CHAPTER 2

LITERATURE REVIEW

Mathematical modeling of tumour growth

2.1 The early models of tumour growth.

The earliest mathematical studies of solid tumours focused purely on growth dynamics when Mayneord (1932) developed a mathematical model which studied the effect of different distributions of actively dividing cells. This model illustrated that when the entire tissue volume was growing exponentially with the growth rate gradually reducing as the region of active growth was progressively restricted to an outer shell of tissue of decreasing thickness, ultimately arriving at a linear growth rate.

Hill (1928) set the scene for many later mathematical models of solid tumours. He used mathematical approaches to study a number of important physiological processes such as the diffusion of oxygen into a solid where it is consumed by metabolic processes, the outward diffusion of lactic acid from a solid which produces it by metabolic processes and the diffusion of oxygen away from a blood vessel into a region with an oxygen debt.

Thomlinson and Gray (1955) proposed a mathematical model of the diffusion and consumption of oxygen to supplement an experimental investigation of some types of bronchial carcinomata which grow in solid rods which are devoid of capillaries and which comprise cells nourished by diffusion of metabolites inwards from the

immediately surrounding stroma. Large tumours of this kind often consist of necrotic centres surrounded by ‘intact tumour cells which appear as rings’.

Burton (1966) developed a diffusion model which examined both the distribution of oxygen in a spherical tumour where the blood supply is completely confined to the surface and the resulting relative radius of the central zone to the total radius, which was then used to explain how the growth curve cold fit a Gompertzian expression.

2.2 Early models of avascular tumours and multicell spheroids

The emerging interest in both the avascular nodules as well as the multicell spheroid model encouraged various new approaches to the mathematical modeling of solid tumours.

Greenspan (1972) extended the models by Burton (1966) and Thomlinson and Gray (1955) by introducing a surface tension among the living cancer cells in order to maintain a compact, solid mass. He made an assumption that necrotic cellular debris continually disintegrates into simpler chemical compounds that are freely permeable through cell membranes. In this way, the tissue volume loss due to necrosis would be replaced by the inward motion of cells from the outer region as a result of the forces of adhesion and surface tension, thereby explaining the existence of a steady-state tumour size. Greenspan also assumed that a chemical is produced somewhere within the tumour which inhibits the mitosis of cancer cells without causing their death once the concentration

reaches a critical level. These effects were combined in an integro-differential equation for the evolution of the tumour radius, and a reaction-diffusion equation for both the concentration of nutrient and that of inhibitor.

Two different possibilities were then considered separately. While the first model assumed that the chemical inhibitor was a result of inadequate nutrient supply and a product of necrosis, the second model assumed that the inhibitor was produced purely by the metabolic processes of living cells, with no katabolites associated with necrosis. Qualitatively, the two models predicted some overall similarities in the development of the spheroid, with three distinct growth phases: an initial exponential growth phase, followed by some degree of retardation, culminating in a final phase where retardation by both mitotic inhibition and cell death ultimately gave rise to dormancy. Nevertheless, each of the two models predicted a distinctly different growth pattern prior to arriving at a steady state.

Glass (1973) developed a one dimensional mathematical model which predicted patterns of mitotic activity in a growing tumour. Mitotic inhibitors called chalones were assumed to be produced uniformly throughout the tissue, which then diffused beyond the tissue boundaries and decayed. The regulation of growth by a ‘switch mechanism’, was introduced where mitosis occurred below a critical value of chalone concentration, and was completely above this value. He considered, no volume loss mechanism such as necrosis , and stable tissue growth was assumed to occur when the chalone concentration was less than the mitotic threshold throughout the tissue.

This is contrast to Greenspan's (1972). This model has been extended to two and three dimensions, by Shymko and Glass (1976) attempting to determine the effect of different geometries on the pattern and growth stability. Greenspan (1976) also consider the stability to asymmetric perturbations of the spherical shape of an equilibrium-sized tumour. This formulation considered a thin proliferating layer near the surface and a large, central necrotic core, where the birth or death of cells produces internal pressure differentials which cause the motion of cellular material.

Deakin (1975) then extended the formulations of Burton (1966) and Greenspan (1972, 1974) to incorporate an oxygen consumption which was propotional to oxygen concentration within critical limits. Beyond an upper critical value of oxygen concentration, oxygen consumption was considered a constant, while necrosis occurred at a lower critical value below which no oxygen would be consumed.

McElwain and Ponzo (1977) developed a model which investigated the effect of non-uniformity of oxygen consumption. This is a model on a tumour's growth rate produced three distinct phases in the tumour's development which is different with Deakin (1975) which restricted to the non-uniformity of oxygen consumption on the variable rim thickness. In the first phase, oxygen concentration is above the upper critical value everywhere, so that all cells consume oxygen at a uniform rate, giving rise to exponential growth. While in the second phase, the growth rate reduces as oxygen concentration reduces in the central region, with an associated decrease in the effective

proliferation rate and a slowing in the overall growth. The tumour reaches a viable dormant state I the final phase with an outer proliferating layer, an intermediate layer where overall proliferation is reduced and an inner necrotic core.

