Chapter 1

1 Introduction

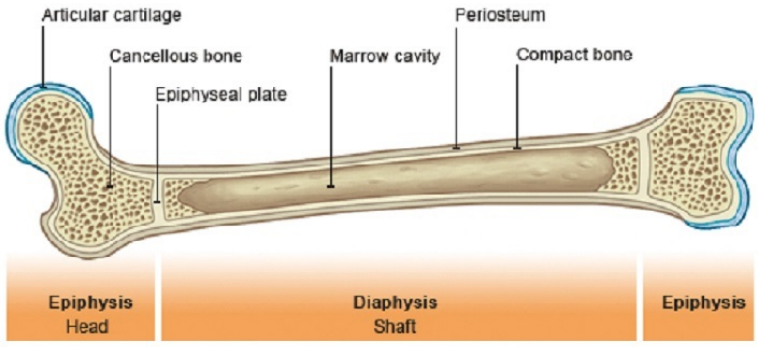

Figure 1: Bone Structure

Bone in our body is a living tissue that remains to be worked out and repair itself throughout our life [18, 57]. Experimental results show that collagen strands and lifeless bone minerals cover about 60-70 percent area of the bone at a local site, while remaining proportion carries water [41, 28]. An infant body contains 270 bones while an adult skeleton is made of 206 bones, this happens due to the continuous process of bone resorption and formation. There are two forms of bone called cortical and trabecular (also known as cancellous) [22]. Cortical bone is an external layer of bone which is hard and thick, whereas a spongy and soft structure lying inside the bone is called trabecular bone [40, 33]. The main functioning of the bone includes the support to body and provides the base to marrow. There are numerous kinds of bone cells [29] but mainly three cells named as osteoclast (C),osteoblast (B) and osteocytes take part in the functioning and maintenance of bone. The main activity of osteoclast includes the resorption of mineralized tissues while osteoblasts are bone forming cells. Osteocytes are bone cells lying at

the deep rooted area of bone.

Osteoclasts(C)

Osteoclasts were firstly introduced by Kolliker in 1873. Osteoclasts are polynuclear (more than one nucleus) cells that prolifirate from one cell type to another known as macrophage [25]. It a clinical apparatus which is used for break bones [10, 14]. They are released from marrow and are concerned with white blood cells. They are composed of many cells which make a mesh together that's why they are multinuclear cells. They live on the external layer of bone and resorb bone. Osteoclasts produce digestive enzymes that help them in bone resorption. The concentration of osteoclasts is very rare and only 2-3 cells reside per mm of bone.

Osteoblasts(B)

Osteoblasts are the main cellular part of bone. Osteoblasts turns the plasma into mineral form in bone making process [40]. The mass of bone is preserved in the equilibrium form by the balanced concentration of osteoblasts (bone forming cells) and the osteoclasts (bone resorbing cells) [74]. An osteon is a group of systematized osteoblastic cells which is composed by a unit of bone cells [18].

Osteoblasts are the special cells which provide different products to the mesenchymal stem cells that make bone dense, and by further process they make the organic matrix of bone.

Osteocytes

An osteocyte is a star shaped cell and oftenly found cell in the adult bone cells, and live with the organism till its end. There are approximately 42 billion osteocyte cells in the mature human body. The average half life of these cells is about 25 years and there is no further divisibility in these cells. The osteocytes come from

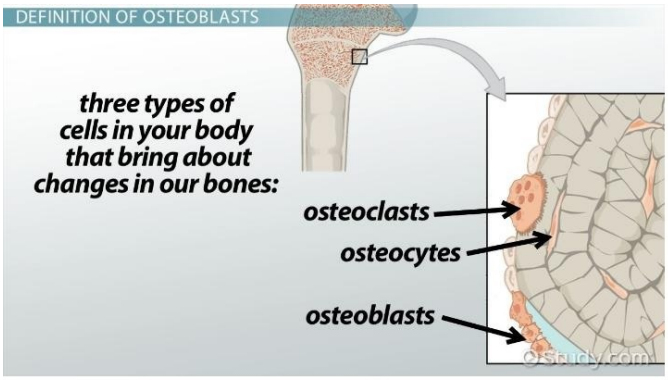

Figure 2: Bone Cells

osteoprogenitors from which some cells are segregate into active osteoblasts. When the bone becomes aged and perfect then the osteocytes and their progressions live inside the spaces which are known as lacunae [27]. Osteocytes are joined to each other through lengthy cytoplasmic linkages that have small canals known as canaliculi, that are used to interchange the minerals and waste via gap stations [42]. They are mostly involved in regular turnover of bone via several mechanisms. They resorb the bone through rapid mechanism.

1.1 Bone Remodeling

Bone guarantees redesigning for the duration of whole life in spatially and transiently discrete destinations in an organized procedure including resorption trailed by formation of new bone [53, 38, 63]. Bone remodeling is accountable for development and mechanically instigated adaptation of bone and entails the processes of bone formation and resorption, however globally correlated, take place separately at anatomical different sites [56]. Such tightly correlated event needs the harmonized activities of multicellular components to confirm that bone removal and making takes place successively at the identical anatomical place to preserve bone volume [10]. One of the major functions of bone is to redesign for the

whole life-time period in spatially and temporarily distinct destinations as a well-organized procedure which includes resorption by C, straggled on account of the arrangement of new bone by B [4]. There are multifarious elements which proffer paracrine coupling among C and B and exclusively autocrine circles for the sake of input of each cell type whether positive or negative [42]. Pro-resorptive cytokine receptor activator of atomic factor B Ligand and its bait receptor OPG [26] are included among the most paramount ingredients, which are transmitted by B and C [10]. There are various elements which carry TGF-β that is released and enacted through resorbing C and affects C and B and IGF which is further discharged by B and from the lattice through resorbing C, that strengthens and develops B [71]. The process of remodelling is carried out due to B and C activities and disabilities and deteriorations like micro-fractures are established again through coupling as shown in figure 3.

The procedure that usually controls the mechanical characteristics of vertebrate bone is called renovating which takes place intermittently at various locales in the development of skeleton [48]. It also includes the unpredictable exchange of three multifarious cell kinds. The redesigning of bone is a perpetual dynamic strategy in which more settled bone tissue is taken out of the skeleton by C and new bone cell is generated by B [2]. In case a remodelling bone imbalance is still there after the completion of a rejuvenating cycle, the deterioration of bone will get worse resulting in osteoporosis [41] In the remodelling process of bone, one of the core issues is osteoporosis which triggers expensive therapeutic medication. Bone mass reduction is a bone disease which is caused by a net addition of bone resorption over bone formation [18]. There are certain medications which are specifically made for the treatment of osteoporosis such as calcium or vitamin D, estrogen, bisphosphonates and denosumab . In a homeostatic coordination, resorption and development are settled with the purpose that the old bone is

consistently replaced and substituted by new bone cell so that it may have adapted to mechanical cumbrance and laceration. Both B and C are almost incorporated in the remodelling process at BMU. Bone is possessed of multifarious capacities in vertebrates which also includes various significant organs and hematopoietic marrow, special support for muscles and the potential of different particles such as calcium and progressive factors are set into the lattice. Bone gets recuperated in the developed skeleton in a constant manner on account of a variety of boosts in the process of bone remodelling. It involves emptying of cavities or the bone passage ways from the surfaces of hard and spongy bones, separately by C [10]. In this way, B is filled out in these cavities by setting down a fresh bone network. This kind of progression is same like what happens in the trabeculae form in the strengthening of endochondral but not same like when resorption excels in its arrays for the development of medullary hole inside bone. Finally, the development in a bone tallies resorption amongst the process of bone remodelling. It stands without any doubt that the procedures which are responsible for bone remodelling are yet not elaborated with clarification. However, they tend to affect adversely some parts of a bone, and in the process, mechanical powers which follow amendments, fit in accordance with weight and exercise and nearly approaching of cytokines of the progress factors owing to sequential adjustments in the basic hormonal levels. It is a strongly established procedure which takes place after resorption in the targeted area of bone and there are approximately one million foci for redesigning of the skeleton of an adult. According to the recent investigations, it has been proven that in the event of mechanical powers, osteocytes give direction to the enrolment of C towards the destinations of bone resorption by inspiring the declaration of RANKL by B tissues in the close-lying smaller scale condition [20]. Despite this propelling, the precise sub-atomic components which monitor the initiation, movement and the closing of redesigning at any designated area remain inefficiently help up.

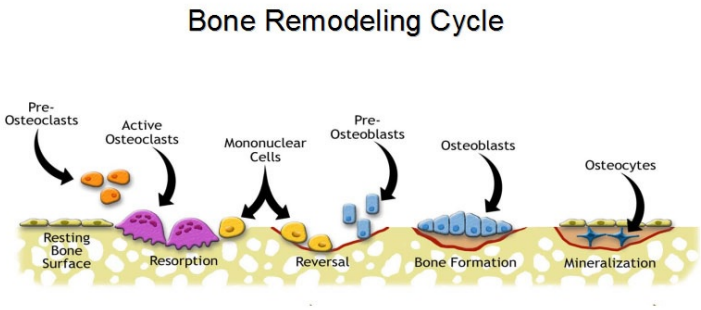

Figure 3: Bone Remodeling process

Osteocytes are categorically sifted out B which are twisted plainly and put up in the osteoid grid in which they were setting down. They remain intact with each other and with B tissues on the surface of overlying bone and by them with B tissues in the bone marrow cavity [11].

1.2 Communication between Osteoclasts and Osteoblasts

As discussed in previous section, two cells mainly responsible for remodeling process are osteoclasts and osteoblasts. The key role of both kinds of cells is quite opposite; osteoclasts are bone resorbing cells, while osteoblasts function as bone forming cells [56, 2]. Osteoclasts are lethally differentiated myeloid multinucleated osteoclast precursors that are exclusively transformed to eradicate mineralized bone milieu. Precursors of osteoclasts flow in the blood and bone marrow and adult osteoclasts are produced from synthesis of the precursors. Such evolution takes place after the signaling through receptor activators of NF-$\kappa\beta$ and its ligand. During bone resorption, osteoclasts append to the bone and develop tight seals with the underlying bone matrix in roughly circular extensions of their cytoplasm, and within these sealed zones they form ruffled border membranes [56]. By this sealing and secretory means, the bone matrix is concurrently degraded and bone

minerals are dissolved [18], while protecting neighboring cells from the harmful effects of HCl. Osteoblasts are mono nucleated cellular units derived from osteoblast precursors. They are responsible for manufacturing of the major proteins of bone as well as type 1 collagen like osteocalcin and osteopontin, which compile the organic milieu of bone. These cells are also accountable for the mineralization of bone and fabricate enzyme alkaline phosphates. Recent investigations exhibit the role of osteoblasts as an imperative component in governing osteoclastogenesis [77]. Another type of bone cells namely osteocytes, a latent state of osteoblasts, also participate in bone maintenance and mineralization. Many therapies of different bone disorders effect through osteocytes [40].

