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ABSTRACT

The mathematical analysis of the tumour growth attracted a lot of interest in the last two decades. However, as of today no generally accepted model for tumour growth exists. This is due partially to the incomplete understanding of the related pathology as well as the extremely complicated procedure that guides the evolution of a tumour. Moreover, the growth of a tumour does depend on the available tissue surrounding the tumour and therefore it represents a physical case which is realistically modelled by ellipsoidal geometry. The remarkable aspect of the ellipsoidal shape is that it represents the sphere of the anisotropic space. It provides the appropriate geometrical model for any direction dependent physical quantity. In the present work we analyze the stability of a spherical tumour for four continuous models of an avascular tumour and the stability study of an ellipsoidal tumour. For all five models, conditions for the stability are stated and the results are implemented numerically. For the spherical cases, it is observed that the steady state radii that secure the stability of the tumour are different for each of the four models, and that results to differences in the stable and unstable modes. As for the ellipsoidal model, it is shown that, in contrast to the highly symmetric spherical case, where stability is possible to be achieved, there are no conditions that secure the stability of an ellipsoidal tumour. Hence, as in many physical cases, the observed instability is a consequence of the lack of symmetry.
"Μπαίνοντας ο εικοστός αιώνας, στο τελευταίο του τέταρτο, αισθάνομαι άστεγος και
περιττός. Όλα είναι κατειλημμένα - ως και τ΄ άστρα. Οι άνθρωποι έχουν απαλλαγεί
από κάθε παιδεία... Οι κολεγιόπαιδες λύνουν εκπληκτικές εξισώσεις με μιαν ευκολία
που είναι ν΄ απορείς: συν, πλην, διά, επί - άρα. Το μυστικό στη ζωή αυτή, φαίνεται,
δεν είναι αν είσαι δούλος ή όχι. Είναι να οδηγείσαι με συνέπεια σε κάποιο «άρα» και
να ήξεις έτοιμη την απάντηση."
Οδυσσέας Ελύτης

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1. Introduction

In this section the biology of the tumours is being presented followed by an outline of this thesis.

1.1. Introduction to Tumour Biology

1.1.1. From a normal cell to neoplasia

During growth and development, tissue cells rapidly divide in a controlled manner. The proliferation rate of cells is dictated by the tissue type and function. For example, the proliferation rate is arrested in nerve cells, after development, whilst the cells of the intestinal epithelium continue to proliferate at a high rate, throughout life. Both the organ size and the cell number are controlled by mechanisms that regulate the mitotic activity of cells, keeping a balance between programmed cell death (apoptosis) and cell proliferation. Cell proliferation is necessary for tissue regeneration following injury or as part of the normal cell turnover (gut epithelium, skin). For example, the cells of the skin are constantly shed off and thus, multiply in a higher rate than the neuronal cells, which rarely to never proliferate. However, there are cases where cells proliferate at a higher rate than genetically dictated, as mentioned in the work of Michor et al. (2004) and Roose et al. (2007). In particular, increased mitosis is observed in hyperplasia, metaplasia, dysplasia and neoplasia, see Chaplain & Sleeman (1993).

Chaplain & Sleeman (1993) define that hyperplasia occurs in cells, like liver cells
and ovarian cells, when the proliferation rate is increased due to functional requirements. Metaplasia is the process of cell alteration from one type to another (usually from more specialized to less specialized cells). This process is initiated by chronic conditions. A typical example of metaplasia is the conversion of cells of the respiratory track from mucus-secreting, ciliated, columnar epithelium to non-ciliated, squamous epithelium incapable of secreting mucus when are subjected to continuous inhalation of smoke. Dysplasia occurs when there is a disorganized cell pattern in epithelial tissues, such as skin and oesophagus, as a result of a chronic irritation or inflammation. The dysplastic cells increase in number and hence epithelium thickens. Both metaplasia and dysplasia are reversible when the original stimulus ceases to exist. These conditions are also referred as precancerous states since they often lead to neoplasia, when the initial stimulus persists (Melicow (1982)).

Neoplasia is also a state of uncontrollable and abnormal cell proliferation, as stated by Ward & King (1997), Melicow (1982) and Maini et al. (2006). Tumours can arise from all kinds of tissue cells resulting into a large variety of structurally and functionally different tumours (see Chaplain & Sleeman (1993), Fukunari et al. (2003) and Jones et al. (2011)). The main difference between neoplasia and the precancerous states described previously (metaplasia and dysplasia) is that the changes in the cells persist even after the initial stimulus is removed. Plus, the tumour cells have the ability of multiplying and producing same type tumour cells.

Here we quote a basic definition of cancer from Chaplain & Sleeman (1993): “A tumour is a mass of tissue formed as a result of abnormal, excessive and inappropriate (i.e. purposeless) proliferation of cells, the growth of which continues indefinitely and regardless the mechanisms which control normal cellular proliferation.”

At the generic level of description, cancer could be viewed as a cellular disease in which mutations in genes that control growth and maintain homeostasis occur, as referenced by Ward & King (1997), Roose et al. (2007), Byrne et al. (2005), Michor et al. (2004), Maini et al. (2006), Byrne et al. (2006a), Byrne et al. (2006b) and Hanahan & Weinberg (2000). However, because of the variety of tumour types, a more broad definition is needed as suggested by Byrne et al. (2006b). Thus, a cell
is characterized as cancerous when we notice the following characteristics:

- increased proliferating rate,
- decreased apoptotic rate,
- alteration of signalling pathways,
- tendency to form or presence of vascular network,
- insensitivity of anti-growth signals,
- genetic instability and high numbers of mutation incidents,
- tumour-promoting inflammation,
- altered energy metabolism and
- destruction of immune cells (macrophages) that invade the tissue in question.

The above characteristics can be found in the original work of Hanahan & Weinberg (2000) and its extension by Hanahan & Weinberg (2011).

1.1.2. From a single cancer cell to metastatic tumours

As described in Section 1.1.1, genetic mutations in cells result in the development of cancer cells. The cancerous cells aggregations (known as tumour colonies) obtain their nutrients (oxygen and glucose) and release waste products in a similar fashion to the other non-cancerous cells, via simple diffusion. At these early stages, the tumour increases at an exponential rate (Jones et al. (2011)), since all cells are well-nourished and proliferate at their highest rate possible, as supported by the work of Byrne & Preziosi (2003).

As the colony increases in size, the amount of nutrient, in particular oxygen, that reaches the cells close to the tumour centre decreases, since the nutrients are consumed en route from the outside to the inside of the tumour. The proliferation rate of central cells is gradually reduced. Further reduction in the concentration of nutrients below a threshold value, especially oxygen, reversibly arrests cell proliferation.
The non-dividing cells remain alive (see Freyer & Schor (1987)). The cells with arrested proliferation are termed quiescent and they can recover to proliferating cells once the nutrient supply is restored. As the tumour increases in size further, the concentrations of nutrients fall even further. Once they reach a second threshold value, the cell in the centre cannot support their basic metabolic needs and eventually die forming a collection of necrotic tissue.

A tumour cross-section consists of an outer zone of fully proliferating cells, an intermediate zone of quiescent cells and a central core of necrotic tissue and cell debris (Greenspan (1972)), as depicted histologically in Figure 1.1 and schematically in Figure 1.2. Once these three regions are formed, the outer zone remains constant in size. Every new layer of cells on the outside of the outer ring is accompanied by a newly formed layer of quiescent cells at the intermediate zone interface. As the tumour continues to develop, the rim of adequate nourished viable cells at the surface becomes roughly constant in size, leading to a phase of near linear growth, as suggested by Conger & Ziskin (1983), Freyer & Sutherland (1986) and Byrne (2010). Eventually due to the diffusion-limited accumulation of nutrients and wastes, the action of necrotic disintegration, the mitotic inhibitory factors and the delayed proliferation rate, the tumour reaches a maximal size (see the work of Vaupel et al. (1981), Freyer (1988), Landry et al. (1981), Inch et. al. (1970), Folkman & Hochberg (1973) and Haji-Karim & Carlsson (1978)). This dynamic steady state occurs when the death rate equals the proliferation rate, as supported by the work of Roose et al. (2007), Byrne et al. (2005), Maini et al. (2006), Byrne et al. (2006a), Byrne et al. (2006b), Byrne (2012), Perfahl et al. (2011), Owen et al. (2009), Connor et al. (2012), Panovska et al. (2007), Araujo & McElwain (2004), Byrne & Preziosi (2003) and Byrne (2000). Experiments of in vitro growth of nodular carcinomas which are described by Folkman (1971), Inch et. al. (1970) and Sutherland et al. (1971), as well as those of those involving techniques for the in vivo isolation of tumours (see Folkman (1972), Folkman et al. (1971) and Thomlison & Gray (1955)) corroborate the existence of a dormant, but viable steady state described also in Folkman.
& Hochberg (1973) and Sutherland & Durand (1984). If we assume that this is a spherical-like configuration, its diameter measures only a few millimeters (around 2 mm as observed by Folkman & Hochberg (1973)). This structure is the definition of an avascular tumour, which as the term implies, is a tumour without its own blood network.

There are tumours that remain in the avascular stage indefinitely. However, under hypoxic stimulation, most tumours exhibit the angiogenic tendencies. A brief description of angiogenesis tailor-made for mathematicians is found in the book written by Jones et al. (2011). Tumour angiogenesis is driven by hypoxia. The cancerous cells release tumour angiogenic factors (TAFs), a family of proteins that promote angiogenesis in tumours. An important member of TAFs is vascular endothelial growth factor (VEGF). VEGF acts on the neighbouring vasculature and promotes chemotactic and haptotactic angiogenesis (Araujo & McElwain (2004)). The result of VEGF action is the sprouting of capillary ends towards the tumour following
the VEGF gradient. Capillary tips that come into close proximity join together, forming anastomoses, through which circulating blood can flow. Secondary sprouts emanate from the new loops and so the process continues, with increasing numbers of capillary tips being formed until the new vessels penetrate the tumour (Figure 1.3). The newly formed vessels restore the nutrient supply and the proliferation rate of the tumour increases. Now the tumour is characterized as vascular (Figure 1.4) and its size continues to grow beyond the size at the saturation level (steady state size), as described by Folkman (1971).

The formation of blood vessels is a dynamic process. Vessel formation is incomplete because the vessel walls lack muscular tone. As a result they can collapse under the pressure of the surrounding tissue proliferation. Consequently, the areas around the collapsed vessels are deprived of oxygen. The resulting hypoxia promotes further angiogenesis, that restores tissue perfusion. So, the hypoxic cells will once again secrete VEGF and the process described above will recur (see Secomb, T. W. et al. (2000) and Pries et al. (2001)). The neovascularisation supports further tissue proliferation, as the local nutrient levels increase. In this way, the tumour’s spatial structure changes dynamically with periods of cell proliferation alternating with pe-
The presence of blood vessels that connect the tumour with the adjacent vasculature does not only serve for the nourishment of the colony. Small clusters of tumour cells can detach from the original aggregation and travel to distant tissues via the blood network of the host. If the conditions there are favourable, they will establish secondary tumours or metastases that further weaken the host (see Ward & King (1997)). When that happens, the tumour has reached the metastatic phase. Moreover, the rapid growth of vascular tumours may impair the function of neighbouring organs. Invasion is another key characteristic of tumours. Byrne et al. (2005) sug-
gest that contact with the surrounding tissue stimulates the production of enzymes
that digest the tissue, liberating space into which the tumour cells migrate.

1.1.3. On the differences between avascular and vascular tumours

Tumours are classified into two categories; benign and malignant. The benign type
often refers to the slow and relatively harmless avascular state of tumour growth,
mainly because the colony can stay in this dormant state without any clinical
symptoms to the host. Even a rather controversial hypothesis suggests that all
humans have small dormant avascular tumours in their bodies and yet appear and
feel healthy. On the other hand, the malignant type is the rapid and potentially
life-threatening vascular type of cancer. From now, the use of the term benign will
substitute the term avascular, and so the use of the term malignant for the term
vascular.

In reality, as supported in the work of Chaplain & Sleeman (1993), these two types
(avascular-benign & vascular-malignant) really represent the extremes of a spectrum
of tumour growth characteristics. Avascular tumours turn vascular as already de-
scribed, via the process of angiogenesis as depicted in Figure 1.5.

In general, benign tumours are highly differentiated, remain localized, neither in-
vading the surrounding tissues nor giving rise to secondary colonies (metastases).
On the contrary, malignant tumours are less well differentiated, have a higher rate
of proliferation, invade the tissues locally and are able to metastasize.

We proceed in describing the main differences between avascular and vascular tu-
mours, concentrating on the degree of differentiation, the rate of growth, the spread
pattern and the distribution of hypoxic regions.

- Differentiation: by this term we refer to the high order specification of cells
  within a multicellular organism in the interest of fulfilling different functions.
  In the specific context of tumours, a tumour is said to be highly differentiated
  when its structure holds a close resemblance to the tissue of origin. This
  requires that the tumour cells hold resemblance to the adult cells of the tissue of
origin in their morphology, in their arrangement in relation to one another and to the stroma and blood vessels and in their functional activities. However, the tumours are easily distinguishable from the non-neoplastic tissue only because they form a discrete mass. On the other hand, some malignant tumours can be anaplastic (no differentiation resemblance to the native tissue). The individual tumour cells have a primitive, undifferentiated appearance with little attempt at forming special structure. This almost structureless appearance makes the determination of histogenesis extremely difficult. Yet again, there is a spectrum of differentiation of tumour cells, ranging from the well-differentiated cells of the benign to the undifferentiated of the anaplastic. The majority of malignant cells lie in the middle of this spectrum (see Chaplain & Sleeman (1993)). In addition to poor differentiation, malignant tumour cells also vary abnormally in shape and size (even within the same tumour), in their arrangement in relation to one another. These changes combined with the mitotic activity, are sometimes collectively termed cellular atypia. These factors are mostly found in highly, malignant, poorly differentiated cancers in which cellular variability
(pleomorphism) is sometimes extreme (see Chaplain & Sleeman (1993)). Plus, Byrne (2000) suggests that vascular tumours typically contain many cell types, including tumour cells, macrophages and endothelia cells, which are embedded in a tissue matrix, with variable growth rates and cell composition.

- Rate of growth: the rate of increase in the number of tumour cells depends on the rate of cell production and the rate of cell loss. The rate of cell production depends on the number of cells undergoing mitosis and on the time needed to complete a cell cycle. Estimates of cell production can be obtained experimentally upon administration of certain drugs, like colchicin, vinconstine or radio-active (tritiated) thymidine. In vivo animal experiments have shown that benign tumours start by growing at an exponential rate but soon reach a saturation size (see Section 1.1.2). Same experimental techniques reveal that malignant tumours show logarithmic growth at first, but as the tumour enlarges, cell loss increases and the rate of growth gradually slows down. Thus, increase is partly due to the cells of malignant tumours being abnormal and having a rather short average lifespan, which varies for individual tumours. Another cause of cell loss is hypoxia. As the tumour enlarges, it tends to outgrow its blood supply especially if the growth is rapid, as in many malignant tumours. Hypoxia inhibits mitoses and causes the death of individual cells and groups of cells. At the end, an avascular tumour is much smaller than a vascular one, mostly because of the lack of vasculature, which provides constant nutrient supply to the latter.

- Spread of tumours: Benign tumours proliferate locally and grow by expansion. They compress the surrounding tissue, causing atrophy and disappearance of its cells. The stroma of the surrounding tissue is more resistant and becomes condensed to form a fibrous capsule around the tumour. This results to a well-defined edge for benign tumours. However, some benign tumours have little or no capsule but still the margin between the tumour and the surrounding tissue remains sharp without evidence of local invasion. Clinical effects produced by benign tumours arise mainly from mechanical effects such as pressure on
nerves and organs. A benign tumour remains *in situ* for years without caus-
ing ill effects and if detected it is easily removed from its capsule by surgery. On the other hand, malignant tumours grow both by expansion and by pen-
etrating the surrounding tissues. They are not incapsulate and their edges are ill-defined. Projections of tumour cells extend from the main site into sur-
rounding tissues like the legs of a crab (in fact the word cancer comes from the Latin word for crab). Their cells also invade the walls of the lymphatics and blood vessels in and around the tumour and are carried away to other parts of the body where they may proliferate, giving rise to secondary tumours and metastases. Malignant tumours can be eliminated if they are recognized and successfully removed by surgery before the stage of metastasis. Nonetheless, the aggressive behaviour of malignant tumours presents the major obstacle to their complete removal and once metastatic spread has occurred, surgical removal of the primary tumour has no positive effect.

- Hypoxic region: A key feature of many solid tumours growing *in vivo* or as tumour spheroids *in vitro* is the presence of regions of low oxygen as evidenced by microelectrode measurements and staining for hypoxia induced factors. In avascular tumours or in spheroids, cultured *in vitro*, hypoxic regions form when the tumour reaches a critical size when the diffusion of oxygen and other nutrients from the surrounding medium is insufficient to meet the metabolic demands of cells in the interior as mentioned by Owen *et al.* (2004). The same mechanism is believed to trigger the appearance of hypoxia in vascularized tumours. Blood vessels within malignant tumours are typically surrounded by an annulus of proliferating cells a few cells thick, followed by a poorly oxy-
genated or hypoxic layer. Often there are regions that the cells are unable to survive and form a necrotic region. Cells respond to hypoxia in a number of ways. Typically, they reduce their rates of proliferation. As a result, become less responsive to chemotherapies that target rapidly dividing cells. They may also produce a range of chemicals, including VEGF which stimulate the angio-
genesis (for further information refer to Maxwell *et al.* (1997) and Owen *et al.*
This process is fully described in Section 1.1.2.
1.2. Outline of the thesis

In this section we present the outline of the thesis. An introduction to tumour biology has already been presented. More specifically, Section 1.1.1 refers to the different types of over-proliferating cells and especially to the conditions that transform a normal cell to a cancer cell. Then, in Section 1.1.2 there is a description of the evolution of a tumour colony, from a single cancer cell to vascular and metastatic tumours. Section 1.1.3 focuses on the differences between avascular and vascular tumours, most commonly described as benign and malignant tumours, respectively. The present section (Section 1.2) is devoted to the outline of the thesis.

A literature review on mathematical models concerning tumours can be found in Chapter 2. Section 2.1.1 is devoted to the literature review of models in the genesis of cancer, especially in modelling the sequence and timing of mutations that lead to carcinogenesis and modelling the effect of environmental conditions on tumour progressions. In Section 2.1.2, there is a list of models for avascular tumour growth, where Section 2.1.3 refers to models for tumour invasion. Sections 2.1.4 and 2.1.5 focus on the newest models on tumour angiogenesis and vascular tumour growth which are more complicated than the models in previous Sections with a less analytical and a more numerical approach. This Chapter would be far from complete if Sections 2.1.6 and 2.1.7 were missing. Section 2.1.6 is dedicated to the reasons why researchers keep working on modelling the avascular tumour growth, since this stage is relative harmless to the patient, while Section 2.1.7 gives reason on choosing between a continuum or a discrete, cell-based model according to the specific needs of the problem we are addressing. The next three sections are dedicated the three models from the literature on the stage between avascular and tumour invasion which served as a inspiration for this thesis. In Section 2.2 there is a detailed description of the Greenspan model for a spherical tumour. This model serves as a guideline for both stating the problem of tumour growth and performing a stability study on perturbed colonies. Section 2.3 is dedicated to non-homogeneous model for
an ellipsoidal tumour, while Section 2.4 hosts the reduction of the non-homogeneous model from an ellipsoidal tumour to a spherical one.

Chapter 3 includes original work for this thesis. This chapter is dedicated to two new models for spherical tumour growth that are derived from the models described in Section 2.2 and 2.4. In Section 3.1, there is a detailed description of the non-homogeneous Greenspan model for a spherical tumour, focusing on the differences and similarities with the homogeneous Greenspan model and the non-homogeneous modified spherical case. Section 3.2 refers to the homogeneous modified model for a spherical colony, in comparison to the models of Section 2.2 and 2.4.

Chapter 4 is dedicated to the original work of studying perturbation on spherical tumours. Each section includes a different model, but they share in common the $\vartheta - \varphi$ dependence of the perturbation. In details, Section 4.1 contains the study of $\vartheta - \varphi$ dependent perturbation of the homogeneous Greenspan model, while Section 4.2 holds the relevant study for the non-homogeneous Greenspan model. Sections 4.3 and 4.4 are dedicated to stability study of the homogeneous and non-homogeneous modified model, respectively.

The main core of this thesis ends up with the stability analysis of the non-homogeneous ellipsoidal model. This model, because of its complexity and importance, comprises the whole 5th Chapter of this thesis.

This work would be incomplete if Appendices and a list of literature papers were missing. In details, Chapter 5 is followed by the Bibliography, while in the end of this manuscript there are appendices dedicated on spherical and ellipsoidal geometry, spherical and ellipsoidal perturbation, plus an appendix on calculations from unperturbed to perturbed models.
2. Mathematical models of Tumour Growth

This chapter begins with a literature review of mathematical modelling of tumour growth (Section 2.1). In Section 2.2, we present the Greenspan model for a spherical tumour colony as presented by Greenspan (1976), plus some graphs on pressure and nutrient distribution produced for the thesis only. In Section 2.3 we refer to the model for an ellipsoidal tumour proposed by Dassios et al. (2012). At the end of Section 2.3 we plot the pressure and nutrient profiles of an ellipsoidal tumour for a more complete presentation of the model. Lastly, Section 2.4 contains the reduction of the ellipsoidal tumour which is described in Section 2.3, to a spherical one. The latter model was also proposed by Dassios et al. (2012). Section 2.4 also includes our figures for the pressure within the tumour and the nutrient concentration distribution across our domain of interest.

2.1. Literature review in mathematical modelling of tumours

In this section, we present a literature review on mathematical modelling of tumours. There are models for the genesis of tumours, namely for the sequence and timing of mutations, as well as the effect of environmental conditions on tumour progressions (Section 2.1.1). In Section 2.1.2 we present the most popular models for avascular tumour growth and in Section 2.1.3 models for tumour invasion. Next, following the evolution of tumour, we proceed to the models of tumour angiogenesis (Section 2.1.4) and vascular tumour growth (Section 2.1.5). The last two sections (2.1.5 and
2.1.6) are literature evidences on why it is important to keep modelling the avascular state of tumour growth and on whether it is better to use continuum or discrete cell-based models.

In this section, we focus on Sections 2.1.2 and 2.1.3 as those are the growth stages that we are interested in for this study.

2.1.1. Models for the sequence and timing of mutations and the effect of environmental conditions on tumour progressions

In this section we will focus on the models describing the birth of cancer cells. These models describe mathematically the frequency of mutations and how environmental conditions can lead to tumour initiation.

Armitage & Doll (1954) suggested that the age distribution of a cancer is connected to the number of changes (not necessarily mutations) needed for its progression in a proportional way. This model serves as an excellent description for cancers of colon, stomach and pancreas, but fails to describe others like breast and prostate cancer.

Research on gene mutations has gone a long way since 1954. Based on the work of Hanahan & Weinberg (2000), newer models are now being used to investigate how the sequence and timing of mutations and the environmental conditions influence tumour progression.

Here we briefly present models of evolution on studying the effect and/or chromosomal instability and microsatellite instability on tumour initiation (see Komarowa et al (2008) and Siegmund et al. (2009)).

Komarowa et al (2008) used optimal control theory to identify from a set of time-varying mutation rates, the mutation rate that enables a population of cancer cells to rapidly attain a given size. Their analysis showed that, for most choices of parameter values, the optimal strategy for the tumour could be characterized by a mutation rate that is initially high and reduces over time. This prediction is consistent with the behaviour of many cancers that show a high degree of genetic instability during early growth and stabilize as the disease progresses.
By exploiting increase in computing power and the availability of large data sets, Siegmund et al. (2009) have recently applied statistical methods to DNA methylation patterns to infer the genetic evolution of colorectal cancer cells at several sites of the tumour. As the ancestral trees from different sites revealed a common ancestor at the time of transformation, they went on to conclude that the cancers were probably initiated by a period of rapid clonal expansion, rather than being established at different times by different cells.

2.1.2. Models for Avascular Tumour Growth

As mentioned in Chapter 1, once normal cells mutate to cancer cells, a tumour colony starts growing by simple nutrient diffusion. This avascular state is approached by using either 1) continuum mathematical models that use space averaging and thus consisting of partial differential equations or 2) discrete cell population models that consider processes that occur on the single cell scale and introduce cell-cell interaction using cellular automata-type computational machinery. Mathematical models describing continuum cell populations and their development classically consider the interactions between the cell number density and one or more chemical species that provide nutrients or influence the cell cycle events of a tumour cell population. Thus these models typically consist of reaction-diffusion-convection equations (see Roose et al. (2007)).

On the other hand, because of advances in biotechnology, large amounts of data on phenomena occurring on a single cell scale are now available. This, combined with in vitro experiments using tumour spheroids and high power confocal or multiphoton laser microscopy that enables tracking of individual cells in space and time, has allowed the modelling single-cell-scale phenomena and then using the techniques of upscaling to obtain information about the large-scale phenomena of tumour growth (Roose et al. (2007)). There are several upscaling techniques, with the most popular being the cellular automata as seen in the works of Anderson et al. (2000), Duchting & Vogelsaenger (1985), Qi et al. (1993), Kansal et al. (2000a), Kansal et al. (2000b),

The early models on avascular models concentrated on spatio-temporal aspects of the growth (see Burton (1966) and Greenspan (1972)). The researchers focused on describing how the size and structure of three dimensional multicellular spheroids (MCS) change when culture conditions are manipulated. The simplicity and reproducibility of the experimental assays for MCS, the availability of reliable data on the size and composition of the spheroids and information about the spatial distributions of key metabolites like oxygen and glucose, and chemotherapeutic drugs, made MCS attractive subjects for mathematical modelling.

