Models of Bone Cancers - Part I. Mathematical Models of Cancers. An Introduction

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Institute of Computer Science
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Technical report No. 1178

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Abstract:

In biology and medical sciences mathematical models play an important role. The role of mathematical models are then to explain a set of experiments, and to make prediction which will then be tested by further theoretical and/or experimental approaches. During the last four decades, various neoplasms (tumors and cysts) models have been developed, analyzed and discussed. Some of these models are based on simple assumptions ignoring the spatial effects of tumour growth. These models are based on ordinary differential equations (ODEs) only. On the other hand the models which take spatial effects into considerations lead to models which are based on formulations using partial differential equations (PDEs). They also need to take into considerations the facts that the tumor regions are changing in time and that the boundaries are unknown in advance.

The submitted paper represents an introductory course to study model problems of loaded long bones, bones of spine (vertebrae) and/or of jaw-bones with cancers. The study will be divided into several parts and will be concerned with mathematical models of cancers, the mathematical models of loaded bones with cancers and the models of fracturing as well as microfracturing of bones with tumors and numerical methods for their solutions.

Keywords:
Neoplasms, cancers, long bones, spine, jaw-bones, growth of tumors, mathematical models, numerical methods, algorithms

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1 Introduction

At present cancers are fundamental and social problems as they represent the main causes of morbidity and mortality in the world. World Health Organization – WHO's studies show that cancers are leading causes of death world wide, accounting of about 12–14% of all world's deaths. Bone tumors represent a great number of diseases occurred in the human population. Therefore, the fundamental cancer's research is needed and advanced countries investing large sums of money into these research programs, namely to molecular biology, cell biology, drug delivery research, but also into mathematics. The PubMed bibliographic data base shows that more then 1.5 million papers in the area of cancer research were written. In the area of the mathematical modelling of cancers the number of present research results represent of about 100,000 papers. J. E. Cohen characterizes the usefulness of mathematics in these studies as follows: "Mathematics is Biology's next microscope, only better", and moreover, "Biology is Mathematics' next Physics, only better."

The goal of this study is to give an idea, how to better understand of the highly nonlinear processes passing in the bone tissue during the evolution of cancer under the influence of stresses (pressures and tensions) in the loaded bone tissue and the influence of the tumour mass onto the bone strength and its possible resistance to fracturing (i.e., the fracture strengthens). Moreover, the ultimate goal in the clinical practice is to use mathematical modelling to help design therapeutic strategies. Using analysis and nonlinear numerical simulations, we investigate, and then in general, we can explore the effects of the interaction between the genetic characteristics of the tumor and the tumor microenvironment on the resulting tumor progression and morphology. We will present a model for solid tumor growth and then the ensuing model of the loaded long bone and/or of the spine and/or of the jaw-bone with cancers.

Cancer arises from one single cell. The transformation from the normal cell into a tumour cell is a multistage process. The evolution of a cell is regulated and controlled by the genes contained in its nucleus. Receptors on the surface of cell(s) can receive signals which are then transmitted to the cell nucleus. These genes are then activated or suppressed [105]. These processes are in progress in the sub-cellular scales. But there can be situations that particular signals induce uncontrolled **proliferation** or on the other hand induce **cell death**, the so-called **apoptosis** and/or induce **the programmed cell death**.

A tumour is a mass of tissue that forms when cells divide uncontrollably, i.e., by an overproduction of cells. A bone tumors are abnormal growth of cells within the bone that are (i) noncancerous, we speak about **benign bone tumors**, or (ii) cancerous, and we speak about **malignant bone tumors**. Bone tumors are of **primary types**, originating within the bone tissues, or of **secondary types**, which result from the spread cancer cells from the primary tumors located in other tissues in the human body and we speak about **metastasis** (see e.g. [36, 31, 69]. Another type of neoplasms are **cysts,** except that they are filled by fluid. Growing tumors replace healthy tissue with abnormal benign or malignant tissues. Benign tumors are not life-threatening, expecting such benign tumors that are changed into malignant tumors.

Benign bone tumors do not metastasize, that is, they do not spread to other tissues but remain situated in the bone or in the other tissue. Bone cells, the so-called osteoblasts, produce osteomas, while cartilage cells, the so-called **chondroblasts**, produce **chondromas**. Tumors, which are built from both types of bone and cartilage cells produce **osteochondromas**, which are the common type of benign bone tumors.

There exist many types of benign bone tumors, namely Giant cell tumor, Osteochondroma, Ecchondroma, Fibrous dysplasia, non-ossifying fibromaunicameral bone cyst (neo-ossifying fibroma), simple bone cyst, aneurysmal bone cysts, osteoid osteoma, osteoblastoma, osteoma, chondroblastoma, chondromyxoid fibroma. Benign tumors and cysts are located also in the jaw-bone and that are most often odontogenic, meaning that they originate from tissue related to the teeth. Another type of odontogenic cyst is the so-called odontogenic keratocyst, which are frequently situated in the mandible, but it is observed also in maxilla. It grows relatively very quickly.

Remark 1 *The problems of cysts are studied in the number of papers e.g. [95, 94, 68, 99, 101, 108, 82, 83] and the papers and books quoted here.*

Bone tumors are most classified according to their histogenesis. Tumors are of benign or malignant types. Malignant bone tumors are of primary and secondary types and the secondary types (metastasis) are frequently occurred than the primary types ($\leq 1\%$). Primary bone cancers, known as sarcomas, originate in different types of bones or of soft tissues, like cartilage, muscles, nerves, connective tissues.

Primary bone cancers are different than secondary bone cancers. The most common types of primary bone cancer are

(i) Multiple Myeloma, which is a malignant tumor of bone marrow; most are observed in patients between the ages of 50 and 70 years old.

(ii) Osteosarcomas, which are bone-forming sarcoma that develop primarily at the ends of the bones (children and young adults) and located in the knee, hip and shoulders areas. They are classified due to the cells of origin, their size, location, and degree of proliferation – mitoses. Surgery remains the standard for osteosarcomas with adjective systemic chemotherapy.

(iii) Ewing's Sarcoma develop most frequently in the middle of long bones as the upper and lower limbs, pelvis, ribs.

(iv) Chondrosarcomas arise from cartilage and are observed in the upper and lower limbs, pelvis and ribs; they may also develop from benign enchondromas and osteochondromas.

(v) Fibrosarcomas arise from connective tissue – tendons, ligaments or muscles, and may affect the bone of the jaw and limbs.

(vi) Giant cell tumors (GCTs) are benign but locally aggressive tumors. When they are located in the spine and sacrum, the surgical resection is complicated and is associated with excessive blood loss. Moreover, radiotherapy is also complicated.

Bone sarcomas occur in 0.2% of all neoplasms. Cancer registry data with histological stratification show that osteosarcoma is the most common primary malignant tumor of bone, which accounting $\sim 35\%$ of carcinomas; chondrosarcomas of about $\sim 25\%$ and Ewing sarcoma of about $\sim 16\%$ of carcinomas. Chordomas and malignant fibrous histiocytoma occur in 8% or 5% of bone tumors, respectively.

Osteosarcomas occurs predominantly in younger patients, less than 20 years old, and moreover, in 80% of this sarcomas occur in long bones of the limbs, while a smaller part of cases are located in other part of the skeleton, that is, in craniofacial bones, the spine, and the pelvis. In the case of patients older than fifty, osteosarcoma of the limbs occur in $\sim 50\%$ of cases, and in the pelvis and craniofacial bones it occurs in about of 20% of cases.

Chondrosarcomas, more than 50% of cases, occur in the long bones of the limbs; their incidence rates show a gradual increase up to age 75. The other their major locations are the pelvis, ribs and sternum, that are high risk sites for malignant cartilage tumors.

Ewing sarcoma has a epidemiological feature similar to those of osteosarcoma. Ewing sarcoma mainly occur in the diaphysis of long bones, while the osteosarcomas tend to occur in the metaphyseal areas of long bones. The incidence mirrors those of osteosarcoma with the major peak occurring during the second decade of life, with a rapid decrease in incidence after age 20.

The bone cancers were studied in a great number of papers, e.g. [92, 93, 71, 52, 19, 106, 29, 67, 53, 30, 31, 69, 13, 38, 50, 96] and in many other papers.

Some types of bone tumors and other neoplasms can be found e.g. in WHO Classification of Bone Tumors [91, 98, 13, 86, 75, 55, 27, 85, 87] and `http//:njms2.umdnj.edu/tutorweb/introductory.htm`.

From the etiology point of view bone malignancies are of different origins. While radiation and chronic inflammantory states were established, other exposures and conditions, like chromium, nickel, cobalt, aluminium, titanium, methyl-methacrylate as well as polyethylene, have been suspected, but at present not confirmed. Therefore, at present attentions have been focused on some bone sarcomas arising as a consequences of implanted metallic joint prostheses and metallic hardware used in orthopaedy.

The clinical features of bone tumors are non-specific, and therefore, during a long time they are not diagnosed. As the cardinal symptoms that lead to diagnosis of bone tumors are pains, swelling as well as discomfort of patients and limitation of their mobility and spontaneous fractures of bones. Swelling may be of very long duration, especially in benign neoplasms with practically no additional difficulties for patients. Swellings are observed if there are extraosseous parts of the tumors or the bones are expanded by the tumorous processes. But in malignant tumors, swellings develop more rapidly as the growth of malignant tumors are of millimeters per day, while in the case of benign tumors the growths of tumors are millimeters per year. In some cases pathologic fractures are diagnosed. They may occur with no prior symptoms at all, as they are frequently the cases in juvenile cysts and in some non-ossifying bone fibromas. But in the cases of malignant bone tumors, fractures are rare primary events, as they occur in advanced stages for the patients. Diagnoses of tumors are based on the radiological or CT/MRI and histological criteria. Focal extents and staging are based on MRI because the main advantages are represented by high contrasts. Bone metastases are best detected on radionuclide bone scans, on computer tomography (CT) and/or on positron emission tomography (PET), respectively. Histological gradings are attempts to predict the biological behavior of malignant tumors based on histological features. The relative amount of cells compared to matrix (known as cellularity), and nuclear features of the tumor cells are the most important criteria used for grading in bone tumor analyses. For bone tumors the universal classification TNM staging system used for most carcinomas is not commonly applied for bone sarcomas because of their special behaviors and their metastasize to lymph nodes. Therefore, the special staging system (TNM system) was adopted for the musculoskeletal system.