1.3 RANK-RANKL-OPG Signalling Pathway

Various growth factors give paracrine coupling amongst C and B and additionally autocrine cycles for positive and negative input control every cell kind. The most essential components are the proresorptive cytokine receptor activator of nuclear factor β ligand (RANKL) and its decoy receptor osteoprotegerin (OPG), which are communicated by B and corresponding control of C [70, 51]. Complex formation of OPG and RANK with RANKL give anabolic and catabolic effects on bone, respectively. Several other elements like transforming growth factor-β (TGF-β) and parathyroid hormone (PTH) also incorporate in such phenomena [73]. Both C and B are the main cells which are oftenly involved in bone turnover. These cells plays counter action on bone cells , earlier they resorb bone and after resorbing they form bone cells [61]. The stability between the forming and resorbing of bone tissues is crucial to maintain the mass of the bone. Formation of bone goes through four phases namely: stimulation of osteoclast precursors, absorption of bone, reversal C inhibition, and stimulation of osteoblast precursors. Hence the osteoclast genesis is the start of whole process [2]. C are derived from hematopoitic

and degrade bone mass in different separating processes. First of all, a process starts in which osteoblastic precursors multiplied to each other and form a long chain and placed itself on the bone's surface, where other factors like cytokine, hormones and TGF-β stimulates and activate C [65]. When C are stimulated they start resorbing the bone mass and make holes on bone surface. In the third step of the cycle, the death of the osteoclasts procurers starts which stimulates B precursors and bone rebuilding process starts. When new bone is achieved then it normalises its mineralization [41].

Once new bone is formed then the osteoblasts precursors generates osteocytes or convert into bone apparent tissues. The imbalance of resorbing bone turnover goes during the whole life [30]. Osteoporosis is a bone disease which occur when the bone mass is continuously degraded and brings bone in breakable condition which increase the danger of bone fracture, particularly hip, vertebral and prime fractures which may cause decrease in the sovereignty and improved morality in ageing. A main significant approach is obtained to stop the absorption of bone mass. A precarious signalling network consisting of three main factors OPG, RANK, and RANKL was introduced for the cellular bone formation process. OPG was firstly introduced in 1997 First time OPG was found in the mice cells which is in the form of arbitrary clones together with long chain of genes that was confirmed to encrypt a new bone receptor namely tumour necrosis factor (TNF). OPG is the part of TNF receptor family, it is typical because it released some secretions from the trans-membrane region. It consists of four homologous regions to complete its objective i.e RANKL. There are many kinds of tissue produced by OPG like B, endothelial cells, vascular smooth muscle and many other cells rising the query of this protein in the bone mass regulation. It has been recognised that for the activation of B a protein osteoclastogensis required by two freshly well-known molecules that are RANKL and macrophage colony-stimulating factor (M-CSF). These are necessary

for the activation of genes which are permitting the transcription of C separation. RANKL is also an other supporter of TNF ligand group. It is the production of B networking cell chain and they stimulate the T-cells [46]. RANKL and M-CSF are the corresponding actions. M-CFS proliferate the group of C precursors and RANKL fixes its receptor RANK which communicate with the C precursors and developed C which increase the differentiation of C, and stimulates the activation of RANK by preventing its apoptosis [20]. The RANKL was introduced in late 90s and plays an important role for the transduction of RANKL signals.

1.4 Transforming Growth Factor-β (TGF-β)

Multiple and dispensable activities of TGF-β family incorporate monitoring of various characteristics and outcomes of cell functions, including growth, prolifiration, and dispersal, in all organisms of the human body. TGF-β plays a vital role in administrating the perpetuation of bone metabolic homeostasis [39]. TGF-β is discharged and enacted by resorbing osteoclasts and gives an anabolic effects on bone by directly influencing the osteoblasts [52, 83]. Although TGF-β directly takes part in the emergence of osteoclasts during the latent state of osteoblasts but hinders bone removal by diminishing the expression of RANKL on osteoblasts [45]. TGF-β is a polyfunctional protein that belongs to a family that have four isomers namely (TGF-β1, TGF-β2, TGF-β3, TGF-β4) [61, 16, 49]. The main function of these four factors and many other networking proteins is to produce white blood cell meshes in the body. In order to make serine enzyme TGF-β merge to other factors that fixes TGF-β receptors that is the composition of β1 and β2 precursors [48]. After the composition of TGF-β, it plays a bi-directional role such that the precursers of β1 stimulates the β2 receptors that stimulates a networking flow which tends the stimulation of different substrate and and regulation of protein. TGF-β plays a cruicel role in bone remodling. The bone morphogenetic

protein (BMS) which is also the member of TGF-β superfamily highly activates the osteoblast precursers in bone formation. As we described above that TGF-β plays a bi-directional way so it also stimulates the osteoclast precurcers in bone resorption. TGF-β also plays an important role in the metastasis of cancer of bone resorption. So, the specific role of TGF-β in osteoclasts and bone resorption seems to be fairly complicated.

1.5 Parathyroid Hormone (PTH)

The parathyroids produce a hormone called parathyroid hormone (PTH) [33]. The parathyroid glands are placed within the neck, simply behind the butterfly-shaped ductless gland [21]. Parathyroid hormone is secreted from four parathyroid glands, that are the smallest glands in this neck area, set behind the ductless gland, and the size of these four tiny glands is about the grain of rice and weighs close to 30 milligram and 3-4 millimeters in diameter [13]. Parathyroid hormone are responsible for the regulation of calcium level in the blood, largely by increasing the levels when they are too low. It does this through its actions on kidneys, bones and intestine:

1. Bones: PTH stimulates the discharge of Calcium (Ca) from messavi calcium stores within the bones into the blood. This will increases bone destruction and reduces the formation of latest bone [50].

2. Kidneys: PTH reduces loss of Ca in water. PTH additionaly stimulates the assembly of active vitamin-D in kidneys [5].

3. Intestine: PTH indirectly increases Ca absorption from food within the intestine, via its effects on vitamin-D metabolism.

Parathyroid hormone is generally controlled by the negative feedback of Ca levels within the blood to the PTH secretions, where low Ca level in the blood stimulate PTH secretion, whereas high Ca levels within the blood stop the dis-

charge of PTH.

A primary drawback within the PTH, manufacturing an excessive amount of PTH causes raised Ca levels within the blood (hypercalcaemia) and this is often cited as primary gland disease. There is an identical but rare condition known as tertiary hyper parathyroidism that causes hyper calcaemia because of additional PTH production on the rare drop of all four glands being active. Secondary hyper parathyroidism arises in response to low blood Ca levels and is caused by alternative mechanisms, for example, renal disorder and vitamin-D deficiency. Mild primary hyper parathyroidism often causes few, if any symptoms and is usually diagnosed by finding a high Ca concentration on a routine biopsy. Treatment could also be surgical removal of the affected gland(s) (parathyroidectomy). Furthermore, on the symptoms for every condition will be found within the individual articles.

Too little PTH or hypo-parathyroidism, may be a rare medical condition. It may end up in low levels of Ca wthin the blood (hypo-calcaemia) [23]. It's typically treated medically with oral Ca and vitamin-D analogues however, the provision of PTH replacement medical aid might amendment the approach to treatment for few patients.

The four endocrine glands create additional or less PTH in response to the extent of calcium within the blood. If the ca in our blood goes too low, the endocrine glands produce additional PTH. Increased in the concentration of PTH causes the more ca into the blood. Hence,The parathyroid glands are four tiny glands, located in the neck, that control the body's calcium levels.

PTH employs typical actions on bone metabolism by triggering its receptor on target cells [32, 19]. Its main functioning includes calcium regulation. PTH has dual effects on bone turnover process. Constant exposure to PTH gives a negative feedback, while sporadic contact to low quantity of PTH is coupled with positive

effects. A number of studies have been conducted to investigate the effect of PTH drug in dysregulated bone remodeling and showed anabolic effects on bone.

1.6 Sclerostin

Sclerostin, encrypted by SOST gene, is an extravasated glycoprotein expressed by osteocytes [8, 76, 69]. It is a C-terminal cysteine knot-like (CTCK) domain and has resemblance to the DAN family of bone morphogenetic protein (BMP) antagonists. Animal's models have been found potentially valuable for investigating sclerostin for the reason that it has high conservancy over vertebrates (the percentages of the sequences of amino acids measured in the mouse and rate are 88 and 89, respectively which are quite similar to human sequences) [8]. Binding of sclerostin to its coreceptors expressed on the surface of osteoblasts constrains the Wntβ-catenin signaling [17], consequently suppressing differentiation, production and undertakings of osteoblastic cells [65]. Experimental study on SOST knockout mice showed high levels of bone mass phenotype [60], whereas the results were rather contrasting i.e., a low mass phenotype were observed in a transgenic mice with an over expression of SOST gene [77]. Therefore, osteoblast movement is self-synchronized by a negative feedback setup.

1.7 Mechanical Stress

Poroelasticity is the study based on the relation among deformation and fluid flow in a fluid drenched malleable medium [3]. Main activities of bone fluid include the transportation of nutrients to cells engrossed in medium and moving waste of cells away [22]. It also provides minerals to bone tissue for relocation. Mechanosensory system of bone and bone fluid both are strongly interconnected [55, 81]. Mechanical stress plays a vital role in supplying the bone fluid. Mechanical strain supports the bone deformation process which in turn produces the fluid flow [59, **?**]. Bone

cells also get affected through such mechanism of mechanical strain [68, 15]; it helps in maintaining the bone remodeling process. Many bone diseases like osteoporosis have been examined by applying a continuous mechanical stress; such stress gave anabolic effects on bone formation [6, 7] while catabolic effects on bone resorption [47].

1.8 Osteoporosis

A disparity among RANKL/OPG signaling equipoise gives rise to several bone pathological processes mostly associated with ageing, called osteopenia and with more extremity, osteoporosis [61, 24, 62]. Osteoporosis is a bone related disorder regarded as skeletal infirmity with low Bone Mineral Density (BMD), which subsequently causes recurrent micro harms and impulsive cracks; it is a persistent syndrome demanding long-term cure [9]. Middle aged women and elderly people are the prime targets of osteoporosis and currently its influence is intensely rising socially and economically; WHO has declared it as the second foremost healthcare issue [35]. In a regular bone remodeling process, RANKL/OPG is prudently balanced ; the rise in RANKL plays a vital part in supporting resorption via osteoclast development, activities, and persistence [16, 62]. As the human body gets older the density of the osteons expands and the cortical sponginess and architectural damages of bone also rises due to the execution of a large number of remodeling cycles [12, 1, 79]. This scenario initiates a vicious cycle where micro harms occur often, consequently weakening bone configuration and increasing proportion of impulsive fractures [11]. Furthermore, latest analyses on bone remodeling propose that plasma levels OPG and RANKL are contrariwise linked to BMD and take part into the growth of osteoporosis in postmenopausal women [72].

1.9 Osteomyelitis

The bacterium called S. aureus is the main cause of osteomyelitis, which is bone infectivity. A contact of bacterium with bone produces severe bone damage and failure of the vasculature along with a continual chronic contamination [35, 31]; this is more complex as a result of the hasty emergence of anti damages of S. aureus. Experimental results have confirmed that the virus intercepts production, stimulates apoptosis and hinders mineralization of osteoblastic cells. In an ostemyelitc bone, the bacterium stimulates the bone resorption by stimulating the RANKL expression and inhibiting the OPG expression in osteoblasts [65]. Bisphosphonates is the drug therapy which induces the OPG expression which in turn slows down the formation of RANK-RANKL complex formation, eventually hindering bone resorption[22, 75]. The increase in OPG is probable to activate the osteoblastic induced bone development [35]. We think that a mathematical system of the virus might give a structure for a better analysis and comprehending the antibiotic intercession. Here we present a hybrid mathematical system for uniting and disentangling the relations of cellular and molecular statistics [65]. Our perception is that this attempt would be beneficial in developing improved therapies to control the spread of the diseases.