It all began with Thomlison & Gray (1955) who related the diffusion of nutrients and tumour heterogeneity. Then, the paper written by Burton (1966) was the first to suggest that diffusion and nutrient consumption might be limiting factors to the solid tumour growth. In details, Burton (1966) was the one who extended the work of Thomlison & Gray (1955) to link tumour growth with the size of the region in which the nutrient concentration is greater than some critical level.

Greenspan (1972) proposed a model which attempts to capture all the phases of avascular growth by adding the action of mitotic inhibitor (produced within the tumour) and necrotic decomposition and by dividing the tumour into distinct compartments of proliferating, quiescent and necrotic cells. Today, these models can seem extremely simple, and perhaps even naive, especially when compared to the detailed computational models that are currently being developed to study solid tumour growth. To this extent, early models simplified the problem by assuming that the spheroids are radially symmetric and their growth regulated by a single, diffusible growth factor that is supplied externally, like oxygen or produced internally like the tumour necrosis factor. Another example of oversimplification was that the threshold values of oxygen alone can delineate regions of cell proliferation (high oxygen), quiescence (intermediate oxygen) and necrosis (low oxygen).
Owing to their simplicity, the early models of MCS have limited applicability. For example, the spheroids are assumed to comprise a single population of cells and stochastic effects are ignored, so that the emergence of different clonal subpopulations cannot be investigated. Equally, cell metabolism is assumed to be controlled by a single diffusible species, whereas in practice multiple metabolites are involved. In particular, as tumour cells become starved of oxygen they switch from aerobic to anaerobic respiration (Byrne (2010)).

There was also misguided evidence of those models that they were working in a good enough manner. Analytical expressions for the size of the spheroid at the onset of quiescence and the width of its outer, proliferating shell during the linear growth phase can be used to estimate model parameters and predict the effect of changing the concentration of the key growth factor being supplied to the spheroid (see Araujo & McElwain (2004)). The agreement between the experimental data on MCS and the dynamics of mathematical modelling indicates that the models provide a realistic description of the biological processes that regulate the growth of MCS. Such agreement does not constitute a “proof” that these mechanisms alone regulate MCS (Byrne (2010)).

So, throughout the years, some corrective assumptions have been made in the modelling approaches. Although the initial focus of MCS models was on the diffusible growth factors, the introduction of cell movement and pressure marked a conceptual change to accommodate mechanical effects. For example, in the model presented by Araujo & McElwain (2004) pressure gradients, generated by differences in cell proliferation and death, cause cells to move from regions of high cell proliferation and pressure (near the tumour periphery) to regions of net cell death and lower pressure (at the tumour centre).

Additionally, either surface tension of cell-cell adhesion is assumed to maintain the compact nature of the tumour mass and counter the expansive forces that are associated with tumour growth. Routine model analysis reveals that the strength of cell-cell adhesion - the affinity of cells to remain as a coherent mass-strongly influences spheroid morphology, strong cell-cell adhesion yields radially symmetric
spheroids, and weak adhesion yields irregular, fractal-like spheroid boundaries. Mutations that weaken cell-cell adhesion might be a characteristic feature of highly invasive tumours.

Other authors have developed biomechanical models in which the tumour is seen as a mixture of interacting phases, for example cells and extracellular fluid cultured in suspension (Ward & King (1997) and Byrne et al. (2003)) or embedded in a tissue matrix. Tissue mechanics models consider the mechanical interactions between tumour cells with the aim of answering questions about how the mechanical properties of the tumour, and the tissue in which the tumour grows influence tumour growth. Several independent models (Heimlinger et al. (1997) and Roose et al. (2003)) have shown that the growth-induced compression of a compliant tissue matrix (or gel) that surrounds a tumour spheroid can generate restraining forces that arrest the growth of the spheroid, even when nutrients are freely available.

Stiffer tissues give rise to smaller spheroids. These results suggest that knowledge of the mechanical properties of a tumour and its surrounding tissue might be important for characterizing invasive potential. They also explain how therapies designed to alter the mechanical properties of the tissue stroma by, for example, neutralizing the action of matrix-degrading proteases, might retard invasion. In practice, the tissue stroma surrounding a tumour is heterogeneous and subject to continuous remodelling (see Radisky et al. (2007) and Bertheim et al. (2004)).

Byrne (2012) have used cellular automata to investigate how the microenvironment (specifically, the local oxygen concentration and extracellular matrix density) influences and is influenced by the growth dynamics and phenotypic diversity of a tumour. Their simulations predicted that when oxygen levels are low the tumour will rapidly diverge from its initial phenotype and exhibit high levels of population diversity, with aggressive phenotypes quickly becoming dominant.

Due to the advantages of both the continuum and the discrete models (see Section 2.1.6), researchers tried to combine them into hybrid models. Byrne & Drasdo (2009) have developed complementary cell based and continuum models of MCS growth that exhibited similar growth kinetics. By fitting the pro-
files for the tumour radius and pressure distribution generated by each model they estimated parameters for the continuum model from parameters in the cell-based model. In this way, they have shown how cell-based models can be used as an intermediate step to measurable biophysical properties of individual cells to parameters that appear in continuum models of MCS.

Kim et al. (2007) have developed a new type of hybrid model in which a continuum model is used in regions with a high tumour cell density and a discrete model is used in regions with a tumour cell density that it is too low to justify the use of a continuum model.

2.1.3. Models for Tumour Invasion

When the tumour reaches the maximum saturation size, VEGF is produced within the tumour in order to attract capillary tips and sprouts from the nearby vasculature. At this stage, the tumour loses its symmetric shape and surface deviations are formed. In this context, some of the earliest continuum models of tumour angiogenesis are based on an analogy with fungal growth, where both phenomena exhibit interconnected, branched structures that evolve in response to environmental signal (see Alarcón et al. (2005)).

Greenspan (1976) was the first to model surface perturbation on an initially spherical tumour. This model is described in details in Section 2.2. The extensions and modifications to Greenspan’s original model of MCS are now so numerous that it is impossible to do justice to them (Araujo & McElwain (2004), Preziosi (2003), Tracqui (2009) and Roose et al. (2007)). Important developments include relaxing the assumption of radially symmetric growth (Araujo & McElwain (2004), Byrne & Chaplain (1996) and Cristini et al. (2003)) and distinguishing different cell populations within the spheroid (see Ward & King (1997)). For example, whereas Greenspan (1976) used analytical techniques to predict how the invasive boundary of a tumour initially develops, Greenspan (1976) used sophisticated numerical methods to solve the system of nonlinear equations and realte the irregular shapes
adopted by the tumour to the values of key model parameters.

If the tumour is assumed as an incompressible fluid and contains no voids or holes, then cell proliferation and death generate spatial variations in the pressure within the tumour which drive cell motion, with cells moving down pressure gradients, away from regions of net cell proliferation and toward regions of net cell death. Surface tension is also incorporated into the model as a mechanism for maintaining the compactness of the tumour and counteracting the expansive forces caused by cell proliferation (Byrne (2012)).

Byrne (2012) presented an analysis that provided a mechanism which may explain how the irregular morphology characterizing invasive tumours may be initiated. To understand this, Byrne (2012) considered a uniform cluster of tumour cells for which the surface tension coefficient is significantly large than the underlying radially-symmetric solution is linearly stable to symmetry-breaking perturbations including the use of Legendre polynomials. This particular analysis predicted that such a cluster would remain radially symmetric through its development.

Suppose now that the cells undergo a transformation which weakens the surface tension forces holding the tumour cells together. If the reduction is significant, then the tumour will become unstable to a finite range of asymmetric perturbations and will develop an irregular morphology. Byrne (2012) noted that similar quantitative behaviour is obtained if, instead of invoking surface tension (and the associated jump in the pressure across the tumour boundary), the nutrient concentration is assumed to be discontinuous across the tumour boundary, with a jump related to the local curvature. The physical motivation for this boundary condition is that the nutrients (or its energy-equivalents) are utilized by cells on the tumour boundary to maintain its compactness.

Avascular tumours that possess irregular boundaries have been reported. In order to understand how such non-uniform boundaries may form, several authors have used linear techniques to investigate the stability of radially symmetric tumour configurations to asymmetric perturbations, the underlying spherically symmetric state resembling avascular nodules, as predicted by the work of Greenspan (1976), Chap-
lain (1993) and Byrne & Chaplain (1996). Recently, Byrne (1999) has used weakly nonlinear analysis to resolve these problems. They studied the global stability of quasi-steady solutions for a simple mathematical model describing the growth of a spherical vascularized tumour consisting only of living cells. By assuming the rates of proliferation and absorption to be increasing nonlinear functions of the nutrient concentration, they establish the existence of a non-trivial steady solution and conditions for the existence and uniqueness of a quasi-steady solution for each initial configuration. Also, we prove that all these quasi-steady solutions converge uniformly to a non-trivial steady solution. The quasi-steady approach is justified by the smallness of the parameter that measures the ratio between the timescales for the diffusion of nutrients and growth of the tumour (Bueno et al. (2005)).

2.1.4. Models for Tumour Angiogenesis

Some of the earliest continuum models of tumour angiogenesis are based on an analogy with fungal growth, both phenomena exhibiting interconnected, branched structures that evolve in response to environmental signals (see Alarcón et al. (2005)). Balding & McElwain (1985) adapted a fungal growth model develop by Edelstein (1982). They focused on three key physical variables: a generic, diffusible chemical produced by the tumour and termed as TAF, capillary tips and capillary sprouts. Their one dimensional model consisted of three nonlinear partial differential equations that were derived by applying the principle of mass balance to each species (see Alarcón et al. (2005)). Balding & McElwain (1985) proposed a simple model of tumour angiogenesis to describe the experiments in which tumour cells implanted in the rabbit cornea stimulated the formation, growth and migration of new blood vessels from the limbus to the tumour (Folkman (1974)). The model focused on a generic, tumour-derived chemical, termed as TAF. The model was set up so that TAF produced by the tumour cells was assumed to diffuse towards neighbouring vessels and to undergo a
natural decay at the same time. In addition, the tumour was assumed to produce TAF at a constant rate so that the concentration of TAF at the tumour boundary was maintained at a constant value. The capillary tips were assumed to emanate from existing vessels and tips at rates proportional to TAF levels, to move by chemotaxis up spatial gradients of TAF and to form tip-to-tip anastomosis. Numerical simulations of Balding and McElwain’s model and its subsequent extensions (Byrne & Chaplain (1995)) reproduced many characteristic features of angiogenesis, including acceleration of the developing vasculature towards the tumour and a peak in the density of capillary tips preceding a peak in the density of blood vessels, as predicted by Muthukkaruppan et al. (1982).

The basic models have also been extended to account for tumour growth during angiogenesis and the increase in nutrient availability associated with the expanding vasculature (Panovska et al. (2007)). Many modifications have been developed, like the work by Byrne & Chaplain (1995) and Orme & Chaplain (1996), in terms of different production and removal terms of the TAF and the capillary tips. However in each case, the results are similar and exhibit many of the characteristic features of angiogenesis that have been observed in vivo (Muthukkaruppan et al. (1982)).

Expansions of the early models of tumour angiogenesis to two and three spatial dimensions highlighted their main weaknesses (see Orme & Chaplain (1997)) which are described next. Since the vessels were treated as a single model variable, only variations in their concentration were considered and details of the morphology of the vascular network are ignored. Consequently, such models were unable to distinguish between a tissue perfused by a large vessel and another perfused by a large number of small vessels, even though the amount of oxygen being delivered to the two tissues might vary markedly. Vascular remodelling and the effect of blood flow on the evolving vasculature were also neglected. Moreover the models did not distinguish between anastomosis and capillary tip death, even though the former would have increase nutrient supply to the tissue while the latter would not. Finally, no account is taken of vascular remodelling and in particular, the impact of blood flow and haematocrit on the evolving vasculature. In spite of these weaknesses, the mod-
els do provide useful insights into the ways in which different physical mechanisms (eg the strength of the chemotactic response, the rate of TAF production, the rate of capillary tip formation) influence angiogenesis. In particular, the success of angiogenesis is tightly controlled by the balance between endothelial cell proliferation and migration: as the strength of the chemotactic response increase, the tips migrate towards the tumour more rapidly, thereby reducing both the time available for tip proliferation and the density of vasculature when the tumour is reached (Orme & Chaplain (1996)).

These weaknesses described above have stimulated the development of a new class of hybrid models that account for the detailed morphology of the angiogenic network. Hybrid models combine two or more different modelling approaches. For example, reaction-diffusion equations for nutrient transport and consumption can be coupled to a cellular automaton that describes how normal and tumour cells interact.

Stokes & Lauffenburger (1991) coupled a probabilistic equation for the movement of individual endothelial cells to a diffusion equation for TAF. Their simulations revealed that a chemotactic response to a TAF is necessary for stimulating directed vascular network growth and that a substantial level of random motion is required for vessel anastomosis and capillary loop formation - an overly strong response produced networks largely devoid of these features. By obtaining independent qualitative and quantitative agreement of heir model with *in vitro* and *in vivo* experiments, they not only demonstrated that *in vitro* migration assays can be used to test putative inhibitors and activators of angiogenesis but also highlighted an important role of mathematical modelling as a bridge between *in vivo* and *in vitro* experiments.

Recently, Anderson & Chaplain (1998) have developed a hybrid model in which capillary tips movement is treated as a random walk, which is biased towards higher levels of TAFS and blood flow is included (McDougall *et al.* (2002)).

In the work published by Levine *et al.* (2000) and Levine *et al.* (2002), the researchers proposed a model to account for specific angiogenic and anti-angiogenic factors (such as vascular endothelial growth factor A (VEGFA), angioprotein 1 (ANGPT1) and 2 (ANGPT2), anti-angiogenic compounds (such as endostatin and angiostatin) and
protease inhibitors) and interactions between the endothelial cells that line the blood vessels and other cell types (such as pericytes and macrophages). They developed highly complex models that account for detailed knowledge of specific chemicals and biochemistry involved. They account for interactions between endothelial cells, angiogenic factors and cells as pericytes an macrophages that are also involved in angiogenesis. They based their work on the theory of reinforced random walks. Panovska (2004) showed that enhanced migration together with tip production from the vessels via branching, rather than endothelial cell proliferation, can be alternative to constant migration and additional proliferation of the endothelial cells in the tips for successful angiogenesis.

Anderson & Chaplain (1998) developed a continuum-discrete model in which the movement of the tips of the vessels was modelled by the means of a biased random walk whose transition probabilities were derived by discretization of a previously developed partial differential equations model. In this work, the role of haptotaxis (migration upward gradient of adhesive molecules, in particular fibronectin) was examined and shown to be a key factor in successful angiogenesis. Whilst it is straightforward to extend Baldwing and McElwain’s model to two and three dimensions, the resulting models highlight some of the shortcoming of using a continuum framework to study angiogenesis. This is primarily because angiogenesis is a two or three dimensional process, with tips sprouting in directions other than of the propagating vascular front, and it is not immediately clear how the snail trail should be generalized in higher space dimensions (Alarcón et al. (2005) and Orme & Chaplain (1996)).

Alarcón et al. (2003) developed a mathematical model that shows how blood flow and red blood cell heterogeneity influence the growth of systems of normal and cancerous cells. First, they determined the distribution of oxygen in a native vascular network incorporating into the model features of blood low and vascular dynamics such as structural adaptation, complex rheology and red blood cell circulation. Once they had calculated the oxygen distribution, they then studied the dynamics of a colony of normal and cancerous cells, placed in such a heterogeneous environment.
During the second stage, they assumed that the vascular network did not evolve and was independent of the dynamics of the surrounding tissue. The cells were considered as elements of a cellular automaton, whose evolution rules were inspired by the different behaviour of normal and cancer cells. Their most important result was that environmental inhomogeneity restricted dynamically the ability of malignant colonies to grow and invade healthy tissue. This was because non-uniform oxygen perfusion led to the existence of very poorly oxygenated regions which the cancer cells failed to populate. One weakness of the model in question was the fact that the vasculature was independent of the dynamics of the surrounding tissue. However, this situation was not realistic. For it is known that vasculature adapts to the needs of the tissue. In order to couple the dynamics of the tissue with the structural adaptation of the vessels, growth factors should be introduced to the model proposed by Alarcón et al. (2003).

2.1.5. Models for Vascular Tumour Growth

Hahnfeldt et al. (1999) proposed a simple model, formulated as a system of differential equations, coupling the growth of the tumour mass and its vasculature. Similar models, including systems of differential equations, have been developed to investigate the contributions of angiogenesis and vasculogenesis to the growth and treatment of vascular tumour (Stoll et al. (2003) and Stamper et al. (2007)). More detailed models that also account for the influence of VEGF and the angioproteins on vessels maturation have been used to show how the strength of the angiogenic response affects the growth rate of a tumour, as the model by Arakelyan et al. (2005) showed. In particular, Arakelyan et al. (2005) low vessel maturation rates in tumours with low background vessels densities will give rise to slowly growing tumours that possess large proportions of immature vessels and might exhibit oscillatory growth dynamics. Cristini et al. (2003) predicted that highly vascularized tumours would remain compact in shape while they grow, whereas those with limited nutrient availability would
develop invasive fingers leading to tumour fragmentation. Following the model published by McDougall et al. (2002), similar hybrid models of vascular tumour growth have been developed to investigate interactions between a tumour and its vasculature.

By coupling a cellular automaton model with a system of reaction-diffusion equations for key metabolites, Patel et al. (2001) studied the effect of vascular density and tumour metabolism on the invasive potential of tumour cells that could survive at lower pH levels than normal cells. The vasculature was modelled as a series of localized sources (sinks) of glucose. Numerical simulations revealed a range of vascular densities for which tumour growth and invasion were optimal: at lower densities, excessively low pH levels cause both normal and tumour cells to die and at higher densities the vessels network rapidly eliminated any acid that is produced so it is maintained at low levels and the tumour cells lose their competitive advantage over normal cells.

In practice, the tumour vasculature is a highly dynamic network, with new vessels being produced to meet the metabolic demands of under-perfused, hypoxic tumour regions while redundant vessels, with low flow, are pruned at other sites. For example, Macklin et al. (2009) have shown that the inclusion of extracellular matrix degradation by tumour cells can hinder newly formed blood vessels from penetrating the tumour mass. This results in the generation of vascular networks that encapsulate the tumour mass and are inefficient at delivering nutrients to the tumour. Araujo & McElwain (2004) have developed a computational framework that couples processes that function at the subcellular, cellular and tissue scales.

2.1.6. Why is it good to keep modelling the avascular growth?

When attempting to model any complex system it is wise to try and understand each of the components as well as possible before they are all put together. Avascular tumour growth is much simpler to model mathematically and yet contains many of the phenomena which are needed to address in the general case of vascular tumour
growth modelling. Moreover, the reproducibility of experiments with avascular tumours implies that the quality and quantity of experimental evidence exceeds that for vascular tumours, for which it is often difficult to isolate individual effects (Roose et al. (2007)).

In contrast to avascular tumours, which can be easily studied in the laboratory and have highly reproducible growth patterns, vascular tumours must be grown in \textit{in vivo} and their growth dynamics are extremely diverse. Indeed, owing to the interplay between the rapidly proliferating tumour cells and the evolving vasculature, the composition of a single tumour can be highly heterogeneous in both space and time. For example, a functioning blood vessel can, over time, become occluded or collapse when the pressure exerted on it by the increasing number of tumour cells that it supports. The associated reduction in nutrient supply could stimulate the tumour cells to produce angiogenic factors that will regulate the growth of new blood vessels into the region (see Folkman (1974), Folkman (2002) and Jain (1988)). These factors combined with the technical challenge of collecting information about how the spatial composition of a vascular tumour changes over time, have frustrated mathematicians in attempting to model vascular tumour growth.

Thus we see the modelling of avascular tumours as a first step toward building models for fully vascularized tumours. There are parallels between avascular tumour growth and the growth of a tumour tissue in the microregion supported by a single blood vessel inside a vascular tumour. Thus, avascular tumour modelling can be of use when making predictions and designing experiments on vascular and metastatic tumours, which are much more time consuming and difficult as they have to be performed \textit{in vivo} (Roose et al. (2007)).

2.1.7. Continuum or discrete, cell-based model?

In practice, the question of whether to use a continuum or a cell-based model strongly depends on the questions that the particular model addresses and the type of data available. In general, cell-based models can be more easily extended to account
for additional data on subcellular signaling pathways and/or the cell type, whereas continuum models contain fewer parameters and, as a result, should give better fits to the data (Byrne (2010)).

In details, models as Greenspan (1976), Byrne & Chaplain (1996), Cristini et al. (2003), Ward & King (1997), Byrne et al. (2003), Helmlinger et al. (1997), Chen et al. (2001), Roose et al. (2003), Radisky et al. (2007) and Bertheim et al. (2004) are continuum models because they describe how cell populations and concentrations change and, in contrast to discrete cell-based models, they do not distinguish between individual cells. Therefore, continuum models share several common features: the tumours are seen as continuous masses that contain a small number of distinct populations, stochastic effects are usually neglected and subcellular phenomena are ignored (Byrne (2010)).

As such, they are well suited to studying the growth kinetics of tumour spheroids that contain a large number of cells but less well suited to small clusters of tumour cells, such as metastases (Byrne (2010)).

For studying small spheroids, discrete models (such as cellular automata) that view the tumour as a collection of interacting cells, each assigned their own set of parameter values and behavioural rules, are gaining in popularity and have been used to study tumour invasion (Anderson (2005)).

When comparing cell-based and continuum models of tumour growth, an obvious advantage of cell-based models is the relative ease with which parameters to model their behaviour can be chosen using measurable biological and biophysical quantities, such as cell growth rates during the cell cycle and membrane deformation in response to mechanical loading (Byrne (2010) and Osborne et al. (2010)). Discrete models have the advantage that they are perfectly adapted to modelling internal signaling networks within each cell. There is in addition no requirement that all cells be the same; indeed each can behave differently with no extra complication. Also, the validity of the averaging over cells implicit in writing down a continuum model is questionable, especially when cells of more than one type are considered (Roose et al. (2007)).
On the other hand, given that tumour growing in vitro and in vivo typically contain between $10^6$ and $10^{11}$ cells, it might be more practical to use a continuum rather than a cell-based model to simulate their development (Byrne (2010)) Moreover, continuum models have the advantage of being more amenable to mathematical analysis and understanding, and one thus better be able to aid intuition and give insight into underlying physical and biological principles. In addition they are likely to contain fewer parameters and can build on existing bodies of knowledge on continuum mechanics in other fields. The main problem with discrete models is that it is very difficult to build in realistic movement and growth laws based on biology and physics. In addition, they usually contain many more parameters and can only be analyzed computationally.
2.2. The Greenspan model for a spherical tumour

In this section, we present the Greenspan model for a spherical tumour. First, we introduce the equations and the boundary conditions that approach the avascular growth state of the spherical tumour. Then we introduce the perturbed variables assuming that they depend on both $\vartheta$ and $\varphi$ spherical angles in contradiction to the assumption of Greenspan (1976) for $\vartheta$–dependence only. To conclude, we state the solutions for the pressure distribution, the nutrient concentration and the radius evolution for the case of complete spherical symmetry and we plot those variables in graphs to visualise the results. The analysis for the perturbed case can be found in Section 4.1.

Every minute new cells are born, while old ones die. This dynamic process alters the number of cells in a tumour, and thus internal pressure changes occur. On its turn, internal pressure results in cellular motion. This action is assumed to be governed by the equation

$$ q (x, y, z, t) = -\nabla p , $$

(2.1)

where $q$ is the particle velocity and $p (x, y, z, t)$ denotes the internal pressure. We substitute $q$ with either $-\nabla p$ or $dr/dt$, the boundary velocity, depending on the case, to avoid using a lot of different parameters. Mass conservation within the tumour volume combined with a constant rate of volume loss per unit volume ($S_1$) is expressed in terms of

$$ \Delta p = S_1 , \ r < r_P . $$

(2.2)

A cross-section of the colony is depicted in Figure 2.1. This Figure reflects the homogeneity within the tumour in terms of pressure distribution. In other words, we assume that the rate of volume loss per unit volume is the same in every part of the tumour colony regardless of necrotic core or living layer and this is depicted as a same colour everywhere. We assume that both the tumour and its environment are in a state of diffusive equilibrium for the nutrient concentration ($\sigma$) at all times,
throughout our domain of interest

\[\Delta \sigma = 0 .\]  \hspace{1cm} (2.3)

We also assume that far away from the tumour, there is a source of constant nutrient supply \((\sigma_\infty)\),

\[\sigma \to \sigma_\infty, \text{ as } r \to \infty .\]  \hspace{1cm} (2.4)

On the evolving tumour surface, the pressure should equal the surface-tension force. This condition show that the tumour is a compact and continuous mass and mathematically is expressed as

\[p = \alpha \kappa ,\]  \hspace{1cm} (2.5)

where \(\alpha\) is a constant and \(\kappa\) the mean curvature. Due to mass conservation, the mass/volume flow of cells out of the sphere equals to the rate of mass/volume production within this volume, that is

\[\frac{dr}{dt} \cdot \hat{n} = -\hat{n} \cdot \nabla p + \lambda \sqrt{\sigma} ,\]  \hspace{1cm} (2.6)
where \( \hat{n} \) is the normal unit vector on the tumour surface, \( \lambda \) is a parameter of order 1 for the volume of the proliferating layer and \( \sqrt{\sigma} \) at the boundary is governed by the following equation

\[
\sqrt{\sigma} = \frac{2\sigma_\infty}{\mu r_P + \sqrt{\mu^2 r_P^2 + 4\sigma_\infty}}.
\]  

(2.7)

Assuming continuity across the area of living cells, we obtain

\[
\frac{dr}{dt} \times \hat{n} = -\nabla p \times \hat{n}.
\]  

(2.8)

Similarly with the pressure, the rate at which the nutrient diffuses through the boundary equals the rate at which the nutrient is consumed, that is

\[
\hat{n} \cdot \nabla \sigma = \mu \sqrt{\sigma},
\]  

(2.9)

where \( \mu \) is the parameter for the volume of the proliferating layer in the case of nutrient concentration. We introduce a perturbation of the pressure distribution, the nutrient concentration and the radius in the following form,

\[
p(r, \vartheta, \varphi, t) = \bar{p}(r, t) + \varepsilon \bar{p}(\vartheta, \varphi, t),
\]  

(2.10)

\[
\sigma(r, \vartheta, \varphi, t) = \bar{\sigma}(r, t) + \varepsilon \bar{\sigma}(\vartheta, \varphi, t),
\]  

(2.11)

\[
r(\vartheta, \varphi, t) = r_P(t) + \varepsilon \xi(\vartheta, \varphi, t),
\]  

(2.12)

where \( \varepsilon \) is a small parameter, \( \bar{p}, \bar{\sigma}, r_P \) are variables of the spherical tumour (pressure, nutrient concentration and radius respectively) and \( \bar{p}, \bar{\sigma}, \xi \) are variables of the perturbed part depending on both spherical angles, in contradiction to Greenspan (1976), where he proposed perturbations depending only on \( \vartheta \).