2 The classification of bone tumors

2.1 The structure and functions of bones

The skeleton is the framework of the body. It supports the softer tissues and provides areas of attachment for most skeletal muscles. The purpose of the skeletal system is to protect many of the body's internal organs, e.g., vertebrae protect the spinal cord, the ribcage protect the heart and lungs, cranial bones protect the brain, etc., and provide kinematic links and muscle attachment sites, and facilitate muscle action and body movement. Since skeletal muscles are attached to bones, then when the associated muscles contract they cause bones to move.

A bone tissue is a connective type of tissue whose solid composition enhances its supportive and protective roles. It consists of cells and of an organic extracellular matrix of fibres and a ground substances produced by the cells. Bone tissues store several minerals, including calcium Ca and phosphorus P, which are combined intimately with the organic matrix. These inorganic components make bone tissues hard and rigid; organic components give a bone its flexibility and elasticity. These inorganic components consist of calcium and phosphate in the form of small crystals of $Ca_{10}(PO_4)_6(OH)_2$. Bone minerals are embedded in various oriented fibres of the protein collagen, and the inorganic matrix. From a macroscopic point of view bones are divided into two main types of osseous tissue – that is, (i) cortical or compact bones and (ii) trabecular or spongy or cancellous bones. **Cortical bones** form the outer cover of the bones and they have dense structures. **Cancellous bones** are composed of thin plates, or trabeculae, in loose mesh structures, where the interstices between the trabeculae are filled with a red marrow. The cancellous bone tissue is arranged in concentric lacunae-containing lamellae. Bone tissues behave like composite biomaterials. The red bone marrows are occurred inside of some larger bones where blood cells are produced. With a bone increase the bone marrow changes from the red bone marrow to the yellow bone marrow. Bone marrow produces stem cells, such as erythrocytes, that is, the red blood cells, and the leucocystes, that is, the white blood cells. Yellow bone marrow consists mainly of adipose cells, and a few blood cells, and it represents an important chemical energy reserve. For more details see e.g. [43, 47, 24, 86, 38, 70, 85].

Types of bones are the following:

- Axial and appendicular. The appendages are the arms and legs, which contain approximately of about 30 bones each.

- The head bones, which contain of about 22 bones.
- The spine, which contain 33 bones; include 7 cervix (neck), 12 thorax, 5 lumbar, 5 sacral, 4 coccyx.
- The pelvic girdle, which is fused to the sacrum at the sacro-iliac joint. The pelvis is the part of the skeleton that is added onto the spine.
- The thorax (chest) consists of 12 pairs of ribs.
- The shoulder girdle consists of the scapula (shoulder blade) and the clavicle (collar bone).

Categories of bones are the following:

- Long bones, which have greater length than width (e.g., the femur, the tibia, the fibula, the humerus, the ulna, the radius) and which consist of a shaft and a variable number of extremities (endings). They are usually somewhat curved for strength.
- Short bones, which are roughly cube-shaped and have approximately equal length and width, e.g., the ankle or wrist bones.
- Flat bones, which have a thin shape/structure and provide considerable mechanical protection and extensive surfaces for muscle attachments, e.g., the cranial bones, the sternum and the ribs, protecting the inner organs in the thorax, and the scapular (shoulder blades).
- Irregular bones, which have complicated shapes. Their shapes are due to the functions they fulfil in the skeletal body, like the vertebrae protecting the spinal cord, or some facial bones.
- Sesamoid bones, which develop on some tendons in locations where there is considerable friction, tension, and physical stress, e.g. the patellae (kneecaps).
- Sutural bones, which are classified by their locations rather than by their shapes. They are small bones located e.g. within the sutural joints between the cranial bones.

Cartilages are related to bones. Bones are caltified cartilages. Long bones originate from cartilage tissues in limb buds during embryonic development and increase in length through endochondral ossification in which cartilage tissue is calcified and subsequently replaced by bone matrix near the ends of the bones. They increase in width by periosteal matrix apposition by osteoblasts; the marrow space increases in diameter in proportion to the length of the growing bone by endosteal resorption of cortical bone by osteoclasts. New cancellous, known also as trabecular, bones are laid down rapidly following resorption of calcified cartilage at the growth plate. Most of them are quickly removed by osteoclastic resorption to maintain a medullary cavity as the bone grows. Mutations in genes regulate limb bud development.

Bones grow from their ends - extremities. Under normal circumstances bones stop growing when the owner reaches teens or early twenties. Bone components are articulatory cartilage, which reduces friction and absorbs shocks at freely moveable joints; spongy bone; bone marrow; endosteum, which is membrane that lines the cavity of a bone; compact bone; periosteum, which is a though fibrous membrane that surrounds the outside of bones whenever they are not covered by articular cartilage; medullary cavity, that in adults contains fatty yellow bone marrow (Figs 2.1). For the structure of long bones see e.g. [21, 44, 86, 85].

The ideal reconstructions of long bones with tumors would have biological affinity, resistance to infection, sufficient biomechanical strength, and durability. Distraction osteogenesis involved three different procedures – bone transport, shortening distraction, or both combined with the use of an intramedullary nail. For illustration of useful techniques the treatment of osteosarcoma situated in the femur is presented. For such type of reconstruction in the diaphysis area the bone transport or shortening-distraction techniques can be used. Reconstruction of long bones are classified as follows:

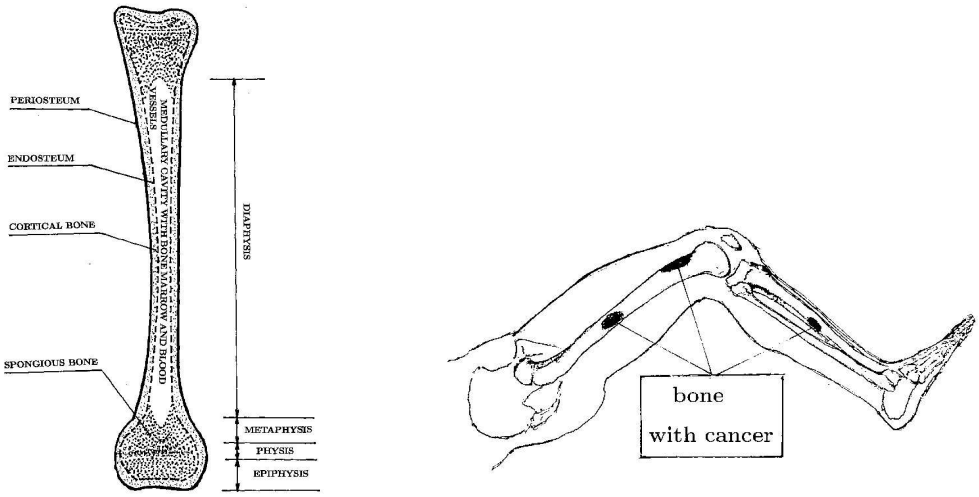

Figure 2.1: Long bones, their structure and locations of bone cancers: (a) cross section through the tibia - the Diaphysis, Metaphysis, Physis and Epiphysis and its structure, (b) locations of some cancers in the femur and the tibia.

Type 1. Diaphyseal reconstruction.

Type 2. Metaphyseal reconstruction.

Type 3. Epiphyseal reconstruction.

Type 4. Subarticular reconstruction.

Type 5. Arthrodesis.

The classification of reconstruction by distraction osteogenesis using bone transport or shortening distraction is presented in [98]. Distraction osteogenesis involved three different procedures – bone transport, shortening distraction, or both combined with the use of an intramedullary nail. Reconstruction of femur using distraction osteogenesis is presented at Fig. 2.2 due to [98]. Mathematical simulations of these types of reconstructions can be based on the modified methods and algorithms discussed in [78, 79, 80, 81, 82, 83, 84, 85] and also in the next part of the paper.

Between bone tumors **primary vascular tumors of bone**, which represent a heterogeneous group of bone entities, are also observed. Vascular tumors of bone consist of a wide variety of different clinicopathologic entities, ranging from begin lesions on one hand and malignant tumors at the other hand [38]. Vascular tumors of bone are of

(A) benign type, that are

  (i) Hemangioma, that are cavernous and capillary; located in the skull or vertebrae;

  (ii) Hemangiomatosis, that are

    * non-aggressive and regional;
    * non-aggressive, disseminated (cystic angiomatosis);
    * aggressive or massive osteolysis and/or Gorham Stout's Disease;

(B) intermediate (locally aggressive, rarely metastasizing) type, that is, Epithelioid hemangioma; located in long tubular bones;

(C) malignant type, that are,

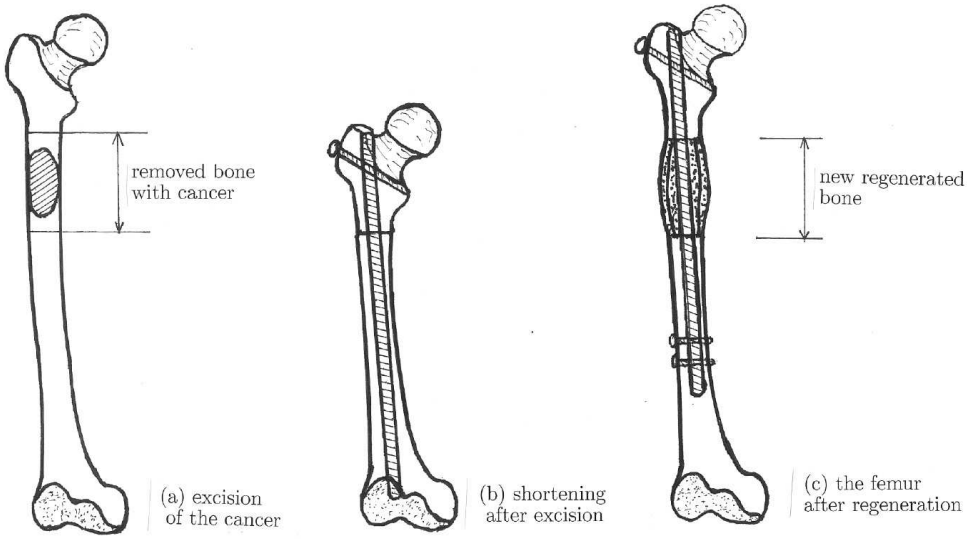

Figure 2.2: Some reconstruction of bones after Osteosarcoma in the femur and distraction osteogenesis. Schematic figure of distraction osteogenesis based on shortening-distraction with using an intramedullary nail (modified after [98]).

(i) Epithelioid hemangioendothelioma; located in long tubular bones of extremities;

(ii) Angiosarcoma, located in long tubular bones of extremities and in spine; that are

- Primary;
- Irradiation-induced;
- Bone infraction associated.