Chapter 2

2 Review of Literature

Recently, many researchers have developed several mathematical models of bone remodeling to study the deep dynamics of intracellular and intercellular mechanisms of bone. Some of the models allow just the estimation of cell population dynamics and alteration in bone density; the first attempt in this regard was by Komarova et al [34], while some of them deals with several bone diseases including the tight coupling between bone cells and their potential therapies based on their efficacy; firstly introduced by Lemaire et al [80]. Komarova et al [34] model depicts that the dynamical behavior of bone remodeling strictly depends on the regulation of bone resorbing cells by autocrine factors, and the osteoclast-osteoblast communication produces a complex, nonlinear structure, which cannot be figured out from the analysis of each cell class alone [54, 44]. Many researchers extended the model of Komarova et al afterwards. Ayati et al [11] developed a model to study myeloma bone disorder and demonstrated how therapeutic strategies might be examined through such computational systems. Benito M. Chen-Charpentier et al [71] introduced delays in the model of Komarova et al [34] and checked the stability and bifurcation. Ryser et al [66] developed a mathematical model based on partial differential equations with time delays to simulate the dynamics of bone multicellular units. Their system illustrates the RANKL/OPG signaling pathway along with the osteoclast-osteoblast communication. Lemaire et al [80] proposed a mathematical framework comprising of cellular control and biochemical feedback systems responsible for the modulation of bone remodeling. Their model also incorporates to simulate the growth of several metabolic disorders such as osteoporosis, estrogen dearth or vitamin-D deficiency and determines possible treatments based on their effectiveness [67]. Since RANK/RANKL/OPG signal-

ing pathway is a main signaling cascade synchronizing bone turnover, so practical insinuation of particular RANKL/OPG expression profiles on bone density were profoundly investigated by Pivonka et al [58]. They developed a model comprising of the dynamics of bone cellular units, based on the work of Lemaire et al [80] integrating the RANK/RANKL/OPG pathway along with the modulating effect of TGF-β on bone cells. Pivonka et al [43] first time introduced PK model of drug denosumab along with a PD model of bone remodeling and analyzed the effect of denosumab on bone [37] through this PK/PD model [36].

Remodeling of bone period should lie in a state which is stable, where in the non presence of the external stimuli and under physiological circumstances, the osteoblast and osteoclast populations remains almost constant over time. This type of stable state is called dynamical and has to be power full against the changes in the parameters of the models.[25] stated that the physiological state of the remodeling of the bone mechanism is likely described by values of the parameters near to a point of bifurcation. This happens at the time when system shows the energetic feedback of steady states to parameter variations. Zumsande et al. (2011) practiced a modeling methodology which was generalized for the testing of the several models according to their properties of bifurcations. The outcomes of the simulations showed that in a two dimensional model the steady state stability need OPG domination over the RANKL. Many diseases related to bones like osteoporosis, osteopenia, Paget's disease and postmenopausal osteoporosis are results of dysfunctions in the remodeling of the bone. They recommended that such type of the disorderness (diseases) provoked by steady state transition because of the instability in a Hopf bifurcation (HB), however this concept is still confirmed.

For trabecular bones by following the Rayser et al (2007) model , the model of Pivonka et al. (2008) was further elaborated by Buenzli's (2011). And suggested another spatio-temporal model (STM) to find out the factors that are regulatory in

cortical bone and the distribution of the cell. The model of Buenzli's combined the most important connecting pathways that are present between the osteoblastics and osteoclastic cells. And was built up by froming the numbers of extra material-balance-equations. The Basic Multicellular Unit structure at descriptive stage it is well understandable [23 , 24], although, for the identification of the connection between underlying cellular interaction phenomena and the Basic Multicellular unit structure no any work had been performed yet. The model of Buenzli construct such kind of connections and also tested capabilities of these to rebuild the spatio-temporal dynamics (STD) of the single Basic Multicellular Units (BMUs). Cell distributions of cortical Basic Multicellular units that were experimentally seen was got under special circumstances. Regulatory factors spatial distributions could also be calculated.

The Komarovas's et al. model (2003) rebuilt the changes in osteobasts and osteoclasts population, and mass of the bone at the time of bone remodeling period at a seperate spot, and anticipated the occurance of changing modes of dynamical behaviors of the Basic Multicellular Units (BMU) during the period of remodeling of bones. Nonetheless, the autocrine regulation loops and paracrine regulation loops were described by the parameters range which outstripped the biological potential. Additionally, osteocytes are missing in this model, infact they are very much important in bone remodeling regulation [14, 13] model was extended further by Moroz's et al. (2006) by describing the paracrine parameters and autocrine parameters within the biological capacity. And by adding the osteocyte apoptosis role, in remodeling of bone mechanism. Moroz's model comprises of 4 components (4-ODE), which show temporal changes in the osteoclast population, osteoblast population, osteocytes population and volume of bone. The model of moroz's determined the presence of the steady states that is basic, with the occurrence of a 4 dimensional surface "bone-osteoblast-osteoclast-osteocytes" space shows the

existance of is present a 1st integral for the dynamical structure that is under consideration, by conservative value that can be demonstrated. Moroz's model also explained the recovering potential existence, which is assisted against the biochemical bone damage and mechanical bone damage. By comparison with the normal remodeling of bone mechanism the Moroz's model was justified. Nonetheless, in order to examine the extensive range of contents more work is required.

Chapter 3

3 Main Results

3.1 Osteoporotic model

A simplified version of *LIó*'s model [4] has been described here to depict the temporal variations in osteoclasts (C) and osteoblasts (B) cells concentrations during an osteoporotic bone turnover. The following assumptions have been made by taking into account the dysregulated bone remodeling process defined in the previous section.

1. Number of osteoclasts (osteoblasts) includes the populations of osteoclast (osteoblast) precursors and osteoclasts (osteoblasts).

2. The death rate of bone resorbing and bone forming cells is proportional to the present populations of that particular cell.

3. As the ageing factor (a_{ageing}) plays a crucial role in the development of osteoporosis and weakens the bones by destroying the bone cells so this effect has been included in bone removal and forming bone cells.

4. No external effects have been included on the population system.

Based on the above assumptions, following model gives a more general view of temporal changes in both bone cells concentrations:

$$\begin{aligned} \frac{dC}{dt} &= a_1 g_1(C,B) - a_{ageing} b_1 C \\ \frac{dB}{dt} &= a_2 g_2(C,B) - a_{ageing} b_2 B \end{aligned} \tag{1}$$

where C, B represent the population of bone resorbing and bone forming cells, respectively, a_i; $i = 1, 2$ are the proliferation rates of osteoclasts and osteoblasts precursors, respectively and b_i; $i = 1, 2$ are the apoptosis rates of C and B, respectively. The function $g_i(C, B)$; $i = 1, 2$ illustrates the communication between C and B depending on the autocrine and paracrine factors involved in growth rate of both cells.

Now considering the function $g_i(C, B)$; $i = 1, 2$ in a power law approximation form provided in [4], our system (1) takes the following form:

$$\begin{aligned} \frac{dC}{dt} &= a_1 C^{\delta_{11}} B^{\delta_{21}+\delta_{OL}} - a_{ageing} b_1 C \\ \frac{dB}{dt} &= a_2 C^{\delta_{12}} B^{\delta_{22}} - a_{ageing} b_2 B \end{aligned} \tag{2}$$

In system (2), δ_{ij}; $i, j = 1, 2$ represents the net effect of several growth factors participating in bone turnover process and producing autoregulations in osteoclasts and osteoblasts or effecting one cell type through the other. We supposed that the quantity of these growth factors [82, 78] depend on the donor cells population at any instant. The brief description of δ_{ij}; $i, j = 1, 2$ is as follows:

δ_{11} net effect of osteoclasts autocrine factors,

δ_{21} osteoblasts-released paracrine factors activating osteoclasts,

δ_{12} osteoclasts-released paracrine factors activating osteoblasts,

δ_{22} net effect of osteoblasts autocrine factors.

Due to an imbalance in bone turnover practice in an osteoporotic bone, a disruption in OPG-RANKL complex formation occurs which influences the paracrine effect produced by osteoblasts on osteoclasts. To incorporate this aspect, a supplementary factor (δ_{OL}) has been added in the model. A change in bone density (Y) occurs as the C and B concentrations exceed their steady state level, this aspect is described in the following equation.

$$\frac{dY}{dt} = -s_1 max(C - \bar{C}, 0) + s_2 max(B - \bar{B}, 0) \tag{3}$$

In the above equation, $\bar{C}$ and $\bar{B}$, represent the steady state values of C and B, respectively and s_i; $i = 1, 2.$ are the normalized activities of bone resorption and formation, respectively.

A numerical evidence of system (2) along with equation (3) is provided in [4]. In this article, a theoretical analysis of this system has been conducted to provide the evidence of the existence of a periodic solution. We modify the system (2) by making the following assumptions:

- $C^{\delta_{11}} \propto C$ and $B^{\delta_{22}} \propto B$
- $\delta_1 = \delta_{21}$ and $\delta_2 = \delta_{12}$, where δ_i; $i = 1, 2$ represents the paracrine effects produced by RANK-RANKL-OPG signalling pathway and other factors including PTH and TGF-β. In addition, the effect of δ_1 is catabolic as it represses the concentration of osteoclasts while δ_2 stimulates the production of osteoblasts so produces an anabolic effect on osteoblasts population.

So based on these assumptions system (2) takes the following form.

$$\begin{aligned} \tfrac{dC}{dt} &= a_1 C B^{\delta_1+\delta_{OL}} - a_{ageing} b_1 C \\ \tfrac{dB}{dt} &= a_2 C^{\delta_2} B - a_{ageing} b_2 B \end{aligned} \tag{4}$$

Here we discussed few mathematical models of bone remodeling including osteoporotic model, Zero dimensional bone model without tumor, Zero dimensional bone model with tumor, Osteomyelitis effect on bone remodeling, stability analysis of the model, osteoporotic model and numerical simulations. Now we drive a simplified Komarova's model to describe the temporal changes of the osteoclasts and osteoblasts populations and the bone mass at a certain cite of bone based on the previous biological considerations. The basic model is,

$$\frac{du_1}{dt} = \alpha_1 u_1 u_2^{\gamma_1} - \beta_1 u_2$$

$$\frac{du_2}{dt} = \alpha_2 u_1^2 u_2 - \beta_2 u_2$$

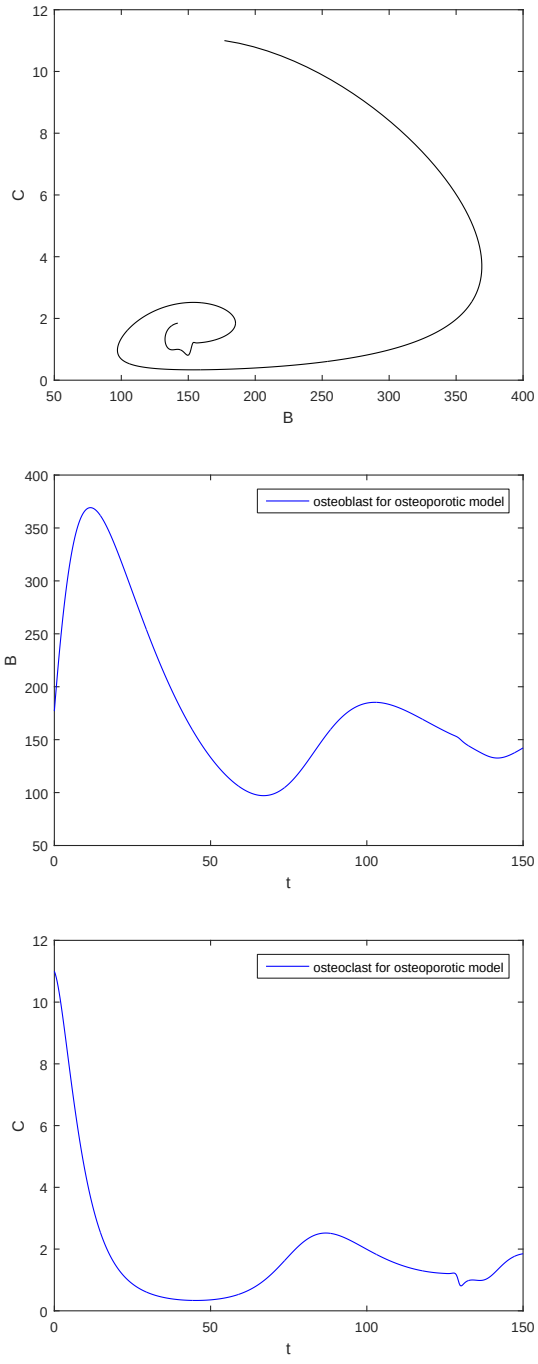

Figure 4: Graphical depiction of model.