McElwain and Morris (1978) extended the previous models to include a constant cell loss rate in the entire viable region, with the consequence that a dormant state could be reached with or without a central necrotic region. In considering apoptosis as a cell loss mechanism, this model is an antecedent to much of the subsequent mathematical literature relating to tumour development.

It is important to note that ‘since random fluctuations are fundamental to the population processes, the probabilistic or stochastic of evolving populations is essential whenever one considers populations whose size may assume small values. As a result, various stochastic models of solid tumour growth also developed (Wette *et al.* 1974). The behaviour of small populations is predominantly statistical, and the random component of the growth kinetics of a population, such as exhibited in the spontaneous extinction in even supercritical growth, may indeed become more important than the average behaviour.

2.3 Early models of tumour invasion and metastasis

Metastasis, the spread of cancer to distant sites in the body, is in fact what makes cancer so lethal Ruoslahti (1996). For that reason, metastasis and the invasion of normal tissue by cancer cells are the hallmarks of malignancy.

Saidel *et al.* (1976) proposed a compartmental model of the haematogenous metastatic process from a solid tumour. In this model, five sub-populations were considered-tumour cells, vascular surfaces, invading tumour cells on the inner vessel surface, viable tumour cells arrested in pulmonary vessels and pulmonary metastatic foci. They used the assumption of a Michaelis-Menten form for the processes of tumour cell proliferation and vessel surface formation.

Liotta *et al.* (1976) proposed a stochastic model of metastasis formation to complement this model in order to distinguish amongst tumour clumps and metastatic foci. Simulation of the dynamics of the metastatic process was then accomplished by combining the numerical solution of the deterministic model given by Saidel *et al.* (1976) with the analytical stochastic model. This gives good agreement with experimental data for the mean and variance of macroscopic metastatic foci.

Saidel *et al.* (1976) work was also extended by Liotta *et al.* (1974) in a diffusion model which coupled diffusion equations with source and sink terms were proposed in spherical polar coordinates (with spherical symmetry) to describe the density of both the

tumour cells as well as the surface area of tumour vessels as functions of time and radial position.

2.4 Models of tumour growth in the 1980s

Adam (1986) had noted the important experimental findings on the role of growth inhibitors in tumour development (Bullough, 1965; Bullough and Deol, 1971; Weiss, 2000). While Glass (1973) had assumed that regulation of growth occurred by a discontinuous switch mechanism for the control of mitotic activity with a spatially uniform production of inhibitor, Adam (1986) maintained that a spatially-dependent mitotic control function best reflected experimental observations and warranted further theoretical study.

This new model demonstrated the sensitivity of the growth of the tissue to a non-uniform source of inhibitor. Adam soon extended this simple model to investigate the roles of both non-uniform mitotic inhibition and geometry on the stability of growth (Adam, 1987a). The model prediction was compared with the experimental results of Adam (1987b). Adam cautiously noted that although the combination of spherical geometry and a certain spatial variation in inhibitor production gave rise to an excellent fit with the published data. This fit did not prove the necessity of spatial variations in mitotic control to explain such observations. It is particularly noteworthy that the models proposed by Adam (1986, 1987a,b) did not incorporate a volume loss mechanism such as

necrosis, so that stability could only occur by complete growth inhibition throughout the tissue—a somewhat incongruous notion in the context of cancer.

Clearly, the effects of a necrotic core would be an important consideration on the extension of these models. It is essential to recognize that the necrotic core was simply incorporated as a source of growth inhibition (Adam and Maggelakis, 1989), rather than representing a mechanism for volume loss.

Landry *et al.* (1982) considered the geometric and physical characteristics of multicellular spheroids in a mathematical model which attempted to relate growth rate. While the model did provide an explanation for the linear growth of multicellular spheroids, it predicted an infinite linear expansion and was unable to explain the growth saturation of large spheroids.

On the other hand, Maggelakis and Adam (1990) studied a non-uniform growth inhibition in a model which examined the growth rate of a spherically-symmetric prevascular carcinoma when both nutrient consumption and inhibitor production were spatially non-uniform. An additional parameter was introduced into the model to account for the effects of the inhibitor production on nutrient consumption rate. This formulation bestowed the potential to adopt a four-layered structure. In the first phase, all cells could obtain sufficient nutrients, allowing mitosis to proceed normally throughout the tissue. The second phase commenced when nutrient concentration reduced sufficiently in the central region to cause mitotis to decrease there, thereby beginning to slow the overall

growth of the spheroid. A two-layered structure prevailed during this phase, with an outer layer proliferating normally, and an inner layer in which proliferation was reduced. The third phase was a further period of retarded growth where the structure comprised an additional layer of necrosis at the centre, which constituted a volume loss mechanism. While this could give rise to dormancy, further growth ensued if the retardation by necrotic volume loss and consumption decrease was insufficient, giving rise to a fourth phase which could be characterized by either the aforementioned three-layered structure, or a four-layered structure comprising an additional quiescent layer.