Secondary bone cancers originate when malignant (tumor) cells from primary cancer locations in bones spread, that is, metastasize to another site(s) in bone(s) and the tumor malignant cells are those of the original tumor. It can also metastasized to the jaw-bones. Most cancers, like prostate, lung, breast, etc., can metastasize. The primary tumors cannot reach a size of about few mm^3 without nourishment from new blood vessels. Tumor angiogenesis is a necessary proliferation of a network of blood vessels that penetrates into cancerous tissues and supplies nutrients, that is, the glucose and oxygen, and remove waste products. An undesirable consequence is that neovascularization favors cancer cells metastasis. Metastatic areas can develop hypervascularization. Bone metastases are often hypervascularized [39, 59].

Tumor metastases to bone are not a random process, but rather a result of anatomical factors, tumor cell phenotype, and suitability of the metastatic site for tumor growth. Blood flows from the primary sites are significant determinant of the sites of metastases. Metastasis is a very complicated process that consists of a cascade of linked sequential events. Mechanisms of tumor cell metastasis to bone consists of several stages, that are, (i) a tumor cell(s) is detached from the primary site; (ii) creation of new vessel system and ensuing circulation and invasion of tumor cells; (iii) survive host immune response and physical force in the circulation; (iv) arrest in distant capillary bed in bone; (v) escape the capillary bed; (vi) tumor cell proliferation and creations metastases in bone. Cancer metastasis to bone tissue causes bone destruction or osteolysis. When localized in the bone marrow, tumor cells release growth factors and cytokineses that can modify the microenvironment and the bone remodelling, that is, parathyroid hormone-related protein (PTHrP), transforming growth factor beta (TGFβ), colony stimulating factor (CSF-1), granulocyte-monocyte CSF (GC-CSF), and chemokineses and other growth factors and cytokineses [49, 77]. Since bones are composed of hard

mineralized tissues, they are more resistent to destruction than other soft tissues. The bone matrix is a favorable microenvironment, rich in sequestered growth factors, that is, bone morphogenetic proteins (BMPs) insulin-like growth factors (IGF-1) and transforming growth factor beta (TGFβ). Bone matrix degradation by osteoclasts releases the entrapped growth factors that promote tumor cell proliferation. The vasculature in the bone marrow consists of sinusoidal capillaries that have a larger diameter than capillaries of other tissues. The sinusoidal capillaries have discontinuous walls made of endothelial cells with no tight junctions, therefore, the structure of the marrow sinusoids and the blood flow make an advantageous ability for tumor cells to invade the bone marrow.

Since bone tissues are mainly composed of hard mineralized tissues, and therefore, they are more resistant to destruction of bone tissues, thus they must possesses the capacity to cause bone destruction for cancer cells to grow in bone [52]. A production of bone – resorbing factors depends on the type of malignancies in which bone metastases occur. Several tumor types, such as prostate, lung, renal cell, and thyrozoid, are associated with osteolytic lesions, while osteoblastic metastases are more often manifest in prostate cancer. Mixed osteolytic and osteoblastic lesions are often observed in breast and prostate cancers [67, 49, 31, 105].

The detailed discussions about all these above mentioned problems see e.g. in [65, 66, 62, 37, 36, 98, 14, 49, 31, 69, 15, 63, 38, 76, 75, 40, 105] and in the references presented here.

Limbs with sarcomas are treated by chemotherapy, radiological evaluation and surgical techniques. The last one is connected with the implants and with the technology of materials for hardware. Complications such as deep infections, fractures, bone resorption, and breakage of prostheses still occur.

2.2 Classification of bone tumors

The classification of tumors is based on the matrix produced by the tumor and the cytologic findings. Several systems have been introduced for classifying tumors of bones, based on morphologic differences between different lesions or based on clinical and radiographic parameters or on histologic differences as well as etiology, respectively, that will be modified with our knowledge in regard to the primary tumors of bones. Ewing [34, 35], Budd and McDonald [17], Coley [23]) modified the classification of bone tumors of the Registry of Bone Sarcoma and later the classification of tumors arising in bones was introduced by Lichtenstein [65]. This classification, reflecting current concepts of his time, provides within its framework a place for all known primary neoplasms of bone including pathological entities known in his time. His classification includes the benign as well as the malignant primary tumors. Significant progress has been made in the histological and genetic typing of bone tumors, introduced by the WHO Classification of Bone Tumors [38], where the morphology code of the International Classification of Diseases for Oncology (ICD-O) and the Systematized Nomenclature of Medicine (see `http://snomed.org`) are used.

WHO Classification of Bone Tumors:

A. Cartilage Tumors

1. Osteochondroma
2. Chondroma
   a. Enchondroma
   b. Periosteal chondroma
   c. Multiple chondromatosis
3. Chondroblastoma
4. Chondromyxoid fibroma
5. Chondrosarcoma
   a. Central, primary, and secondary
   b. Peripheral
   c. Dedifferentiated
   d. Mesenchymal
   e. Clear cell

B. Osteogenic tumors

1. Osteoid osteoma
2. Osteoblastoma
3. Osteosarcoma
   a. Conventional
      - chondroblastic
      - fibroblastic
      - osteoblastic
   b. Telangiectatic
   c. Small cell
   d. Low grade central
   e. Secondary
   f. Parosteal
   g. Periosteal
   h. High grade surface

C. Fibrogenic tumors

1. Desmoplastic fibroma
2. Fibrosarcoma

D. Fibrohistiocytic tumors

1. Benign fibrous histiocytoma
2. Malignant fibrous histiocytoma

E. Ewing sarcoma/primitive neuroectodermal tumor

1. Ewing sarcoma

F. Hematopoietic tumors

1. Plasma cell myeloma
2. Malignant lymphoma, NOS

G. Giant cell tumor

1. Giant cell tumor
2. Malignancy in giant cell tumor

H. Notochordal tumors

1. Chordoma

I. Vascular tumors

1. Hemangioma
2. Angiosarcoma

J. Smooth muscle tumors

1. Leiomyoma
2. Leiomyosarcoma

K. Lipogenic tumors

1. Lipoma
2. Liposarcoma

L. Neural tumors

1. Neurilemmoma

M. Miscellaneous tumors

1. Adamantinoma
2. Metastatic malignancy

N. Miscellaneous lesions

1. Aneurysmal bone cyst
2. Simple cyst
3. Fibrous dysplasia
4. Osteofibrous dysplasia
5. Langerhans cell histiocytosis

6. Erdheim-Chester disease
7. Chest wall hamartoma

O. Joint lesions

1. Synovial chondromatosis.

Malignant bone tumors are classified, e.g., in the American Joint Commission on Cancer (AJCC) tumor-node-metastasis (T-N-M) staging system as follows:
T0 – no tumor, T1 – tumors $\leq$ 8cm, T2 – tumors $\geq$ 8cm, T3 – tumors in more locations on the same bone;
N0 – no spread, N1 – spread to lymph nodes;
M0 - no distant spreading, M1 - distant metastasis.

For alternate group T-N-M staging system the Roman numeral I-IV (ranging from the absence of incremental increases in metastasis) or assigns G1-G4 (lower numbers indicate low-grade tumors, higher numbers indicate high-grade tumors) are used.

Odontogenic tumors are either of epithelial, mesenchymal, or of unknown origins [64].

Classification of odontogenic tumors:

A. Benign epithelial odontogenic tumors:

1. Tumors producing minimal inductive change in the connective tissue:
   a. Ameloblastoma;
   b. Calcifying epithelial odontogenic tumor, the so-called Pindborg tumor;
   c. Odontogenic adenomatoid tumor, that is, adenomeloblastoma, adenomatoidodontogenic tumor;
   d. Calcifying odontogenic cyst, the so-called Gorlin's cysts;
2. Tumors producing extensive change in the connective tissue:
   a. Ameloblastic fibroma;
   b. Ameloblastic fibroodontoma;
   c. Ameloblastic odontoma, the so-called odontoameloblastoma;
   d. Odontoma;
   - Compound-composite odontoma;
   - Complex odontoma.

B. Mesenchymal odontogenic tumors

l. Odontogenic fibroma;
2. Odontogenic myxoma;
3. Cementoma:
   a. Periapical cemental dysplasia;
   b. Cementifying fibroma;
   c. Benign cementoblastoma;
4. Dentinoma.

C. Tumors of unknown origins:

1. Melanotic neuroectodermal tumor of infancy.

D. Malignant odontogenic tumors:

1. Primary interosseous carcinoma;
2. Ameloblastic fibrosarcoma;
3. Ameloblastic dentisarcoma;
4. Ameloblastic odontosarcoma.

Bones in the human skeleton are renewed by the process known as **remodelling**, which is generally heterogeneous, with regular but asynchronous cycles, so that every bone in the skeleton is periodically remodelled. Moreover, bone-remodelling depends on external loads, which produce stress and strain patterns in the bone, which are considered as mechanical stimuli [102, 103, 33]. Bone contains sensor-cell detecting mechanical stimuli. The intensity of the stimuli then affect the activity of the osteoclasts

and osteoblasts. Together with genetic, metabolic and hormonal factors, that is, the mechanism by which the morphology (density) of the bone changes. Normal loading and consequently a normal stimulus distribution lead to the homeostatic equilibrium with normal bone density, in which the amount of bone formation is in balance with the amount of bone resorption. Unnatural load evoke the stimulus patterns and the adaptive bone-remodelling leads to a new equilibrium state. In the case of cancer disease, e.g., the multiple myeloma, patients have abnormal remodelling, where formation and resorption are out of balance, resulting in the end that bone formation decreases and bone resorption increases. Carcinoma cells are occurred in close association with locations of active bone resorption, and their ability to stimulate osteoclast formations and activities are characteristic. Since the cancer disease progresses in time, bone formation rapidly decreases, that can result bone fracture during loading of this part of the skeleton. This problem will be also of our interest in this paper and will be discussed in the next part of this study.

The paper will be divided into several parts and will be concerned with evolutions of a tumors and their growth, with mathematical models of loaded bones with cancers and mathematical methods and algorithms for their solutions. The bone-remodelling, microfracturing and fracturing of bones will be also studied and shortly discussed.

3 Cancer evolution

Cancer evolution is characterized by several stages of development. The first stage of development, known as **carcinogenesis**, is characterized by a sequence of genetic mutations, i.e., many gene mutations take place in the human body during one humans' lifetime or epigenetic mutations, that creates the first single abnormal cell(s), that gives rise to a tumor. These gene mutations arise increase of oncogeneses, circumvent apoptotis, that is, inactivation or less of tumor suppressor genes. There are two ways by which a gene start to be abnormal, firstly, a stimulating gene turns to be hyperactive, or upregulated, and we speak about **oncogenes**; and secondly, an inhibitory gene turns to be inactive, or downregulated, and we speak about **tumor suppressive genes**. Such gene is, e.g., the p53 gene that controls the initiation of the cell cycle.