In this Section, we focus on the unperturbed part of the model. So, we are interested only on the \( \bar{\ } \) variables. More details about the calculations from the full model to the separated unperturbed and perturbed models can be found in the Appendix E. Under the hypothesis of complete spherical symmetry, all cell variables depend only on \( r \) and \( t \) because of the assumed spherical geometry. In fact, the tumour grows as a sphere of radius \( r_P = r_P(t) \). The boundary value problem from equations
(2.2)-(2.3) reduces to

\[
\frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \bar{p}}{\partial r} \right) = S_1, \quad r < r_P(t), \quad (2.13)
\]

\[
\frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \bar{\sigma}}{\partial r} \right) = 0, \quad (2.14)
\]

with \( \bar{\sigma} \to \sigma_\infty \) as \( r \to \infty \). On \( r = r_P(t) \), equations (2.5), (2.6) and (2.9) are written now as

\[
\bar{p} = \frac{\alpha}{r_P(t)}, \quad (2.15)
\]

\[
\frac{d r_P(t)}{dt} = -\frac{\partial \bar{p}}{\partial r} + \lambda \sqrt{\bar{\sigma}}, \quad (2.16)
\]

\[
\frac{\partial \bar{\sigma}}{\partial r} = \mu \sqrt{\bar{\sigma}}. \quad (2.17)
\]

The final solutions for the unperturbed part are

\[
\bar{p}(r, t) = \frac{S_1}{6} \left( r^2 - r_P^2 \right) + \frac{\alpha}{r_P}, \quad (2.18)
\]

\[
\bar{\sigma}(r, t) = \sigma_\infty - \frac{\mu r_P^2}{r} \frac{2 \sigma_\infty}{\mu r_P + \sqrt{\mu^2 r_P^2 + 4 \sigma_\infty}}, \quad (2.19)
\]

\[
\frac{d r_P}{dt} = -\frac{S_1 r_P}{3} + \frac{2 \lambda \sigma_\infty}{\mu r_P + \sqrt{\mu^2 r_P^2 + 4 \sigma_\infty}}, \quad (2.20)
\]

for the pressure distribution, the nutrient concentration and the radius evolution, respectively. Note that the tumour radius depends on time \( (r_P = r_P(t)) \).

Greenspan (1976) assumed that after a considerable amount of time, the tumour colony would reach state steady, where further tumour growth is ceased. This state is mathematically described by a zero first derivative of the tumour radius, that is

\[
\frac{d r_P}{dt} = 0. \quad (2.21)
\]

Equation (2.20) in the steady state case results in an exterior radius given by

\[
r_{P\infty} = \frac{3 \lambda}{S_1} \left( \frac{\sigma_\infty}{1 + \frac{3 \lambda \mu}{S_1}} \right)^{\frac{3}{2}}, \quad (2.22)
\]
which is regulated mainly by the order of the rate of volume loss.

Table 2.1 contains parameters for plotting the resulting equations of the unperturbed model. These parameters have these values for two reasons

- we had to construct the radius evolution of the colony in the same way as Greenspan (1976) and
- we needed parameters that would work well with all four spherical models, as well as the ellipsoidal model.

Note that these cannot be the only set of parameters suitable for this model. However, a further investigation will only be possible along with experimental data as part of a future work.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
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<td>$r_p(t = 0)$</td>
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<tr>
<td>$\beta/d_t$</td>
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Table 2.1.: Parameters for plotting the graphs

Using the parameters from Table 2.1, we plot the radius evolution in time taking into account equation (2.20) and we obtain Figure 2.2. From this figure, the steady state radius is approximately 0.5669, which coincides with the value that we will obtain if we substitute the same parameters to equation (2.22).

This Section would be far from complete, if we did not add the graphs for pressure and nutrient distribution, using Equations (2.18) and (2.19) and the parameters from Table 2.1.

Figure 2.3 depicts the pressure distribution within the tumour colony. The negative values are a result of the parameters used for this model. However, it is interesting to compare the pressure value inside the necrotic core to the pressure near to the tu-
Figure 2.2.: Radius evolution in the unperturbed case when using the Greenspan model (1976).

Figure 2.3.: Pressure profile versus radius within the tumour colony.

mour radius. Note that the term pressure mainly includes the stress forces between the cells. The pressure inside the tumour is negative and larger in absolute value compared to the pressure on the tumour radius which is slightly positive. Negative pressure in the necrotic core means a positive particle velocity, and in this case a high velocity. This can be supported by the fact that within the necrotic core, only
dead cells and debris can be found, so movement in this region is easier than the living layer which is stuffed with cells. In the proliferating part, the particle velocity is negative and smaller as a absolute value, a result of the high cellular density of the area.

Greenspan (1976) focused only on the nutrient concentration outside the tumour colony. This is depicted in Figure 2.4. We can observe that the curve slowly reaches the value $\sigma_\infty = 1$, but by the time the nutrient reaches the tumour outer surface ($r_p = 0.5669$), the nutrient concentration is over 0.6, which means that a large amount of nutrient is lost to diffusion to the environment.

![Figure 2.4. Nutrient concentration profile outside the tumour colony.](image-url)
2.3. The non-homogeneous modified model for an ellipsoidal tumour

This section includes the model proposed by Dassios et al. (2012) for the avascular growth stage of an ellipsoidal tumour. The authors adjusted the Greenspan model to fit the needs of the complex ellipsoidal geometry. In this Section, we introduce perturbation on pressure, nutrient concentration and tumour boundary evolution, so we obtain two separate models, one for the unperturbed part, which matches the model proposed by Dassios et al. (2012), and one for the perturbed part, which is explicitly described in Chapter 5. At the end of this Section, we simulate the radius evolution of an unperturbed ellipsoidal tumour, as well as the pressure and nutrient profiles within the tumour colony.

To model an avascular tumour, we keep the assumption of the original paper (Dassios et al. (2012)) of a three-layered structure for its interior cell distribution. The interior structure can be schematically given by Figure 2.5. In the centre of the tumour there is a necrotic core occupied of dead cells and debris (red ellipsoid). This core is enveloped by a quiescent layer of live but not proliferating cells (quiescent cells) (blue ellipsoidal shell), whereas close to the tumour boundary there is a thin layer of live proliferating cells (green ellipsoidal shell). For this approach they
assume that all three layers are of ellipsoidal shape as part of the confocal ellipsoidal family with focii \((\pm h_2, 0, 0), (\pm h_3, 0, 0), (0, \pm h_1, 0)\). The ellipsoidal system is defined by

\[
\begin{align*}
    x_1 &= \frac{\rho \mu \nu}{h_2 h_3}, \\
    x_2 &= \frac{\sqrt{\rho^2 - h_2^2} \sqrt{\mu^2 - h_3^2} \sqrt{h_3^2 - \nu^2}}{h_1 h_3}, \\
    x_3 &= \frac{\sqrt{\rho^2 - h_3^2} \sqrt{h_2^2 - \mu^2} \sqrt{h_2^2 - \nu^2}}{h_1 h_2},
\end{align*}
\]

where \((\rho, \mu, \nu)\) and \((x_1, x_2, x_3)\) are the ellipsoidal and Cartesian coordinates respectively. Note that \(\rho \in [h_2, \infty), \mu \in [h_3, h_2]\) and \(\nu \in [0, h_3]\). The reference ellipsoid is given by

\[
\frac{x_1^2}{\alpha_1^2} + \frac{x_2^2}{\alpha_2^2} + \frac{x_3^2}{\alpha_3^2} = 1, \quad 0 < \alpha_3 < \alpha_2 < \alpha_1 < \infty,
\]

in Cartesian coordinates, where

\[
\begin{align*}
    h_1^2 &= \alpha_2^2 - \alpha_3^2, \quad h_2^2 = \alpha_1^2 - \alpha_3^2, \quad h_3^2 = \alpha_1^2 - \alpha_2^2,
\end{align*}
\]

are the semi-focal distances.

The difference between the three areas of the tumour lies in differences of the nutrient concentration \(\sigma\). Cells proliferate while the nutrient concentration is larger than the critical level \(\sigma_1\). A cell stays alive but do not proliferate when the nutrient supply remains over the critical level \(\sigma_2\) and under \(\sigma_1\). When the nutrient concentration falls under \(\sigma_2\), the cell is found in the necrotic core. For that, we distinguish the tumour and its surroundings into four regions \((\Omega_N, \Omega_Q, \Omega_P, \Omega_S)\). \(\Omega_N\) denotes the ellipsoidal necrotic core, the ellipsoidal shell \(\Omega_Q\) consists of quiescent cells, the ellipsoidal shell \(\Omega_P\) hosts the proliferating cells and \(\Omega_S\) stands for the area outside the tumour. In
terms of nutrient concentration, the ellipsoidal regions are specified as

\[
\Omega_N = \{ (\rho, \mu, \nu) : h_2 \leq \rho < \rho_N, \quad \sigma(r) < \sigma_2 \}, \quad (2.28)
\]

\[
\Omega_Q = \{ (\rho, \mu, \nu) : \rho_N < \rho < \rho_Q, \quad \sigma_2 < \sigma(r) < \sigma_1 \}, \quad (2.29)
\]

\[
\Omega_P = \{ (\rho, \mu, \nu) : \rho_Q < \rho < \rho_P, \quad \sigma(r) > \sigma_1 \}, \quad (2.30)
\]

\[
\Omega_S = \{ (\rho, \mu, \nu) : \rho > \rho_P, \quad \sigma_1 < \sigma(r) < \sigma_\infty \}, \quad (2.31)
\]

for every \((\mu, \nu)\) where \(\sigma(r)\) is the nutrient concentration at the point \(r = (\rho, \mu, \nu)\) and \(\sigma_\infty\) is the nutrient concentration from a nutrient source that constantly supplies the tumour. \(\rho_N\) stands for the boundary of the necrotic core, while \(\rho_Q\) for the boundary of the quiescent layer. We assume that the nutrient concentration is in a diffusive steady state, so

\[
\Delta \sigma_i(r) = 0, \quad r \in \Omega_i, \quad i = N, L, S \quad (2.32)
\]

where \(\sigma_N(r), \sigma_L(r), \sigma_S(r)\) denote the nutrient concentrations at the point \(r\) of \(\Omega_N, \Omega_L = \Omega_Q \cup \Omega_P\) and \(\Omega_S\) respectively. If we assume that the tumour resembles an incompressible fluid, changes in cell population will result in motion within the structure and thus in alterations in pressure distribution. This is expressed as

\[
\Delta p = S_1 \mathcal{H}( |r| - |r_N| ) + S_2 \mathcal{H}( |r_N| - |r| ), \quad (2.33)
\]

where \(S_1\) is the constant net rate of cell loss due to apoptosis in the liveing area (proliferating and quiescent layer) and \(S_2\) is the cell loss rate because of necrosis in the necrotic core. \(\mathcal{H}\) is the Heaviside step function and \(r_N\) denotes a point on the surface of the necrotic area. On the boundary of the necrotic core, \(\partial \Omega_N\), we assume continuity for the nutrient concentration, the pressure distribution and its gradient

\[
\sigma_N(r_N) = \sigma_L(r_N), \quad (2.34)
\]

\[
p_N(r_N) = p_L(r_N), \quad (2.35)
\]

\[
\hat{n} \cdot \nabla p_N \bigg|_{r=r_N} = \hat{n} \cdot \nabla p_L \bigg|_{r=r_N}, \quad (2.36)
\]
where \( p_N \) denotes the pressure in the necrotic region, \( p_L \) the pressure in the living layer and \( \hat{n} \) the unit normal vector. On the boundary of the tumour, \( \partial \Omega_P \), the following conditions coincide with the Greenspan model

\[
\hat{n} \cdot \nabla \sigma_L \bigg|_{r=r_P} = \frac{\gamma}{k} s(r_P), \tag{2.37}
\]

\[
\sigma_L(r_P) = \sigma_S(r_P), \tag{2.38}
\]

\[
\frac{dr}{dt} \cdot \hat{n} \bigg|_{r=r_P} = -\hat{n} \cdot \nabla p \bigg|_{r=r_P} + \frac{\beta}{dt} s(r_P), \tag{2.39}
\]

\[
\frac{dr}{dt} \times \hat{n} \bigg|_{r=r_P} = -\hat{n} \times \nabla p \bigg|_{r=r_P}, \tag{2.40}
\]

where \( \gamma \) denotes the rate of mass/volume consumption, \( k \) the diffusion constant \( \beta \) the mass/volume production, \( d_t \) the mass density of the tumour colony and \( s(r_P) = h_P^P(\rho_P - \rho_Q) \) the local thickness. The latter parameter is the key difference from the Greenspan approach, as instead of using a square root law we introduce the local thickness \( s \). Note that \( h_P^P \) is one of the metric coefficients defined in the Appendix B. Furthermore, on the outer boundary \( \partial \Omega_P \), we assume that the pressure satisfies the Young–Laplace relation (see Dassios (2014))

\[
p_L(r_P) - p_S(r_P) = \alpha \kappa(r_P), \tag{2.41}
\]

where \( p_L(\rho_P) = g(\rho_P) \) and \( p_S \) denotes the pressure in the surrounding area of the tumour. As \( |r| \to 0 \), \( p_N \) must be smooth. The source of nutrient is assumed to be constant far away from the tumour, that is

\[
\sigma_S = \sigma_\infty \text{ as } r \to \infty. \tag{2.42}
\]

Following Greenspan’s approach, we introduce a perturbation on the \( \rho \) ellipsoidal coordinate which is relevant to the radial coordinate of the spherical coordinate system. We are interested for deviations of the outer tumour boundary, that is

\[
\rho(t) = \rho_P(t) + \varepsilon f(\mu, \nu, t), \tag{2.43}
\]
where $\varepsilon$ is a small parameter and $f(\mu, \nu)$ is the spatial variable of the perturbed part depending on $\mu, \nu$, the angular coordinates of the ellipsoidal geometry, and on time. We introduce the same perturbation factor in the pressure distribution

$$p_N = \bar{p}_N + \varepsilon \tilde{p}_N , 
(2.44)$$
$$p_L = \bar{p}_L + \varepsilon \tilde{p}_L , 
(2.45)$$
$$p_S = \bar{p}_S + \varepsilon \tilde{p}_S , 
(2.46)$$

and the nutrient concentration

$$\sigma_N = \bar{\sigma}_N + \varepsilon \tilde{\sigma}_N , 
(2.47)$$
$$\sigma_L = \bar{\sigma}_L + \varepsilon \tilde{\sigma}_L , 
(2.48)$$
$$\sigma_S = \bar{\sigma}_S + \varepsilon \tilde{\sigma}_S , 
(2.49)$$

where $\bar{p}_N, \bar{p}_L, \bar{p}_N, \bar{\sigma}_N, \bar{\sigma}_L, \bar{\sigma}_S, \bar{\sigma}_N, \bar{\sigma}_L, \bar{\sigma}_S$ are the variables of the ellipsoidal tumour and $\tilde{p}_N, \tilde{p}_L, \tilde{p}_N, \tilde{\sigma}_N, \tilde{\sigma}_L, \tilde{\sigma}_S$ the variables of the perturbed part. Because of the complexity of the geometry, the same applies for the curvature of the outer boundary

$$\kappa = \bar{\kappa} + \varepsilon \tilde{\kappa} , 
(2.50)$$

and the interior pressure on the outer boundary

$$g(\rho_p) = \bar{g}(\rho_p) + \varepsilon \tilde{g}(\rho_p). 
(2.51)$$

Detailed calculations about the transition from the full model to the two separate models, the unperturbed and the perturbed, can be found in Appendix E.

For the unperturbed ellipsoidal part of the tumour, we obtain Laplace equations for the nutrient concentration in the necrotic core, the living layer and outside the
tumour as

\[ \Delta \bar{\sigma}_N = 0 , \quad (2.52) \]
\[ \Delta \bar{\sigma}_L = 0 , \quad (2.53) \]
\[ \Delta \bar{\sigma}_S = 0 . \quad (2.54) \]

In this mode, we assume two different rates of cell death that translates into two different Poisson equations for the pressure distribution in the core of the tumour, \( \bar{p}_N \), and the shell of living layers, \( \bar{p}_L \),

\[ \Delta \bar{p}_N = S_1 , \quad (2.55) \]
\[ \Delta \bar{p}_L = S_2 . \quad (2.56) \]

On the interface between the necrotic core and the living layer we assume continuity for the nutrient concentration, the pressure and its gradient

\[ \bar{\sigma}_N = \bar{\sigma}_L , \quad (2.57) \]
\[ \bar{p}_N = \bar{p}_L , \quad (2.58) \]
\[ \frac{\partial \bar{p}_N}{\partial \rho} = \frac{\partial \bar{p}_L}{\partial \rho} . \quad (2.59) \]

As for the outer tumour boundary, equations (2.37)-(2.39)

\[ \frac{\partial \bar{\sigma}_L}{\partial \rho} = \frac{\gamma}{k} (h_P)^2 (\rho_P - \rho_Q) , \quad (2.60) \]
\[ \bar{\sigma}_L = \bar{\sigma}_S , \quad (2.61) \]
\[ (h_P)^2 \frac{d\rho_P}{dt} = - \frac{\partial \bar{p}_L}{\partial \rho} + \beta \frac{\partial \bar{p}_L}{\partial t} (h^P_P)^2 (\rho_P - \rho_Q) . \quad (2.62) \]

Equation (2.40) represents the evolution of cells on the outer surface of the tumour and results to the following equations

\[ (h^P_\mu)^2 \frac{d\mu}{dt} = \frac{\partial \bar{p}_L}{\partial \mu} , \quad (2.63) \]
\[ (h^P_\nu)^2 \frac{d\nu}{dt} = \frac{\partial \bar{p}_L}{\partial \nu} . \quad (2.64) \]
By assuming that
\[ \bar{p}_L = \bar{g}(\rho_P) , \]  
(2.65)
where \( \bar{g}(\rho_P) \) is a function of \( \rho \), constant on the boundary \( \rho = \rho_P \), the exterior pressure on the outer boundary of the tumour is given by
\[ \bar{p}_S = \bar{g}(\rho_P) - \alpha \bar{\kappa} . \]  
(2.66)
The nutrient source uniformly supplies the tumour
\[ \bar{\sigma}_S \to \sigma_\infty \text{ as } r \to \infty . \]  
(2.67)
As in Dassios et al. (2012), the nutrient concentration within the necrotic region is defined as
\[ \bar{\sigma}_N = \sigma_2 - \frac{\sigma_\infty - \sigma_2}{\lambda - \lambda'} \frac{I_1^1(\rho_P)}{I_0^1(\rho_P)} \frac{E_1^1(\rho)S_2^1(\mu, \nu)}{I_2^1(\rho_P)} - 1 + \frac{\sigma_\infty - \sigma_2}{\lambda - \lambda'} \frac{I_2^2(\rho)}{I_0^2(\rho_P)} \frac{E_2^2(\rho)S_2^2(\mu, \nu)}{I_2^2(\rho_P)} - 1 , \]  
(2.68)
where \( I_n^m(x) \) are the elliptic integrals, \( E_n^m(x) \) the Lamé functions and \( S_n^m(\mu, \nu) \) the surface ellipsoidal harmonics, all of them defined in the Appendix B. \( V(\rho_P) \) stands for the volume of the tumour and is given by
\[ V(\rho_P) = \frac{4 \pi}{3} \rho_P \sqrt{\rho_P^2 - h_2^2} \sqrt{\rho_P^2 - h_2^2} . \]  
(2.69)
For the nutrient concentration outside the necrotic core, we obtain
\[ \bar{\sigma}_L = \bar{\sigma}_S = \sigma_\infty - (\sigma_\infty - \sigma_2) \frac{I_1^1(\rho)}{I_0^1(\rho_P)} \frac{E_1^1(\rho)S_2^1(\mu, \nu)}{I_2^1(\rho_P)} - 1 + \frac{\sigma_\infty - \sigma_2}{\lambda - \lambda'} \frac{I_2^2(\rho)}{I_0^2(\rho_P)} \frac{E_2^2(\rho)S_2^2(\mu, \nu)}{I_2^2(\rho_P)} - 1 . \]  
(2.70)
Next we state the expression for the pressure distribution in the core of the tumour

\[
\bar{p}_N = \left[ \tilde{g}(\rho_P) + (S_1 - S_2) \frac{V(\rho_N)}{4\pi} I_0^1(\rho_N, \rho_P) + \frac{S_1}{6} (\rho_N^2 - \rho_P^2) + \frac{S_2}{6} (\rho^2 - \rho_N^2) \right] \\
- \left[ (S_1 - S_2) \frac{V(\rho_N)}{4\pi} I_1^1(\rho_N, \rho_P) + \frac{S_1 (\rho_N^2 - \rho_P^2)}{6E_1^1(\rho_N)E_1^1(\rho_P)} + \frac{S_2 (\rho^2 - \rho_N^2)}{6E_1^1(\rho)E_1^1(\rho_N)} \right] \frac{E_2^1(\rho)}{\Lambda - \Lambda', \rho_N} \\
+ \left[ (S_1 - S_2) \frac{V(\rho_N)}{4\pi} I_2^1(\rho_N, \rho_P) + \frac{S_1 (\rho_N^2 - \rho_P^2)}{6E_2^1(\rho_N)E_2^1(\rho_P)} + \frac{S_2 (\rho^2 - \rho_N^2)}{6E_2^1(\rho)E_2^1(\rho_N)} \right] \frac{E_2^2(\rho)}{\Lambda - \Lambda'} ,
\]

(2.71)

where \( V(\rho_N) \) is the volume of the ellipsoidal necrotic core and is given by

\[
V(\rho_N) = \frac{4\pi}{3} \rho_N \sqrt{\rho_N^2 - h_3^2} \sqrt{\rho_N^2 - h_2^2} ,
\]

(2.72)

The pressure distribution in the living shell is given by

\[
\bar{p}_L = \left[ \tilde{g}(\rho_P) + (S_1 - S_2) \frac{V(\rho_N)}{4\pi} I_0^1(\rho, \rho_P) + \frac{S_1}{6} (\rho^2 - \rho_P^2) \right] \\
- \left[ (S_1 - S_2) \frac{V(\rho_N)}{4\pi} I_1^1(\rho, \rho_P) + \frac{S_1 (\rho^2 - \rho_P^2)}{6E_1^1(\rho)E_1^1(\rho_P)} \right] \frac{E_2^1(\rho)}{\Lambda - \Lambda', \rho_P} \\
+ \left[ (S_1 - S_2) \frac{V(\rho_N)}{4\pi} I_2^1(\rho, \rho_P) + \frac{S_1 (\rho^2 - \rho_P^2)}{6E_2^1(\rho)E_2^1(\rho_P)} \right] \frac{E_2^2(\rho)}{\Lambda - \Lambda'} .
\]

(2.73)

Lastly, we introduce equation (2.74) for the evolution of the unperturbed ellipsoidal outer boundary of the tumour

\[
\frac{d\rho_P}{dt} = - \left[ S_1 \frac{V(\rho_P) - V(\rho_N)}{V(\rho_P)} + S_2 \frac{V(\rho_N)}{V(\rho_P)} \right] \frac{\rho_P (\rho_P^2 - h_3^2) (\rho_P^2 - h_2^2)}{3E_1^1(\rho_P)E_2^1(\rho_P)} \\
+ \frac{\beta}{\alpha} (\rho_P - \rho_Q) .
\]

(2.74)

Using the parameters in Table 2.2 below we plot Equation (2.74) in time and the result is depicted in Figure 2.6. These parameters are the same used in Table 2.1, in order to be able to compare the spherical models with the ellipsoidal model. The initial ellipsoidal tumour has the same volume as the initial spherical tumour.
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<td>$\rho_P(t = 0)$</td>
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Table 2.2.: Parameters for plotting the graphs for the ellipsoidal tumour.

![Graph of $\rho_P$ vs $t$]

Figure 2.6.: Boundary evolution of the unperturbed part versus time.

It shows that the unperturbed boundary soon reaches the steady state value, 1.9598, from the initial value of 0.1228.