Various models relating to oxygenation and radio-sensitivity of solid tumours were developed Liapis *et al.* (1982), Arve and Liapis (1988), King *et al.* (1986a,b) and Schultz and King (1987). In addition, some models of drug transport in tumours given by Jain and Wei (1977) and Swan (1981) were advanced.

2.5 New approaches to the study of tumour invasion and metastasis

Orme and Chaplain (1996) continued the study of tumour growth and vascularisation assumed that tumour cells react to the presence of blood vessels in a similar manner to that of 'taxis', so that tumour cells move up a gradient of capillary vessels. They made an assumption that a necrotic core develop as a consequence of the overcrowding of tumour cells and eventual collapse of blood vessels. Moreover, interactions between tumour cells and capillary vessels were considered in more detail, yielding a somewhat more complicated partial differential equation model.

Perumpaini and Norbury (1999) developed a mathematical model of malignant invasion brought about by a combination of proteolysis and haptoxis. The spatial dynamics of invasive cells were modeled by a directed cell movement up an extracellular gradient, while neglecting random cell motility. The proliferation of the tumour cells was incorporated using the logistic growth equation, while a simple passive degradation described the dynamics of the extracellular matrix. In addition, while the production of protease was assumed to depend on the local concentrations of both tumour cells and extracellular matrix, its decay was assumed to be linear with a specified half-life.

Both theoretical and experimental methods were combined in a publication by Perumpaini and Byrne (1999). Gatenby (1991, 1995a,b, 1996a,b), Gatenby and Gawlinski (1996) and Webb *et al.* (1999) advanced works on tumour invasion by investigating alternative mechanistic bases for experimentally-observed behaviour. Gatenby (1991, 1995a, 1996b) used methods from population biology in treating tumour cells as an invading species.

Chaplain and Sleeman (1993) that the degree of tumour differentiation maybe characterized mathematically by a strain energy function, thereby linking the potential for invasion and metastasis to the constitutive nature of the tissue. This approach afforded an emphasis on the activity of the layer of proliferating cells at the tumour periphery, which may invade the surrounding host tissue.

Sleeman and Nimmo (1998) extended the model of fluid transport in vascularized by introducing a pressure – curvature condition to the tumour periphery. A perturbation analysis was conducted to show how small deviations from spherical symmetry could enhance asymmetric growth, enabling the tumour to invade and metastasize.

2.6 Further models of avascular tumours and multicell spheroids

Chaplain *et al.* (1994) relating to the loss of coupling between tumour cells and proposed that the diffusion of growth inhibitory factors between cells may not be constant. This new model introduced a non-linear, spatially-dependent diffusion coefficient to describe the diffusion of a growth inhibitory factor which is in contrast to earlier models (Adam, 1986, 1987a,b; Adam and Maggelakis, 1989) which incorporated only non-linear *production* of mitotic inhibitors. In addition, both uniform inhibitor production, as well as the non-linear production term proposed by Britton and Chaplain (1992) and Chaplain and Britton (1993) were considered. The model demonstrated that the introduction of a non-linear, spatially-dependent diffusion coefficient was sufficient to produce a profile of growth inhibitor concentration. Furthermore, since the combination of non-linear diffusion and a non-linear production term was also able to reflect experimental observations, it is not possible to distinguish between the effects of non-linear diffusion and non-linear production of inhibitors from a mathematical point of view.

The role of apoptosis (that is, programmed cell death) in tumour growth has also spawned several novel mathematical models. New antitumour strategies which focus on apoptosis are emerging (Hickman *et al.,* 1994). Bryne and Chaplain (1996a) considered both apoptosis and necrosis as distinct cell loss mechanisms in a model which studied the effects of nutrients and inhibitors on the existence and stability of time-independent solutions for a multicell spheroid.

Byrne (1997) developed a mathematical model which studied the effect of time delays on the dynamics of avascular tumour growth because of these time delays, the tumour's evolution depended not only on its composition at a particular instant, but also on its composition at some earlier time. Two types of time delay in the net cell proliferation rate were considered where the first one was regulated by the cell itself (autocrine control) and represented the time taken for the cells to undergo mitosis. The second type of delay, was influenced by neighbouring cells (paracrine control) and represented the time for cells to upregulate the production rate of a particular growth factor and for the growth factor to modify the rate of apoptotic cell loss.