A first tumor cell(s) starts to indirectly divide (Figs 3.1), we speak that a cell(s) undergoes **mitosis**, the new cells born and start to press the neighboring cells, that generates displacements of these neighboring cells. This stage is devoted as **carcinogenesis**. In this stage the nutrition of cells depends on the nutriment in neighboring cells.

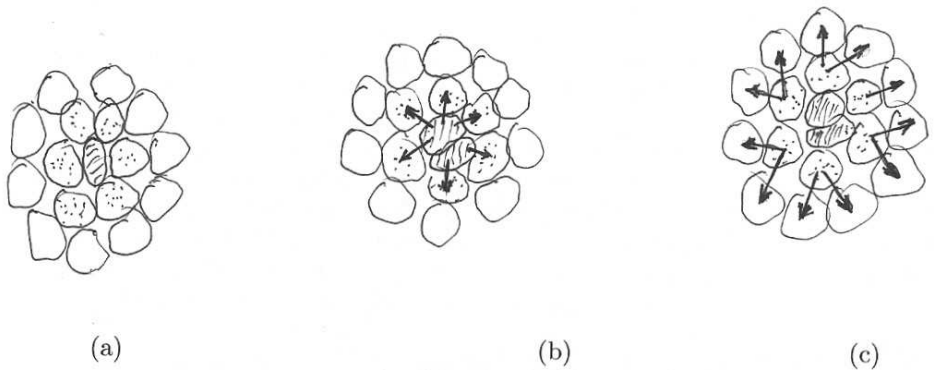

Figure 3.1: Evolution of tumor cells: (a) initial state; (b) mitosis and pressure acting on the neighboring cells; (c) cell movements and the pressure field evoked by mitosis.

This leads to growth of the tumor [18, 90] and many others. The tumor is not surrounded by capillaries. The early mitosis can be studied in laboratory by culturing tumor cells. Further, the tumor cells proliferate and form an in situ tumor. The nutrition of tumor cells, because the tumor is not surrounded by capillaries, are depended on the nutriment from the neighboring cell area. The

tumor tends to assume a limit radius corresponding to a situation with balance between mitosis and disintegration (decomposition) of tumor cells into some waste products and water. The tumor cells produce chemical factors that diffuse into the tumor mass (tissue) and into the surrounding tissue. These chemical factors are the so-called **growth inhibitor factor (GIF)** and the so-called **tumor angiogenesis factor (TAF)**. The former has an influence onto the mitotic rate of tumor cells, that arises the proliferation of endothelial cells. The diffusion of tumor angiogenesis factor initiates a new phase, called **tumor angiogenesis**. The endothelial cells within a TAF release some enzymes degrading their basement membrane – the matrix-degrading enzymes, and subsequent degradation of the extracellular matrix (ECM) play a main role in providing some space for the tumor to expand into the surrounding tissue [4, 5].

This stage is the second stage of tumor development and is characterized by its **avascular phase** and we speak about the avascular growth of tumor.

Nutrients, e.g. glucose and oxygen, are still received by diffusion through the surrounding tissue. With the further increasing of the tumor less nutrient reaches the inner central part of the tumor, the interior cells begin to die and we speak about **necrotic cells**, which are broken up by enzymes. The necrotic cells in the interior of the tumor balances with cell proliferation on the boundary, and thus the tumor reach a certain diffusion-limited size $\sim$ 2–4 mm of a spherical or irregular shapes (firstly the tumors can be observed if they reach a size of about $\sim$1 mm, which obtain approx. 1.0×10^6 cells). When tumor cells are in a high nutrient environment, they proliferate, in low nutrients the tumor cells trigger cell death – called **apoptosis**, in intermediate nutrient levels the tumor cells stay **quiescent** (Fig. 3.2). Therefore, we see that tumor cells consume nutrients, which diffuse into the tumor tissue from the surrounding tissue in the avascular stage. If the tumor is very large, then the nutrients cannot reach the inner parts of the tumor and the cells become gradually extinct and creak the necrotic tissue of the tumor. Only in the relatively thin layer being in a contact with healthy tissues the tumor cells proliferate, because their tumor cells are in a high nutrient environments, while below this layer the tumor cells are in intermediate nutrient environments, and therefore, they are quiescent.

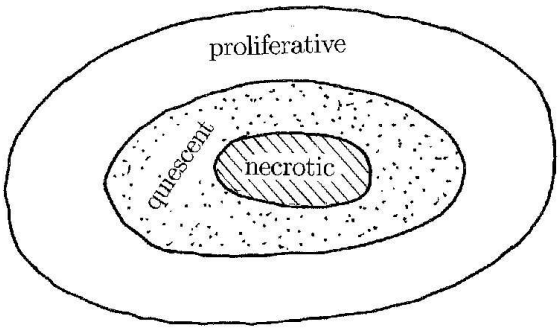

Figure 3.2: Tumor – schematic cross-section.

The third stage of tumor evolution is characterized by the development of neovasculature by the process described above and known as **angiogenesis.** A tumor-induced neovasculature grows, capillary sprouts then form by accumulation of endothelial cells. If first capillary sprouts reach the tumor surface and penetrate through it into the tumor interior, the tumor obtain much more nutrient and the tumor cells become to be very aggressive, their mitotic rate strongly increase and the tumor rapidly growth (Figs 3.3) [51, 57].

The final stage of the tumor evolution is the called **vascular phase or vascular growth**, which is characterized by a dense system of capillaries that provide the tumor by large amounts of nutrients, e.g. the glucose and oxygen.

The cancers are distinguished by the tissue from which they originate and by the cell types of their involvement. Therefore, we speak about **leukemia**, which is a cancer of white blood cells, or about

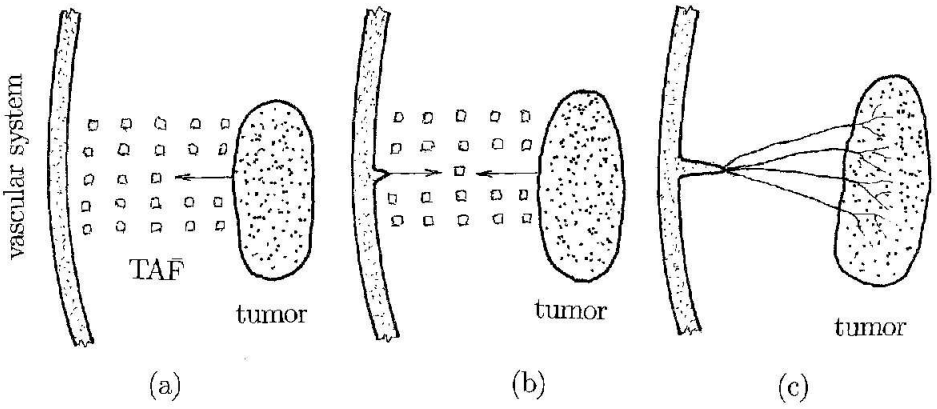

Figure 3.3: The tumor angiogenesis: (a) production of TAF factors; (b) stimulation of proliferation of endothelial cells with invasion of the extracellular matrix and migration towards the tumor cells; (c) formation of new capillary sprouts.

sarcoma, which is a cancer originating in connective and muscle tissues, or about **carcinoma**, which is a cancer originating from epithelial cells.

We saw that the **tumor** – the **neoplasm**, is a growing mass of abnormal cells. The tumor is said to be **benign** if the mass of abnormal cells remains clustered together and confined to the cavity. The tumor is said to be **malignant** if the tumor has emerged out of the cavity, by breaking out through the basal membrane and proliferating into extracellular matrix, and/or stroma. When the cancer cells invade into the blood vessels or into the lymphatic vessels, then they are transported into the other localities, where they create new cancer deposits, the **secondary tumors**, while about the tumors in the initial localities we speak as about the **primary tumors**. The process of creation of the secondary tumors is denoted as **metastasis.** A solid tumor of a ~ 1 cm size obtain 10^9 cells, tumor and normal cells. It is a size when the solid tumor can be reliably detected.

4 Mathematical models of tumor growth

In the mathematical oncology mathematical modelling and simulation of tumor growth play an important role and can have a great influence on the quality of the patient's life and also for better understanding of processes concerning with the evolutions of tumors as well as for the development of the applied mathematics. Applied mathematics can provide better interpretation of experimental data, and qualitative analysis of external actions to control tumor growth. The development of mathematical theories might not only provide a detailed description of the spatial evolution of the tumor in time, but can help to understand of the processes concerning with the evolution of tumors. Such studies are aimed on processes on the sub-cellular and cellular scale and on processes on the macroscopic scale, that is, on the organism, when the tumor grows and spreads.

Processes in the sub-cellular scale are processes of the cells evolution, which are regulated by the genes contained in their nuclei, cell proliferation or cell death (the so-called **apoptosis**) and programmed cell death. Unregulated proliferations induce interactions between tumors cells and host cells with the activation or inactivation of immune cells.

Processes in the cellular scale are processes concerning with the cell-cell interactions. These interactions represent the main elements at the stages of tumor formations, that is, among tumor cells and host cells, or among tumor cells themselves.

Processes on the macroscopic scale are processes such as blood vessel formation, invasion, vital continuation tumor growth. The angiogenic process occurs through migration, proliferation, and cell-cell signalling, that is, through processes at the cellular scale, but nevertheless this process is studied from the macroscopic point of view. After vascularization the tumor continuously grows and becomes to build a heterogeneous tissue (Fig. 4.1), created by proliferating layer, quiescent layer, necrotic inner nuclei and always the islands of non-cancerous tissues. In each of these layers, interactions between tumor and immune cells and blood vessels have the meaningful role in the growth of the tumor and in its malignant progress. At this stage the overlaps of phenomena at the cellular level and of phenomena of macroscopic behaviors, such as the diffusion, the mass balance or tumor size, are stated. All these processes are mathematically simulated and analyzed. While the processes on the cellular scale lead to study systems of coupled ordinary differential equations or Boolean networks, the multicellular systems lead to study (i) nonlinear integro-differential equations, similar to those in the nonlinear kinetic theory, based on solutions of the Boltzman equation, or (ii) partial differential equations for systems concerning with the internal structures, and then to study the corresponding discrete solutions. The processes on the macroscopic scale lead to solve (i) systems of nonlinear partial differential equations, and the corresponding discrete solutions, (ii) discrete models, such as cellular automata. Models at the cellular scale are based namely on the population dynamics, the population dynamics with internal structure, the kinetic theory for active particles as well as variety of these theories and methods. For more details see [104, 97, 32, 10, 105, 9] and the references in these papers and books.