Our model takes the following form,

$$\frac{dO_c}{dt} = \alpha_1 O_c^{g_{11}} O_b^{g_{21}+g_{por}} - g_{ageing}\beta_1 O_c \tag{5}$$

$$\frac{dO_b}{dt} = \alpha_2 O_c^{g_{12}} O_b^{g_{22}} - g_{ageing}\beta_2 O_b \tag{6}$$

Put $g_{11} = 1 = g_{22}$, then,

$$\frac{dO_c}{dt} = \alpha_1 O_c O_b^{g_{21}+g_{por}} - g_{ageing}\beta_1 O_c$$

$$\frac{dO_b}{dt} = \alpha_2 O_c^{g_{12}} O_b - g_{ageing}\beta_2 O_b$$

The bone mass equation is,

$$\frac{dz}{dt} = -k_1 max[O_c^{g_{11}} - O_c, 0] + k_2 max[O_b^{g_{22}} - O_b, 0] \tag{7}$$

For equilibrium solution of (5) and (6), put $\frac{dO_c}{dt} = 0 = \frac{dO_b}{dt}$

$$\alpha_1 O_c O_b^{g_{21}+g_{por}} - g_{ageing}\beta_1 O_c = 0$$

$$\alpha_2 O_c^{g_{12}} O_b - g_{ageing}\beta_2 O_b = 0$$

$$O_c(\alpha_1 O_b^{g_{21}+g_{por}} - g_{ageing}\beta_1) = 0$$

$$O_b(\alpha_2 O_c^{g_{12}} - g_{ageing}\beta_2) = 0$$

$$O_b^{g_{21}+g_{por}} = g_{ageing}\frac{\beta_1}{\alpha_1}$$

$$\bar{O_b} = (g_{ageing}\frac{\beta_1}{\alpha_1})^{\frac{1}{g_{21}+g_{por}}}$$

and,

$$\bar{O_c} = (g_{ageing}\frac{\beta_2}{\alpha_2})^{\frac{1}{g_{12}}}$$

The steady state solution which always exist is a,

$$(\bar{O_c}, \bar{O_b}) = [(g_{ageing}\frac{\beta_2}{\alpha_2})^{\frac{1}{g_{12}}}, (g_{ageing}\frac{\beta_1}{\alpha_1})^{\frac{1}{g_{21}+g_{por}}}] \tag{8}$$

Solution of equation (5) and (6) having initial conditions (O_c^0, O_b^0) is,

$$O_{c(t)} = O_c^0 exp(\int \alpha_1 O_b^{g_{21}+g_{por}} - g_{ageing}\beta_1 ds) \tag{9}$$

$$O_{b(t)} = O_b^0 exp(\int \alpha_2 O_c^{g_{12}} - g_{ageing}\beta_2 ds) \tag{10}$$

Jacobian matrix of system after linearizing around $(\bar{O}_c, \bar{O}_b)$ is

$$J(\bar{O}_c, \bar{O}_b) = \begin{bmatrix} \alpha_1 O_b^{g_{21}+g_{por}} - g_{ageing}\beta_1 & \alpha_1(g_{21}+g_{por})O_c O_b^{g_{21}+g_{por}-1} \\ \alpha_2 g_{12} O_c^{g_{12}-1} O_b & \alpha_2 O_c^{g_{12}} - g_{ageing}\beta_2 \end{bmatrix}$$

Trace and determinant of above system is

$$T_r(J(\bar{O}_c, \bar{O}_b)) = \alpha_1 O_b^{g_{21}+g_{por}} - g_{ageing}\beta_1 + \alpha_2 O_c^{g_{12}} - g_{ageing}\beta_2$$

$$= \alpha_1 O_b^{g_{21}+g_{por}} + \alpha_2 O_c^{g_{12}} - g_{ageing}(\beta_1 + \beta_2)$$

Theorem 1 *Equation (5)and (6) with positive initial conditions and verifying the condition $\gamma_1\gamma_2 \leqslant 0$ has a unique positive periodic solution which oscillates around the equilibrium point.*

Proof.

Dividing the equation (5) by the equation (6) then we have

$$\frac{dO_b}{dO_c} = \frac{O_b(\alpha_2 O_c^{g_{12}} - g_{ageing}\beta_2)}{O_c(\alpha_1 O_b^{g_{21}+g_{por}}) - g_{ageing}\beta_1}$$

$$\frac{\alpha_1 O_b^{g_{21}+g_{por}}) - g_{ageing}\beta_1}{O_b}(\frac{dO_b}{dO_c}) = \frac{(\alpha_2 O_c^{g_{12}} - g_{ageing}\beta_2)}{O_c}$$

$$(\frac{\alpha_1 O_b^{g_{21}+g_{por}}}{O_b} - \frac{g_{ageing}\beta_1}{O_b})dO_b = (\frac{(\alpha_2 O_c^{g_{12}} - g_{ageing}\beta_2)}{O_c})dO_c$$

Now, integrating we have,

$$\frac{\alpha_1 O_b^{g_{21}+g_{por}}}{g_{21}+g_{por}} - g_{ageing}\beta_1 ln(O_b) = \frac{\alpha_2 O_c^{g_{12}}}{g_{12}} - g_{ageing}\beta_2 ln(O_c) + lnC$$

$$\frac{\alpha_1 O_b^{g_{21}+g_{por}}}{g_{21}+g_{por}} = \frac{\alpha_2 O_c^{g_{12}}}{g_{12}} + ln(O_c^{-g_{ageing}\beta_2}) + lnC - ln(O_b^{-g_{ageing}\beta_1})$$

$$\frac{\alpha_1 O_b^{g_{21}+g_{por}}}{g_{21}+g_{por}} = \frac{\alpha_2 O_c^{g_{12}}}{g_{12}} + ln(\frac{C.O_c^{-g_{ageing}\beta_2}}{O_b^{-g_{ageing}\beta_1}})$$

$$Exp(\frac{\alpha_1 O_b^{g_{21}+g_{por}}}{g_{21}+g_{por}} - \frac{\alpha_2 O_c^{g_{12}}}{g_{12}}) = \frac{C.O_c^{-g_{ageing}\beta_2}}{O_b^{-g_{ageing}\beta_1}})$$

$$Exp(\frac{\alpha_1 O_b^{g_{21}+g_{por}}}{g_{21}+g_{por}}).Exp(\frac{\alpha_2 O_c^{g_{12}}}{g_{12}}) = \frac{C.O_c^{-g_{ageing}\beta_2}}{O_b^{-g_{ageing}\beta_1}})$$

$$O_b^{-g_{ageing}\beta_1} Exp(\frac{\alpha_1 O_b^{g_{21}+g_{por}}}{g_{21}+g_{por}}) = C.O_c^{-g_{ageing}\beta_2} Exp(\frac{\alpha_2 O_c^{g_{12}}}{g_{12}})$$

Now let,

$$y = O_b^{-g_{ageing}\beta_1} Exp(\frac{\alpha_1 O_b^{g_{21}+g_{por}}}{g_{21}+g_{por}})$$

also,

$$y = C.O_c^{-g_{ageing}\beta_2} Exp(\frac{\alpha_2 O_c^{g_{12}}}{g_{12}})$$

Now we calculate the first derivative $\frac{dy}{dO_c}$

$$\frac{dy}{dO_c} = C[-g_{ageing}\beta_2 O_c^{-g_{ageing}\beta_2-1} Exp\frac{\alpha_2 O_c^{g_{12}}}{g_{12}} + O_c^{-g_{ageing}\beta_2} Exp\frac{\alpha_2 O_c^{g_{12}}}{g_{12}}.\frac{\alpha_2}{g_{12}} g_{12} O_c^{g_{12}-1}]$$

$$\frac{dy}{dO_c} = CExp\frac{\alpha_2 O_c^{g_{12}}}{g_{12}}[-g_{ageing}\beta_2 O_c^{-g_{ageing}\beta_2-1} + O_c^{-g_{ageing}\beta_2-1}\alpha_2 O_c^{g_{12}}]$$

$$\frac{dy}{dO_c} = CExp\frac{\alpha_2 O_c^{g_{12}}}{g_{12}} O_c^{-g_{ageing}\beta_2-1}[-g_{ageing}\beta_2 + \alpha_2 O_c^{g_{12}}]$$

$$\frac{dy}{dO_b} = -g_{ageing}\beta_1 O_b^{-g_{ageing}\beta_1 - 1} Exp\frac{\alpha_1 O_b^{g_{21}+g_{por}}}{g_{21}+g_{por}} + O_b^{-g_{ageing}\beta_1}$$

$$Exp\frac{\alpha_1 O_b^{g_{21}+g_{por}}}{g_{21}+g_{por}}.\frac{\alpha_1}{g_{21}+g_{por}}.g_{21} + g_{por}O_b^{g_{21}+g_{por}-1}$$

$$\frac{dy}{dO_b} = Exp\frac{\alpha_1 O_b^{g_{21}+g_{por}}}{g_{21}+g_{por}}(-g_{ageing}\beta_1 O_b^{-g_{ageing}\beta_1-1} + O_b^{-g_{ageing}\beta_1-1}.\alpha_1 O_b^{g_{21}+g_{por}})$$

■

3.2 Zero-dimensional Bone Model without Tumor

A normal bone remodeling model at a single discrete site is made. The model contains a system of ordinary differential equations that gives the populations of bone cells in the basic multicellular unit The model equations are;

$$\frac{d}{dt}C(t) = \alpha_1 C(t)^{g_{11}} B(t)^{g_{21}} - \beta_1 C(t) \tag{11}$$

$$\frac{d}{dt}B(t) = \alpha_2 C(t)^{g_{12}} B(t)^{g_{22}} - \beta_2 B(t) \tag{12}$$

The initial conditions for the system are $C(0) = C_0, B(0) = B_0$. The power law approximation gives the expansion of OC and OB strength in terms of equations. The parameters $g_{11}, g_{12}, g_{21}, g_{22}$ has positive and negative effect. The factor ($g_{11} > 0$) is the autocrine signalling and has positive response on osteoclast growth, and The factor ($g_{21} < 0$) is the paracrine signalling and has negative response on osteoclast growth,The factor ($g_{22} > 0$) is the autocrine signalling and has positive response on osteoblast growth, and The factor ($g_{12} > 0$) is the paracrine signalling and has positive response on osteoblast growth.Now we have to calculate the the equilibrium points for the system [64]. for equilibrium points equate above two equations to zero then we have,

$$\alpha_1 C(t)^{g_{11}} B(t)^{g_{21}} - \beta_1 C(t) = 0$$

$$\alpha_2 C(t)^{g_{12}} B(t)^{g_{22}} - \beta_2 B(t) = 0$$

from equation we have,

$$\beta_1 C(t) = \alpha_1 C(t)^{g_{11}} B(t)^{g_{21}}$$

$$C(t)^{1-g_{11}} = \frac{\alpha_1}{\beta_1} B(t)^{g_{21}}$$

$$C(t) = (\frac{\alpha_1}{\beta_1} B(t)^{g_{21}})^{\frac{1}{1-g_{11}}} \tag{13}$$