This section would be incomplete if we did not add the graphs for the pressure and nutrient profiles across the tumour. However, these graphs are not as straightforward as the relative graphs in Section 2.2, because both pressure and nutrient concentration (equations (2.68)-(2.73)) depend on $\mu$ and $\nu$. In order to tackle this difficulty, we first search for minimum and maximum when we set $\rho$ as constant.
Then, from equation (2.71) we obtain

\[
\bar{p}_N = w_1 + w_2 E_1^1(\mu) E_2^1(\nu) + w_3 E_2^2(\mu) E_2^2(\nu),
\]  

(2.75)

where

\[
w_1 = \bar{g}(\rho_P) + (S_1 - S_2) \frac{V(\rho_N)}{4\pi} I_0^1(\rho_N, \rho_P) + S_1 \frac{(\rho^2_N - \rho^2_P)}{6} + S_2 \frac{\rho^2 - \rho^2_N}{6},
\]

\[
w_2 = \frac{E_1^2(\rho)}{\Lambda + \Lambda'} \left[ (S_1 - S_2) \frac{V(\rho_N)}{4\pi} I_2^1(\rho_N, \rho_P) + S_1 \frac{(\rho^2_N - \rho^2_P)}{6E_1^1(\rho_N)E_2^1(\rho_P)} + S_2 (\rho^2 - \rho^2_N) \right],
\]

\[
w_3 = \frac{E_2^2(\rho)}{\Lambda - \Lambda'} \left[ (S_1 - S_2) \frac{V(\rho_N)}{4\pi} I_2^2(\rho_N, \rho_P) + S_1 \frac{(\rho^2_N - \rho^2_P)}{6E_2^2(\rho_N)E_2^1(\rho_P)} + S_2 (\rho^2 - \rho^2_N) \right],
\]

for \( \rho \) constant, where \( \rho_N \) and \( \rho_P \) are the values of the necrotic core outer surface and the living layer surface, respectively, at the steady state. The analytical approach for finding minimum or maximum was proven extremely difficult and useless at the end, because of the existence of several parameters with different signs and orders of magnitude to obtain results from analytical expressions only. This is why we used numerics to find the sets of \((\mu, \nu)\) for maximum or minimum pressure within the necrotic core for specific \( \rho \)'s and we obtain Figures 2.7-2.8.

Figure 2.7 gives the pressure profile for the \( \mu - \nu \) contour at the case of \( \rho = \)

![Figure 2.7.](image-url)
In this Figure, the maximum is located close to the position where \((\mu, \nu) = (h_2, 0)\), whereas the minimum close to the position where \((\mu, \nu) = (h_3, 0)\).

The same trend is observed in Figure 2.8, where both maximum and minimum are in the same places as in Figure 2.7. the only difference lies on the fact that now we are situated on the necrotic core boundar.In other words, this Figures depicts the situation on the interface between necrotic core and the quiescent layer.

Similarly, the pressure distribution within the living layer for \(\rho\) constant is given by

\[
\bar{p}_L = w_4 + w_5 E_2^1(\mu) E_2^1(\nu) + w_6 E_2^2(\mu) E_2^2(\nu),
\]

where

\[
w_4 = \bar{g}(\rho_P) + (S_1 - S_2) \frac{V(\rho_N)}{4\pi} I_0^1(\rho, \rho_P) + S_1 \frac{(\rho^2 - \rho_P^2)}{6},
\]

\[
w_5 = \frac{E_2^1(\rho)}{-\Lambda + N} \left[ (S_1 - S_2) \frac{V(\rho_N)}{4\pi} I_0^1(\rho, \rho_P) + \frac{S_1 (\rho^2 - \rho_P^2)}{6 E_2^1(\rho) E_2^1(\rho_P)} \right],
\]

\[
w_6 = \frac{E_2^2(\rho)}{-\Lambda + N} \left[ (S_1 - S_2) \frac{V(\rho_N)}{4\pi} I_0^1(\rho, \rho_P) + \frac{S_1 (\rho^2 - \rho_P^2)}{6 E_2^2(\rho) E_2^2(\rho_P)} \right].
\]

Again, the analytical approach was proven extremely demanding and the global minimum and maximum depended strongly on the choice of parameters. This is
why we used numerics for the living layer also and we obtain Figures 2.9-2.10. In Figures 2.9-2.10 we have the same trend as in Figures 2.7-2.8 as for the position of

![Figure 2.9](image1.png)

Figure 2.9.: Pressure profile of the living layer in the vicinity of the necrotic core.

![Figure 2.10](image2.png)

Figure 2.10.: Pressure profile in an intermediate surface of the living shell.

the maximum and the minimum. So overall, the location for maximum of the pressure is at \((\mu, \nu) = (h_2, 0)\) and for minimum of the pressure at \((\mu, \nu) = (h_3, 0)\). The positions of the maximum and minimum are far from random. In terms of cartesian coordinates (see Figure B.2 in Appendix B), when \((\mu, \nu) = (h_2, 0)\), \(\mu\)-curve ends
at the $x_1x_2$—plane, while the $\nu$—curve ends at the $x_2x_3$—plane, so the only common ground is the $x_2$—axis, where lies the $\alpha_2$ semiaxe. Similarly, when $(\mu, \nu) = (h_3, 0)$, $\mu$—curve ends at the $x_1x_3$—plane, while the $\nu$—curve ends at the $x_2x_3$—plane, so the only common ground is the $x_3$—axis, where lies the $\alpha_3$ semiaxe. Comparing these two semiaxes, $\alpha_3 < \alpha_2$, we conclude that at the shortest semiaxe, we have the minimum pressure value. In addition, equation (2.41) predicts that the maximum difference between pressure in living layer and pressure of the surrounding environment can only be found at the position of the minimum curvature which is at the $\alpha_3$ semiaxe. So, if assuming that the pressure of the surrounding environment does not dramatically alter, the Young-Laplace equation coincides with our finding of the maximum on the $\alpha_2$ semiaxe. In other words, high curvature is sustained high pressure, as the Young Laplace equation predicts. Taking into consideration that the locations of the minimum and the maximum are fixed, we plot the pressure distribution versus $\rho$ for the values of $\mu$ and $\nu$ that represent the maximum and the minimum and we obtain Figure 2.11.

In Figure 2.11 the green line stands for the minimum values of pressure, the blue line for the maximum values of pressure, whereas the red line denotes the difference between the extreme pressure values. Unfortunately, the complexity of the ellipsoidal

Figure 2.11.: Pressure profile on the outer boundary of the tumour colony.
geometry makes the interpretation of this Figure extremely difficult. However, there are a few observations that are worth mentioning. First, we observe the jump on the necrotic core boundary on all three curves, which is because of the existence of two distinct part of the tumours when it comes to the pressure distribution and the cell loss rates. We also notice that the pressure distribution follows different pattern from the pressure profile of the Greenspan model (Figure 2.3). Instead of a increased function, we get a curve with a twisted bell shape. However, if we focus on the necrotic core, the pressure distribution changes from smaller absolute values to larger ones. This coincides with the fact that deep within the necrotic core we can find more dead cells and debris than the region close to the necrotic boundary, so within the necrotic core there is more room for movement and higher cellular velocity than closer to the interface between necrotic and living parts. The bell-shape of the pressure distribution can only be explained by the choice of parameters and thus, a further investigation along with experimental data is suggested. To conclude, all curves end up at the same value at the tumour outer boundary, because the pressure at that point only depends on $\rho_P$ (Equation (2.65)).

Despite the fact that we followed the same technique for the nutrient concentration inside and outside of the tumour, things did not turn out as smoothly as in the case of the pressure distribution. We begin with Figures 2.12 and 2.13, where $\rho = \frac{h_2 + \rho_N}{2}$ and $\rho = \rho_N$, respectively. From these Figures, it seems that the maximum is found at the location $(\mu, \nu) = (h_3, 0)$ while the minimum is found at the location $(\mu, \nu) = (h_2, h_3)$. However, the nutrient values from the numerical simulations showed no significant difference, at least no difference comparable to the accepted numerical error.

Figures 2.14-2.19 follow a similar trend when it comes to the values of minimum and maximum nutrient concentration. Despite the fact that there are locations for maximum and minimum, the nutrient concentration does not differ overall. Plus, the location of the minimum is changed to $(\mu, \nu) = (h_3, 0)$ and of the maximum to $(\mu, \nu) = (h_3, h_2)$. This might be a result of the choice of parameters or because of the fact that the boundary conditions concerning the nutrient concentration do not
Figure 2.12.: Nutrient concentration profile at an intermediate surface within the necrotic region.

Figure 2.13.: Nutrient concentration profile in the vicinity of the necrotic core boundary.

depend on the angular coordinates of the ellipsoidal geometry.

For that, we continued in plotting the values of nutrient concentration at the positions \((\mu, \nu) = (h_3, 0)\), \((\mu, \nu) = (h_3, h_2)\), \((\mu, \nu) = (h_2, 0)\), and \((\mu, \nu) = (h_2, h_3)\), versus the third coordinate of ellipsoidal geometry, \(\rho\) and we obtained Figure 2.20. This graph shows that they are no significant differences of the nutrient concentration, in other words neither maximum nor minimum values for a fixed value of \(\rho\). Moreover,
we can observe that the majority of the nutrient is consumed within the living layer, which coincides with the fact that the living layer contains highly proliferating cells. Then the nutrient concentration decreases towards the necrotic core until it reaches the plateau of $\sigma_2 = 0.4$ inside the necrotic region. This happens because in that area of the tumour there are no cells to consume the nutrient, so the concentration remains stable.
Figure 2.16.: Nutrient profile of the living shell in the vicinity of the outer tumour boundary.

Figure 2.17.: Nutrient profile of the surrounding environment at a distance $\rho = 2\rho_P$. 
Figure 2.18.: Nutrient profile of the surrounding environment at a distance $\rho = 5\rho_P$.

Figure 2.19.: Nutrient profile of the surrounding environment at a distance $\rho = 10\rho_P$. 
Figure 2.20.: Nutrient concentration profile.
2.4. The non-homogeneous modified model for a spherical tumour

In this section we focus on the model proposed by Dassios et al. (2012) as a reduction from the ellipsoidal tumour to a spherical one. We introduced and perturbation in pressure, nutrient concentration and radius, so the original model is divided into an unperturbed and a perturbed part, which can be found in Section 4.2. At the end of this Section, we also include plots of the pressure and the nutrient profiles of this model for a spherical tumour.

This model have two main differences with the Greenspan model (Section 2.2),

- the assumption of two separate compartments inside the tumour, the living part and the necrotic core in terms of different cell loss rates and
- the assumption of the significance local thickness on the outer boundary over the square root law proposed by Greenspan.

The schematic cross-section of the tumour is depicted in Figure 2.21. The red circles denotes the necrotic area, whereas the other two areas form the living part (blue colour for the quiescent part and green colour for the proliferating layer). The line that separates the quiescent shell from the proliferating is dashed because there is no difference between the two regions as far as the model concerns.

By combining a mass conservation law with Darcy’s law we obtain the following Poisson equation for the pressure distribution

\[ \Delta p = S_1 \mathcal{H}(|r| - |r_N|) + S_2 \mathcal{H}(|r_N| - |r|), \]  

inside the tumour, where \( S_1 \) is the cell loss rate due to apoptosis in the living part of the tumour and \( S_2 \) the cell loss rate due to necrosis occurring in the necrotic core alone. \( \mathcal{H} \) stands for the Heaviside function. \( p_L \) stands for the pressure distribution inside the living layer and \( p_N \) inside the necrotic core. Note that according to this approach, the living layer consists of both the proliferating and the quiescent layer.

The nutrient concentration is still dictated by Laplace equation (2.3) and the nutrient is uniformly distributed by a remote source (2.4). We denote \( \sigma_N \) as the nutrient
concentration inside the necrotic core and $\sigma_L$ inside the living layer. In the interior boundary of the tumour, we assume continuity for the nutrient concentration, the pressure distribution and its gradient

$$\sigma_N(r_N) = \sigma_L(r_N), \quad (2.78)$$
$$p_N(r_N) = p_L(r_N), \quad (2.79)$$
$$\mathbf{n} \cdot \nabla p_N(r_N) = \mathbf{n} \cdot \nabla p_L(r_N). \quad (2.80)$$

Equations on the boundary of the tumour are obtained from the ellipsoidal tumour reduction. In contrast to Greenspan, we assume the Young-Laplace condition that represents the energy needed to maintain the intercellular bonds on the outer boundary

$$p_{\text{out}}(r_P) = g(r_P) - \frac{\alpha}{r_P}. \quad (2.81)$$
Furthermore, on the boundary of $\Omega_P$, the following conditions coincide with the Greenspan model

$$\frac{dr}{dt} \cdot \hat{n} = -\hat{n} \cdot \nabla p + \frac{\beta}{dt}(r_P - r_Q), \quad (2.82)$$

$$\frac{dr}{dt} \times \hat{n} = -\hat{n} \times \nabla p , \quad (2.83)$$

where $\beta$ is the mass/volume production and $d_t$ the mass density of the tumour colony. As for the gradient of nutrient, we assume that it is proportional to the width of the proliferating cell layer.

$$\hat{n} \cdot \nabla \sigma = \frac{\gamma}{k}(r_P - r_Q) \text{ at } r = r_P , \quad (2.84)$$

where $\gamma$ is the rate of mass/volume consumption and $k$ is the diffusion constant. This approach differs from the Greenspan model, where the gradient of the nutrient obeys a square root law on the tumours’ outer boundary. Furthermore, as $r \to 0$, $p_N$ must be smooth. Following the same routine as before, we introduce perturbation in pressure distribution, nutrient concentration and radial evolution, as in equations (2.10)-(2.12).

The final solutions for the unperturbed part of this model are derived in the paper Dassios et al. (2012). The results for pressure in the living layer and the necrotic core, for the nutrient concentration and the radius evolution are summarized as

$$\bar{p}_L(r,t) = g(r_P) + \frac{S_1}{6}(r^2 - r_P^2) + \frac{S_1 - S_2}{3}r_N^3\left( \frac{1}{r} - \frac{1}{r_P} \right), \quad (2.85)$$

$$\bar{p}_N(r,t) = g(r_P) + \frac{S_1 r_P^2 - S_1 r_P^2}{6} + (S_1 - S_2)r_N^3\left( \frac{1}{2r_N} - \frac{1}{3r_P} \right), \quad (2.86)$$

$$\bar{\sigma}(r,t) = \sigma_\infty - \frac{\gamma r_P^2(r_P - r_Q)}{k} \frac{1}{r}, \quad (2.87)$$

$$\frac{dr_P}{dt} = -\frac{S_1 r_P}{3} + \frac{S_1 - S_2 r_N^3}{3r_P} + \frac{\beta}{d_t}(r_P - r_Q). \quad (2.88)$$

Noting that $\sigma_1$, $\sigma_2$ are the critical nutrient concentrations on the necrotic core boundary and the quiescent layer boundary respectively, we obtain the radius of
the necrotic core and the radius of quiescent layer, respectively, from Equation (2.87)

\begin{align}
    r_N &= \frac{\sigma_\infty - \sigma_1}{\sigma_\infty - \sigma_2} \frac{\gamma r_P^3}{k (\sigma_\infty - \sigma_1) + \gamma r_P^3}, \\
    r_Q &= \frac{\gamma r_P^3}{k (\sigma_\infty - \sigma_1) + \gamma r_P^3}.
\end{align}

(2.89)  

(2.90)

In Figure 2.22, we plot the solution of equation (2.88) versus time. As seen in Section 2.2, the radius still reaches a steady state value which in this case is approximately 0.3781.

Figure 2.22.: Radius evolution in the unperturbed case when using the non-homogeneous modified model.

Moreover, we plot the pressure and nutrient profiles of this model, using the parameters from Table 2.1.

Figure 2.23 follows the same trend as the relevant Figure 2.3. Within the necrotic core, the decreased and negative values of pressure reflect a higher ability for movement, because of the existance of desintegrated cells and materials. As we move closer to the outer boundary, the movement becomes more difficult, as there are a lot of cells and little room to move, and this is depicted by the positive and small values of pressure in the area.
Figure 2.23.: Pressure distribution within the tumour colony.

Figure 2.24 shows that the nutrient concentration decreases as we move towards the necrotic core, as expected from the physiology of the problem. However, we can still observe that an amount of nutrient is lost before reaching the tumour boundary due to diffusion to the surrounding area. The large domain that we choose to plot this graph is not ideal to have a clear picture for the nutrient profile within the tumour, but it is still obvious that the majority of the nutrient is consumed within a narrow
zone inside the tumour close the outer boundary, because of the steep decrease of the curve.
3. Two particular models

In this chapter, we present our two new models that are inspired from the homogeneous Greenspan model and the non-homogeneous modified model described in Chapter 2. Section 3.1 is dedicated to the model that we refer to as the non-homogeneous Greenspan model. This model resembles to the Greenspan model with the exception of assuming two different cell loss rates which separate the tumour cells into necrotic cells and living cells. In this Section, we present the model with its initial equation and then we introduce perturbation in the pressure, the nutrient concentration and the radius evolution. Section 3.1 is concluded with plots of the radius evolution in time, as well as plots of pressure and nutrient concentration profile within the tumour. Section 3.2 contains the homogeneous modified model which is based on the non-homogeneous modified model, but instead of two cell loss rates, we only have one. The same approach as in all other models is used, and Section 3.2 starts with the model equation, then perturbation is introduced and the Section is concluded with figures of radius versus time and pressure and nutrient concentration versus the tumour radius.

3.1. The non-homogeneous Greenspan model for a spherical tumour

In this model, we consider the Greenspan model and assume two different rates of cell extinction; one for the apoptosis inside the living layer and one for the necrosis
in the necrotic core. As depicted in Figure 3.1, the two distinct colours (red and green) stand for two different cell loss rates. This assumption is mathematically formulated in equation (2.2) with

$$\Delta p = S_1 \mathcal{H}(|r| - |r_N|) + S_2 \mathcal{H}(|r_N| - |r|) \ , \ r < r_P$$

(3.1)

while equation (2.3), which is the Laplace equation for nutrient concentration, remains the same. The condition for the nutrient source at infinity, as well as all boundary conditions on the tumour surface remain as in Greenspan’s model (2.4)-(2.9). However, because of the presence of a necrotic core, we have to assume continuity for the nutrient concentration, the pressure distribution and its gradient.
on the necrotic-living interface as

\[
\sigma_N(r_N) = \sigma_L(r_N),
\]
\[
p_N(r_N) = p_L(r_N),
\]
\[
\hat{n} \cdot \nabla p_N(r_N) = \hat{n} \cdot \nabla p_L(r_N),
\]

just like the non-homogeneous modified model (Section 2.4). In a similar way, as in Sections 2.2 and 2.4, we introduce perturbations in the pressure distribution, the nutrient concentration and the radius evolution by substituting equations (2.10)-(2.12) into the equations of this model and we obtain equations for the unperturbed and the perturbed part, separately.

Here, we provide the solutions for the unperturbed part of the model. The equations describing the unperturbed part coincide with the equations of the full model, but in order to distinguish them, we will use \( \bar{p}, \bar{\sigma} \) when referring to the unperturbed sphere.

The first two equations describe the pressure distribution inside the necrotic core (\( \bar{p}_N \)) and the living region (\( \bar{p}_L \)) respectively.

\[
\bar{p}_N(r,t) = \frac{\alpha}{r_P} + \frac{1}{6} \left( S_2 r^2 - S_1 r_P^2 \right) + \left( S_1 - S_2 \right) r_N^3 \left( \frac{1}{2r_N} - \frac{1}{3r_P} \right),
\]
\[
\bar{p}_L(r,t) = \frac{\alpha}{r_P} + \frac{S_1}{6} \left( r^2 - r_P^2 \right) + \left( S_1 - S_2 \right) r_N^3 \left( \frac{1}{r} - \frac{1}{r_P} \right),
\]

where \( r_P \) is a time-dependent variable, and more specifically the tumour radius at a specific time.

The solution for the nutrient concentration is the same as in Greenspan (2.19)

\[
\bar{\sigma}(r,t) = \sigma_\infty - \frac{2\mu r_P^2 \sigma_\infty}{\mu r_P + \sqrt{\mu^2 r_P^2 + 4\sigma_\infty r}}.
\]

The radius for the unperturbed part is given by the differential equation

\[
\frac{dr_P}{dt} = -\frac{S_1 r_P}{3} + \frac{S_1 - S_2}{3} r_P^2 + \frac{2\lambda \sigma_\infty}{\mu r_P + \sqrt{\mu^2 r_P^2 + 4\sigma_\infty}}.
\]
On the boundary of the necrotic core, the nutrient concentration obtains a critical value $\sigma_2$, so

$$\sigma(r_N) = \sigma_2,$$  

(3.9)

from where we deduce

$$r_N = \frac{2\mu r_p^2 \sigma_{\infty}}{(\sigma_{\infty} - \sigma_2) \left( \mu r_p + \sqrt{\mu^2 r_p^2 + 4\sigma_{\infty}} \right)}.$$  

(3.10)

In Figure 3.2 we plot the evolution of the tumour radius in time when we substitute parameters from Table 2.1 to the equation (3.8).

For this model, the radius finally reaches a steady state value which is around 0.1558. This value is smaller than the steady state radius of the homogeneous model which is the Greenspan model, presented in Section 2.2, where the steady state radius is found 0.5669. In the Greenspan model, we have only one cellular population fully proliferating ($S_1 = 4$) while in the non-homogeneous Greenspan model, we have two distinct population with different cell loss rates. Most importantly, $S_2$, which is the cell loss rate of necrotic core is 250 times larger than $S_1$, which stands for the net cell loss rate of proliferating cells. This results into a much smaller tumour colony in
the non-homogeneous model, even if both models initiate from spheres of same radii. In addition, from the timescale we can see the tumour colony of the non-homogeneous model reaches quicker the steady state radius (approximately at t=0.25) comparing to the homogeneous Greenspan model (at t=3). This can be explained by the different cell loss rates and especially by the existance of the large $S_2$ at the non-homogeneous model.

To conclude, we plot the pressure profile within the tumour colony, as well as the nutrient concentration profile within the tumour and at the surrounding environment. Figure 3.3 shows that the pressure follows the same trend as in all relevant figures of spherical models. The pressure starts from negative but large values to end up with slightly positive values. This coincides with the ability of cells to move quicker within the necrotic core because of absence of structure, while close to the boundary the area is highly populated with proliferating cells which leaves no room for cell movement. In this Figure, we can also observe a difference in the curvature between the necrotic core and the living layer. The point of inflection is on the necrotic core boundary, and this is related to the different cell loss rates.

Figure 3.4 depicts equation (3.7) using parameters from Table 2.1. As described

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{pressure_profile}
\caption{Pressure profile within the tumour colony.}
\end{figure}

in previous Figures that relate the nutrient concentration with the radius, there is
an amount of nutrient that never reaches the tumour radius due to diffusion in the surrounding area. Then, the nutrient concentration decreases drastically in the area that stands for the living part of the spherical tumour.

Figure 3.4.: Nutrient concentration profile inside and outside of the tumour.
3.2. The homogeneous modified model for a spherical tumour

This model is based on the model proposed by Dassios et al. (2012) as a reduction of the relevant ellipsoidal model described in the literature. This model will be referred as the homogeneous modified model.

The only difference lies in assuming homogeneity for the inside of the tumour in terms of cell loss rate. This is depicted in Figure 3.5, where the dashed line is used to separate the tumour colony section not in the notion of two different cellular population, but because we are using the width of the proliferating layer in the model boundary conditions. Cell populations are only distinguished on their position, close or way from the tumour boundary, and the nutrient concentration at that position. Especially, the relation of the nutrient concentration to the critical values, $\sigma_1$ and $\sigma_2$. Apart from that, we assume that the cell populations are identical in terms of pressure distribution and cell loss rate. By combining a mass conservation law with Darcy’s law we obtain the following Poisson equation for the pressure

![Cross-section of a spherical tumour colony when assuming the homogeneous modified model.](image-url)
distribution

\[ \Delta p = S_1 \]  \hspace{1cm} (3.11)

inside the tumour, (see Greenspan (1976)). We preserve the assumption of Greenspan for a steady state diffusion for nutrient concentration

\[ \Delta \sigma = 0, \]  \hspace{1cm} (3.12)

outside the tumour. The source of nutrient is assumed to be constant far away from the tumour, that is

\[ \sigma \to \sigma_\infty \text{ as } |r| \to \infty. \]  \hspace{1cm} (3.13)

In contrast to Greenspan, we assume the Young-Laplace condition that represents the energy needed to maintain the intercellular bonds on the outer boundary

\[ p_{\text{out}}(r_P) = p_L(r_P) - \frac{\alpha}{r_P}, \]  \hspace{1cm} (3.14)

where \( p_L(r_P) = g(r_P) \). Furthermore, on the boundary of \( \Omega_P \), the following conditions coincide with the Greenspan model

\[ \frac{dr}{dt} \cdot \hat{n} = -\hat{n} \cdot \nabla p + \frac{\beta}{d_t} (r_P - r_Q), \]  \hspace{1cm} (3.15)

\[ \frac{dr}{dt} \times \hat{n} = -\hat{n} \times \nabla p, \]  \hspace{1cm} (3.16)

where \( \beta \) is the mass/volume production and \( d_t \) the mass density of the tumour colony. As for the gradient of nutrient, we assume that it is proportional to the width of the living cell layer.

\[ \hat{n} \cdot \nabla \sigma = \frac{\gamma}{k} (r_P - r_Q) \text{ at } r = r_P, \]  \hspace{1cm} (3.17)

where \( \gamma \) is the rate of mass/volume consumption and \( k \) is the diffusion constant. This approach differs from the Greenspan model, where the gradient of the nutrient obeys a square root law on the tumours’ outer boundary.

Furthermore, as \( r \to 0 \), \( p_N \) must be smooth. Following the same routine as in
Greenspan, we introduce perturbation in pressure distribution, nutrient concentration and radial evolution, see equations (2.10)-(2.12). The pressure and nutrient concentrations are substituted by their upper-bar equivalents. Apart from that, all equations that describe the model remain the same. For this model, pressure distribution, nutrient concentration and radius evolution for the unperturbed part are given by

\[
\bar{p}(r,t) = g(r_P) + \frac{S_1}{6} \left(r^2 - r_P^2\right),
\]
\[\quad (3.18)\]

\[
\bar{\sigma}(r,t) = \sigma_\infty - \gamma r_P^2 \left(\frac{r_P - r_Q}{k}\right)\frac{1}{r},
\]
\[\quad (3.19)\]

\[
\frac{dr_P}{dt} = -\frac{1}{3} S_1 r_P + \beta \left(\frac{r_P - r_Q}{d_t}\right).
\]
\[\quad (3.20)\]

On \(r = r_Q\), nutrient concentration has a critical value \(\sigma_1\) which when introduced to equation (3.19), we obtain

\[
r_Q = \frac{\gamma r_P^3}{\gamma r_P^2 + (\sigma_\infty - \sigma_1)k}.
\]
\[\quad (3.21)\]

As we can observe in Figure 3.6, the radius is increasing in time until it reaches a

Figure 3.6.: Radius evolution in the unperturbed case when using the homogeneous modified model.
plateau which corresponds to the steady state case and that value is 0.4471. If comparing this value to the value of 0.3781 steady state radius of the non homogeneous modified model, we can see once more that the homogeneity of the cell loss rates results to a larger tumour colony. As explained in Section 3.1, this is because of the large value of $S_2$ in the non-homogeneous modified model, which results to a smaller colony. In addition, the same parameter results to a quicker reach of the steady state radius. In other words, it takes 2.5 time dimensions for the non-homogeneous modified model to reach the steady state radius, while the homogenous modified model needs 3 time dimensions to reach a larger steady state radius. In conclusion, the presence of $S_2$ results in a smaller steady state radius, but reaches this state in a shorter amount of time.