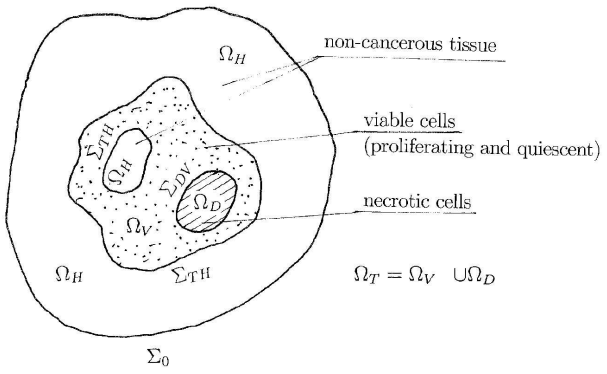

Figure 4.1: Heterogeneous tissue of the tumor – mathematical model of the tumor.

Models at the macroscopic scale are models which link the cellular tissue scale to the macroscopic tissue scale and typically macroscopic properties of the tumors, e.g. tumor malignancy, sustained angiogenesis, and tissue invasion as well as metastasis. The reality is much more complicated due to genetic cell mutations and evolutionary selection. These processes are situated by using two types of models: (i) the **discrete models**, that allows to study the behavior of individual cells such as e.g. cellular automata, random walk, etc.; (ii) the **continuum models**, that allow to study the average behavior of the densities of populations or components.

These types of models are studied by a great number of mathematical methods, which allow to describe phenomenological interactions between cells or mechanical interactions based on measuring stresses and strains of the system. In both types of models the methods require some a priori assumptions about cells behaviors, e.g. that cells move through a process like diffusion, or the cellular components act like (visco-)elastic fluid. For more details see e.g. [48, 45, 100, 6, 88, 89, 11, 12, 4, 5, 20]. The detailed history of the study of solid tumor growth and mathematical modelling with wide literature is presented in the paper of Araujo and McElwain ([7]).

Another class of models views the tumor tissue as a mixture of cells living in porous medium made of extracellular matrix (ECM) and filled by extracellular liquid, where the Darcy's law is used to model both fluid flow and cell motion ([46, 9]).

One of the most useful methods based on the continuum models are the moving boundary models, representing problems with the free boundary and firstly introduced by [48, 1, 3]. In these models it is assumed that growth of solid tumors occurs in an environment, where nutrients nurture their development under the influence of chemical factors that inhibit growth, while the immune system restrains growth of tumors ([28, 88, 89, 11, 41, 42]).

4.1 Advection-diffusion models of tumor growth

Multicell models describe the evolution of tumor growth from the avascular stage to the vascular stage. A primary tumor grows up to cca 1 mm size without new nutriments. By the angiogenic process, described in Section 3 about evolution of the tumor, the tumor vascularized and we speak about the vascular phase. With new nutriments the tumor further grows.

The model problem is composed from a system of partial differential equations of parabolic types, describing the evolution of the densities of viable cells (proliferating and quiescent cells, that is, living cells), nutrients, capillaries and growth inhibitory factor as well as tumor angiogenesis factor. To this system of parabolic equations a hyperbolic equation, describing the evolution of the density of death cells, is added. This system of equations is defined on a time varying domain, representing the whole domain, inside the tumor, that is, the viable and necrotic regions and/or outside the tumor, that is, the non-cancerous tissues, with boundaries between them, that are boundaries of free types. More precision three of them are defined in the whole domain, and remaining three equations are defined inside the tumor, that is, inside the viable and necrotic parts of the tumor. The boundaries between non-cancerous (healthy) tissue(s) and the tumor tissue(s) and between the viable and necrotic tissues, and moreover, the boundary between the proliferating and quiescent cells regions, are the free boundaries that change in time. To derive the model we introduce the density of cells $\mathbf{u} = (u_V, u_D, u_C, u_{GIF}, u_{TAF}, u_N)$, where

u_V is the density of living (viable) tumor cells,
u_D is the density of dead tumor cells,
u_T is the density of tumor cells, $u_T = u_V + u_D$,
u_C is the density of new capillaries,
u_{GIF} is the density of growth inhibitory factor - GIF,
u_{TAF} is the density of tumor angiogenesis factor - TAF,
u_N is the density of nutrient (glucose and oxygen).

The variable u_V, u_D and u_C are connected with cells, while the variables u_{GIF}, u_{TAF} and u_N are referred to macro-molecules. The derivation of the mathematical model will be based on the mass balance law in its integral form.

In our mathematical models of tumor growth we will define the number of a certain type of cells as well as of chemical factors, we denote them as $N(\mathbf{x}, t)$, contained in a volume V fixed in a space by

$$N(\mathbf{x}, t) = \int_V u\,(\mathbf{x}, t)\, d\mathbf{x}, \tag{4.1}$$

and their density $n\,(\mathbf{x}, t)$ by

$$n\,(\mathbf{x}, t) \sim N\,(\mathbf{x}, t)\, d\mathbf{x}, \tag{4.2}$$

where $\mathbf{x} = (x_i)$, $i = 1, \ldots, N$, $N = 2, 3$, is a point in the tumor region and t is time. These quantities can change due to these facts:

- advective flux through the boundary ∂V of V related to cells moving with velocity $\mathbf{v}$;

- diffusive flux through the boundary ∂V of V related to random motion of cells;

- generation and destruction of cells.

To develop the governing equations the mass balance equation in integral form due to above mentioned facts will be used. Thus

$$\frac{d}{dt}\int_V u d\mathbf{x} = -\int_{\partial V} u\mathbf{v}\cdot\mathbf{n} ds - \int_{\partial V} \mathbf{J}\cdot\mathbf{n} ds + \int_V \Gamma d\mathbf{x} - \int_V Lu d\mathbf{x}, \tag{4.3}$$

where $\mathbf{n}$ is the outward normal to ∂V, Γ represents the proliferating term and L is the death coefficient.

Using the Gauss theorem, then, under the regularity assumptions, we obtain

$$\frac{\partial u}{\partial t} = -\nabla \cdot (\mathbf{v}u) - \nabla \cdot \mathbf{J} + \Gamma - Lu, \tag{4.4}$$

representing the mass balance equation in its differential form, setting $\mathbf{J} = -D\nabla u$, where D corresponds to diffusion processes, then Eq. (4.4) leads to

$$\frac{\partial u}{\partial t} + \nabla \cdot (\mathbf{v}u) = \nabla \cdot (D\nabla u) + \Gamma - Lu. \tag{4.5}$$

Eq. (4.5) is the advection-diffusion partial differential equation and it describes the **advection-diffusion models**, that determine the diffusion, proliferation, death and movement (drift) processes, therefore, the diffusion (D), proliferation (Γ), death (L) and movement (drift) ($\mathbf{v}$) coefficients must be specified, and, their dependence of the state variables must be given.

For the generalized model of tumor evolution we will assume the following:

- mitosis of the tumor cells is occurred when a sufficient amount of nutriments exists for survival of their existence;
- proliferation is generated by the so-called growth inhibitory factor (GIF), that inhibits mitosis and by the amount of nutriment;
- with insufficient nutriments the tumor cells die, they do not move; they disintegrate into waste products, namely water; outside tumor the dead tumor cells are consumed by macrophages;
- there exists close packing overall density – a **threshold density** $\overline{u}$, characterized by the fact that if the total density of all cells in a point is above it, then tumor cells are pressed by their neighboring cells and tend to migrate towards a region with lower total density;
- living (viable) cells produce the chemical factors, that is, growth inhibitory factor (GIF) and tumor angiogenesis factor (TAF), that diffuse in the region occupied by the tumor and in the neighboring non-cancerous tissue and their diffusion mechanism is the same and depend on the effective overall density, and it can be different inside and outside the tumor, and moreover, the chemical factors can degrade;
- angiogenesis is influenced by such a way that when stimulated by TAF endothelial cells proliferate; proliferation decreases with the density of new capillaries. New-born endothelial cells move randomly and migrate toward the source of angiogenic stimulus and formate capillary sprouts, and thus, they undergo natural deaths and old capillaries are constantly replaced. Proteins (e.g. angiostatins) are assumed to have the ability of stopping the proliferation of endothelial cells.
- nutrient diffusion is a main way how to nourish the cells after the first stage of evolution (i.e., carcinogenesis). Since the tumor lacks a vasculature, nutriments (glucose and oxygen) in this avascular state of evolution are received by diffusion from the neighboring tissue. Later nutrients are mainly carried by the capillary system and smaller part of nutriments diffuse through the environment outside the capillary system. Nutriment is absorbed by living tumour cells.

The movement of cell, located in the place $\mathbf{x}$ due to the above assumption, is related to the total density u of cells around it and on its local gradient. The total density of cells u is the sum of densities of living tumor cells u_V, dead tumor cells u_D, new capillaries u_C as well as of pre-existing capillaries u_{C_0}

$$u = u_V + u_D + u_C + u_{C_0}, \quad u_V = u_p + u_q, \tag{4.6}$$

where the density of living tumor cells u_V is the sum of the density of proliferating cells u_p and the density of quiescent cells u_q. In the undeformed tumor all cells are assumed to be a sphere of the same radius, the threshold density $\overline{u}$ corresponds to the close packing density of monodisperse mixture of spherulites; if the radii are different, then the threshold density $\overline{u}$ corresponds to a polydisperse

mixture of spherulites [28]. But in the reality the situation is much more complicated, because the dead cells occupy the other space than the living cells, and moreover, the shape of cells that are pressed by resulting pressures evoked during mitosis also produce deformable spheres, then (4.6) can be modified as

$$u = u_V + \varepsilon_1 u_D + \varepsilon_2 \left(u_C + u_{C_0}\right), \quad u_V = u_p + u_q,$$

where $\varepsilon_i \neq 0$ or $\varepsilon_i = 0$, $i = 1, 2$.

When a new tumor cells are generated (see Fig. 3.1), we saw that the pressures generate a motion of the neighboring cells. In absence of other phenomena, the new steady configuration will have $u = \overline{u}$ everywhere.

Let p be the pressure mentioned above, then it can be taken as a function of the local density of the cells u (see [28]). The pressure p is equal to zero for $u = \overline{u}$, that is, if the total density u is equal to the close packing overall density (threshold density); it is positive for $u > \overline{u}$, corresponding to the repulsive forces in compression; it is negative for $u < \overline{u}$, corresponding to the attractive forces among the cells (Fig. 4.2), u_M is the maximal density achieved by compressing the cells. Fig. 4.2 describes the pressure-overall density relation determining cell motion.