Put this value in first equation, we have,

$$\beta_2 B(t) = \alpha_2 [(\frac{\alpha_1}{\beta_1} B(t)^{g_{21}})^{\frac{1}{1-g_{11}}}]^{g_{12}} .(B(t)^{g_{22}}$$

$$B(t) = \frac{\alpha_2}{\beta_2} (\frac{\alpha_1}{\beta_1})^{\frac{g_{12}}{1-g_{11}}} (B(t))^{\frac{g_{12}g_{21}}{1-g_{11}}} .(B(t)^{g_{22}}$$

$$B(t) = \frac{\alpha_2}{\beta_2} (\frac{\alpha_1}{\beta_1})^{\frac{g_{12}}{1-g_{11}}} (B(t))^{\frac{g_{12}g_{21}}{1-g_{11}} + g_{22}}$$

$$B(t) = \frac{\alpha_2}{\beta_2} (\frac{\alpha_1}{\beta_1})^{\frac{g_{12}}{1-g_{11}}} (B(t))^{\frac{g_{12}g_{21}+g_{22}-g_{11}g_{22}}{1-g_{11}}}$$

$$\frac{\beta_2}{\alpha_2} .(\frac{\beta_1}{\alpha_1})^{\frac{g_{12}}{1-g_{11}}} = (B(t))^{\frac{g_{12}g_{21}+g_{22}-g_{11}g_{22}-1+g_{11}}{1-g_{11}}}$$

Let,

$$\Gamma = g_{12}g_{21} - 1 + g_{11} + g_{22} - g_{11}g_{22},$$

Then,

$$\frac{\beta_2}{\alpha_2} .(\frac{\beta_1}{\alpha_1})^{\frac{g_{12}}{1-g_{11}}} = (B(t))^{\frac{\Gamma}{1-g_{11}}}$$

Now,

$$B(t) = (\frac{\beta_2}{\alpha_2})^{\frac{1-g_{11}}{\Gamma}} .[(\frac{\beta_1}{\alpha_1})^{\frac{g_{12}}{1-g_{11}}}]^{\frac{1-g_{11}}{\Gamma}}$$

$$B(t) = (\frac{\beta_2}{\alpha_2})^{\frac{1-g_{11}}{\Gamma}} .(\frac{\beta_1}{\alpha_1})^{\frac{g_{12}}{\Gamma}} \tag{14}$$

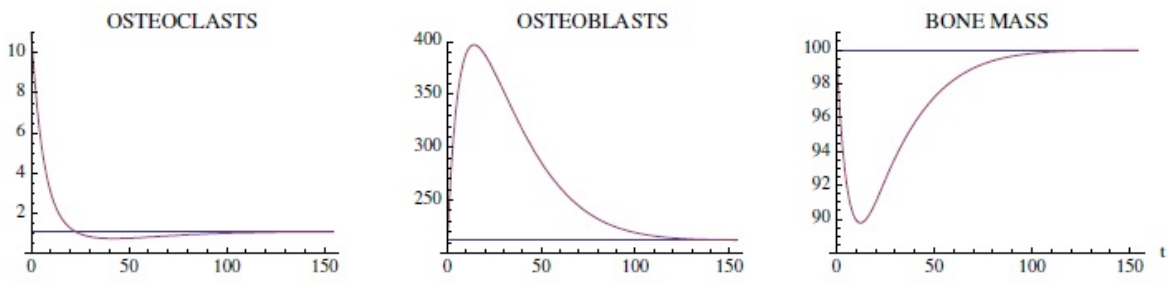

Figure 5: Bone Cells regulation

Put this value in equation (13),we get

$$C(t) = (\frac{\alpha_1}{\beta_1})^{\frac{1}{1-g_{11}}}.(\frac{\beta_1}{\alpha_1})^{\frac{g_{12}}{\Gamma}\cdot\frac{g_{21}}{1-g_{11}}}.(\frac{\beta_2}{\alpha_2})^{\frac{1-g_{11}}{\Gamma}\cdot\frac{g_{21}}{1-g_{11}}}$$

$$C(t) = (\frac{\beta_1}{\alpha_1})^{\frac{-1}{1-g_{11}}+\frac{g_{12}g_{21}}{(1-g_{11})\Gamma}}.(\frac{\beta_2}{\alpha_2})^{\frac{g_{21}}{\Gamma}}$$

$$C(t) = (\frac{\beta_1}{\alpha_1})^{\frac{g_{12}g_{21}-g_{12}g_{21}+1-g_{11}-g_{22}+g_{11}g_{22}}{(1-g_{11})\Gamma}}.(\frac{\beta_2}{\alpha_2})^{\frac{g_{21}}{\Gamma}}$$

$$C(t) = (\frac{\beta_1}{\alpha_1})^{\frac{(1-g_{11})-g_{22}(1-g_{11})}{(1-g_{11})\Gamma}}.(\frac{\beta_2}{\alpha_2})^{\frac{g_{21}}{\Gamma}}$$

$$C(t) = (\frac{\beta_1}{\alpha_1})^{\frac{1-g_{22}}{\Gamma}}.(\frac{\beta_2}{\alpha_2})^{\frac{g_{21}}{\Gamma}} \tag{15}$$

Equation (14) and (15) has unique non trivial steady state of equation (40) and (41). And the equations (11) and (12) has periodic solution when

$$\Psi = \beta_1(g_{11} - 1) + \beta_2(g_{222} - 1)$$

3.3 Zero-dimensional Bone Model with Tumor

we find that the customary cycles of the typical bone model above are bothered by the nearness of myeloma. The tumor parameters yield annoyances of the typical cycles that appear in confine cycles, which are either damped motions that join to the nontrivial unfaltering state or undamped motions that diverge far from the non inconsequential enduring state. The factors for the model with tumor are C(t), B(t), and T(t).equations of the system are as follows:

$$\frac{d}{dt}C(t) = \alpha_1 C(t)^{g_{11}(1+r_{11}\frac{T(t)}{L_T})} B(t)^{g_{21}(1+r_{21}\frac{T(t)}{L_T})} - \beta_1 C(t) \tag{16}$$

$$\frac{d}{dt}B(t) = \alpha_2 C(t)^{g_{12}(1+r_{12}\frac{T(t)}{L_T})} B(t)^{g_{22}-r_{22}\frac{T(t)}{L_T}} - \beta_2 C(t) \tag{17}$$

$$\frac{d}{dt}T(t) = \gamma_T T(t)\log(\frac{L_T}{T(t)}) \tag{18}$$

Where, the initial conditions are $C(0) = C_0$,$B(0) = B_0$ and $T(0) = T_0$ and $Z(t)$ represent the bone mass and $T(t)$ is the density of tumor, and γ_t is the tumor growth constant and $\gamma_t > 0$. As γ_t is the consatnat, so it is independent of bone mass and $r_{11}, r_{12}, r_{21}, r_{22}$ are the tumor parameters and are all non-negative. The different cases for tumor presence are as: (1)-the autocrine progress of osteoclast increased so, $(g_{11}(1 + r_{11}\frac{T(t)}{L_T}) > g_{11}$,because $g_{11} > 0)$, (2)- the paracrine retardation of osteoclast is reduced so $(-g_{21} > -g_{21}(1 + r_{21}\frac{T(t)}{L_T})$,because $-g_{21} < 0)$, (3)- The paracrine progress of osteoblast reduced so, $(g_{12}(1 + r_{12}\frac{T(t)}{L_T}) < g_{21}$,because $g_{21} < 0)$ and, (4)- the paracrine retardation of osteoclast is reduced so $(g_{22}-r_{22}\frac{T(t)}{L_T}$,because $g_{22} > 0)$ To find equilibrium points, put above equations equal to zero then by equation (18) we have,

$$\gamma_T T(t)\log(\frac{L_T}{T(t)}) = 0$$

As $\gamma_t \neq 0, T(t) \neq 0$, then

$$\log(\frac{L_T}{T(t)}) = 0$$

$$T(t) = L_T \tag{19}$$

Then equation (16) becomes

$$\beta_1 C(t) = \alpha_1 C(t)^{g_{11}(1+r_{11})} B(t)^{g_{21}(1+r_{21})}$$

$$C(t)^{1-g_{11}(1+r_{11})} = \frac{\alpha_1}{\beta_1} B(t)^{g_{21}(1+r_{21})}$$

$$C(t) = [\frac{\alpha_1}{\beta_1} B(t)^{g_{21}(1+r_{21})}]^{\frac{1}{1-g_{11}(1+r_{11})}}$$

$$C(t) = (\frac{\alpha_1}{\beta_1})^{\frac{1}{1-g_{11}(1+r_{11})}} B(t)^{\frac{g_{21}(1+r_{21})}{1-g_{11}(1+r_{11})}} \tag{20}$$

Now equation (17) becomes,

$$\beta_2 C(t) = \alpha_2 [(\frac{\alpha_1}{\beta_1})^{\frac{1}{1-g_{11}(1+r_{11})}} B(t)^{\frac{g_{21}(1+r_{21})}{1-g_{11}(1+r_{11})}}]^{g_{12}(1+r_{12})} B(t)^{g_{22}-r_{22}}$$

$$C(t) = \frac{\alpha_2}{\beta_2} (\frac{\alpha_1}{\beta_1})^{\frac{g_{12}(1+r_{12})}{1-g_{11}(1+r_{11})}} (B(t))^{\frac{g_{12}g_{21}(1+r_{12})(1+r_{21})}{1-g_{11}(1+r_{11})} + g_{22}-r_{22}}$$

$$C(t) = \frac{\alpha_2}{\beta_2} (\frac{\alpha_1}{\beta_1})^{\frac{g_{12}(1+r_{12})}{1-g_{11}(1+r_{11})}} (B(t))^{\frac{g_{12}g_{21}(1+r_{12})(1+r_{21}) + (g_{22}-r_{22})(1-g_{11}(1+r_{11}))}{1-g_{11}(1+r_{11})}}$$

$$\frac{\beta_2}{\alpha_2} (\frac{\beta_1}{\alpha_1})^{\frac{g_{12}(1+r_{12})}{1-g_{11}(1+r_{11})}} = (B(t))^{\frac{g_{12}g_{21}(1+r_{12})(1+r_{21}) + (g_{22}-r_{22})(1-g_{11}(1+r_{11})) - 1 - g_{11}(1+r_{11})}{(1-g_{11}(1+r_{11}))}}$$

$$\frac{\beta_2}{\alpha_2} (\frac{\beta_1}{\alpha_1})^{\frac{g_{12}(1+r_{12})}{1-g_{11}(1+r_{11})}} = (B(t))^{\frac{g_{12}g_{21}(1+r_{12})(1+r_{21}) + (1-g_{11(1+r_{11})(g_{22}-r_{22}-1)})}{1-g_{11}(1+r_{11})}}$$

$$\frac{\beta_2}{\alpha_2} (\frac{\beta_1}{\alpha_1})^{\frac{g_{12}(1+r_{12})}{1-g_{11}(1+r_{11})}} = (B(t))^{\frac{g_{12}g_{21}(1+r_{12})(1+r_{21}) - (1-g_{11(1+r_{11})(1-g_{22}+r_{22})})}{1-g_{11}(1+r_{11})}}$$

Let,

$$\Lambda = g_{12}g_{21}(1+r_{12})(1+r_{21}) - (1 - g_{11(1+r_{11})(1-g_{22}+r_{22})})$$