Byrne and Gourley (1997) study the relationship between cell proliferation and apoptosis through a consideration of the internal production of growth factors. Here, a growth factor was first produced in an active form during cell proliferation, and later activated upon binding to a tumour cell. Growth factors which enhanced apoptosis did not alter the qualitative behaviour of the tumour, while growth factors which suppressed apoptosis could induce asymmetric pulsing of the tumour radius.

Ward and King (1997, 1999, 2000) have made a significant contribution on avascular tumour growth. There are models are quite distinct from previous one since they do not appeal to the theory of porous media and theory of mixtures. Ward and King (1997) presented a system of non-linear partial differential equations as a continuum model which assumed cells to be either living or dead (depending on the concentration of a generic nutrient). The aim is to make predictions about tumour heterogeneity and growth, without making any prior assumptions about the spatial structure of the tumour. A velocity field developed as a consequence of local volume changes due to cell proliferation and cell death, where in contrast to previous models, dying cells contracted at a rate which depends on the availability of nutrients. The model used of a generalized Michaelis-Menten form for the rate constants for cell proliferation and death. This formulation predicted an early exponential growth phase followed by linear growth, corresponding to experimental observations in the intermediate phase of spheroid growth. An additional interesting prediction peculiar to this modelling framework was the existence of two phases of growth retardation following the exponential growth. The first of these phases was a consequence of nutrient diffusion limitations, with the second retardation coinciding with the formation of a necrotic region. In addition, well-defined tumour regions were predicted with a distinct viable rim and a necrotic core.

Ward and King (1999a) extended the model by incorporating a necrotic volume loss in order to consider growth saturation. However, they considered only necrotic cell death and proposed two distinct mechanisms for the removal of the necrotic debris: leakage and consumption by neighbouring cells. The latter mechanism was postulated on

the basis of experimental observations of cells consuming neighbouring dead cells (having undergone apoptosis), as reported by Kerr *et al.* (1987). Depending on the choice of parameter regime, this measure enabled the long-time solutions to exhibit either traveling wave or growth saturation.

Byrne and Chaplain (1997), proposed a model which comprised some very novel approaches and constituted a quite general formulation for the growth of multicell spheroids. A key aspect of the model was the assumption that the nutrient concentration satisfied the Gibbs-Thompson relation on the tumour boundary. This is a relation which states that "the nutrient concentration at a point on the tumour boundary is less than the external concentration by a factor which is proportional to the local curvature there" .

Sherrat and Chaplain (2001) have also developed a novel avascular tumours model by considering continuum densities of proliferating, quiescent and necrotic cells, together with a generic nutrient or growth factor. This model predicted the development of the characteristic layered structure of a proliferating rim, an underlying quiescent layer and a necrotic core without making any priori assumptions about the spatial structure of the tumour. The model also incorporated cell movement. An additional novel feature of the model was that the thin, approximately disc-shaped tumour could be supplied with nutrients from underlying tissue, a situation which would arise in the context of a tumour growing within an epithelium. The numerical solutions and accompanying analysis illustrated that tumour structure could be altered significantly by this aspect.

Chaplain (1996) discusses the various stages of tumour growth (avascular, vascular, angiogenesis and metastasis) by presenting a variety of mathematical ideas (Chaplain and co-workers (1993; 1994) presented a unified treatment of the entire process of tumour development.

In a similar manner, a general discussion of a number of modeling frameworks, including lattice schemes and continuum models comprising either a single phase or multiple phases for the study of the tumour growth at the macroscopic level. De Angelis and Preziosi (2000), Anderson and Chaplain (1998) and Anderson *et al.* (2000) gave summaries of various aspects of the model for an overview of the subjects of avascular tumour growth, angiogenesis, invasion and tumour-host interactions. De Angelis and Preziosi (2000) model is particularly noteworthy since it describes the continuous evolution of a tumour from the avascular stage to the vascular stage via the process of angiogenesis. The study of tumour interactions with the immune system has also attracted an abundance of mathematical models. An overview of this field of research has been published by Adam and Bellomo (1997).

In general, the mathematical model of tumour describes the evolution of tumour growth from the early stage (microscopic level) toward later stage (macroscopic level). The model becomes more complex when it involves the interaction between tumour cell and their surrounding. A system of nonlinear partial differential equation has been established for describing this interaction. Since this involving many parameters like concentration of cell, tumour density etc., the solution of nonlinear partial differential

equations are mainly numerical like finite difference method. None of it was being solved analytically. In this study, the mathematical models of tumour from avascular until metastasis stage are solved via Adomian Decomposition Method (ADM) and Homotopy Perturbation Method (HPM). These methods produced approximate analytical solution in a series form. From our knowledge, this is the first time that ADM and HPM were being used in solving tumours model.