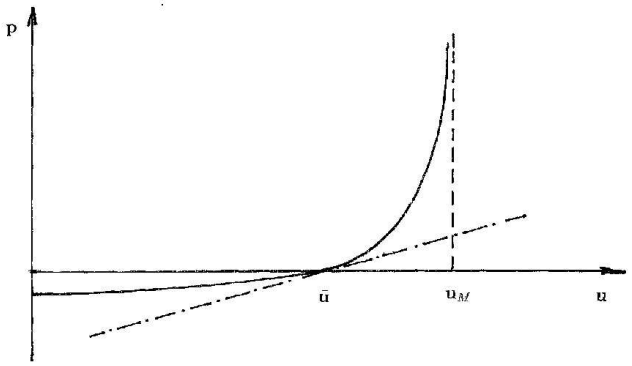

Figure 4.2: The pressure p as a function of the local density of the cells (modified after [28]).

Since in real situations u does not differ from the threshold density $\overline{u}$, then

$$p\left(u\right) = \gamma\left(u - \overline{u}\right),$$

where γ is the curve slope of $p\left(u\right)$ at the point $u = \overline{u}$. The velocity $\mathbf{v}$ of moving cells in the tumor, we denote it as $\mathbf{v}_T$, due to the phenomenological relation ([28])

$$h\mathbf{v}_T = -\nabla p = -p'\left(u\right)\nabla u,$$

where $p'\left(u\right)$ is a derivation of $p\left(u\right)$, can be written as

$$\mathbf{v}_T = -\frac{\gamma}{h}\nabla u, \tag{4.7}$$

being similar to the Darcy law. If the effective overall density u has a stationary point, that is, if $\nabla u = \mathbf{0}$, then $\mathbf{v}_T = \mathbf{0}$.

Due to the above assumptions, cells will proliferate if they have sufficient amount of nutriments u_N, that is, $u_N \geq \overline{u}_N u_V$, where $\overline{u}_N$ is a threshold of nutriment, and it is increasing with available nutriments, and it is decreasing under the presence of GIFs. Proliferation is made by mitosis of living tumor cells, then the growth term is proportional to the density of living tumor cells

$$\Gamma_T = \lambda_T u_V, \tag{4.8}$$

where λ_T is the nutriment uptake rate by proliferating tumor cells.

In the case, if the nutriment u_N is insufficient for nutriment of tumor cells, that is, $u_N < \overline{u}_N u_V$, where $\overline{u}_N$ is a threshold of nutriment, then tumor cells will die, and then a death coefficients L_T is defined as follows:

$$L_T = \lambda_D u_V,$$

where λ_D is a nutrient decay rate.

Evolution of avascular and vascular tumors

Next, we limit ourselves to model evaluation of avascular and vascular tumors only that being sufficient for our further investigations.

Let a tumor occupy a region $\Omega(t)$ with boundary $\partial\Omega(t)$ at time t and let $\Omega(t) = \Omega \times t$, $t \in [t_0, t_p] \equiv \overline{I}$, $\Omega = \Omega_V \cup \Omega_D \cup \Omega_H$, where Ω_V is a region occupied by a viable (living) part of the tumor, that is, a region, where nutriments, oxygen and glucose, are sufficient for a tumor cell viability; Ω_D is a necrotic region, that is, a region occupied by dead tumor cells and their cellular debris due to low nutriments and enzymes that break down to some wastes and water, and Ω_H is a region occupied by a healthy, non-cancerous, tissue (Fig. 4.1), which contains the extracellular matrix (ECM) and a mixture of non-cancerous cells, fluid, and cellular debris.

The nutriment is governed by the reaction-diffusion equation. Denoting by $D = D(\mathbf{x}, t)$ the nutrient diffusivity, by λ_V the nutrient uptake rate by proliferating tumor cells, by λ_D the nutrient decay rate and because in Ω_H there is only little cellular debris, therefore, we can assume that there is no nutrient decay in this region Ω_H and because tumor cells uptake nutrient at a greater rate than non-cancerous cells, then in Ω_H the nutrient uptake can be omitted. Then for the nutriment in $\Omega(t) = (\Omega_V \cup \Omega_D \cup \Omega_H) \times t$, $t \in [t_0, t_p]$, the governing equations in the case of **avascular tumors** are as follows

$$\varepsilon_0 \frac{\partial u_N}{\partial t} = \nabla \cdot (D \nabla u_N) - \lambda(\mathbf{x}, t)\, u_N, \quad \mathbf{x} \in \Omega, \quad t \in I, \tag{4.9}$$

where $u = (u_N, u_D, u_H)^T \equiv (u_p, u_q, u_D, u_H)^T$, and where for $t \in I$ the coefficient of nutriment diffusivity is defined as

$$D(\mathbf{x}, t) \equiv D = \begin{cases} D_V & \text{for } \mathbf{x} \in \Omega_V \equiv \{\mathbf{x} \in \Omega; u \geq \overline{u}\},\ D_V = \{D_p, D_q\},\ t \in I, \\ D_D & \text{for } \mathbf{x} \in \Omega_D \equiv \{\mathbf{x} \in \Omega; u < \overline{u}\},\ t \in I; \\ D_H & \text{for } \mathbf{x} \in \Omega_H \equiv \{\mathbf{x} \in \Omega \setminus \Omega_V \setminus \Omega_D\},\ t \in I, \end{cases} \tag{4.10}$$

where D_p is the coefficient of nutrient diffusivity in proliferating region of the tumor, D_q is the coefficient of nutriment diffusivity in quiescent region of the tumor, and where

$$\lambda(\mathbf{x}, t) \equiv \lambda = \begin{cases} \lambda_V, & (\mathbf{x}, t) \in \Omega_V(t) = \Omega_V \times I,\ \lambda_V = \{\lambda_p, \lambda_q\},\ \Omega_V = \Omega_p \cup \Omega_q, \\ \lambda_D, & (\mathbf{x}, t) \in \Omega_D(t) = \Omega_D \times I, \\ 0, & (\mathbf{x}, t) \in \Omega_H(t) = \Omega_H \times I = (\Omega \setminus \Omega_V \setminus \Omega_D) \times I. \end{cases} \tag{4.11}$$

Because nutrient diffusion (uptake, absorption) and decay all occur much more quickly than tumor growth, then $\frac{\partial u}{\partial t} \simeq 0$, and the problem can be studied as quasi-steady problem. In general $\lambda = \lambda(\mathbf{x}, t, u)$ because the region $\Omega_D = \Omega_D(u, t)$ depends on nutriment, therefore, it is a function of u and t. In practice the problem can be simplified by its linearization, that is, putting $\lambda_D = \lambda_V$, then $\lambda = \lambda_V$ in $(\Omega_V \cup \Omega_D) \times I$. In some models the ratio of the nutrient diffusion time scale T_{diff} to the tumor growth time scale T_{growth}, denoted as ε_0, is small as $\varepsilon_0 = \frac{T_{\text{diff}}}{T_{\text{growth}}} \ll 1$, because $T_{\text{diff}} \sim 1$ minute, $T_{\text{growth}} \sim 1$ day. In a general case of the model of tumor evolution Eq. (4.9) is a nonlinear equation, and therefore, the model is also nonlinear.

For **vascular tumors** Eq. (4.9) will be replaced by

$$\varepsilon_0 \frac{\partial u_N}{\partial t} = \nabla \cdot (D \nabla u_N) + \Gamma_B (u_{VT} - u_N) - \lambda u_N, \tag{4.12}$$

where u_{VT} is the nutrient density (concentration) in the vasculature, Γ_B is the rate of the blood-tissue transfer. The term $\Gamma_B (u_{VT} - u_N)$ represents the nutrient density (concentration) after the process of angiogenesis.

Let us denote by Σ_{TH} the boundary between the tumor and the healthy, non-cancerous, cellular tissues, and by Σ_{DV} the boundary between the necrotic (Ω_D) and viable cellular (Ω_V) tissues. Further, let us denote by $[w]^{sm} = w|_{\Omega_s} - w|_{\Omega_m}$ the jump across the boundary $\Sigma_{sm} = \Omega_s \cap \Omega_m$, $s \neq m$.

Let $\mathbf{n}$ be the outward unit normal across the boundaries Σ_{TH} and Σ_{CV}. Across these boundaries the nutriment and nutrient flux are continuous, that is,

$$\begin{array}{l} [u_N] = 0, \\ [D\nabla u_N \cdot \mathbf{n}] = 0, \end{array} \qquad \mathbf{x} \in \Sigma = \Sigma_{TH} \cup \Sigma_{DV}, t \in I. \tag{4.13}$$

In a sufficiently large distance from the tumor (that is, at the boundary $\sum_0$) the nutriment is constant, that is,

$$u_N = u_{N_0}, \quad \mathbf{x} \in \Sigma_0 \equiv \partial\left(\Omega_V \cup \Omega_D \cup \Omega_H\right), \tag{4.14}$$

as we can assume that nutrient delivery by the blood and uptake by non-cancerous cells are in balance outside the region $\Omega_V \cup \Omega_D \cup \Omega_H$.

The cells and the extracellular matrix in the host tissue Ω_H and the viable tumor tissue Ω_V are affected by a variety of forces, that is, these forces evoke the cellular velocity field $\mathbf{v}$. Proliferating tumor cells in Ω_V evoke hydrostatic stresses, called **oncotic mechanical pressure**, that also exert forces on the surrounding non-cancerous tissue in Ω_H. But tumor and non-cancerous cells as well as the extracellular matrix (ECM) can respond to these oncotic pressure variations by overcoming cell-cell and cell-extracellular matrix adhesion and moving within the skeleton (framework) of collagen and fibroblast cells (that is, created the ECM) that provided structure to the host tissue; the resulting ECM in Ω_H can be deformed in response to the oncotic pressure. Since these tissues are assumed to be a porous medium, then the response of the cells and the ECM to the oncotic pressures is described by the Darcy's law

$$\mathbf{v} = -\beta_m \nabla p, \quad \mathbf{x} \in \Omega_V \cup \Omega_H, \quad t \in I, \quad \beta_m = \beta_m(\mathbf{x}), \tag{4.15}$$

where $\beta_m > 0$ is the cellular mobility, measuring the overall ability of tissue to respond to the oncotic pressure as well as the permeability of the tissue to tumor cells. By the adhesion is meant a concrescence of neighboring tissues.