Then, we have

$$\frac{\beta_2}{\alpha_2}(\frac{\beta_1}{\alpha_1})^{\frac{g_{12}(1+r_{12})}{1-g_{11}(1+r_{11})}} = (B(t))^{\frac{\Lambda}{1-g_{11}(1+r_{11})}}$$

$$B(t) = (\frac{\beta_1}{\alpha_1})^{\frac{g_{12}(1+r_{12})}{\Lambda}}(\frac{\beta_2}{\alpha_2})^{\frac{1-g_{11}(1+r_{11})}{\Lambda}} \tag{21}$$

Now equation (20) becomes,

$$C(t) = (\frac{\alpha_1}{\beta_1})^{\frac{1}{1-g_{11}(1+r_{11})}}[(\frac{\beta_1}{\alpha_1})^{\frac{g_{12}(1+r_{12})}{\Lambda}}(\frac{\beta_2}{\alpha_2})^{\frac{1-g_{11}(1+r_{11})}{\Lambda}}]^{\frac{g_{21}(1+r_{21})}{1-g_{11}(1+r_{11})}}$$

$$C(t) = (\frac{\beta_1}{\alpha_1})^{\frac{-1}{1-g_{11}(1+r_{11})}}(\frac{\beta_1}{\alpha_1})^{\frac{g_{12}g_{21}(1+r_{12})(1+r_{21})}{(\Lambda)(1-g_{11}(1+r_{11}))}}(\frac{\beta_2}{\alpha_2})^{\frac{g_{21}(1+r_{21})}{\Lambda}}$$

$$C(t) = (\frac{\beta_1}{\alpha_1})^{\frac{-1}{1-g_{11}(1+r_{11})}}(\frac{\beta_1}{\alpha_1})^{\frac{g_{12}g_{21}(1+r_{12})(1+r_{21})-\Lambda}{(\Lambda)(1-g_{11}(1+r_{11}))}}(\frac{\beta_2}{\alpha_2})^{\frac{g_{21}(1+r_{21})}{\Lambda}}$$

$$C(t) = (\frac{\beta_1}{\alpha_1})^{\frac{-1}{1-g_{11}(1+r_{11})}}(\frac{\beta_1}{\alpha_1})^{\frac{g_{12}g_{21}(1+r_{12})(1+r_{21})-g_{12}g_{21}(1+r_{12})(1+r_{21})-(1-g_{11(1+r_{11})}(1-g_{22}+r_{22}))}{(\Lambda)(1-g_{11}(1+r_{11}))}}$$

$$(\frac{\beta_2}{\alpha_2})^{\frac{g_{21}(1+r_{21})}{\Lambda}}$$

$$C(t) = (\frac{\beta_1}{\alpha_1})^{\frac{1-g_{22}+r_{22}}{\Lambda}}(\frac{\beta_2}{\alpha_2})^{\frac{g_{21}(1+r_{21})}{\Lambda}} \tag{22}$$

3.4 Osteomyelitis effect on bone remodeling

The model equations are:

$$\frac{dC}{dt} = a_1 C^{u_{11}(1+v_{11}\frac{X}{s})}B^{g_{21}(1+v_{21}\frac{X}{s})} - b_1 C \tag{23}$$

$$\frac{dB}{dt} = a_2 C^{u_{12}(1+v_{12}\frac{X}{s})}B^{u_{22}-v_{22}\frac{X}{s}} - b_2 B \tag{24}$$

$$\frac{dX}{dt} = (\gamma_X - V)X\log(\frac{s}{X}) \tag{25}$$

Where C represents osteoclast ,B represents osteoblast, where X is the strength of bacteria, and γ_X is the growth rate of bacteria and s is the carrying capacity of of bacteria(i.e the maximum size) also, v_{ij} is the effects of infection on the paracine

and autocrine factors u_{ij}. This model is the inspiration of Ayati's work on myeloma disease and the difference in this model is the factor $v_{ij}\frac{X}{s}$ that is the product of density of bacteria and the maximum size. The parameters $v_{11}, v_{12}, v_{21}, v_{22}$ are all non negative, and the affects of X on normal bone remodeling os given by;

1- retardation of B progression rate: reducing the paracrine progression of C $u_{12}(1 + v_{12}\frac{X}{s}) < u_{12}, because u_{12} > 0$ and autocrine progress of C also reduce $u_{22} - v_{22}\frac{X}{s} < u_{22}$

2-Accelerating RANKL and retarding OPG expressions: As we describe above that paracrine inhibitate C so that its power is negative that is the effective difference between OPG and RANKL signalling, as $u_{21}(1 - v_{21}\frac{X}{s}) > u_{21}$ that is the increament in RANKL and retardation in OPG. Now to find the equilibrium points put above three equations equal to zero then we get, From equation (25) we have,

$$(\gamma_X - V)X \log(\frac{s}{X}) = 0$$

Here, $\gamma_X \neq 0, v \neq 0$, then

$$\log(\frac{s}{X}) = 0$$

$$X = s \tag{26}$$

Then equation (23) becomes

$$b_1 C = a_1 C^{u_{11}(1+v_{11})} B^{u_{21}(1+v_{21})}$$

$$C^{1-u_{11}(1+v_{11})} = \frac{a_1}{b_1} B^{u_{21}(1+v_{21})}$$

$$C = [\frac{a_1}{b_1} B^{u_{21}(1+v_{21})}]^{\frac{1}{1-u_{11}(1+v_{11})}}$$

$$C = (\frac{a_1}{b_1})^{\frac{1}{1-u_{11}(1+v_{11})}} B^{\frac{u_{21}(1+v_{21})}{1-u_{11}(1+v_{11})}} \tag{27}$$

Now equation (24) becomes,

$$b_2C = a_2[(\frac{a_1}{b_1})^{\frac{1}{1-u_{11}(1+v_{11})}} B^{\frac{u_{21}(1+v_{21})}{1-u_{11}(1+v_{11})}}]^{u_{12}(1+v_{12})} B^{u_{22}-v_{22}}$$

$$C = \frac{a_2}{b_2}(\frac{a_1}{b_1})^{\frac{u_{12}(1+v_{12})}{1-u_{11}(1+v_{11})}} B^{\frac{u_{12}u_{21}(1+v_{12})(1+v_{21})}{1-u_{11}(1+v_{11})}+u_{22}-v_{22}}$$

$$C = \frac{a_2}{b_2}(\frac{a_1}{b_1})^{\frac{u_{12}(1+v_{12})}{1-u_{11}(1+v_{11})}} B^{\frac{u_{12}u_{21}(1+v_{12})(1+v_{21})+(u_{22}-v_{22})(1-u_{11}(1+v_{11}))}{1-u_{11}(1+v_{11})}}$$

$$\frac{b_2}{a_2}(\frac{b_1}{a_1})^{\frac{u_{12}(1+v_{12})}{1-u_{11}(1+v_{11})}} = B^{\frac{u_{12}u_{21}(1+v_{12})(1+v_{21})+(u_{22}-v_{22})(1-u_{11}(1+v_{11}))-1-u_{11}(1+v_{11})}{(1-u_{11}(1+v_{11}))}}$$

$$\frac{b_2}{a_2}(\frac{b_1}{a_1})^{\frac{u_{12}(1+v_{12})}{1-u_{11}(1+v_{11})}} = B^{\frac{u_{12}u_{21}(1+v_{12})(1+v_{21})+(1-u_{11(1+v_{11})(u_{22}-v_{22}-1)})}{1-u_{11}(1+v_{11})}}$$

$$\frac{b_2}{a_2}(\frac{b_1}{a_1})^{\frac{u_{12}(1+v_{12})}{1-u_{11}(1+v_{11})}} = B^{\frac{u_{12}u_{21}(1+v_{12})(1+v_{21})-(1-u_{11(1+v_{11})(1-u_{22}+v_{22})})}{1-u_{11}(1+v_{11})}}$$

Let,

$$\Delta = u_{12}u_{21}(1+v_{12})(1+v_{21}) - (1-u_{11(1+v_{11})(1-u_{22}+v_{22})})$$

Then, we have

$$\frac{b_2}{a_2}(\frac{b_1}{a_1})^{\frac{u_{12}(1+v_{12})}{1-u_{11}(1+v_{11})}} = B^{\frac{\Delta}{1-g_{11}(1+v_{11})}}$$

$$B = (\frac{b_1}{a_1})^{\frac{u_{12}(1+v_{12})}{\Delta}}(\frac{b_2}{a_2})^{\frac{1-u_{11}(1+v_{11})}{\Delta}} \tag{28}$$

Now equation (27) becomes,

$$C = (\frac{a_1}{b_1})^{\frac{1}{1-u_{11}(1+v_{11})}}[(\frac{b_1}{a_1})^{\frac{u_{12}(1+v_{12})}{\Delta}}(\frac{b_2}{a_2})^{\frac{1-u_{11}(1+v_{11})}{\Delta}}]^{\frac{u_{21}(1+v_{21})}{1-u_{11}(1+v_{11})}}$$

$$C = (\frac{b_1}{a_1})^{\frac{-1}{1-u_{11}(1+v_{11})}}(\frac{b_1}{a_1})^{\frac{u_{12}u_{21}(1+v_{12})(1+v_{21})}{(\Delta)(1-u_{11}(1+v_{11}))}}(\frac{b_2}{a_2})^{\frac{u_{21}(1+v_{21})}{\Delta}}$$

$$C = (\frac{b_1}{a_1})^{\frac{-1}{1-u_{11}(1+v_{11})}}(\frac{b_1}{a_1})^{\frac{u_{12}u_{21}(1+v_{12})(1+v_{21})-\Delta}{(\Delta)(1-u_{11}(1+v_{11}))}}(\frac{b_2}{a_2})^{\frac{u_{21}(1+v_{21})}{\Delta}}$$

$$C = (\frac{b_1}{a_1})^{\frac{-1}{1-u_{11}(1+v_{11})}}(\frac{b_1}{a_1})^{\frac{u_{12}u_{21}(1+v_{12})(1+v_{21})-u_{12}u_{21}(1+v_{12})(1+v_{21})-(1-u_{11(1+v_{11})(1-u_{22}+v_{22})})}{(\Delta)(1-u_{11}(1+v_{11}))}}$$

$$(\frac{b_2}{a_2})^{\frac{u_{21}(1+v_{21})}{\Delta}}$$

$$C = (\frac{b_1}{a_1})^{\frac{1-u_{22}+v_{22}}{\Delta}}(\frac{b_2}{a_2})^{\frac{u_{21}(1+v_{21})}{\Delta}} \tag{29}$$

3.4.1 Theoretical Investigation of the Model

we will study the qualitative aspects of system 4 only, as the equation (3) is decoupled from the system. Let (C_0, B_0) be the initial condition of the system, then a unique solution of 4 exists if $\delta_1 + \delta_{OL}, \delta_2 \geq 0$ and $C_0, B_0 > 0$. It is easy to see that 4 can be written as

$$\begin{aligned} \frac{dC}{C} &= a_1 B^{\delta_1+\delta_{OL}} - a_{ageing} b_1 dt \\ \frac{dB}{B} &= a_2 C^{\delta_2} - a_{ageing} b_2 dt, \end{aligned} \tag{30}$$

which gives the following solution

$$\begin{aligned} C &= C_0 e^{\int_{t_0}^{t} a_1 B^{\delta_1+\delta_{OL}} - a_{ageing} b_1 dx} \\ B &= B_0 e^{\int_{t_0}^{t} a_2 C^{\delta_2} - a_{ageing} b_2 dx}. \end{aligned} \tag{31}$$