Figure 3.7 represents the pressure distribution inside the tumour colony versus

![Figure 3.7: Pressure profile across the tumour colony when assuming the homogeneous modified model.](image)

the radius. As before, it starts from negative large values to end up with positive small numbers at the boundary of the colony. This is supported by the biological description of the avascular tumour. At the necrotic core, there are only dead cells and cellular debris, so cellular movement is easier and the particle velocity is increased. As we get closer to the outer boundary of the tumour, the region has
a more strict structure, movement becomes more difficult and the particle velocity decreases. As already mentioned, a decreased particle velocity equals a increased pressure (living layer), while decreased values of pressure stand for increased cellular mobility (necrotic core).

Figure 3.8 represents the nutrient concentration at different points, inside and outside of the tumour. Once more, the amount of nutrient that reaches the outer boundary of the colony is smaller than the concentration of the source, due to diffusion in the exterior environment. Then, the curve shows a drastic drop in the living layer.
4. On the stability of tumours in spherical geometry

In this section we will present the perturbed part and their solutions of the four spherical models. We begin with the stability study of the homogeneous Greenspan model (Section 4.1), while Section 4.2 contains the stability study of the non-homogeneous Greenspan model. Sections 4.3 and 4.4 are dedicated to the stability study of the modified models, and more specifically, the perturbed part of homogeneous modified model is described in Section 4.3, while Section 4.4 includes the perturbed part of the non homogeneous modified model.

4.1. The \( \vartheta \), \( \varphi \) dependent perturbation of the Greenspan model

In this section we present the perturbed part of the homogenous Greenspan model (the unperturbed part can be found in Section 2.2) and we follow the same approach as Greenspan in his 1976 paper. The difference is that we assume perturbations depending on both angles of the spherical coordinate system, \( \vartheta \) and \( \varphi \), whereas he considered only a perturbation depending on \( \vartheta \). It is important for this model, to express the unit normal vector in terms of \( \varepsilon \) by

\[
\hat{n} = \hat{r} - \frac{\varepsilon \xi_{\vartheta}}{r_p} \hat{\vartheta} - \frac{\varepsilon \xi_{\varphi}}{r_p \sin \vartheta} \hat{\varphi} + \mathcal{O}(\varepsilon^2).
\]  

(4.1)
where $\hat{r}$, $\hat{\vartheta}$, $\hat{\varphi}$ are the orthogonal unit vectors of the spherical coordinate system. Similarly, the Gaussian or mean curvature of the surface is expressed as

$$\kappa = \frac{1}{2} \nabla \cdot \hat{n} = \frac{1}{r_P} - \frac{\varepsilon}{2r_P^2} \left( 2\xi + \xi_{\vartheta\vartheta} + \frac{\xi_{\varphi\varphi}}{\sin^2 \vartheta} + \frac{\xi_{\varphi} \cos \vartheta}{\sin \vartheta} \right) + \mathcal{O}(\varepsilon^2). \quad (4.2)$$

Detailed calculations for the derivation of the normal unit vector and the Gaussian curvature in terms of $\varepsilon$ can be found in Appendix C. If we apply the transformation

$$x = \cos \vartheta, \quad (4.3)$$

$$\sin \vartheta = \sqrt{1 - x^2}, \quad (4.4)$$

$$\frac{\partial \xi}{\partial \vartheta} = -\sqrt{1 - x^2} \xi_x, \quad (4.5)$$

$$\frac{\partial^2 \xi}{\partial \vartheta^2} = -x \xi_x + \xi_{xx} (1 - x^2), \quad (4.6)$$

then the curvature assumes the expression

$$\kappa = \frac{1}{r_P} - \frac{\varepsilon}{2r_P^2} \left\{ 2\xi + \frac{\partial}{\partial x} \left[ (1 - x^2) \frac{\partial \xi}{\partial x} \right] + \frac{\xi_{\varphi\varphi}}{1 - x^2} \right\} + \mathcal{O}(\varepsilon^2). \quad (4.7)$$

Schematically, a perturbed spherical colony is depicted in Figure 4.1. In details, the green circle represents the unperturbed part of the colony, while the white half-circle stands for the perturbation of the radius. Now, the problem for the perturbed part is given by

$$\Delta \tilde{p} = 0, \quad r < r_P, \quad (4.8)$$

$$\Delta \tilde{\sigma} = 0, \quad r > r_P, \quad (4.9)$$

for pressure distribution inside the tumour colony and nutrient concentration in the tumour environment, respectively. The conditions on the boundary surface,
Figure 4.1.: Schematical cross-section of a spherical tumour colony, when assuming the Greenspan model, plus a perturbation on the radius direction.

For $r = r_P$ are

$$\xi \ddot{p}_r + \ddot{p} = -\frac{\alpha}{2r_P^2} \left[ 2\xi + \frac{\partial}{\partial x} \left( (1-x^2) \frac{\partial \xi}{\partial x} \right) + \frac{\xi \phi \phi_1}{1-x^2} \right] , \quad (4.10)$$

$$\xi \ddot{t} = -(\xi \ddot{p}_r + \ddot{p}_r) + \lambda \frac{\xi \ddot{r} + \ddot{r}}{2\sqrt{\sigma}} , \quad (4.11)$$

$$\xi \ddot{\sigma}_r + \ddot{\sigma}_r = \mu \frac{\xi \ddot{r} + \ddot{r}}{2\sqrt{\sigma}} , \quad (4.12)$$

where all parameters are calculated on $r = r_P$ and

$$\sqrt{\sigma} = \frac{2\sigma_\infty}{\mu r_P + \sqrt{\mu^2 r_P^2 + 4\sigma_\infty}} \quad (4.13)$$

on $r = r_P$. To solve the perturbed part of the problem, we use an expansion in terms of the Legendre polynomials. Hence, we assume the following modal forms.
for pressure distribution, nutrient concentration and radial perturbation

\[
\tilde{p}(r, \vartheta, \varphi, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{n} A_n^m(t) r^n P_n^m(\cos \vartheta) e^{im\varphi}, \tag{4.14}
\]

\[
\tilde{\sigma}(r, \vartheta, \varphi, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{n} B_n^m(t) \frac{P_n^m(\cos \vartheta) e^{im\varphi}}{r^{n+1}}, \tag{4.15}
\]

\[
\xi(\vartheta, \varphi, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{n} C_n^m(t) P_n^m(\cos \vartheta) e^{im\varphi}, \tag{4.16}
\]

where \(A_n^m, B_n^m, C_n^m\) depend only on time. By substituting equations (4.14)-(4.16) to equations (4.10)-(4.12), we arrive at

\[
A_n^m(t) = \frac{C_n^m(t)}{r_P^n(t)} \left[ -\frac{S_1 r_P}{3} - \frac{\alpha n (n + 1)}{2 r_P^2} \right], \tag{4.17}
\]

\[
B_n^m(t) = -\frac{C_n^m(t) \mu \sqrt{\sigma} r_P^{n+1}(t) [\mu r_P + 4 \sqrt{\sigma}]}{\mu r_P + 2(n + 1) \sqrt{\sigma}}, \tag{4.18}
\]

\[
C_n^m(t) = C_n^m(t) \left( -\frac{S_1}{3} + \frac{\lambda \mu}{2} \right) - n A_n^m(t) r_P^{n-1}(t) + \frac{\lambda B_n^m(t)}{2 r_P^{n+1}(t) \sqrt{\sigma}}. \tag{4.19}
\]

Following Greenspan, we concentrate on the coefficient \(C_n^m\) which determines the shape and structure of the colony. Obviously, growth is characterized as unstable if \(\xi\) amplifies which is determined by the sign of

\[
\frac{C_n^m(t)}{C_n^m(t)} = (n - 1) f(n, r_P) \tag{4.20}
\]

with

\[
f(n, r_P) = \frac{S_1}{3} - \frac{\alpha n (n + 2)}{2 r_P^3(t)} + \frac{\lambda \mu \sqrt{\sigma}}{\mu r_P + 2(n + 1) \sqrt{\sigma}}. \tag{4.21}
\]

If we compare equation (4.21) to the relevant equation by Greenspan (1976), we conclude that they are exactly the same. So, the assumption of two spherical angles instead of two does not alter the condition of stability for a spherical tumour.

For the Greenspan model, we take into account equation (4.20) together with equation (4.21). For \(n = 0\), \(\frac{C_n^m}{C_n^m}\) is negative, so the perturbation decays and the shape of the tumour remains spherical. For \(n = 1\), \(\frac{C_n^m}{C_n^m}\) equals zero, which results in \(C_1^1\) being
Figure 4.2.: Different $\alpha'$s for the Greenspan model and $n=2$, where the green curve stands for $\alpha_1 = 0.001$ and the blue curve for $\alpha_2 = 0.005$.

Figure 4.3.: The $n=10$ mode for the Greenspan model, where the green curve stands for $\alpha_1 = 0.001$ and the blue curve for $\alpha_2 = 0.005$.

A constant, a mode representing a translation of axes. For $n \geq 2$, $\frac{C_{m'}}{C_m}$ could be positive, negative or zero depending on the sign of equation (4.21). When $f(n, r_P)$ equals zero, this radius is called minimum critical radius. In Figure 4.2, we take two different values for the parameter $\alpha$, so that the left curves denotes the curve with lowest value of $\alpha$. As a result, $f(2, r_P)$ switches from negative to positive in different
values of \( r \). From Figure 2.2, we have that the steady state radius is approximately at 0.5669. In Figure 4.2, for both \( \alpha' \)s (green line with diamond points) the minimum critical radius for stability is smaller than the steady state radius. This means that the boundary of a tumour colony will become unstable at a definite time because those surface deviations will amplify and therefore alter the shape of the tumour, resulting to finger-like formations. These deformations mark the transmission from
the avascular state of the tumour to a possible vascularized state, as these forma-
tions are likely to attract blood capilaries near the tumour. For $n = 10$, we have
two cases for assessment of stability of the tumour. For the lowest value of $\alpha$, the
minimal critical radius is smaller than the steady state radius. Hence this case will
lead to an unstable tumour. In the case of a higher $\alpha$, the minimum critical radius
is larger than the steady state radius (Figure 4.3). This means that the surface
perturbation will decay and the tumour will regain its spherical shape.

In Figures 4.4 and 4.5, we present the modes $n = 2$ and $n = 10$ together for the
same $\alpha$. In Figure 4.5, which presents the case of the smaller value of $\alpha$, both modes
have minimum critical radii smaller than the steady state radius, so both will result
to unstable tumours. In Figure 4.4, the modes show different behaviour, with the
$n = 2$ mode to result to an unstable colony, while the $n = 10$ mode to a tumour
that regains its initial symmetric spherical shape.
4.2. The $\theta$, $\phi$ dependent perturbation of the non-homogeneous Greenspan model

This section is dedicated to the stability study of the non-homogeneous Greenspan model, which is described in Section 3.1. The non-homogeneous Greenspan model resembles to the original Greenspan model with the exception of assuming different cell death rates between the necrotic and the living layer. A cross-section is depicted in Figure 4.6, where the red circle stands for the necrotic region, the green shell for the living layer, while the white half circle represents the perturbation. As described already, the perturbed variables are those with the wingle on the top. From introducing perturbation in pressure, nutrient concentration and radius evolution, we get equations for both the perturbed and unperturbed part. For the perturbed part, and especially for the pressure distribution we obtain

$$\Delta \tilde{p} = 0 , \ r < r_p.$$  \hfill (4.22)
Laplace equation is needed to describe the nutrient concentration

$$\Delta \tilde{\sigma} = 0.$$  \hspace{1cm} (4.23)

The conditions on the boundary give

$$\xi \tilde{p}_r + \tilde{p} = -\frac{\alpha}{2r^2} \left\{ 2\xi + \frac{\partial}{\partial x} \left[ (1 - x^2) \frac{\partial \xi}{\partial x} \right] + \frac{\xi \varphi \varphi}{1 - x^2} \right\},$$  \hspace{1cm} (4.24)

$$\xi_t = -\xi \tilde{p}_{rr} - \tilde{p}_r + \lambda \xi \tilde{\sigma}_r + \tilde{\sigma},$$  \hspace{1cm} (4.25)

$$\xi \tilde{\sigma}_{rr} + \tilde{\sigma}_r = \mu \frac{\xi \tilde{\sigma}_r + \tilde{\sigma}}{2\sqrt{\sigma}}.$$  \hspace{1cm} (4.26)

where \(x = \cos \vartheta\) and \(\bar{\sigma}\) is given by equation (4.13), while\n
$$\tilde{\sigma} \to 0, \text{ as } r \to \infty.$$  \hspace{1cm} (4.27)

To solve the perturbed part we assume modal solutions for \(\tilde{p}, \tilde{\sigma}\) and \(\xi\), in the form

$$\tilde{p}(r, \vartheta, \varphi, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{n} A_n^m(t) r^n P_n^m(\cos \vartheta) e^{im\varphi},$$  \hspace{1cm} (4.28)

$$\tilde{\sigma}(r, \vartheta, \varphi, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{n} B_n^m(t) \frac{P_n^m(\cos \vartheta)}{r^{n+1}} e^{im\varphi},$$  \hspace{1cm} (4.29)

$$\xi(\vartheta, \varphi, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{n} C_n^m(t) P_n^m(\cos \vartheta) e^{im\varphi}.$$  \hspace{1cm} (4.30)

The coefficients \(A_n^m\), \(B_n^m\) and \(C_n^m\) are given when substituting equations (4.28)-(4.30) to (4.24)-(4.26) and finally

$$A_n^m(t) = \frac{C_n^m(t)}{r_P^2} \left[ \frac{\alpha (n - 1)(n + 2)}{2r_P^2} + \frac{S_1 - S_2}{3} \frac{r_N^3}{r_P^3} - \frac{S_1}{3} r_P \right],$$  \hspace{1cm} (4.31)

$$B_n^m(t) = -C_n^m(t) \frac{\mu \sqrt{\sigma} r_P^{n+1}}{2(n + 1) \sqrt{\sigma}} \left( \mu r_P + 4 \sqrt{\sigma} \right).$$  \hspace{1cm} (4.32)
and most importantly,

\[
\frac{C_{n}'}{C_{n}} = (n - 1) \frac{S_{1}}{3} - \frac{\alpha n(n - 1)(n + 2)}{2r_{P}^3} - (n + 2) \frac{S_{1} - S_{2}}{3r_{P}^3} r_{N}^3 + \frac{(n - 1)\lambda \mu \sqrt{\sigma}}{\mu r_{P} + 2(n + 1)\sqrt{\sigma}} \tag{4.33}
\]

Equation (4.33) controls the stability of the tumour. More specifically, the sign of the right-hand-side of Equation (4.33), namely

\[
\frac{C_{n}'}{C_{n}} = (n - 1) \left[ \frac{S_{1}}{3} - \frac{\alpha n(n + 2)}{2r_{P}^3} - \frac{n + 2}{n - 1} \frac{S_{1} - S_{2}}{3r_{P}^3} r_{N}^3 + \frac{\lambda \mu \sqrt{\sigma}}{\mu r_{P} + 2(n + 1)\sqrt{\sigma}} \right], \tag{4.34}
\]

and \( f(n, r_{P}) \) which is used for the stability plots is described by

\[
f(n, r_{P}) = \frac{(n - 1)S_{1}}{3} - \frac{\alpha n(n - 1)(n + 2)}{2r_{P}^3} - \frac{(n + 2)(S_{1} - S_{2})}{3r_{P}^3} r_{N}^3 + \frac{(n - 1)\lambda \mu \sqrt{\sigma}}{\mu r_{P} + 2(n + 1)\sqrt{\sigma}} \tag{4.35}
\]

Figure 4.7.: The \( n = 0 \) mode for the non-homogeneous Greenspan model.

For the \( n = 0 \) mode and for the range of radius that we are interested in, Figure 4.7 shows that \( f(0, r_{P}) \) based on the parametric values that we choose. Hence, the tumour becomes unstable in this mode. For \( n = 1, \), the tumour colony be-
Figure 4.8.: The $n = 1$ mode for the non-homogeneous Greenspan model.

Figure 4.9.: The $n = 2$ mode for the non-homogeneous Greenspan model for different $\alpha'$s, where the smallest value is represented by the green curve, while the blue curve stands for $\alpha_2 = 0.005$.

comes unstable since the start of the deviation because the perturbation amplifies $(f(1, r_P) \geq 0)$. For $n = 2$, and for the same choice of $\alpha'$s, the tumour becomes unstable after some time and a possible source of metastasis (Figure 4.9), while for $\alpha$’s the minical critical radius is smaller than the steady state radius, which for the non-homogeneous model equals to 0.1558. For $n = 10$, we have the same trend as
Figure 4.10.: The $n = 10$ mode for the non-homogeneous Greenspan model, where the green curve stands for $\alpha_1 = 0.001$ whereas the blue curve for $\alpha_2 = 0.005$.

Figure 4.11.: The $n=2$ and $n=10$ modes for the non-homogeneous Greenspan model for $\alpha = 0.001$.

in the homogeneous Greenspan model. Depending on the value of $\alpha$, which is a characteristic of the membrane compactness, we can either have stable or unstable tumours. More specifically, when assuming a smaller value for $\alpha$, the $n = 10$ mode results to an unstable tumour (green line with diamond points) because the minimal critical radius of this case is smaller than the steady state radius. On the other
hand, when applying a larger value for $\alpha$ we have a case of stable tumour. Next we present Figures 4.11 and 4.12 where we plot both $n=2$ and $n=10$ modes for the same value of $\alpha$. In these Figures, the $n=2$ mode is represented by the lines with the cross points, while $n=10$ is denoted by the lines with the diamond points.
4.3. The $\theta$, $\varphi$ dependent perturbation of the homogeneous modified model

This section contains the stability study for the homogeneous modified model, which is schematically depicted in Figure 4.13. The same approach was followed as in all spherical models. In the perturbed part, both pressure and nutrient concentrations are harmonic

\[
\Delta \tilde{p} = 0 , \quad (4.36)
\]
\[
\Delta \tilde{\sigma} = 0 . \quad (4.37)
\]

Figure 4.13.: Schematic cross-section of a perturbed spherical tumour colony when assuming the homogeneous modified model.
The conditions at the far field and on the boundary are given by

\[ \tilde{\sigma} \rightarrow 0 \text{ as } r \rightarrow \infty , \] (4.38)
\[ \xi \tilde{p}_r + \tilde{p} = 0 \text{ at } r = r_P , \] (4.39)
\[ \xi_t = - (\xi \tilde{p}_{rr} + \tilde{p}_r) \text{ at } r = r_P , \] (4.40)
\[ \xi \tilde{\sigma}_{rr} + \tilde{\sigma}_r = 0 \text{ at } r = r_P . \] (4.41)

For the perturbed parameters, we assume spherical harmonic functions, so that

\[ \tilde{p}(r, \vartheta, \varphi, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{n} A_{nm}^m(t) r^n P_n^m(\cos \vartheta) e^{im\varphi} , \] (4.42)
\[ \tilde{\sigma}(r, \vartheta, \varphi, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{n} B_{nm}^m(t) \frac{P_n^m(\cos \vartheta) e^{im\varphi}}{r^{n+1}} , \] (4.43)
\[ \xi(\vartheta, \varphi, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{n} C_{nm}^m(t) P_n^m(\cos \vartheta) e^{im\varphi} . \] (4.44)

where the coefficients are calculated when we apply equations (4.42)-(4.44) to equations (4.39)-(4.41).

\[ A_{nm}^m(t) = - \frac{C_{nm}^m(t)}{3} S_1 r_P^{1-n}(t) , \] (4.45)
\[ B_{nm}^m(t) = - C_{nm}^m(t) 2\gamma (r_P - r_Q) (n + 1) k r_P^{n+1}(t) , \] (4.46)
\[ \frac{C_{nm}^{m'}(t)}{C_{nm}^m(t)} = \frac{(n - 1)}{3} S_1 , \] (4.47)

where we focus on the sign of the parameter \( f(n, r_P) \)

\[ f(n, r_P) = \frac{(n - 1)}{3} S_1 . \] (4.48)

Equation (4.48) is important for concluding whether a perturbed tumour will evolve to an unstable colony, or regain its original spherical shape. However, it is obvious from the form of this Equation, that \( f(n, r_P) \) is independent of the radius of the tumour and depends only on the mode \( (f(n, r_P) = f(n) ) \) This is the reason behind the form of Figure 4.14. For the \( n = 0 \) mode, \( f(0) \) is negative and that results to a

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stable tumour, while for $n = 1$, $f(1) = 0$ and $C_1^{\infty}$ is constant. For $n \geq 2$, all modes are unstable, because $f(n)$ is positive.
4.4. The $\vartheta$, $\varphi$ dependent perturbation of the non-homogeneous modified model

This section refers to the stability study of the non homogeneous modified model which can be found in Section 2.4. Figure 4.15 stands for the perturbed part of the non homogeneous modified model. The equations describing the perturbed part of this model are

$$\Delta \tilde{p} = 0, \quad r < r_P$$

$$\Delta \tilde{\sigma} = 0, \quad 0 < r < \infty.$$
so we seek harmonic solutions for both pressure distribution and nutrient concentration. The accompanying conditions are

\[
\tilde{\sigma} \rightarrow 0 \text{ as } r \rightarrow \infty, \quad (4.51)
\]

\[
\xi \tilde{p}_r + \tilde{p} = 0 \text{ at } r = r_P, \quad (4.52)
\]

\[
\xi_t = -\xi \tilde{p}_{rr} - \tilde{p}_r \text{ at } r = r_P, \quad (4.53)
\]

\[
\xi \tilde{\sigma}_{rr} + \tilde{\sigma}_r = 0 \text{ at } r = r_P. \quad (4.54)
\]

For the perturbed part, we assume expansions in Legendre polynomials as

\[
\tilde{p}(r, \vartheta, \varphi, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{n} A_m^n(t) r^n P_n^m(\cos \vartheta) e^{im\varphi}, \quad (4.55)
\]

\[
\tilde{\sigma}(r, \vartheta, \varphi, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{n} B_m^n(t) \frac{P_n^m(\cos \vartheta) e^{im\varphi}}{r^{n+1}}, \quad (4.56)
\]

\[
\xi(\vartheta, \varphi, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{n} C_m^n(t) P_n^m(\cos \vartheta) e^{im\varphi}. \quad (4.57)
\]

By applying the conditions of the perturbed part, we obtain the following expressions for the coefficients

\[
A_m^n(t) = -\frac{C_m^n(t)}{r_P^n(t)} \left( S_1 \left( \frac{S_1 - S_2 r_N^3}{3} \right) \right), \quad (4.58)
\]

\[
B_m^n(t) = -\frac{C_m^n(t) 2^{n+1}(t)}{(n+1)k} (r_P - r_Q), \quad (4.59)
\]

\[
\frac{C_m'(t)}{C_m^n(t)} = \frac{1}{3} \left[ S_1 (n - 1) - (n + 2) (S_1 - S_2) r_N^3 \right]. \quad (4.60)
\]

In order to plot the stability figure, we use the parameter \( f \) which is defined by

\[
f(n, r_P) = \frac{1}{3} \left[ S_1 (n - 1) - (n + 2) (S_1 - S_2) r_N^3 \right]. \quad (4.61)
\]

Equation (4.60) will be used to study the stability of the tumour modelled by the non-homogeneous modified model.