The outward normal velocity v_n of the tumor boundary Σ_{TH} is as follows

$$v_n = \mathbf{v} \cdot \mathbf{n} = -\beta_m \nabla p \cdot \mathbf{n}, \tag{4.16}$$

and similarly for Σ_{DV}. These outward normal velocities over Σ_{TH} and Σ_{DV} are assumed to be continuous across these boundaries, i.e., $[\mathbf{v} \cdot \mathbf{n}] = 0$. Next, we will see, that in the case of the boundary $\sum_{DV}$ this assumption is not wholly correct.

Due to proliferation of cells the number of tumor cells increases, and therefore, the volume of the viable region Ω_V also increases. But on the other hand, apoptosis decreases the total volume of the viable region Ω_V at a constant rate λ_{apt}. In the healthy tissue (Ω_H) birth and death of cells are practically to be in balance, so that, the total volume of the healthy region Ω_H is not changed [25]. The volume loss in Ω_D can be made due to the enzymatic breakdown of necrotic tumor cells throughout the necrotic core Ω_D at a constant rate λ_N. Thus

$$\int_{\sum_{DV}} \mathbf{v} \cdot \mathbf{n} ds = -\int_{\sum_{DV}} \left(\beta_m \nabla p \cdot \mathbf{n}\right) ds = -\lambda_N \left|\Omega_D\right|,$$

where $|\Omega_D|$ represents the volume of Ω_D and $\mathbf{n}$ is the normal to $\sum_{DV}$ with positive direction directed from Ω_V into Ω_D. Thus

$$\nabla \cdot \mathbf{v} = \begin{cases} \beta_m u_N - \lambda_{\text{apt}}, & \mathbf{x} \in \Omega_V, \\ 0, & \mathbf{x} \in \Omega_H, \\ -\lambda_N, & \mathbf{x} \in \Omega_D, \end{cases} \tag{4.17}$$

where β_{apt} is a constant related to the tumor cell mitosis rate. We saw above that the interface boundary Σ_{DV} between Ω_D and Ω_V is determined by the level of nutriments. Therefore, it is not a material boundary. To determine the correct volume change in the necrotic tumor region Ω_D the

extension of the velocity field $\mathbf{v}$ can be advantageously used, and moreover, the extension of the pressure continuously into the necrotic tumor region Ω_D will be assumed. Thus, we have

$$\begin{array}{ll} \mathbf{v} = -\beta_m \nabla p, & \mathbf{x} \in \Omega_D, \\ [p] = 0, & \mathbf{x} \in \Sigma_{DV}, \\ [-\beta_m \nabla p \cdot \mathbf{n}] = 0, & \mathbf{x} \in \Sigma_{DV}. \end{array} \tag{4.18}$$

The condition $[p] = 0$ across Σ_{DV} characterizes low cellular adhesion and it is consistent with increased cellular mobility observed in hypoxic cells. From conditions (4.18a,b,c) the condition $[\mathbf{v} \cdot \mathbf{n}] = 0$ on Σ_{DV} follows immediately. Moreover, conditions (4.18a,b,c) are satisfied for any C^1-smooth solution p.

Remark 2 *Tumor hypoxia is the situation where tumor cells have been deprived of oxygen. It can also be a result of the high degree of cell proliferation undergone in tumor tissue which causes a higher cell density and thus taxes the local oxygen supply ([16]).*

4.2 A free boundary problem modelling tumor growth

In this model problem we will assume that the tumors contain three types of cells: (i) proliferating cells with density $u_p(\mathbf{x}, t)$, quiescent cells with density $u_q(\mathbf{x}, t)$, and dead cells with density $u_D(\mathbf{x}, t)$. A death of living cells comes by (ii) apoptosis, representing certain self-destruction with ensuing suicide when it receives some signals from the outside, or when it becomes aware of unrepairable damage to its machinery, i.e., its DNA, (iii) necrosis, representing a death of living cells owing to an insufficiency (lack) of nutrients. Apoptosis decreases the total volume of the viable region Ω_V at a (constant) rate $K_A(u_N)$. The quiescent cells become proliferating at a rate $K_p(u_N)$ depending on the density (concentration) of nutrients u_N, and can be necrotic or can go into apoptosis at death rate $K_D(u_N)$. Moreover, we will assume that proliferating cells become quiescent at a rate $K_Q(u_N)$ and that their death rate is $K_A(u_N)$. The density of proliferating cells increases due to proliferation at a rate $K_B(u_N)$. We also assume that dead cells are removed from the tumor, because of their decomposition, at a constant rate K_R.

We saw that proliferation and removal of cells evoke a continuous motion of cells within the tumor, which we denoted by $\mathbf{v}$. To derive the governing equations the conservation of mass laws for the densities of the proliferating cells u_p, the quiescent cells u_q, and the dead cells u_D within the tumor region $\Omega_T(t) = \Omega_D(t) \cup \Omega_V(t) = \Omega_D(t) \cup \Omega_p(t) \cup \Omega_q(t)$ are used, and then we have

$$\begin{aligned} \frac{\partial u_p}{\partial t} + div(\mathbf{v}_p u_p) &= (K_B(u_N) - K_Q(u_N) - K_A(u_N)) u_p + K_p(u_N) u_q \text{ in } \Omega_V(t), \\ \frac{\partial u_q}{\partial t} + div(\mathbf{v}_q u_q) &= K_Q(u_N) u_p - (K_p(u_N) + K_D(u_N)) u_q \text{ in } \Omega_V(t), \\ \frac{\partial u_D}{\partial t} + div(\mathbf{v}_D u_D) &= K_A(u_N) u_p + K_D(u_N) u_q - K_R u_D \text{ in } \Omega_D(t) \end{aligned} \tag{4.19}$$

where $\mathbf{v}_p$ and $\mathbf{v}_q$ are the velocity of proliferating cells and quiescent cells and $\mathbf{v}_D$ is the velocity due to removal of cells. The functions $K_B(u_N)$, $K_Q(u_N)$, $K_p(u_N)$ and $K_D(u_N)$ can be defined, e.g., as linear functions:

$$\begin{aligned} K_B(u_N) &= k_B u_N; \quad K_Q(u_N) = k_Q(u_{N0} - u_N); \\ K_p(u_N) &= k_p u_N; \quad K_D(u_N) = k_D(u_{N0} - u_N), \end{aligned} \tag{4.20}$$

where $u_{N0} = const. > 0$, and the coefficients k_B, k_Q, k_p and k_D can be defined as follows

$$k_B = 1;\ k_Q = 0.9;\ k_p = 0.05;\ k_D = 0.1.$$

The velocities $\mathbf{v}_p$ and $\mathbf{v}_q$ are mutually related by the relation ([26])

$$\mathbf{v}_q = \mathbf{v}_p + \chi \nabla u_N,$$

where χ is a chemotactic sensitivity coefficient and is assumed to be a nonnegative constant. This last assumption is based on some evidence that proliferating cells seem to be less motile as they undergo mitosis ([58]). Introducing $u_p + u_q + u_D = N$ (i.e., numbers of proliferating, quiescent and dead cells per unit volume, that is, their densities), that is, the cell density within the tumor is constant, say N, then we can introduce the mean velocity as

$$\mathbf{v} = \frac{1}{N}\left(u_p \mathbf{v}_p + u_q \mathbf{v}_q + u_D \mathbf{v}_D\right),$$

and using (4.19a,b,c) we have

$$\nabla . \mathbf{v} = \frac{1}{N}\left(K_B\left(u_N\right) u_p - K_R u_D\right) \quad \text{in } \Omega\left(t\right).$$

Remark 3 *Assuming that the velocity field in a tumor is uniform, then* $\mathbf{v}_p \equiv \mathbf{v}_q \equiv \mathbf{v}_D \equiv \mathbf{v}_T$.

Nutrient (oxygen and glucose) with concentration u_N is diffusing in $\Omega_T\left(t\right)$ and affects the transition of cells from one type of cells to another, that is,

$$\begin{array}{ll} u_p \to u_q & \text{at rate } K_Q\left(u_N\right), \\ u_q \to u_p & \text{at rate } K_p\left(u_N\right), \\ u_p \to u_D & \text{at rate } K_A\left(u_N\right), \\ u_q \to u_D & \text{at rate } K_D\left(u_N\right), \\ u_p \to u_p & \text{at rate of proliferation } K_B\left(u_N\right). \end{array}$$

Necrotic cells are removed from the tumor at constant rate K_R.

For simplicity we can put $\beta_m = 1$ in (4.15) and $N = 1$. Thus

$$\mathbf{v} = -\nabla p, \quad p \text{ is a pressure.}$$

Let us assume that the total density is constant

$$u_p + u_q + u_D = \text{const} = 1.$$

Adding (4.19a,b,c), then

$$-div\left(\nabla p\right) \equiv -\Delta p = K_B\left(u_N\right) u_p - K_R u_D.$$

We can eliminate the equation for u_D putting

$$u_D = 1 - u_p - u_q$$

in the equation for p. Then

$$\Delta p = -K_B\left(u_N\right) u_p + K_R\left(1 - u_p - u_q\right) = -\left(K_B\left(u_N\right) + K_R\right) u_p - K_R u_q + K_R = -h\left(u_N, u_p, u_q\right). \tag{4.21}$$

Then Eq. (4.9), Eqs (4.19a,b,c) and Eq. (4.21) lead to the following system of equations in $\Omega_T, t > 0$ ([42]):

$$\begin{aligned} \varepsilon_0 \frac{\partial u_N}{\partial t} &= \nabla \cdot \left(D_V u_N\right) - \lambda\left(\mathbf{x}, t\right) u_N, \quad \mathbf{x} \in \Omega_T,\ t > 0, t \in I, \\ \frac{\partial u_p}{\partial t} - \nabla p \cdot \nabla p &= f\left(u_N, u_p, u_q\right), \quad \mathbf{x} \in \Omega_T,\ t > 0, t \in I, \\ \frac{\partial u_q}{\partial t} - \nabla p \cdot \nabla q &= g\left(u_N, u_p, u_q\right), \quad \mathbf{x} \in \Omega_T,\ t > 0, t \in I, \\ \Delta p &= -h\left(u_N, u_p, u_q\right), \quad \mathbf{x} \in \Omega_T,\ t > 0, t \in I, \end{aligned} \tag{4.22}$$

and where

$$\begin{aligned} f\left(u_N, u_p, u_q\right) &= \left[K_B\left(u_N\right) - K_Q\left(u_N\right) - K_A\left(u_N\right)\right] u_p + K_p\left(u_N\right) u_q - h\left(u_N, u_p, u_q\right) u_p, \\ g\left(u_N, u_p, u_q\right) &= K_Q\left(u_N\right) u_p - \left[K_p\left(u_N\right) + K_D\left(u_N\right)\right] u_q - h\left(u_N, u_p, u_q\right) u_q, \\ h\left(u_N, u_p, u_q\right) &= \left[K_B\left(u_N\right) + K_R\right] u_p + K_R u_q - K_R. \end{aligned}$$

On the boundary $\Sigma_{TH} = \partial\left((\Omega_V \cup \Omega_D) \cap \Omega_H\right)$ we have the following conditions

$$\begin{aligned} u_N|_T = u_N|_H = \overline{u}_N \quad & \text{on } \Sigma_{TH}(t),\ t > 0, \\ [p]_T^H = s_0\mathcal{K} \quad & \text{on } \Sigma_{TH}(t),\ t > 0, \\ [\beta_m \nabla p \cdot \mathbf{n}]_T^H = \left[\frac{\partial p}{\partial n}\right]_T^H = -v_n \quad & \text{on } \Sigma_{TH}(t),\ t > 0, \end{aligned} \tag{4.23}$$

where $\overline{u}_N$ is a concentration of nutrients, s_0 is the surface tension coefficient, $\mathcal{K}$ is the mean curvature. The condition (4.23b) shows that the surface tension maintains a compact solid tumor together, and it is attributed to cell-to-cell adhesiveness. The condition (4.23c) represents the kinematic condition ([18]), i.e., Eq. (4.16).