By setting $\frac{dC}{dt} = \frac{dB}{dt} = 0$, following steady states have been obtained.
$(0, 0)$ if $\delta_1 + \delta_{OL}, \delta_2 \geq 0$ and

$$(\underline{C}, \underline{B}) = ((\frac{b_2 a_{ageing}}{a_2})^{\frac{1}{\delta_2}}, (\frac{b_1 a_{ageing}}{a_1})^{\frac{1}{\delta_1+\delta_{OL}}}), \tag{32}$$

which always exists. The jacobian of (4) around the steady state $(\underline{C}, \underline{B})$ is

$$J(\underline{C}, \underline{B}) = \begin{pmatrix} a_1 \underline{B}^{\delta_1+\delta_{OL}} - b_1 a_{ageing} & (\delta_1 + \delta_{OL})\underline{B}^{\delta_1+\delta_{OL}-1}(a_1 \underline{C}) \\ a_2 \delta_2 \underline{C}^{\delta_2-1} \underline{B} & a_2 \underline{C}^{\delta_2} - b_2 a_{ageing} \end{pmatrix} \tag{33}$$

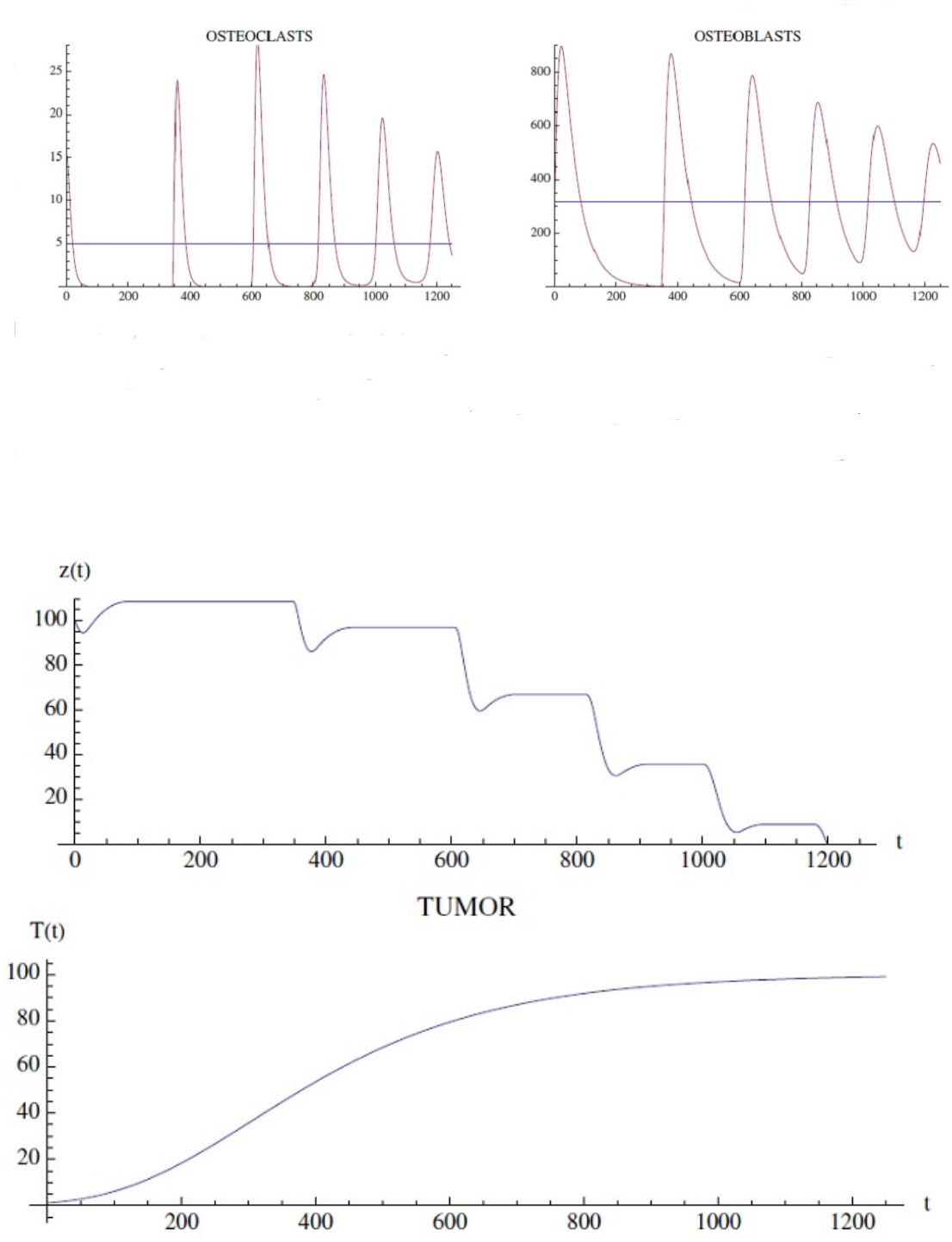

Figure 6: Bone Cells regulation in presence of tumor

The eigen values evaluated at the equilibrium poin $(\underline{C}, \underline{B})$ have a vanishing real part only if $(\delta_1 + \delta_{OL})\delta_2 \leq 0$ which a gives a unique positive periodic solution of 4. In next theorem the oscillatory behaviour of the nonlinear system (4) is shown.

Theorem 2

A unique positive oscillatory solution of nonlinear system (4) exists subjected to positive initial conditions and the property $(\delta_1 + \delta_{OL})\delta_2 \leq 0$.

Proof

System 4 implies

$$\frac{a_1 B^{\delta_1+\delta_{OL}} - a_{ageing} b_1}{B} dB = \frac{a_2 C^{\delta_2} - a_{ageing} b_2}{C} dC$$

which after integration yields

$$B^{-b_1 a_{ageing}} e^{\frac{a_1 B^{\delta_1+\delta_{OL}}}{\delta_1+\delta_{OL}}} = K C^{-b_2 a_{ageing}} e^{\frac{a_2 C^{\delta_2}}{\delta_2}},$$

where C represents the constant of integration. We define a new variable z as follows:

$$z = B^{-b_1 a_{ageing}} e^{\frac{a_1 B^{\delta_1+\delta_{OL}}}{\delta_1+\delta_{OL}}}.$$

Also we have

$$z = K C^{-b_2 a_{ageing}} e^{\frac{a_2 C^{\delta_2}}{\delta_2}},$$

where K is the constant of integration. To investigate the behaviour of $z(C, B)$, we consider the condition $(\delta_1 + \delta_{OL})\delta_2 \leq 0$. In particular let $\delta_1 + \delta_{OL} < 0$. This implies for $B \to 0$ and $B \to \infty$ we have $z \to \infty$, while for $C \to 0$ and $C \to \infty$ we have $z \to 0$. Now we determine the first order derivative of z w.r.t C,

$$\frac{dz}{dC} = K e^{\frac{a_2}{\delta_2} C^{\delta_2}} C^{-b_2 a_{ageing}-1} (-b_2 a_{ageing} + a_2 C^{\delta_2}).$$

A similar argument is obtained for $\frac{dz}{dB}$. It is clear that $\frac{dz}{dC} = \frac{dz}{dB} = 0$ at the equilibrium point $(\underline{C}, \underline{B})$ given in (32). The behaviour of the function z is depicted in Fig.. It is easy to see that as $z \to 0$, C exists but B vanishes. As C increases it intersects just one value of B. A further increment in the value of C gives intersection with two values of B. We have a similar scenario for B over C. It gives a closed curve in CB-phase plane where $B = B(C)$. Hence the solution of the (4) is oscillatory and positive.

3.4.2 External Agents Influencing the Osteoporotic Bone Turnover

In the following model, system (30) has been modified by including an external effects, produced by osteocytes, as a consequence of a mechanical strain applied. Such effect has been depicted in the form of a function $\gamma(t)$ which counts the RANKL produced by osteocytes along with its regulation by Sclerostin inhibition. So the system (30) takes the following form:

$$\begin{aligned} \frac{dC}{dt} &= B^{\delta_{21}+\delta_{OL}}(a_1 C + d_1 \frac{\gamma(t)}{C}) - a_{ageing} b_1 C \\ \frac{dB}{dt} &= a_2 C^{\delta_{12}} B - a_{ageing} b_2 B, \end{aligned} \tag{34}$$

where d_1 represents the proportionality constant. At present no precise functional form of $\gamma(t)$ is constructed so we assume a consistent input of osteoclasts and investigate the stability of the following system:

$$\begin{aligned} \frac{dC}{dt} &= B^{\delta_{21}+\delta_{OL}}(a_1 C + \frac{d_1}{C}) - a_{ageing} b_1 C \\ \frac{dB}{dt} &= a_2 C^{\delta_{12}} B - a_{ageing} b_2 B, \end{aligned} \tag{35}$$

3.4.3 Stability Analysis of the Model

Assume (C_o, B_0) be the initial conditions of system (35) ; $C_0, B_0 \geq 0$, for $\delta_1 \delta_2 < 0$ the system has a unique positive solution. The first equation of the system (35)

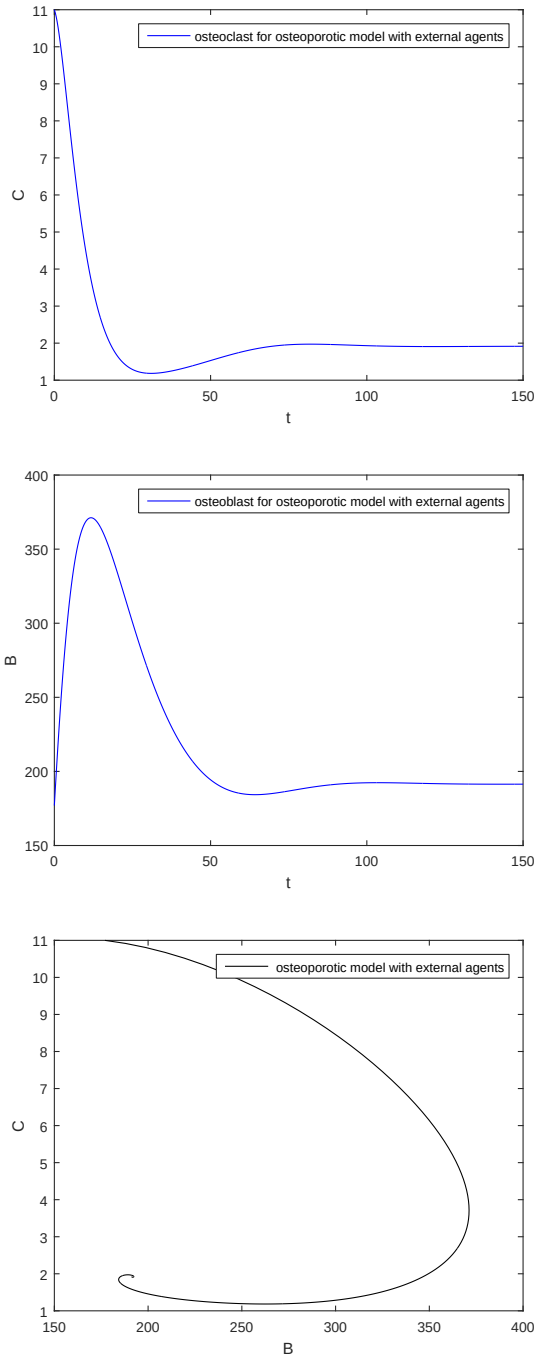

Figure 7: Graphical depiction of model.