For \( n = 0 \) and for the parameters from Table 2.1, equation (4.61) results to negative values (\( f(0, r) < 0 \)). Hence this mode is stable. However, for \( n \geq 1 \), all deviations
Figure 4.16.: Stability Study for the non-homogeneous modified model. 

increase and the tumour becomes unstable from the very start (Figure 4.16).
5. On the stability of tumours in ellipsoidal geometry

This chapter is dedicated solely to the stability study of the perturbed part of the Ellipsoidal model. Calculations for the original model to the equations of the perturbed part can be found in Appendix E. For the perturbed part of the tumour we focus on the variables with the tilde on the top ($\tilde{\sigma}_N$, $\tilde{\sigma}_L$, $\tilde{\sigma}_S$, $\tilde{p}_N$, $\tilde{p}_L$, $\tilde{p}_S$) and the evolution of the perturbation, $f$, which is assumed to depend only on $\mu$, $\nu$ and on time, $t$. The perturbed nutrient concentration is governed by the Laplace equation

$$\Delta \tilde{\sigma}_N = 0 , \tag{5.1}$$
$$\Delta \tilde{\sigma}_L = 0 , \tag{5.2}$$
$$\Delta \tilde{\sigma}_S = 0 , \tag{5.3}$$

in the necrotic core, the living shell and the surrounding area of the tumour, respectively. The perturbed pressure distribution within the tumour could no longer be obtained by solving Poisson equation, but simply by the following Laplace equations

$$\Delta \tilde{p}_N = 0 , \tag{5.4}$$
$$\Delta \tilde{p}_L = 0 , \tag{5.5}$$
where \( \tilde{p}_N \) is the perturbed pressure in the necrotic core and \( \tilde{p}_L \) the perturbed pressure in the living layer. The equations of continuity on the interface between the necrotic part and the living part of the tumour, i.e. equations (2.34)-(2.36), are transformed into the following equations

\[
\tilde{\sigma}_N = \tilde{\sigma}_L , \tag{5.6}
\]
\[
\tilde{p}_N = \tilde{p}_L , \tag{5.7}
\]
\[
\frac{\partial \tilde{p}_N}{\partial \rho} = \frac{\partial \tilde{p}_L}{\partial \rho} , \tag{5.8}
\]

after we introduce equations (2.44)-(2.48) and the expression for the normal unit vector on the interface, which can be found in Appendix D. The boundary conditions on the outer boundary of the tumour are turned into more complicated expressions, due to the fact that the boundary \( (\rho_L) \), the curvature \( (\kappa) \), the normal unit vector \( (\mathbf{n}) \) and the gradient on the outer boundary of the tumour are all expressed in terms of \( \varepsilon \). The expressions for \( \mathbf{n} \) are \( \nabla \) can be found in Appendix D. Finally, equation (2.37) assumes the form

\[
\frac{\partial \tilde{\sigma}_L}{\partial \rho} + \left( -\frac{f \rho_L}{\rho_L^3 - \mu^2} - \frac{f \rho_L}{\rho_L^2 - \nu^2} + \frac{f \rho_L}{\rho_L^2 - h_3^2} + \frac{f \rho_L}{\rho_L^2 - h_2^2} \right) \left[ \frac{\partial \tilde{\sigma}_L}{\partial \rho} + \frac{\gamma}{k} (h_L^L)^2 (\rho_L - \rho_Q) \right] =
\]
\[
= \frac{(h_L^L)^2}{(h_L^L)^2} \left\{ \frac{(h_L^L)^2}{\rho_L^2 - \nu^2} \frac{\partial \tilde{\sigma}_L}{\partial \nu} \left[ f \sqrt{\rho_L^2 - \nu^2} - \frac{\nu f}{\sqrt{\rho_L^2 - \nu^2}} \right] \right. \\
+ \left. \frac{(h_L^L)^2}{\rho_L^2 - \mu^2} \frac{\partial \tilde{\sigma}_L}{\partial \mu} \left[ f \sqrt{\rho_L^2 - \mu^2} - \frac{\mu f}{\sqrt{\rho_L^2 - \mu^2}} \right] \right\} + \frac{\gamma}{k} f , \tag{5.9}
\]

while equation (2.38) retains its simple form

\[
\tilde{\sigma}_L = \tilde{\sigma}_S . \tag{5.10}
\]
The metric coefficients on the outer boundary are also expressed in terms of $\varepsilon$ (Appendix D). Equation (2.39) for the perturbed part has the following form

$$
\left(h^L_\rho\right)^2 f_t + \frac{\partial \tilde{p}_L}{\partial \rho} - \frac{\beta}{d_t} \left(h^L_\rho\right)^2 f + f \rho_L \left( \frac{1}{\rho^2_L - \mu^2} + \frac{1}{\rho^2_L - \nu^2} - \frac{1}{\rho^2_L - h^2} - \frac{1}{\rho^2_L - h^2} \right),
$$

$$
\left(h^L_\rho\right)^2 \frac{d \rho_L}{dt} - \frac{\partial \tilde{p}_L}{\partial \rho} - \frac{\beta}{d_t} \left(h^L_\rho\right)^2 (\rho_L - \rho_Q) + \left( \frac{\mu f}{\rho^2_L - \mu^2} - f \mu \right) \left(h^L_\rho\right)^2 \frac{d \mu}{dt} + \frac{1}{\left(h^L_\mu\right)^2} \frac{\partial \tilde{p}_L}{\partial \mu}
$$

$$
+ \left( \frac{\nu f}{\rho^2_L - \nu^2} - f \nu \right) \left(h^L_\nu\right)^2 \left( \frac{d \nu}{dt} + \frac{1}{\left(h^L_\nu\right)^2} \frac{\partial \tilde{p}_L}{\partial \nu} \right) = 0,
$$

(5.11)

while equation (2.40) splits in three different expressions

$$
\left( f \nu - \frac{\nu f}{\rho^2_L - \nu^2} \right) \left( h^L_\mu \right)^2 \frac{d \mu}{dt} - \frac{\partial \tilde{p}_L}{\partial \mu} = \left( f \mu - \frac{\mu f}{\rho^2_L - \mu^2} \right) \left( h^L_\nu \right)^2 \frac{d \nu}{dt} - \frac{\partial \tilde{p}_L}{\partial \nu},
$$

(5.12)

$$
\frac{\partial \tilde{p}_L}{\partial \mu} = \left( f \mu - \frac{\mu f}{\rho^2_L - \mu^2} \right) \left( h^L_\mu \right)^2 \frac{d \rho_L}{dt} - \frac{\partial \tilde{p}_L}{\partial \rho} + \frac{f \rho_L}{\rho^2_L - \mu^2} \left( h^L_\mu \right)^2 \frac{d \mu}{dt} + \frac{\partial \tilde{p}_L}{\partial \mu},
$$

(5.13)

$$
\frac{\partial \tilde{p}_L}{\partial \nu} = \left( f \nu - \frac{\nu f}{\rho^2_L - \nu^2} \right) \left( h^L_\nu \right)^2 \frac{d \rho_L}{dt} - \frac{\partial \tilde{p}_L}{\partial \rho} + \frac{f \rho_L}{\rho^2_L - \nu^2} \left( h^L_\nu \right)^2 \frac{d \nu}{dt} + \frac{\partial \tilde{p}_L}{\partial \nu}.
$$

(5.14)

Next, the pressure from inside the tumour reaches a constant value on the boundary, $\tilde{g}(\rho_L)$. Depending on the boundary we obtain

$$
\tilde{p}_L = \tilde{g}(\rho_L),
$$

(5.15)

$$
\tilde{p}_S = \tilde{g}(\rho_L) - \alpha \kappa,
$$

(5.16)

because of our assumption of the Young-Laplace equation (2.41). For the perturbed nutrient concentration near the nutrient source we assume

$$
\tilde{\sigma}_S \to 0, \text{ as } |r| \to \infty.
$$

(5.17)
We consider harmonic solutions for the perturbation, the nutrient concentration and the pressure distribution

\[
\begin{align*}
    f &= \sum_{n=0}^{\infty} \sum_{m=1}^{2n+1} a_n^m(t) E_n^m(\rho) S_n^m(\mu, \nu) , \\
    \delta_N &= \sum_{n=0}^{\infty} \sum_{m=1}^{2n+1} b_n^m(t) E_n^m(\rho) S_n^m(\mu, \nu) , \\
    \delta_L &= \sum_{n=0}^{\infty} \sum_{m=1}^{2n+1} \left[ c_n^m(t) + (2n + 1) d_n^m(t) I_n^m(\rho) \right] E_n^m(\rho) S_n^m(\mu, \nu) , \\
    \delta_S &= \sum_{n=0}^{\infty} \sum_{m=1}^{2n+1} (2n + 1) e_n^m(t) I_n^m(\rho) E_n^m(\rho) S_n^m(\mu, \nu) , 
\end{align*}
\]  
(5.18)\mbox{,} (5.19)\mbox{,} (5.20)\mbox{,} (5.21)

where \( a_n^m(t), \ b_n^m(t), \ c_n^m(t), \ d_n^m(t), \ e_n^m(t), \ g_n^m(t), \ h_n^m(t), \ i_n^m(t), \) are time-dependent coefficients, \( E_n^m(\rho) \) are the Lamé functions of the first kind, \( S_n^m(\mu, \nu) \) the ellipsoidal surface harmonics and \( I_n^m(\rho) \) the elliptic integrals. \( E_n^m(\rho), \ S_n^m(\mu, \nu), \ I_n^m(\rho) \) are defined in Appendix A.

In order to determine whether the tumour is stable or not, we need to know whether \( f \) increases or decays. To do that, we need the following equation

\[
\begin{align*}
    \left( h_L^2 \right)^2 \sum_{n=0}^{\infty} \sum_{m=1}^{2n+1} a_n^m(t) E_n^m(\rho) S_n^m(\mu, \nu) + \sum_{n=0}^{\infty} \sum_{m=1}^{2n+1} g_n^m(t) \frac{\partial E_n^m(\rho)}{\partial \rho} S_n^m(\mu, \nu) \\
    - \frac{\beta}{d_t} \left( h_L^2 \right)^2 \sum_{n=0}^{\infty} \sum_{m=1}^{2n+1} a_n^m(t) E_n^m(\rho) S_n^m(\mu, \nu) \\
    - \frac{2}{3} \rho_L^2 \left[ \sum_{n=0}^{\infty} \sum_{m=1}^{2n+1} a_n^m(t) E_n^m(\rho) S_n^m(\mu, \nu) \right] \left( \frac{1}{\rho_L^2 - \mu^2} + \frac{1}{\rho_L^2 - \nu^2} - \frac{1}{\rho_L^2 - h_3^2} - \frac{1}{\rho_L^2 - h_2^2} \right) \left[ S_1 \frac{V(\rho_L) - V(\rho_N)}{V(\rho_L)} + S_2 \frac{V(\rho_N)}{V(\rho_L)} \right] \frac{\rho_L^2 - \mu^2}{E_1(\rho_L) E_2(\rho_L)} = 0 , 
\end{align*}
\]  
(5.24)

which includes the time-derivative of the coefficient of the perturbation, \( a_n^m(t) \). However, there is also the coefficient of \( \delta_L \). So, in need of a second equation between \( g_n^m(t) \) and...
we choose the following equation

\[ a_n^m(t) = \sum_{n=0}^{\infty} \sum_{m=1}^{2n+1} g_n^m(t) E_n^m(\mu) E_n^m(\nu) = \left( \frac{(h_\rho^L)^2}{\sqrt{\rho^2 - \mu^2 - \nu^2}} \frac{\partial}{\partial \mu} \left[ \sqrt{\rho^2 - \mu^2 - \nu^2} \sum_{n=0}^{\infty} \sum_{m=1}^{2n+1} a_n^m(t) E_n^m(\nu L) \right] \right) \cdot \left\{ -\frac{2\rho_L}{3 (h_\rho^L)^2} \left[ S_1 - \left( S_1 - S_2 \right) \frac{V(\rho_X)}{V(\rho_L)} \right] \left( \frac{\rho^2_L - \mu^2}{E_2^2(\rho_L) E^2(\rho_L)} \right) + \frac{\beta}{\delta t} (\rho_L - \rho_Q) \right\} . \]  

In Figures 5.1-5.3, we depict the ratio \( \frac{a_n^m}{a_n^m} \) by combining the Equations (5.24) and (5.25) in the \( \mu - \nu \) contour. In order to conclude whether \( f \) increases, the above fraction must be positive. When the fraction is negative, then \( f \) decays. As seen, in the following figures, using the parameters from Table 2.2, \( f \) increases in all cases. However, it worth mentioning the trends that the figures reveal.

In Figure 5.1 we can observe a maximum at the location where \((\mu, \nu) = (h_2, h_3)\) which corresponds to the \(x_1\) axis in cartesian coordinates, while the minimum is located at \((\mu, \nu) = (h_3, 0)\) which corresponds to \(x_3\) axis in cartesian coordinates. This means that along the longest semiaxis, there lies the maximum of value of \( f \) so the most unstable part of the tumour will be there. On the other hand, along the shortest semiaxis, the perturbation will be smoother.

Figures 5.2-5.3 follow the same trend. The maximum value can be found at the locations where \( \mu = h_2 \), while the minimum value at \( \mu = h_3 \). In cartesian coordinates, \( \mu = h_2 \) represents the \(x_1x_2\)–plane, while \( \mu = h_3 \) represents the \(x_1x_3\)–plane.

When comparing those two planes, \( x_1x_2 \) includes the two longest semiaxes, while \( x_1x_3 \) includes the longest and the shortest semiaxes. In other words, the maximum values are found in the area of the two longest semiaxes, which are located away from the core of the ellipsoidal tumour and are more prone to perturbations.

This contradicts with the spherical case, as predicted by Greenspan, where there were different cases of \( f \) being amplified or decayed depending on the tumour unperturbed radius. However, in the ellipsoidal case, the anisotropy of the shape inclines towards the legitimacy of this result. In other words, in a system less symmetrical than the sphere, we expect the asymmetry to reflect unstable tumour growth from
Figure 5.1.: The $\mu, \nu$ contour for $n = 0$ and $m = 1$.

Figure 5.2.: The $\mu, \nu$ contour for $n = 1$ and $m = 1$.

Figure 5.3.: The $\mu, \nu$ contour for $n = 2$ and $m = 1$. 
the very start of their development.

It is depressing to realize that most tumours do not develop in a symmetric way and therefore no stability of their growth is expected. This is another physical case where instability appears as a result of lack of symmetry.
6. Conclusions

This chapter includes the conclusions from this work as presented in the previous chapters. We conclude with some ideas for future work in order for this model to be more complete and ready to be used by Biologists and Clinicians for tumour analysis.

We begin by comparing the steady state radii of the four spherical models. By using the same parameters for all four models (Table 2.1), the steady state radii range from 0.1558 when assuming the non-homogeneous modified model to 0.5669 in the Greenspan model. When comparing two models with the same boundary conditions, but different to the number of cell loss rates, the homogeneous model always holds the largest radius at the steady state case, even if the initial volumes were the same. For example, the non-homogeneous Greenspan model reaches a radius of 0.3781 in contrast to the 0.5669 of the homogenous Greenspan model. This results from assuming only one cell loss rate within the tumour at the homogenous case, which in our approach is the smaller of the two, so more cells survive than the non-homogeneous case. Lastly, when comparing model with the same number of cell loss rates, the model that holds a boundary condition based on the local thickness instead of a square root law reaches a smaller radius at the steady state case. For example, non-homogeneous model has a steady state radius of 0.1558, while non-homogeneous Greenspan reaches the value of 0.3781. The same applies for homogenous modified model (0.4471) and homogeneous Greenspan (0.5669).

Continuing with the pressure and nutrient profiles of all four spherical models, in all cases the same trends are observed. In the necrotic core we have negative but
large values of pressure, which reflect the high particle velocity expected due to the absence of strict structure in the region. Close to the outer boundary of the tumour, the pressure obtains small but positive values which represent the low mobility of cells due to overpopulation of the region with highly proliferating cells. When comparing the models, the curves of the nonhomogeneous models share the same form, with an inflection point at the necrotic core surface, while the other models share a more smooth curve. In matters of nutrient concentration, an amount of nutrient is lost due to diffusion before it even reaches the outer boundary of the tumour, whereas the largest amount is consumed with the shell of living cells.

However, the value of the steady state “radius” of the ellipsoidal model can be directly compared to the radii of the spherical models. Equation (2.74) reflects the complexity of the ellipsoidal geometry and results to a value of 1.9598 for the steady state. The volume of the ellipsoidal tumour is much larger that the relevant volume of the spherical tumours, so no obvious results can be derived.

Things get even more complicated when we depict the pressure distribution and the nutrient concentration of the ellipsoidal model. The dependence of these two values of $\mu$ and $\nu$ forces us into looking for locations of maximum and minimum of these parameters and then plotting the maximum and minimum values of these parameters. Although, details of the results derived from these Figures can be found in Section 2.3, it is worth mentioning that there is a dependence of pressure and nutrient concentration on the choice of parameters, which does not allow us to make any safe conclusions.

From Chapter 4 and the stability study of the spherical models, we conclude that the stability or not of a spherical tumour does not depend on the angles. Moreover, both homogeneous and non-homogeneous Greenspan model consist of cases of stable and unstable tumours that dependent of their radius. On the other hand, both modified models are independent of the tumour radius, as their cases show no minimum critical radius. For more details on each model and its stability study, we refer the reader to Section 4.1 for the Greenspan model, Section 4.2 for the non-homogeneous Greenspan model, Section 4.3 for the homogeneous modified model and Section 4.4
for the non-homogeneous modified model.

The stability study of the ellipsoidal model is explicitly described in Chapter 5. The complexity of the ellipsoidal geometry is once more reflected to the calculations and to the forms of the results. In the ellipsoidal case, the stability or not of the tumour depends on the angular coordinates of the ellipsoidal tumour, in contradiction to the spherical models where the coefficient of the radial perturbation is independent of both \( \theta \) and \( \varphi \). The main outcome is that, all the modes that we explored result in unstable tumours, as \( f \) is positive at all times. For the \( n = 0 \) mode, the more unstable position of the ellipsoidal tumour is located at the longest semiaxis, while the less unstable at the shortest semiaxis. A similar result, but in the cases of planes, can be observed for greater modes, where the most unstable part can be found at the plane of the two longest semiaxes, whereas the plane of the longest and the shortest semiaxes accounts for the least unstable part of the ellipsoidal tumour.

The goal of this work was to test a model for tumour perturbation in ellipsoidal geometry, which complexity and anisotropy matches the complexity and anisotropy found in tumours in vivo. This complexity is reflecting on the results and more specifically on the fact that the ellipsoidal tumour will become unstable as soon as a perturbation starts to grow on its surface. This coincides with the physicians guidelines, to observe for disturbed ellipsoidal shaped tumours, as studies (see Mills et al. (2014), Feldman et al. (2009), Wapnir et al. (1996) and Alemán-Flores et al. (2004)) have shown that they are prone to become unstable and attract vasculature, in their way of become malignant and final to metastasize.

Unfortunately this work is far from being ready to use for Clinicians, as the parametric values are based on numerical calculations. So, our main goal for the future would be to use parameters from experimental data in order to check the stability of both in vitro and in vivo growing tumours. It would be also interesting to further enhance the model by adding other processes that take place within the tumour, for the model to become more realistic.


CLARK, E.R. (1918) Studies on the growth of blood-vessels in the tail of the frog


**Drasdo, D.** (1998) *A Monte-Carlo approach to growing solid non-vascular tumors*, in *Dynamical Networks in Physics and Biology at the Frontier of Physics and...*


Appendices
A. Introduction to Spherical Geometry

When we model complicated shapes, we are in need of a coordinate system that best fits the problem. In other words, when we model spherical tumours, the spherical coordinate system is closer to the geometry of the problem than the cartesian coordinate system, and hence it is preferable to use. The spherical coordinates \((r, \vartheta, \varphi)\) are connected with the coordinates of the cartesian system \((x_1, x_2, x_3)\) as

\[
\begin{align*}
    x_1 &= r \sin \vartheta \cos \varphi, \\
x_2 &= r \sin \vartheta \sin \varphi, \\
x_3 &= r \cos \vartheta,
\end{align*}
\]

and an illustration of the spherical coordinates and its orthogonal unit vectors in accordance to the cartesian coordinate system is depicted in Figure A.1. Besides the spherical coordinates, we will need the form of the Laplace operator in spherical coordinates, as well as the normal unit vector, the surface gradient and the curvature. These formulae are used in all four models for spherical tumours presented in this thesis.

To begin with, the Laplace operator

\[
\Delta = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial}{\partial r} \right) + \frac{1}{r^2 \sin \vartheta} \frac{\partial}{\partial \vartheta} \left( \sin \vartheta \frac{\partial}{\partial \vartheta} \right) + \frac{1}{r^2 \sin^2 \vartheta} \frac{\partial^2}{\partial \varphi^2}.
\]
So, in order to solve the Laplace equation for a certain function $u(r, \vartheta, \varphi)$, we assume that
\[
u(r, \vartheta, \varphi) = R(r)\Theta(\vartheta)\Phi(\varphi) . \tag{A.5}
\]

If we separate in this way the $u$ function, then the Laplace equation leads to the next three ordinary equations
\[
\frac{d}{dr} \left( r^2 \frac{d}{dr} R(r) \right) - n(n+1) R(r) = 0 , \tag{A.6}
\]
\[
\frac{1}{\sin \vartheta} \frac{d}{d\vartheta} \left( \sin \vartheta \frac{d}{d\vartheta} \Theta(\vartheta) \right) + \left[ n(n+1) - \frac{m^2}{\sin^2 \vartheta} \right] \Theta(\vartheta) = 0 , \tag{A.7}
\]
\[
\frac{d^2}{d\varphi^2} \Phi(\varphi) + m^2 \Phi(\varphi) = 0 , \tag{A.8}
\]
where the separation constant $n$ takes the values 0, 1, 2, ... in order for the function $\Theta(\vartheta)$ to remain bounded for $\vartheta = 0$ and $\vartheta = \pi$, and the separation constant $m$ takes the integral values of the interval $|m| \leq n$ in order to secure rotational symmetry and independence of the solutions.

Equation (A.6) has the interior solutions $r^n$ and the exterior solutions $r^{-(n+1)}$, while (A.8) has the pair of solutions $e^{\pm im\varphi}$. For the equation (A.7) we introduce the substitution $x = \cos \vartheta$ and the equation (A.7) is transformed to the associated
Legendre equation

\[(1 - x^2) \frac{d^2}{dx^2} P_n^m(x) - 2x \frac{d}{dx} P_n^m(x) + \left[ n(n+1) - \frac{m^2}{1-x^2} \right] P_n^m(x) = 0. \]  \hspace{1cm} (A.9)

The associated Legendre equation (reproduced by Dassios (2012)) is solved by the associated Legendre functions of the first kind

\[P_n^m(x) = (1 - x^2)^{m/2} \frac{d^m}{dx^m} P_n(x), m = -n, -n+1, ..., 0, ..., n-1, n, \]  \hspace{1cm} (A.10)

where

\[P_n(x) = \frac{1}{2^n} \sum_{k=0}^{[n/2]} \frac{(-1)^k(2n-2k)!}{k!(n-k)!(n-2k)!} x^{n-2k}, n = 0, 1, 2, ..., \]  \hspace{1cm} (A.11)

and the associated Legendre functions of the second kind

\[Q_n^m(x) = (1 - x^2)^{m/2} \frac{d^m}{dx^m} Q_n(x), m = -n, -n+1, ..., 0, ..., n-1, n, \]  \hspace{1cm} (A.12)

where

\[Q_n(x) = \frac{1}{2} P_n(x) \ln \frac{1+x}{1-x} - \sum_{k=0}^{n-1} \frac{1}{k+1} P_k(x) P_{n-1-k}(x), n \geq 0. \]  \hspace{1cm} (A.13)

In particular,

\[P_1^1(x) = \sqrt{1-x^2}, \]  \hspace{1cm} (A.14)
\[P_2^1(x) = 3x\sqrt{1-x^2}, \]  \hspace{1cm} (A.15)
\[P_2^2(x) = 3(1-x^2), \]  \hspace{1cm} (A.16)
\[P_3^1(x) = \frac{3}{2}(5x^2-1)\sqrt{1-x^2}, \]  \hspace{1cm} (A.17)
\[P_3^2(x) = 15x(1-x^2), \]  \hspace{1cm} (A.18)
\[P_3^3(x) = 15(1-x^2)\sqrt{1-x^2}. \]  \hspace{1cm} (A.19)
and

\[ Q_1^1(x) = \frac{\sqrt{1-x^2}}{2} \ln \frac{1+x}{1-x} + \frac{x}{\sqrt{1-x^2}}, \quad (A.20) \]
\[ Q_2^1(x) = \frac{3x\sqrt{1-x^2}}{2} \ln \frac{1+x}{1-x} + \frac{3x^2-2}{\sqrt{1-x^2}}, \quad (A.21) \]
\[ Q_2^2(x) = \frac{3x(1-x^2)}{2} \ln \frac{1+x}{1-x} + \frac{3x^3+5x}{(1-x^2)}, \quad (A.22) \]
\[ Q_3^1(x) = \frac{(15x^2-3)\sqrt{1-x^2}}{4} \ln \frac{1+x}{1-x} + \frac{x}{\sqrt{1-x^2}} - \frac{15x\sqrt{1-x^2}}{2}, \quad (A.23) \]
\[ Q_3^2(x) = \frac{15x(1-x^2)}{2} \ln \frac{1+x}{1-x} + \frac{2}{1-x^2} + 15x^2 - 10, \quad (A.24) \]
\[ Q_3^3(x) = \frac{15(1-x^2)\sqrt{1-x^2}}{2} \ln \frac{1+x}{1-x} + \frac{8x}{(1-x^2)\sqrt{1-x^2}} + \frac{25x-15x^2}{\sqrt{1-x^2}}, \quad (A.25) \]

On a surface with complete spherical symmetry, the normal unit vector is represented by the \( \hat{r} \),

\[ \hat{n} = \hat{r}, \quad (A.26) \]

while the surface gradient in terms of spherical coordinates is given by

\[ \nabla = \frac{\partial}{\partial r} \hat{r} + \frac{1}{r} \frac{\partial}{\partial \theta} \hat{\theta} + \frac{1}{r \sin \theta} \frac{\partial}{\partial \phi} \hat{\phi}. \quad (A.27) \]

Lastly, the mean curvature on the spherical surface is given by

\[ \kappa = \frac{1}{r_P} \quad (A.28) \]

where \( r_P \) is the spherical radius.
B. Introduction to Ellipsoidal Geometry

This Appendix serves as a brief introduction to ellipsoidal geometry and is based on the book by Dassios (2012). The anisotropy of the ellipsoidal coordinate system serves as a better tool to approach shapes more complicated than simple spheres. The reference ellipsoid is specified, when given any three numbers $\alpha_1$, $\alpha_2$, $\alpha_3$, as

$$\frac{x_1^2}{\alpha_1^2} + \frac{x_2^2}{\alpha_2^2} + \frac{x_3^2}{\alpha_3^2} = 1, \quad 0 < \alpha_3 < \alpha_2 < \alpha_1 < +\infty,$$  \hspace{1cm} (B.1)

where $\alpha_1$, $\alpha_2$, $\alpha_3$ are the three semi-axes of the ellipsoid which in their turn define the semi-focal distances

$$h_1^2 = \alpha_2^2 - \alpha_3^2, \quad h_2^2 = \alpha_1^2 - \alpha_3^2, \quad h_3^2 = \alpha_1^2 - \alpha_2^2.$$  \hspace{1cm} (B.2)

The centre of the ellipsoidal coordinate system is the focal ellipse, an ellipse on the $x_1, x_2$ plane with semi-focal distance $h_3$ and semi-axes $\alpha_1$ and $\alpha_2$.