Cellular proliferation and death at a distance sufficiently far away from the tumor, that is from the boundary $\partial\Omega_{TH}$, we denoted it as Σ_0, then

$$p = p_{\Sigma_0}, \quad (\mathbf{x}, t_0) \in \Sigma_{0t_0}. \tag{4.24}$$

On the boundary Σ_{DV} we have the conditions

$$\begin{aligned} \mathbf{v} = -\beta_m \nabla p, \quad & (\mathbf{x}, t) \in \partial\left(\Omega_D \cap \Omega_V\right) \times I = \Sigma_{DV} \times I; \\ [p] = 0, \quad & (\mathbf{x}, t) \in \Sigma_{DV} \times I, \\ [-\beta_m \nabla p \cdot \mathbf{n}] = 0, \quad & (\mathbf{x}, t) \in \Sigma_{DV} \times I. \end{aligned} \tag{4.25}$$

The condition (4.25c) automatically satisfies $[\mathbf{v} \cdot \mathbf{n}] = 0$, $(\mathbf{x}, t) \in \Sigma_{DV} \times I$. The condition (4.25b), that is, the jump of p across Σ_{DV} models low cellular adhesion and is consistent with an increased cellular mobility, known in the case of hypoxic cells (see [56, 72])).

Moreover, the initial conditions

$$\begin{aligned} u_N(\mathbf{x}, t_0) = u_{N0}(\mathbf{x}) \quad & \text{in } \Omega(0),\ u_{N0}(\mathbf{x}) \geq 0, \\ u_p(\mathbf{x}, t_0) = u_{p0}(\mathbf{x}) \quad & \text{in } \Omega(0),\ u_{p0}(\mathbf{x}) \geq 0, \\ u_q(\mathbf{x}, t_0) = u_{q0}(\mathbf{x}) \quad & \text{in } \Omega(0),\ u_{q0}(\mathbf{x}) \geq 0, \\ u_D(\mathbf{x}, t_0) = u_{D0}(\mathbf{x}) \quad & \text{in } \Omega(0),\ u_{D0}(\mathbf{x}) \geq 0, \end{aligned} \tag{4.26}$$

and where $u_{p0}(\mathbf{x}) + u_{q0}(\mathbf{x}) + u_{D0} = N\ (\equiv 1)$.

The problem (4.22)-(4.26) is studied in a simpler case by Cui and Friedman ([26]) and Friedman ([42]). They assume the radially symmetric tumor, containing only living cells. In this special case of two types of cells, proliferating and quiescent, they proved that there exists a unique spherically symmetric stationary solution of the problem.

In Section 3 about cancer evolution we saw that two important factors (from many chemical factors produced by tumor cells), which diffuse both in the tumor tissue as well as in the surrounding tissue in a space and time, are meaningful. These two main factors, the growth inhibitory factor (GIF) and the tumor angiogenesis factor (TAF), in the surrounding tissue evoke a tumor angiogenesis phase of tumor evolution. Let us denote by u_{GIF} the density of GIF and by u_{TAF} the density of TAF. Active tumor cells produce both chemical factors GIF and TAF by constant rates γ_{GIF} and γ_{TAF} and decay at rates δ_{GIF} and δ_{TAF} and they move by random movements inside the tumor region Ω_T and diffuse into the neighboring tissue region Ω_H. Namely the diffusion of TAF is important in the role of generation of new capillaries (see Fig. 3.3c) during the angiogenesis phase of tumor evolution. When the endothelial cells interact with the TAF factor, they proliferate and the new-born cells tend to migrate towards the source of TAF with formation of capillary sprouts by accumulation of endothelial cells. We will assume that the diffusion mechanisms of both factors are the same, and therefore, the coefficient of diffusion is also the same, we denote it as $K_{GT}(u)$, and in general it depends on the effective overall density. Moreover, it is different inside and outside the tumor.

The evolution of GIF and TAF are described by

$$\begin{aligned} \frac{\partial u_{\mathrm{GIF}}}{\partial t} &= \nabla \cdot \left(K_{\mathrm{GT}}(u) \nabla u_{\mathrm{GIF}}\right) + \gamma_{\mathrm{GIF}} \chi_T u_V - \delta_{\mathrm{GIF}} u_{\mathrm{GIF}}, \\ \frac{\partial u_{\mathrm{TAF}}}{\partial t} &= \nabla \cdot \left(K_{\mathrm{GT}}(u) \nabla u_{\mathrm{TAF}}\right) + \gamma_{\mathrm{TAF}} \chi_T u_V - \delta_{\mathrm{TAF}} u_{\mathrm{TAF}}, \end{aligned} \tag{4.27}$$

where $\chi_T = \chi_T(\mathbf{x}, t)$ is the characteristic function of $\Omega_T(t)$. In a special case, in which the diffusion coefficient K_{GT} is constant, we denote it as k_{GT}, then

$$\begin{aligned}\frac{\partial u_{\mathrm{GIF}}}{\partial t} &= k_{\mathrm{GT}}\Delta u_{\mathrm{GIF}} + \gamma_{\mathrm{GIF}}\chi_T u_V - \delta_{\mathrm{GIF}} u_{\mathrm{GIF}},\\ \frac{\partial u_{\mathrm{TAF}}}{\partial t} &= k_{\mathrm{GT}}\Delta u_{\mathrm{TAF}} + \gamma_{\mathrm{TAF}}\chi_T u_V - \delta_{\mathrm{TAF}} u_{\mathrm{TAF}},\end{aligned} \tag{4.28}$$

where γ_{GIF} is the production coefficient of GIF from living tumor cells, γ_{TAF} is the production coefficient of TAF from living tumor, δ_{GIF} is the degradation coefficient of GIF, δ_{TAF} is the degradation coefficient of TAF. Since TAF diffuses from the solid tumor into the tumor-free neighboring region Ω_H the endothelial cells interact with the TAF, thus these cells proliferate and the new-born cells migrate towards the source of angiogenic stimulus and the accumulated endothelial cells formate capillary sprouts, which further in the next phase develop the vascular system of the tumor.

The balance equation then leads to

$$\frac{\partial u_c}{\partial t} + v_c\nabla\left(u_c\nabla u_{TAF}\right) = k_c\triangle u_c + \gamma_c u_{TAF}\left(\overline{u}_c - u_c\right)_+\left(u_c + \hat{u}_c\right) - \delta_c u_c, \tag{4.29}$$

where u_c is the density of new capillaries, and where we assumed that the diffusion and drift terms are constant, and where

$$(f)_+ = \begin{cases} f & \text{for } f > 0;\\ 0 & \text{otherwise.}\end{cases}$$

The second term on the left-hand side is the drift term, which, in general, is given by $\mathbf{v}_c = v_c(u)\nabla u_{\mathrm{TAF}}$ and is directed towards the source of angiogenic stimulus, and the second term on the right-hand side represents the growth term, that is, $\Gamma_c = \gamma_c u_{\mathrm{TAF}}\left(\overline{u}_c - u_c\right)_+\left(u_c + \hat{u}_c\right)$, where $\hat{u}_c = \hat{u}_c(\mathbf{x})$ represents the density of pre-existing capillaries, which is time-independent, fixed in space and naturally space dependent, $\overline{u}_c$ is the threshold overall density above which capillaries are not generated, k_c is the diffusion coefficient of capillary sprouts, v_c is the migration coefficient of capillary sprouts towards the source of angiogenic stimulus, δ_c is the natural death coefficient of endothelial cells, γ_c is the proliferative coefficient of capillary sprouts.

When the tumor is developed then the nourishment is made by the diffusion of nutriment inside the tumor though the capillaries. Therefore, the coefficient of diffusion depends on u_c and increase with increasing of u_c. The balance equation under the existence of the uptake from the living tumor cells then gives

$$\frac{\partial u_N}{\partial t} = \nabla\cdot\left(\left(k_E + k_N\left(u_c + \hat{u}_c\right)\right)\nabla u_N\right) - \delta_N u_V u_N \quad \text{in } \Omega_T, \tag{4.30}$$

where u_N is the density of nutriment, u_c is the density of new capillaries, $\hat{u}_c$ is the density of the pre-existing capillaries from which new capillaries start to generate, u_V is the density of living tumor cells, k_E is the diffusion coefficient of nutriment outside the capillary network inside the tumor, k_N is the diffusion coefficient of nutriment through the capillary network inside the tumor and δ_N is the absorption coefficient of nutrient from active tumor cells. Outside Ω_T, that is, in Ω_H, the capillary network is assumed to increase linearly with its density. So that on $\sum_{TH} = \partial\Omega_T \cap \partial\Omega_H$ the corresponding interface condition can be written as

$$u_N = \varepsilon_N + \beta_N\left(u_c + \hat{u}_c\right) \quad \text{on } \partial\Omega_T \cap \partial\Omega_H = \Sigma_{TH} \quad \text{or on its part,} \tag{4.31}$$

where ε_N and β_N are some constants.

Remark 4 *The state variables u_{GIF}, u_{TAF} and u_c are defined in the whole environment $\Omega(t)$, while the variables u_V, u_D and u_N are defined in the tumor $\Omega_T(t)$.*

Remark 5 *The free boundary problems were studied, e.g., by Chen and Friedman [22], Bazaliy and Friedman [8], Friedman [41, 42] and many others.*

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