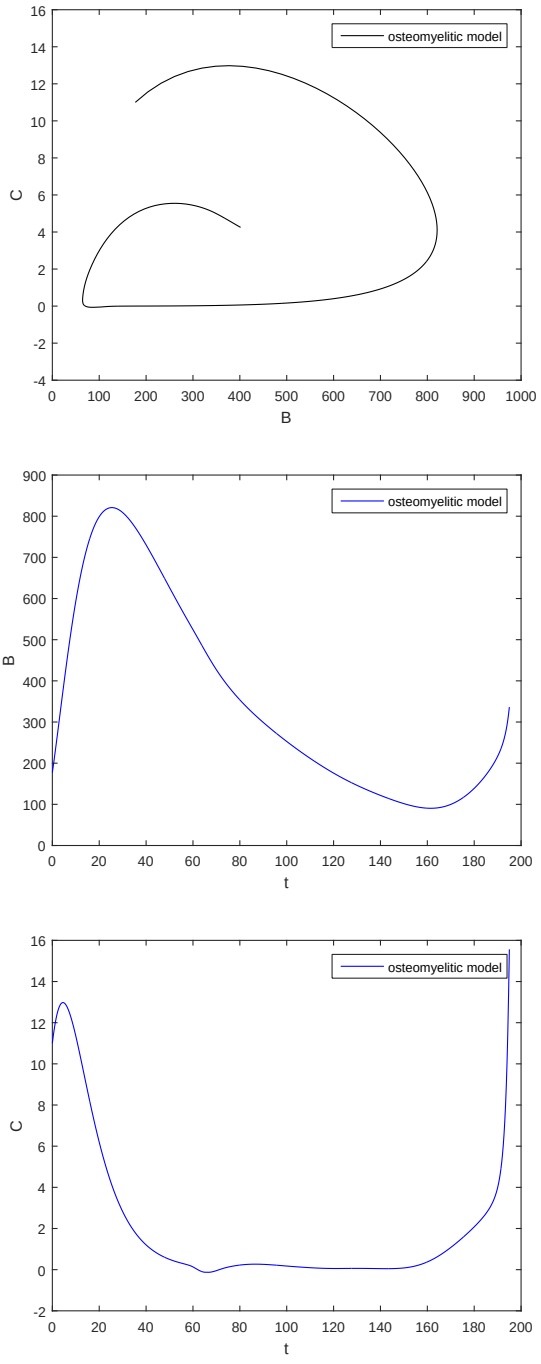

Figure 8: Graphical depiction of model.

gives the following form

$$\frac{dC}{dt} = C(a_1 B^{\delta_1+\delta_{OL}} - a_{ageing}b_1 + d_1\frac{B^{\delta_1}}{C^2}) \Rightarrow \frac{dC}{dt} > C(a_1 B^{\delta_1+\delta_{OL}} - a_{ageing}b_1),$$

which gives the following

$$C > C_0 e^{(\int_{t_0}^{t} a_1 B^{\delta_1+\delta_{OL}} - a_{ageing}b_1 dx)}.$$

Second equation of the system (35) implies

$$B = B_0 e^{(\int_{t_0}^{t} a_2 C^{\delta_2} - a_{ageing}b_2 dx)}.$$

The following unique steady state has been obtained by setting $\frac{dC}{dt} = \frac{dB}{dt} = 0$.
$(\underline{C}, \underline{B}) = ((\frac{b_2}{a_2})^{\frac{1}{\delta_2}}), (\frac{b_1\underline{C}^2}{a_1\underline{C}^2 + d_1})^{\frac{1}{\delta_1+\delta_{OL}}})$
The jacobian matrix of (35) is computes as following

$$J(\underline{C}, \underline{B}) = \begin{pmatrix} a_1\underline{B}\delta_1 + \delta_{OL} - b_1 a_{ageing} - d_1\frac{\underline{B}^{\delta_1+\delta OL}}{\underline{C}^2} & (\delta_1+\delta_{OL})\underline{B}^{\delta_1+\delta_{OL}-1}(a_1\underline{C} + \frac{d_1}{\underline{C}}) \\ a_2\delta_2\underline{C}^{\delta_2-1}\underline{B} & a_2\underline{C}^{\delta_2} - b_2 \end{pmatrix} \tag{36}$$

$\mathrm{tr}(J(\underline{C}, \underline{B}) = 0)$ and $\mathrm{Det}(J(\underline{C}, \underline{B}) > 0)$ at the non-trivial steady state value $(\underline{C}, \underline{B})$; $\delta_1\delta_2 \leq 0$. So dynamically we have a probable fulcrum for the system. Dulac's criterian has been implemented to show the nonexistence of the oscillatory solutions for the system (35).

Theorem 3

The nonlinear system 35 with the initial condition (C_0, B_0) provided that $\underline{C}, \underline{B} > 0$ and $\delta_1\delta_2 \geq 0$ exhibits a positive solution, which shows affinity towards the stable

equilibrium solution $(\underline{C}, \underline{B})$.

Proof

We consider the domain $\Gamma = \mathbb{R}^+ \times \mathbb{R}^+$, a simply connected region of 2D-plane, and the function $f(C,B) = \frac{1}{CB}$ continuously differentiable on Γ. Assume that $h(C,B) = B^{\delta_{21}+\delta_{OL}}(a_1 C + \frac{d_1}{C}) - a_{ageing} b_1 C$, and $k(C,B) = a_2 C^{\delta_{12}} B - a_{ageing} b_2 B$, it is easy to see that the functions $h(C,B)$ and $k(C,B)$ are equal to the R.H.S of system 35. Then

$$f(C,B)h(C,B) = \frac{(a_1 B^{\delta_{21}+\delta_{OL}-1} - a_{ageing} b_1)}{B} + d_1 \frac{B^{\delta_1+\delta_{OL}-1}}{C_1^2}$$

$$f(C,B)k(C,B) = (\frac{a_2 C^{\delta_2} - a_{ageing} b_2}{C}).$$

As

$$\frac{\partial(fh)}{\partial C} + \frac{\partial(fk)}{\partial B} = -2d_1 \frac{B^{\delta_1+\delta_{OL}} - 1}{C^3}$$

is not equal to zero and does not switch sign in the region Γ, so it implies the nonexistence of closed orbits in Γ.

3.5 Osteomyelitic Model

Like (4), taking into account the autocrine and paracrine signaling of osteoclasts and osteoblasts along with the drug therapy of bisphosphonates, the osteomyelitic model is defined as follows:

$$\begin{aligned} \frac{dC}{dt} &= a_1 C^{\delta_{11}(1+\gamma_{11}\frac{V}{m})} B^{\delta_{21}(1+\gamma_{21}\frac{V}{m})} - b_1 C \\ \frac{dB}{dt} &= a_2 C^{\delta_{12}(1+\gamma_{12}\frac{V}{m})} B^{\delta_{22}-\gamma_{22}\frac{V}{m}} - b_2 B \\ \frac{dV}{dt} &= a_V V \log(\tfrac{V}{m}), \end{aligned} \tag{37}$$

where $\delta_{ij}\, i,j = 1,2$ are the autocrine and paracrine factors defined as previously. a_V is the production rate of bacterium (V) and m represents the maximum carrying

capacity of V. This model has been inspired by the Lio's work defined in [**?**]. The term $\gamma_{ij}\frac{V}{m}$ couple the bacterium density and its maximum size to power law for C/B interactions. The following assumptions have been made to incorporate the effects of S.aureus in the model.

- $\delta_{11}(1+\gamma_{11}\frac{V}{m}) > \delta_{11}$ (showing the stimulated expression of osteoclasts autocrine factors),
- $\delta_{21}(1+\gamma_{21}\frac{V}{m}) > \delta_{21}$ (showing the elevated paracrine effect of B onto C produced by decreased OPG and increased RANKL expression),
- $\delta_{12}(1+\gamma_{12}\frac{V}{m}) < \delta_{12}$ (showing decreased osteoclasts-released paracrine effects on osteoblasts),
- $\delta_{22} - f_{22}\frac{V}{m} < g_{22}$ (showing decreased promotion of osteoblasts autocrine factors).

Parameter Values		
Parameter	Description	Value
a_1	C-differentiation rate	3/day
a_2	B-differentiation rate	4/day
b_1	C-apoptosis rate	0.2/day
b_2	B-apoptosis rate	0.02/day
δ_{11}	autocrine effect of C	1.1
δ_{12}	paracrine effect of B onto C	1
δ_{21}	paracrine effect of C onto B	0
δ_{22}	autocrine effect of B	-0.5
γ_{11}	effect of virus on δ_{11}	0.005/day
γ_{12}	effect of virus on δ_{12}	0/day
γ_{21}	effect of virus on δ_{21}	0.2/day
γ_{22}	effect of virus on δ_{22}	0.005/day
s_1	bone removal rate	0.0748/day
s_2	bone formation rate	0.0006395/day
m	virus carrying capacity	100
a_V	virus growth rate	0.005/day
T	effectiveness of treatment	add
T_{treat}	treatment dosage time	(200,400,600) days
a_{ageing}	ageing factor	2
δ_{OL}	RANKL effect	0.1
$\underline{C}$	steady level of C	(Control,Osteoporosis,Osteomyelitis)=(1.16,1.78,5)
$\underline{B}$	steady level of B	(Control,Osteoporosis,Osteomyelitis)=(231.72,177.91,316
C_0	initial value of C	(Control,Osteoporosis,Osteomyelitis)=(11.16,11.78,15)
B_0	initial value of B	(Control,Osteoporosis,Osteomyelitis)=(231.72,177.91,316
Y_0	initial value of Y	(Control,Osteoporosis,Osteomyelitis)=(1,1,1)

Hence, in this section we describe the mathematical models of bone remodeling which are osteoporotic model, Zero dimensional bone model without tumor, Zero dimensional bone model with tumor, Osteomyelitis effect on bone remodeling, stability analysis of the model and osteoporotic model.

3.6 Numerical Simulations

The inspiration behind this scheme is that one can now solve the normalized boundary value problem, although nonlinear, quite easily, both using analytic and numerical schemes. The most widely employed numerical method for the boundary value problems is the collocation method. The advantage of this method is that, it reduces the nth order differential equation(s) into n first order differential equations, thus reducing the computational cost on a large domain with small step size and a range of parameters. We have simplified the three systems using the Generalized Collocation Method (GCM) [71]. Collocation methods are basically implicit Runge-Kutta quadrature techniques [65].

From figure 1 it is obvious that the bone turnover during osteoporosis is more crucial. From figure 2, we can see that the external agents effect the concentration of osteoblast and [10]. Figure 3 provides the bone dynamics of the case where the osteomyelitis diseases effects are taken into account [10]. We can see that the bone dynamics now changes exponentially [4].

Chapter 4

4 Discussion

4.1 Discussion

In this thesis stability analysis of the mathematical models for osteoporotic and osteomyelitic bone turnover is checked. Osteoporosis and osteomyelitis are very common bone disorders having different incident causes. Osteoporosis occurs due to several factors like age, estrogen deficiency or an imbalance in bone remodeling process, while osteomyelitis is caused by a bacterium called Staphylococcus aureus, a type of staph bacteria. We examined the expository signaling among the bone cells named as osteoclast and osteoblast. Main functioning of osteoblasts is bone formation while osteoclasts are bone removal cells. Mathematical frame works for both pathologies comprising of the communication between osteoclasts and osteoblasts have been presented to exhibit the conditions for stability in normal and dysregulated bone turnover. The percentage ratios of the population of osteoblast/osteoclast have been determined via numerical simulations. The remedial upshots of targeting both osteomyelitic and osteoporotic cells participating in such processes are examined. This work not only studies the dynamics of osteoporotic and osteomyelitic bone turnover but also exemplifies how therapeutic approaches might be inspected via such computational methodologies.

4.2 Open Problems

Problem 2 *The models of osteoporosis discussed in the thesis can be extended by adding the role of different drug therapies like denosumab,bisphosphonates and vitamin-D.*

Problem 3 *External Mechanical strain can influence the bone diseases so its effect can also be included in osteoporotic and osteomyletic models.*

Chapter 5

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