As depicted in Figure B.1 the variable $\rho$ defines a family of confocal ellipsoids, the variable $\mu$ defines a confocal family of hyperboloids of one sheet, while the variable $\nu$ defines the confocal family of the hyperboloids of two sheets. The ellipsoidal coordinates are connected with the coordinates of the Cartesian system as

$$x_1 = \frac{\rho \mu \nu}{h_2 h_3}, \quad h_2 < \rho < +\infty,$$  \hspace{1cm} (B.3)

$$x_2 = \sqrt{\frac{\rho^2 - h_3^2 \sqrt{\mu^2 - h_3^2 \sqrt{\nu^2}}}{h_1 h_3}}, \quad h_3 < \mu < h_2,$$  \hspace{1cm} (B.4)

$$x_3 = \sqrt{\frac{\rho^2 - h_2 \sqrt{h_3^2 - \mu^2 \sqrt{h_3^2 - \nu^2}}}{h_1 h_2}}, \quad 0 < \nu < h_3,$$  \hspace{1cm} (B.5)
while the ellipsoidal coordinate curves in the cartesian space are depicted in Figure B.2. The ellipsoidal metric coefficients are

\[
h_\rho = ||r_\rho|| = \sqrt{\frac{\rho^2 - \mu^2 \sqrt{\mu^2 - \nu^2}}{\rho^2 - h_3^2 \sqrt{\rho^2 - h_2^2}}}, \tag{B.6}
\]

\[
h_\mu = ||r_\mu|| = \sqrt{\frac{\mu^2 - \nu^2 \sqrt{\mu^2 - \nu^2}}{\mu^2 - h_3^2 \sqrt{\nu^2 - h_2^2}}}, \tag{B.7}
\]

\[
h_\nu = ||r_\nu|| = \sqrt{\frac{\rho^2 - \nu^2 \sqrt{\rho^2 - \nu^2}}{\rho^2 - h_3^2 \sqrt{\rho^2 - \nu^2}}}. \tag{B.8}
\]

In the Ellipsoidal system, the solutions to the Laplace equation differ depending on the domain wherein they are defined. The interior harmonic solution has the form
of

$$E_n^m(\rho, \mu, \nu) = E_n^m(\rho)E_n^m(\mu)E_n^m(\nu), \quad (B.9)$$

where $E_n^m$ is the Lamé function of the first kind, of degree $n = 0, 1, 2, \ldots$ and order $m = 1, 2, \ldots 2n + 1$, whereas the exterior harmonic solution is defined as

$$F_n^m(\rho, \mu, \nu) = F_n^m(\rho)E_n^m(\mu)E_n^m(\nu), \quad (B.10)$$

where $F_n^m$ is the Lamé function of the second kind. The latter is given by

$$F_n^m(\rho) = (2n + 1)E_n^m(\rho) \int_\rho^\infty \frac{dx}{[E_n^m(x)]^2 \sqrt{x^2 - \hat{h}_3^2 \sqrt{x^2 - \hat{h}_2^2}}. \quad (B.11)$$

The functions $E_n^m(\rho, \mu, \nu)$ and $F_n^m(\rho, \mu, \nu)$ are called Lamé products or interior and exterior ellipsoidal harmonics respectively. The surface ellipsoidal harmonics are given by

$$S_n^m(\mu, \nu) = E_n^m(\mu)E_n^m(\nu), \quad n = 0, 1, 2, \ldots, \quad m = 1, 2, \ldots, 2n + 1. \quad (B.12)$$

W will state the ellipsoidal harmonics of degree less than or equal to two because we are using them in this paper. For $n = 0$, we have the Lame function

$$E_0^1(x) = 1, \quad (B.13)$$

where $x$ is one of the ellipsoidal coordinates, $(\rho, \mu, \nu)$, the interior ellipsoidal harmonic

$$E_0^1(\rho, \mu, \nu) = 1, \quad (B.14)$$

and the exterior ellipsoidal harmonic

$$F_0^1(\rho, \mu, \nu) = \int_\rho^\infty \frac{dx}{\sqrt{x^2 - \hat{h}_3^2 \sqrt{x^2 - \hat{h}_2^2}}. \quad (B.15)$$
For $n = 1$, we have the Lamé functions

\[ E_1^1(x) = x, \quad (B.16) \]
\[ E_1^2(x) = \sqrt{|x^2 - h_3^2|}, \quad (B.17) \]
\[ E_1^3(x) = \sqrt{|x^2 - h_2^2|}, \quad (B.18) \]

the interior ellipsoidal harmonics

\[ E_1^j_1(\rho, \mu, \nu) = \rho \mu \nu = h_2 h_3 x_1, \quad (B.19) \]
\[ E_1^j_2(\rho, \mu, \nu) = \sqrt{\rho^2 - h_3^2} \sqrt{\mu^2 - h_3^2} \sqrt{h_3^2 - \nu^2} = h_1 h_3 x_2, \quad (B.20) \]
\[ E_1^j_3(\rho, \mu, \nu) = \sqrt{\rho^2 - h_2^2} \sqrt{h_2^2 - \mu^2} \sqrt{h_2^2 - \nu^2} = h_1 h_2 x_3, \quad (B.21) \]

and the exterior ellipsoidal harmonics

\[ E_1^j_1(\rho, \mu, \nu) = 3E_1^j_1(\rho, \mu, \nu) \int_0^\infty \frac{dx}{x^2 \sqrt{x^2 - h_3^2} \sqrt{x_2^2 - h_2^2}}, \quad (B.22) \]
\[ E_1^j_2(\rho, \mu, \nu) = 3E_1^j_2(\rho, \mu, \nu) \int_0^\infty \frac{dx}{(x^2 - h_3^2)^{3/2} \sqrt{x_2^2 - h_2^2}}, \quad (B.23) \]
\[ E_1^j_3(\rho, \mu, \nu) = 3E_1^j_3(\rho, \mu, \nu) \int_0^\infty \frac{dx}{\sqrt{x^2 - h_3^2} (x_2^2 - h_2^2)^{3/2}}. \quad (B.24) \]

For $n = 2$, we have the Lamé functions

\[ E_2^1(x) = x^2 + \Lambda - \alpha_1^2, \quad (B.25) \]
\[ E_2^2(x) = x^2 + \Lambda' - \alpha_1^2, \quad (B.26) \]
\[ E_2^3(x) = x \sqrt{|x^2 - h_3^2|}, \quad (B.27) \]
\[ E_2^4(x) = x \sqrt{|x^2 - h_2^2|}, \quad (B.28) \]
\[ E_2^5(x) = \sqrt{|x^2 - h_3^2|} \sqrt{|x^2 - h_2^2|}, \quad (B.29) \]

where

\[ \Lambda = \frac{1}{3} (a_1^2 + a_2^2 + a_3^2) + \frac{1}{3} \sqrt{h_1^4 + h_2^4 h_3^2}, \quad (B.30) \]
\[ \Lambda' = -\frac{1}{3} (a_1^2 + a_2^2 + a_3^2) + \frac{1}{3} \sqrt{h_1^4 + h_2^4 h_3^2}. \quad (B.31) \]
The interior ellipsoidal harmonics for \( n = 2 \) are

\[
\begin{align*}
\mathbf{E}_1^2(\rho, \mu, \nu) &= (\rho^2 + \Lambda - \alpha_1^2)(\mu^2 + \Lambda - \alpha_1^2)(\nu^2 + \Lambda - \alpha_1^2), \\
\mathbf{E}_2^2(\rho, \mu, \nu) &= (\rho^2 + \Lambda' - \alpha_1^2)(\mu^2 + \Lambda' - \alpha_1^2)(\nu^2 + \Lambda' - \alpha_1^2), \\
\mathbf{E}_3^2(\rho, \mu, \nu) &= \rho \mu \sqrt{\rho^2 - h_3^2 \nu \sqrt{\rho^2 - h_3^2 \mu^2}}, \\
\mathbf{E}_4^2(\rho, \mu, \nu) &= \rho \mu \sqrt{\rho^2 - h_3^2 \mu \sqrt{\rho^2 - h_3^2 \nu^2}}, \\
\mathbf{E}_5^2(\rho, \mu, \nu) &= \rho \mu \sqrt{\rho^2 - h_3^2 \nu \sqrt{\rho^2 - h_3^2 \mu^2}}.
\end{align*}
\]

and the exterior ellipsoidal harmonics are given by

\[
\begin{align*}
\mathbf{F}_1^2(\rho, \mu, \nu) &= 5 \mathbf{E}_1^2(\rho, \mu, \nu) \int_{\rho}^{\infty} \frac{dx}{(x^2 + \Lambda - \alpha_1^2)^2 \sqrt{x^2 - h_3^2 x^2 - h_2^2}}, \\
\mathbf{F}_2^2(\rho, \mu, \nu) &= 5 \mathbf{E}_2^2(\rho, \mu, \nu) \int_{\rho}^{\infty} \frac{dx}{(x^2 + \Lambda' - \alpha_1^2)^2 \sqrt{x^2 - h_3^2 x^2 - h_2^2}}, \\
\mathbf{F}_3^2(\rho, \mu, \nu) &= 5 \mathbf{E}_3^2(\rho, \mu, \nu) \int_{\rho}^{\infty} \frac{dx}{x^2 (x^2 - h_3^2)^{3/2} \sqrt{x^2 - h_3^2}}, \\
\mathbf{F}_4^2(\rho, \mu, \nu) &= 5 \mathbf{E}_4^2(\rho, \mu, \nu) \int_{\rho}^{\infty} \frac{dx}{x^2 (x^2 - h_3^2)^{3/2} \sqrt{x^2 - h_3^2}}, \\
\mathbf{F}_5^2(\rho, \mu, \nu) &= 5 \mathbf{E}_5^2(\rho, \mu, \nu) \int_{\rho}^{\infty} \frac{dx}{(x^2 - h_3^2)^{3/2} (x^2 - h_2^2)^{3/2}}.
\end{align*}
\]

The rest of the ellipsoidal harmonics can be found in the book by Dassios (2012) (Appendix F).

For the ellipsoidal mode, we also use the normal unit vector \( \hat{n} \) which is

\[
\hat{n} = \hat{\rho},
\]

while the position vector is given by

\[
r = \frac{\rho}{h_\rho} \hat{\rho} + \frac{\mu}{h_\mu} \hat{\mu} + \frac{\nu}{h_\nu} \hat{\nu}.
\]

The gradient is represented in ellipsoidal coordinates as

\[
\nabla = \frac{1}{h_\rho} \frac{\partial}{\partial \rho} \hat{\rho} + \frac{1}{h_\mu} \frac{\partial}{\partial \mu} \hat{\mu} + \frac{1}{h_\nu} \frac{\partial}{\partial \nu} \hat{\nu}.
\]
Finally, the mean curvature at a surface point \((\rho_P, \mu, \nu)\) of the ellipsoid is given by

\[
\kappa(\rho_P, \mu, \nu) = \left( \frac{1}{\rho_P^2 - \mu^2} + \frac{1}{\rho_P^2 - \nu^2} \right) \frac{\rho_P \sqrt{\rho_P^2 - h_3^2} \sqrt{\rho_P^2 - h_2^2}}{2 \sqrt{\rho_P^2 - \mu^2} \sqrt{\rho_P^2 - \nu^2}}.
\]  

(B.45)
C. Useful formulae in spherical coordinates for perturbed variables

In this section, we will demonstrate the calculations behind the equations for the unit vector and the curvature for the perturbed surface in powers of $\varepsilon$. In the spherical geometry, the orthogonal unit vectors are

$$\hat{r} = \sin \vartheta \cos \varphi \hat{i} + \sin \vartheta \sin \varphi \hat{j} + \cos \vartheta \hat{k}, \quad (C.1)$$

$$\dot{\vartheta} = \cos \vartheta \cos \varphi \hat{i} + \cos \vartheta \sin \varphi \hat{j} - \sin \vartheta \hat{k}, \quad (C.2)$$

$$\dot{\varphi} = -\sin \varphi \hat{i} + \cos \varphi \hat{j}, \quad (C.3)$$

where $\hat{i}, \hat{j}, \hat{k}$ are the unit vectors in cartesian coordinates.

We assume that the perturbation depends on both $\vartheta$ (polar angle) and $\varphi$ (azimuthal angle),

$$r = F(\vartheta, \varphi, t) \hat{r}. \quad (C.4)$$

In order to calculate the unit vector, first we have to calculate $r_{\vartheta}$ and $r_{\varphi}$.

$$r_{\vartheta} = F_{\vartheta} \hat{r} + F \dot{\vartheta}, \quad (C.5)$$

$$r_{\varphi} = F_{\varphi} \hat{r} + F \sin \vartheta \dot{\varphi}. \quad (C.6)$$

Then we need to find $r_{\vartheta} \times r_{\varphi}$

$$r_{\vartheta} \times r_{\varphi} = (F^2 \sin \vartheta) \hat{r} - (F F_{\vartheta} \sin \vartheta) \hat{\vartheta} - (F F_{\varphi}) \hat{\varphi}, \quad (C.7)$$
and its norm

$$||r_\theta \times r_\varphi|| = F \sqrt{F^2 \sin^2 \vartheta + F_\varphi^2 \sin^2 \varphi + F_\theta^2}.$$  \hspace{1cm} (C.8)

The normal unit in terms of $F$ is

$$\hat{n} = \frac{r_\theta \times r_\varphi}{||r_\theta \times r_\varphi||} = \frac{(F \sin \vartheta) \hat{r} - (F_\varphi \sin \vartheta) \hat{\varphi} - (F_\theta) \hat{\theta}}{\sqrt{F^2 \sin^2 \vartheta + F_\varphi^2 \sin^2 \varphi + F_\theta^2}}.$$  \hspace{1cm} (C.9)

Then we calculate the curvature and its form in $F$ is

$$\kappa = \frac{1}{2} \nabla \cdot \hat{n} = \frac{F \sin^3 \vartheta (2F^2 + 3F_\varphi^2 - FF_\varphi)}{2F (F^2 \sin^2 \vartheta + F_\varphi^2 \sin^2 \varphi + F_\theta^2)^{3/2}} + \sin \vartheta \left[ F_\varphi^2 (3F - F_\varphi) - F_\varphi \left( F^2 + F_\varphi^2 \right) + F_\varphi F_\theta (F_\varphi + F_\theta) \right] \frac{1}{2F (F^2 \sin^2 \vartheta + F_\varphi^2 \sin^2 \varphi + F_\theta^2)^{3/2}} - \frac{2 \cos \vartheta F_\varphi F_\theta^2 + F_\varphi \cos \vartheta \sin^2 \vartheta (2F^2 + F_\theta^2)}{2F (F^2 \sin^2 \vartheta + F_\varphi^2 \sin^2 \varphi + F_\theta^2)^{3/2}},$$  \hspace{1cm} (C.10)

because of the following formulae

$$\nabla \cdot \hat{r} = \frac{2}{F},$$  \hspace{1cm} (C.11)

$$\nabla \cdot \hat{\varphi} = \frac{\cos \vartheta}{F \sin \vartheta},$$  \hspace{1cm} (C.12)

$$\nabla \cdot \hat{\theta} = 0,$$  \hspace{1cm} (C.13)

$$\left( \nabla \frac{F \sin \vartheta}{\sqrt{F^2 \sin^2 \vartheta + F_\varphi^2 \sin^2 \varphi + F_\theta^2}} \right) \cdot \hat{r} = 0,$$  \hspace{1cm} (C.14)

$$\left( \nabla \frac{F_\theta \sin \vartheta}{\sqrt{F^2 \sin^2 \vartheta + F_\varphi^2 \sin^2 \varphi + F_\theta^2}} \right) \cdot \hat{\varphi} = \frac{1}{F \left( F^2 \sin^2 \vartheta + F_\varphi^2 \sin^2 \varphi + F_\theta^2 \right)^{3/2}} \cdot \left[ F \sin^3 \vartheta (FF_\varphi - F_\theta^2) + \sin \vartheta (F_\varphi \varphi - F_\theta F_\varphi) + F_\varphi F_\theta^2 \cos \vartheta \right].$$  \hspace{1cm} (C.15)
\[
\left( \frac{F_\varphi}{\sqrt{F^2 \sin^2 \vartheta + F_\varphi^2 \sin^2 \varphi + F_\varphi^2}} \right) \cdot \dot{\varphi} = \sin \vartheta \left( \frac{F^2 F_{\varphi \varphi} + F_{\varphi \varphi} F_\varphi^2 - F F_\varphi^2 - F_\varphi F_{\varphi \varphi}}{F \left( F^2 \sin^2 \vartheta + F_\varphi^2 \sin^2 \varphi + F_\varphi^2 \right)^{3/2}} \right).
\]
(C.16)

If we substitute \( F \) with \( r_P(t) + \varepsilon \xi(\vartheta, \varphi, t) \) then the normal unit in terms of \( \varepsilon \) is given by
\[
\hat{n} = \hat{r} - \frac{\varepsilon \xi_\vartheta}{r_P} \hat{\vartheta} - \frac{\varepsilon \xi_\varphi}{r_P \sin \vartheta} \hat{\varphi},
\]
(C.17)
while the curvature takes the following form
\[
\kappa = \frac{1}{r_P} - \varepsilon \frac{1}{r_P^2} \left[ \xi + \frac{\xi_{\vartheta \vartheta}}{2} + \frac{\xi_{\varphi \varphi}}{2 \sin^2 \vartheta} + \frac{\cos \vartheta \xi_\varphi}{\sin \vartheta} + O(\varepsilon^2) \right].
\]
(C.18)

Substituting \( \vartheta \) in both the normal unit and the curvature with \( x = \cos \vartheta \), from Equations (C.17) and (C.18) we obtain
\[
\hat{n} = \hat{r} + \varepsilon \frac{\xi_x \sqrt{1 - x^2}}{r_P} \hat{\vartheta} - \varepsilon \frac{\xi_\varphi}{r_P \sqrt{1 - x^2}} \hat{\varphi} + O(\varepsilon^2),
\]
(C.19)
\[
\kappa = \frac{1}{r_P} - \varepsilon \frac{1}{r_P^2} \left[ \xi + \frac{\partial}{\partial x} \left( \frac{1 - x^2}{2} \xi_x \right) + \frac{\xi_{\varphi \varphi}}{2(1 - x^2)} + O(\varepsilon^2) \right].
\]
(C.20)

Lastly, we state a few parameters that we need for the spherical models, that is the pressure and the nutrient fields, as well as the factor \( \sqrt{\sigma} \) of the square root law which is frequently used in the models. We obtain the perturbed forms for these variables which are obtained via Taylor expansion
\[
p(r, \vartheta, \varphi, t) = \bar{p}(r_P, t) + \bar{p}_r(r_P, t) \varepsilon \xi + \varepsilon \bar{p}_\vartheta(r_P, \vartheta, \varphi, t) + O(\varepsilon^2),
\]
(C.21)
\[
\sigma(r, \vartheta, \varphi, t) = \bar{\sigma}(r_P, t) + \bar{\sigma}_r(r_P, t) \varepsilon \xi + \varepsilon \bar{\sigma}_\vartheta(r_P, \vartheta, \varphi, t) + O(\varepsilon^2),
\]
(C.22)
\[
\sqrt{\sigma}(r, \vartheta, \varphi, t) = \sqrt{\bar{\sigma}(r_P, t)} + \frac{\varepsilon \left[ \bar{\sigma}_r(r_P, t) \xi + \bar{\sigma}_\vartheta(r_P, \vartheta, \varphi, t) \right]}{2 \sqrt{\bar{\sigma}(r_P, t)}} + O(\varepsilon^2).
\]
(C.23)
D. Useful formulae in ellipsoidal coordinates for perturbed variables

In this appendix, we will present the expressions for the metric coefficients, the normal unit vectors and the gradient for all areas and boundaries of the tumour. We begin with the metric coefficients of the boundary of the necrotic core

\begin{align*}
h^N_\rho &= \frac{\sqrt{\rho^2_N - \mu^2} \sqrt{\rho^2_N - \nu^2}}{\sqrt{\rho^2_N - h^2_N} \sqrt{\rho^2_N - h^2_2}}, \\
h^N_\mu &= \frac{\sqrt{\rho^2_N - \mu^2} \sqrt{\mu^2 - \nu^2}}{\sqrt{\mu^2 - h^2_2} \sqrt{h^2_2 - \mu^2}}, \\
h^N_\nu &= \frac{\sqrt{\rho^2_N - \nu^2} \sqrt{\mu^2 - \nu^2}}{\sqrt{h^2_3} \sqrt{h^2_2 - \nu^2}}.
\end{align*}

(D.1) (D.2) (D.3)

Then, we state the metric coefficients for the boundary of the unperturbed ellipsoidal tumour

\begin{align*}
h^P_\rho &= \frac{\sqrt{\rho^2_P - \mu^2} \sqrt{\rho^2_P - \nu^2}}{\sqrt{\rho^2_P - h^2_3} \sqrt{\rho^2_P - h^2_2}}, \\
h^P_\mu &= \frac{\sqrt{\rho^2_P - \mu^2} \sqrt{\mu^2 - \nu^2}}{\sqrt{\mu^2 - h^2_2} \sqrt{h^2_2 - \mu^2}}, \\
h^P_\nu &= \frac{\sqrt{\rho^2_P - \nu^2} \sqrt{\mu^2 - \nu^2}}{\sqrt{h^2_3} \sqrt{h^2_2 - \nu^2}}.
\end{align*}

(D.4) (D.5) (D.6)
However, on the tumour surface, the metric coefficients are expressed in terms of \( \varepsilon \)

\[
\begin{align*}
    h_\rho &= \frac{\sqrt{\rho^2 - \mu^2} \sqrt{\rho^2 - \nu^2}}{\sqrt{\rho^2 - h_3^2} \sqrt{\rho^2 - h_2^2}} \\
    h_\rho &= h_\rho^P \left[ 1 + \frac{\varepsilon \rho_P f}{\rho_P^2 - \mu^2} + \frac{\varepsilon \rho_P f}{\rho_P^2 - h_3^2} - \frac{\varepsilon \rho_P f}{\rho_P^2 - h_2^2} + \mathcal{O} (\varepsilon^2) \right], \quad (D.7)
\end{align*}
\]

\[
\begin{align*}
    h_\mu &= \frac{\sqrt{\mu^2 - \nu^2} \sqrt{\mu^2 - \nu^2}}{\sqrt{\mu^2 - h_3^2} \sqrt{\mu^2 - h_2^2}} \\
    h_\mu &= h_\mu^P \left[ 1 + \frac{\varepsilon \rho_P f}{\rho_P^2 - \mu^2} + \mathcal{O} (\varepsilon^2) \right], \quad (D.8)
\end{align*}
\]

\[
\begin{align*}
    h_\nu &= \frac{\sqrt{\nu^2 - \mu^2} \sqrt{\nu^2 - \mu^2}}{\sqrt{h_3^2 - h_2^2} \sqrt{h_2^2 - \nu^2}} \\
    h_\nu &= h_\nu^P \left[ 1 + \frac{\varepsilon \rho_P f}{\rho_P^2 - \nu^2} + \mathcal{O} (\varepsilon^2) \right]. \quad (D.9)
\end{align*}
\]

For this model, we will need the reciprocals of the metric coefficients which are

\[
\begin{align*}
    \frac{1}{h_\rho} &= \frac{1}{h_\rho^P} \left[ 1 - \frac{\varepsilon \rho_P f}{\rho_P^2 - \mu^2} - \frac{\varepsilon \rho_P f}{\rho_P^2 - h_3^2} + \frac{\varepsilon \rho_P f}{\rho_P^2 - h_2^2} + \mathcal{O} (\varepsilon^2) \right], \quad (D.10) \\
    \frac{1}{h_\mu} &= \frac{1}{h_\mu^P} \left[ 1 - \frac{\varepsilon \rho_P f}{\rho_P^2 - \mu^2} + \mathcal{O} (\varepsilon^2) \right], \quad (D.11) \\
    \frac{1}{h_\nu} &= \frac{1}{h_\nu^P} \left[ 1 - \frac{\varepsilon \rho_P f}{\rho_P^2 - \nu^2} + \mathcal{O} (\varepsilon^2) \right]. \quad (D.12)
\end{align*}
\]

The boundary of the necrotic core retains its original ellipsoidal shape. This boundary is changing only on the \( \rho \) direction of the ellipsoidal coordinate system. So the normal unit vector is obtained by

\[
\hat{n} = \hat{\rho}_0, \quad (D.13)
\]
and the expression for the gradient on $\partial \Omega_N$ has the following form

$$\nabla = \frac{\hat{\rho}_0}{h_\rho} \frac{\partial}{\partial \rho} + \frac{\hat{\mu}_0}{h_\mu} \frac{\partial}{\partial \mu} + \frac{\hat{\nu}_0}{h_\nu} \frac{\partial}{\partial \nu}. \quad \text{(D.14)}$$

For $\partial \Omega_P$ the normal unit vector is expressed in terms of $\varepsilon$ as

$$\hat{n} = \hat{\rho}_0 + \varepsilon h_\rho^P f \left[ \frac{\nu \hat{\nu}_0}{h_\nu^P (\rho_\mu^P - \nu^2)} + \frac{\mu \hat{\mu}_0}{h_\mu^P (\mu_\rho^P - \mu^2)} \right] - \varepsilon h_\rho^P f \nu \hat{\nu}_0 - \varepsilon h_\mu^P f \mu \hat{\mu}_0 + O(\varepsilon^2), \quad \text{(D.15)}$$

and the gradient on the outer boundary has the following form

$$\nabla = \frac{\hat{\rho}_0}{h_\rho} \frac{\partial}{\partial \rho} + \frac{\hat{\mu}_0}{h_\mu} \frac{\partial}{\partial \mu} + \frac{\hat{\nu}_0}{h_\nu} \frac{\partial}{\partial \nu} - \varepsilon f \rho_\mu \left[ \frac{\mu}{h_\mu^P (\rho_\mu^P - \mu^2)} + \frac{\nu}{h_\nu^P (\rho_\mu^P - \nu^2)} \right] \frac{\partial}{\partial \rho} + \varepsilon f \rho \left[ \frac{\mu}{h_\mu^P (\rho_\mu^P - \mu^2)} + \frac{\nu}{h_\nu^P (\rho_\mu^P - \nu^2)} \right] \frac{\partial}{\partial \mu} + O(\varepsilon^2). \quad \text{(D.16)}$$

When assuming that the perturbation has the form of $\rho(t) = \rho_p(t) + \varepsilon f(\mu, \nu, t)$, then the vectorial representation of the perturbed ellipsoid in cartesian coordinates is given by

$$r = \frac{1}{h_2 h_3} \left[ \rho_p(t) + \varepsilon f(\mu, \nu, t) \right] \hat{x}_1 + \frac{1}{h_1 h_3} \sqrt{\rho_\mu^2 - h_3^2} + 2 \rho_\mu \varepsilon f(\mu, \nu, t) + \varepsilon^2 f^2(\mu, \nu, t) \sqrt{\mu^2 - h_3^2} \sqrt{h_3^2 - \nu^2} \hat{x}_2 + \frac{1}{h_1 h_2} \sqrt{\rho_\mu^2 - h_3^2} + 2 \rho_\mu \varepsilon f(\mu, \nu, t) + \varepsilon^2 f^2(\mu, \nu, t) \sqrt{h_2^2 - \mu^2} \sqrt{h_2^2 - \nu^2} \hat{x}_3. \quad \text{(D.17)}$$

In order to calculate the mean curvature of the perturbed surface, we use the first and second fundamental form on the perturbed ellipsoidal.

The first fundamental form on the perturbed ellipsoid is described by

$$\text{d}r \cdot \text{d}r = E(\text{d}\nu)^2 + 2F(\text{d}\nu \text{d}\mu) + G(\text{d}\mu)^2, \quad \text{(D.18)}$$
where

\[ E = r_\nu \cdot r_\nu, \quad (D.19) \]
\[ F = r_\nu \cdot r_\mu, \quad (D.20) \]
\[ G = r_\mu \cdot r_\mu. \quad (D.21) \]

These coefficients in terms of \( \varepsilon \) are given by

\[ E = (h_{\nu \nu}^P)^2 \left( 1 + \varepsilon f \frac{2\rho_P}{\rho_P^2 - \nu^2} \right) + \mathcal{O}(\varepsilon^2), \quad (D.22) \]
\[ F = \mathcal{O}(\varepsilon^2), \quad (D.23) \]
\[ G = (h_{\mu \mu}^P)^2 \left( 1 + \varepsilon f \frac{2\rho_P}{\rho_P^2 - \mu^2} \right) + \mathcal{O}(\varepsilon^2). \quad (D.24) \]

The second fundamental form is defined by

\[-d\mathbf{r} \cdot d\hat{\mathbf{n}} = L(d\nu)^2 + 2M(d\nu)(d\mu) + N(d\mu)^2, \quad (D.25)\]

where the coefficients are given by

\[ L = \hat{\mathbf{n}} \cdot r_{\nu \nu}, \quad (D.26) \]
\[ M = \hat{\mathbf{n}} \cdot r_{\nu \mu}, \quad (D.27) \]
\[ N = \hat{\mathbf{n}} \cdot r_{\mu \mu}. \quad (D.28) \]

Once substituting Equation (D.17) in Equations (D.26)-(D.28), we obtain

\[ L = -\frac{(h_{\nu \nu}^P)^2}{h_{\mu}^P} \frac{\rho_P}{\rho_P^2 - \nu^2} \]
\[ - \varepsilon h_{\mu}^P f \left[ \frac{(h_{\nu \nu}^P)^2}{(h_{\mu}^P)^2} \frac{\rho_P}{\rho_P^3 - \nu^2} + \frac{(h_{\mu \mu}^P)^2}{(h_{\mu}^P)^2} \frac{\mu^2}{\rho_P^3 - \mu^2} \frac{1}{\mu^2 - \nu^2} \right] \]
\[ - \frac{\nu^2}{\rho_P^2 - \nu^2} \left[ \frac{1}{\nu^2} + \frac{1}{\nu^2 - h_3^2} + \frac{1}{\nu^2 - h_2^2} + \frac{2}{\rho_P^2 - \nu^2} + \frac{1}{\mu^2 - \nu^2} \right] \]
\[ + \varepsilon h_{\mu}^P f_{\mu} \frac{(h_{\nu \nu}^P)^2}{(h_{\mu}^P)^2} \frac{\mu}{\mu^2 - \nu^2} + \varepsilon h_{\nu \nu}^P f_{\nu \nu} + \mathcal{O}(\varepsilon^2), \quad (D.29) \]
\[ M = -\varepsilon h^P_{\rho f} \left( \frac{\mu}{\rho^2_P - \mu^2} + \frac{\mu^2}{\mu^2 \nu^2} \right) f - \varepsilon h^P_{\rho f} \left( \frac{\nu}{\rho^2_P - \nu^2} - \frac{\nu}{\mu^2 - \nu^2} \right) f \]  
\[ + \varepsilon h^P_{\rho f} f f + \mathcal{O}(\varepsilon^2), \quad (D.30) \]

and

\[ N = -\frac{(h^P_{\mu})^2 \rho_P}{h^P_{\rho}} \frac{\rho_P}{\rho^2_P - \mu^2} \] 
\[ - \varepsilon h^P_{\rho f} f \left[ \frac{(h^P_{\mu})^2}{(h^P_{\rho})^2} \frac{\rho_P^2}{(\rho^2_P - \mu^2)^2} + \frac{(h^P_{\nu})^2}{(h^P_{\rho})^2} \frac{\nu^2}{(\rho^2_P - \mu^2)(\mu^2 - \nu^2)} \right] \] 
\[ - \frac{\mu^2}{\rho^2_P - \mu^2} \left( \frac{1}{\mu^2} + \frac{1}{\mu^2 - \rho^2} + \frac{1}{\mu^2 - h^2} + \frac{2}{\rho^2_P - \mu^2} - \frac{1}{\mu^2 - \nu^2} \right) \] 
\[ - \varepsilon h^P_{\rho f} f \frac{(h^P_{\mu})^2}{(h^P_{\nu})^2} \frac{\nu}{\mu^2 - \nu^2} + \varepsilon h^P_{\rho f} f f + \mathcal{O}(\varepsilon^2). \quad (D.31) \]

The mean curvature generally is given by

\[ H = \frac{GL - 2FM + EN}{2(EG - F^2)}, \quad (D.32) \]
which is transformed into

\[
H = -\frac{1}{2h_P^P} \left( \frac{\rho_P}{\rho_P^2 - \mu^2} + \frac{\rho_P}{\rho_P^2 - \nu^2} \right) \\
+ \frac{\varepsilon h_P^P f}{2} \left[ \frac{1}{(h_P^P)^2} \left( \frac{\rho_P^2}{\rho_P^2 - \mu^2} \right)^2 - \frac{1}{(h_P^P)^2} \left( \frac{\mu^2}{\rho_P^2 - \mu^2} \right)^2 \right] \\
\times \left( \frac{1}{\rho_P^2} + \frac{1}{\mu^2 - h_3^2} + \frac{1}{\mu^2 - h_2^2} + \frac{2}{\rho_P^2 - \mu^2} \right) \\
+ \frac{1}{(h_P^P)^2} \left( \frac{\rho_P^2}{\rho_P^2 - \nu^2} \right)^2 \left( \frac{\nu^2}{\rho_P^2 - \nu^2} \right)^2 \\
\times \left( \frac{1}{\rho_P^2} + \frac{1}{\nu^2 - h_3^2} + \frac{1}{\nu^2 - h_2^2} + \frac{2}{\rho_P^2 - \nu^2} \right) \\
+ \frac{\varepsilon h_P^P f_{\mu\mu}}{2} \frac{1}{(h_P^P)^2} + \frac{\varepsilon h_P^P f_{\nu\nu}}{2} \frac{1}{(h_P^P)^2} + \mathcal{O}(\varepsilon^2). \tag{D.33}
\]

in the case of a perturbed ellipsoid. However, for this approach we will need the expression for the evolution of the outer boundary in terms of \(\varepsilon\) and in ellipsoidal coordinates which is

\[
\frac{\mathrm{d}r}{\mathrm{d}t} = h_P^P \left\{ \frac{\mathrm{d}\rho_P}{\mathrm{d}t} + \varepsilon \left[ f_t + f_{\rho\rho} \left( \frac{1}{\rho_P^2 - \mu^2} + \frac{1}{\rho_P^2 - \nu^2} - \frac{1}{\rho_P^2 - h_3^2} - \frac{1}{\rho_P^2 - h_2^2} \right) \frac{\mathrm{d}\rho_P}{\mathrm{d}t} \right] \right\} \hat{\rho}_0 \\
+ h_P^P \left( 1 + \frac{\varepsilon f_{\rho\rho}}{\rho_P^2 - \mu^2} \right) \frac{\mathrm{d}\mu}{\mathrm{d}t} \hat{\mu}_0 + h_P^P \left( 1 + \frac{\varepsilon f_{\rho\rho}}{\rho_P^2 - \nu^2} \right) \frac{\mathrm{d}\nu}{\mathrm{d}t} \hat{\nu}_0 + \mathcal{O}(\varepsilon^2). \tag{D.34}
\]

The Gaussian curvature from its general form of

\[
K = \frac{LN - M^2}{EG - F^2}, \tag{D.35}
\]
obtains the form of

\[
K = \frac{1}{(\rho^2_P - \mu^2)(\mu^2 - \nu^2)} \times \left[ \frac{\rho^2_P}{(h^P_\rho)^2} + \frac{2\varepsilon \rho^3_P f}{(h^P_\rho)^2} \left( \frac{1}{\rho^2_P} + \frac{1}{\rho^2_P - \mu^2} + \frac{1}{\rho^2_P - h^2_\lambda} - \frac{2}{\rho^2_P - \mu^2} - \frac{2}{\rho^2_P - \nu^2} \right) + \frac{\varepsilon \rho^3_P \mu f_\mu}{\mu^2 - \nu^2} (2\mu^2 - h^2_\lambda - h^2_\lambda) - \frac{\varepsilon \rho^3_P \nu f_\nu}{\mu^2 - \nu^2} (2\nu^2 - h^2_\lambda - h^2_\lambda) \right. \\
\left. - \frac{\varepsilon \rho^3_P f_{\mu\mu}}{(h^P_\mu)^2} (\rho^2_P - \mu^2) - \frac{\varepsilon \rho^3_P f_{\nu\nu}}{(h^P_\nu)^2} (\rho^2_P - \nu^2) \right] + O(\varepsilon^2). \quad (D.36)
\]
E. Spherical Model: From the Initial model to the Unperturbed and Perturbed model

In this Appendix we will present the calculations from the initial equations of Green-
pan model to the equations that describe the perturbed and the unperturbed part.
This procedure is followed for all four models.

We will begin with the Laplace equation for the nutrient concentration

\[ \Delta \sigma = 0 \Rightarrow \Delta (\bar{\sigma} + \varepsilon \tilde{\sigma}) = 0 \Rightarrow \Delta \bar{\sigma} + \varepsilon \Delta \tilde{\sigma} = 0 \Rightarrow \Delta \bar{\sigma} = 0 \text{ and } \Delta \tilde{\sigma} = 0, \quad (E.1) \]

while the Poisson equation for the pressure results

\[ \Delta p = S_1 \Rightarrow \Delta (\bar{p} + \varepsilon \tilde{p}) = S_1 + \varepsilon \cdot 0 \Rightarrow \Delta \bar{p} + \varepsilon \Delta \tilde{p} = S_1 + \varepsilon \cdot 0 \Rightarrow \Delta \bar{p} = S_1 \text{ and } \Delta \tilde{p} = 0. \quad (E.2) \]

Next, we state the transformation of boundary conditions on \( \partial \Omega_P \), using the formulae for the perturbed variables from Appendix C.

\[
\begin{align*}
\frac{\text{d}r_P}{\text{d}t} \cdot \hat{n} &= -\hat{n} \cdot \nabla p + \lambda \sqrt{\bar{\sigma}} \Rightarrow \frac{\text{d}r_P}{\text{d}t} = \varepsilon \xi_t = -\bar{p}(r_P, t) - \varepsilon \left[ \xi \bar{p}_{rr}(r_P, t) + \bar{p}_r(r_P, \vartheta, \varphi, t) \right] \\
&\quad + \lambda \sqrt{\bar{\sigma}(r_P, t)} + \frac{\varepsilon \lambda}{2 \sqrt{\bar{\sigma}(r_P, t)}} \left[ \xi \bar{\sigma}_r(r_P, t) + \bar{\sigma}(r_P, \vartheta, \varphi, t) \right] \Rightarrow \\
\frac{\text{d}r_P}{\text{d}t} &= -\bar{p}_r(r_P, t) + \lambda \sqrt{\bar{\sigma}(r_P, t)} \text{ and} \\
\frac{\partial \xi}{\partial t} &= -\xi \bar{p}_{rr}(r_P, t) - \bar{p}_r(r_P, \vartheta, \varphi, t) + \frac{\lambda}{2 \sqrt{\bar{\sigma}(r_P, t)}} \left[ \xi \bar{\sigma}_r(r_P, t) + \bar{\sigma}(r_P, t) \right], \quad (E.3)
\end{align*}
\]
\[ \hat{\mathbf{n}} \cdot \nabla \sigma = \mu \sqrt{\sigma} \Rightarrow \bar{\sigma}_r(r_P, t) + \varepsilon [\xi \bar{\sigma}_{rr} + \bar{\sigma}_R(r_P, \vartheta, \varphi, t)] = \mu \sqrt{\bar{\sigma}(r_P, t)} \Rightarrow \]

\[ \bar{\sigma}_r(r_P, t) = \mu \sqrt{\bar{\sigma}(r_P, t)} \text{ and} \]

\[ \xi \bar{\sigma}_{rr}(r_P, t) + \bar{\sigma}_r(r_P, \vartheta, \varphi, t) = \frac{\mu [\xi \bar{\sigma}_r(r_P, t) + \bar{\sigma}(r_P, \vartheta, \varphi, t)]}{2 \sqrt{\bar{\sigma}(r_P, t)}} , \quad (E.4) \]

and

\[ p = \alpha \kappa \Rightarrow \tilde{p} + \varepsilon [\xi \tilde{p}_r(r_P, t) + \tilde{p}(r_P, \vartheta, \varphi, t)] = \frac{\alpha}{r_P} - \varepsilon \frac{\alpha}{r_P} \left[ \partial_x (1 - x^2) \partial_x \xi + 2\xi \right] \Rightarrow \]

\[ \tilde{p}(r_P, t) = \frac{\alpha}{r_P} \text{ and } \xi \tilde{p}_r(r_P, t) + \tilde{p}(r_P, \vartheta, \varphi, t) = -\frac{\alpha}{r_P^2} \left[ \partial_x (1 - x^2) \partial_x \xi + 2\xi \right] . \quad (E.5) \]

Finally, the condition for the nutrient source changes as follows

\[ \sigma \to \sigma_\infty \Rightarrow \bar{\sigma} + \varepsilon \bar{\sigma} \to \sigma_\infty + \varepsilon \cdot 0 \Rightarrow \bar{\sigma} \to \sigma_\infty \text{ and } \bar{\sigma} \to 0 \text{ as } r \to \infty. \quad (E.6) \]
F. Ellipsoidal Model: From the Initial model to the Unperturbed and Perturbed model

In this appendix, we present details from the calculations of this study. We focus on the calculations from the initial model equations to the unperturbed and perturbed equations. We begin with the Laplace equations for the nutrient concentration

$$\Delta \sigma_i = 0 \Rightarrow \Delta (\bar{\sigma}_i + \varepsilon \tilde{\sigma}_i) = 0 \Rightarrow \Delta \bar{\sigma}_i + \varepsilon \Delta \tilde{\sigma}_i = 0 \Rightarrow \Delta \bar{\sigma}_i = 0 \text{ and } \Delta \tilde{\sigma}_i = 0 , \quad (F.1)$$

where \( i = N, L, S \), and the Poisson equations for the pressure distribution

$$\Delta p_j = S_k \Rightarrow \Delta (\bar{p}_j + \varepsilon \tilde{p}_j) = S_k \Rightarrow \Delta \bar{p}_j + \varepsilon \Delta \tilde{p}_j = S_k \Rightarrow \Delta \bar{p}_j = S_k \text{ and } \Delta \tilde{p}_j = 0 , \quad (F.2)$$

where \( j = N, L \) and \( k = 1, 2 \). On \( \partial \Omega_N \), the boundary conditions from the initial model when introducing the parametric forms of nutrient concentration and pressure distribution, we get

$$\sigma(N, r_N) = \sigma(L, r_N) \Rightarrow \bar{\sigma}(N, r_N) + \varepsilon \tilde{\sigma}(N, r_N) = \bar{\sigma}(L, r_N) + \varepsilon \tilde{\sigma}(L, r_N) \Rightarrow$$

$$\bar{\sigma}(r_N) = \bar{\sigma}(r_N) \text{ and } \tilde{\sigma}(r_N) = \tilde{\sigma}(r_N) \quad (F.3)$$

$$p(N, r_N) = p(L, r_N) \Rightarrow \bar{p}(N, r_N) + \varepsilon \tilde{p}(N, r_N) = \bar{p}(L, r_N) + \varepsilon \tilde{p}(L, r_N) \Rightarrow$$

$$\bar{p}(r_N) = \bar{p}(r_N) \text{ and } \tilde{p}(r_N) = \tilde{p}(r_N) \quad (F.4)$$
\begin{align}
\hat{n} \cdot \nabla_{pN}(r_N) &= \hat{n} \cdot \nabla_{pL}(r_N) \\
&= \hat{\rho}_0 \cdot \left[ \frac{\hat{\rho}_0}{h^N_{\rho}} \frac{\partial}{\partial \rho} (\tilde{\rho}_N + \varepsilon \tilde{\rho}_N) + \hat{\mu}_0 \frac{\partial}{h^N_{\mu}} (\tilde{\mu}_N + \varepsilon \tilde{\mu}_N) + \hat{\nu}_0 \frac{\partial}{h^N_{\nu}} (\tilde{\nu}_N + \varepsilon \tilde{\nu}_N) \right] \\
&= \hat{\rho}_0 \cdot \left[ \frac{\hat{\rho}_0}{h^N_{\rho}} \frac{\partial}{\partial \rho} (\tilde{\rho}_L + \varepsilon \tilde{\rho}_L) + \hat{\mu}_0 \frac{\partial}{h^N_{\mu}} (\tilde{\mu}_L + \varepsilon \tilde{\mu}_L) + \hat{\nu}_0 \frac{\partial}{h^N_{\nu}} (\tilde{\nu}_L + \varepsilon \tilde{\nu}_L) \right] \\
&= \frac{1}{h^N_{\rho}} \frac{\partial}{\partial \rho} (\tilde{\rho}_N + \varepsilon \tilde{\rho}_N) = \frac{1}{h^N_{\rho}} \frac{\partial}{\partial \rho} (\tilde{\rho}_L + \varepsilon \tilde{\rho}_L) \Rightarrow \frac{\partial \tilde{\rho}_N}{\partial \rho} = \frac{\partial \tilde{\rho}_L}{\partial \rho} 	ext{ and } \frac{\partial \tilde{\mu}_N}{\partial \rho} = \frac{\partial \tilde{\mu}_L}{\partial \rho}, \quad (F.5)
\end{align}

where the formula for the normal unit vector is given by the equation (D.13) and the expression for the gradient by (D.14). On \( \partial \Omega_P \) the boundary conditions are more complicated due to the fact that the normal unit vector is given by equation (D.15) and the gradient by equation (D.16).
\[
\begin{align*}
\frac{dr}{dt} \cdot \hat{n} = -\hat{n} \cdot \nabla p + \beta s &\Rightarrow \left\{ h_p^L \left[ 1 + \frac{\varepsilon f \rho p}{\rho_p^2 - \mu^2} + \frac{\varepsilon f \rho p}{\rho_p^2 - \nu^2} - \frac{\varepsilon f \rho p}{\rho_p^2 - h_3^2} - \frac{\varepsilon f \rho p}{\rho_p^2 - h_2^2} + \mathcal{O}(\varepsilon^2) \right] \right\} \\
\cdot \frac{d}{dt} (\rho p + \varepsilon f) \rho_0 + h_p^L \left[ 1 + \frac{\varepsilon f \rho p}{\rho_p^2 - \mu^2} + \mathcal{O}(\varepsilon^2) \right] \frac{d\mu}{dt} + h_p^L \left[ 1 + \frac{\varepsilon f \rho p}{\rho_p^2 - \nu^2} + \mathcal{O}(\varepsilon^2) \right] \frac{dv}{dt} \nu_0 \right\} \\
\cdot \left\{ \hat{\rho}_0 + \hat{\varepsilon}_h^L f \left[ \frac{\nu \hat{\nu}_0}{h_p^L (\rho_p^2 - \nu^2)} + \frac{\mu \hat{\mu}_0}{h_p^L (\rho_p^2 - \mu^2)} \right] - \frac{\hat{\varepsilon}_h^L}{h_p^L} f_\nu \hat{\nu}_0 - \frac{\hat{\varepsilon}_h^L f_\mu \hat{\mu}_0}{h_p^L} + \mathcal{O}(\varepsilon^2) \right\} = \\
= - \left\{ \hat{\rho}_0 + \hat{\varepsilon}_h^L f \left[ \frac{\nu \hat{\nu}_0}{h_p^L (\rho_p^2 - \nu^2)} + \frac{\mu \hat{\mu}_0}{h_p^L (\rho_p^2 - \mu^2)} \right] - \frac{\hat{\varepsilon}_h^L}{h_p^L} f_\nu \hat{\nu}_0 - \frac{\hat{\varepsilon}_h^L f_\mu \hat{\mu}_0}{h_p^L} + \mathcal{O}(\varepsilon^2) \right\} \\
\cdot \left\{ \hat{\rho}_0 \frac{\partial}{\partial \rho} (\bar{p}_L + \varepsilon \bar{\rho}_L) + \hat{\mu}_0 \frac{\partial}{\partial \mu} (\bar{p}_L + \varepsilon \bar{\rho}_L) + \hat{\nu}_0 \frac{\partial}{\partial \nu} (\bar{p}_L + \varepsilon \bar{\rho}_L) \right\} \\
+ \frac{\beta}{d t} h_p^L \left[ 1 + \frac{\varepsilon f \rho p}{\rho_p^2 - \mu^2} + \frac{\varepsilon f \rho p}{\rho_p^2 - \nu^2} - \frac{\varepsilon f \rho p}{\rho_p^2 - h_3^2} - \frac{\varepsilon f \rho p}{\rho_p^2 - h_2^2} \right] (\rho p + \varepsilon f - \rho q) \Rightarrow \right. \\
\left( h_p^L \right)^2 \frac{d\rho p}{d t} - \frac{\beta}{d t} h_p^L \left( \frac{1}{\rho_p^2 - \mu^2} + \frac{1}{\rho_p^2 - \nu^2} - \frac{1}{\rho_p^2 - h_3^2} - \frac{1}{\rho_p^2 - h_2^2} \right) \right) \\
\left. (h_p^L)^2 f_t + \frac{\partial \bar{p}_L}{\partial \rho} - \frac{\beta}{d t} (h_p^L)^2 f + \rho p f \left( \frac{1}{\rho_p^2 - \mu^2} + \frac{1}{\rho_p^2 - \nu^2} - \frac{1}{\rho_p^2 - h_3^2} - \frac{1}{\rho_p^2 - h_2^2} \right) \right) \\
\cdot \left[ (h_p^L)^2 \frac{d\rho p}{d t} - \frac{\partial \bar{p}_L}{\partial \rho} - \frac{\beta}{d t} (h_p^L)^2 (\rho p - \rho q) \right] + \left( \frac{\mu f}{\rho_p^2 - \mu^2} \right) (h_p^L)^2 \left[ \frac{d\mu}{d t} + \frac{1}{(h_\mu^L)^2} \frac{\partial \bar{p}_L}{\partial \mu} \right] \\
+ \left( \frac{\nu f}{\rho_p^2 - \nu^2} \right) (h_p^L)^2 \left[ \frac{dv}{d t} + \frac{1}{(h_\nu^L)^2} \frac{\partial \bar{p}_L}{\partial \nu} \right] = 0, \quad (F.8)
\end{align*}
\]
Finally, the nutrient source will split into two parts, perturbed and unperturbed, and this is shown below

\[ \sigma \rightarrow \sigma_\infty \Rightarrow \bar{\sigma} + \varepsilon \bar{\sigma} \rightarrow \sigma_\infty + \varepsilon \cdot 0 \Rightarrow \bar{\sigma} \rightarrow \sigma_\infty \text{ and } \bar{\sigma} \rightarrow 0 \text{ as } r \rightarrow \infty. \]  

(F.10)
Curriculum Vitae

Vasiliki Christina Panagiotopoulou was born in Nottingham on 14/10/1985. She studied at the department of Chemical Engineering of the University of Patras and graduated in 2003 (8.11/10) after submitting her thesis “Solid Tumour Growth in Ellipsoidal Geometry”. Then, she studied at the School of Mathematical Sciences at the University of Nottingham (2008-2011), resulting to an MPhil thesis entitled “A theoretical and experimental study of cell membrane electrosstatics and transport”. She enrolled at the department of Chemical Engineering on February 2012. As a result, she presented her PhD thesis “Modelling tumour surface perturbation in ellipsoidal coordinates” (17/12/2014). Three of her papers have been published in peer review journals. She participated in international, european and local conferences with three oral presentations and two poster presentations.

PAPERS

- Panagiotopoulou, Vasiliki, Richardson Giles, Jensen, Oliver E. & Rauch Cyril

PRESENTATIONS


