A DYNAMIC SIMULATION MODEL FOR LONG TERM BONE MASS HOMEOSTASIS AND OSTEOPOROSIS

by

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ABSTRACT

A DYNAMIC SIMULATION MODEL FOR LONG TERM BONE MASS HOMEOSTASIS AND OSTEOPOROSIS

Osteoporosis is a skeletal disorder related to low bone mass and increased risk of fracture. Although it is seen in both sexes, the disease is more prevalent among women after menopause. Decreased estrogen level, altered physical activity and insufficient dietary calcium supplementation are the basic causes of the disease. A considerable percent of postmenopausal and women aged over 80 are affected by osteoporosis. There is an increasing mortality and morbidity rate related to osteoporotic fractures. The goal of this thesis is to construct a dynamic simulation model that can realistically reproduce long term behaviour of postmenopausal bone loss. For this purpose, a system dynamics model is built which focuses on bone's mechanical properties and its interactions with calcium homeostasis system in blood. Comparisons with available data indicate that the model realistically reproduces the behaviour of bone loss for both menopausal and nonmenopausal causes in women. Experiments with the model demonstrate that keeping peak strains above disuse threshold is essential in bone health. Both medical and non-medical interventions work for treating bone loss after menopause, but drug therapies are most influential in treating osteoporosis. For avoiding non-menopausal losses, simulation experiments show that calcium supplementation is essential in pre and post-menopausal years.

ÖZET

UZUN DÖNEMLİ KEMİK KÜTLESİ ÖZDENGESİ ve KEMİK ERİMESİ ÜZERİNE BİR DİNAMİK BENZETİM MODELİ

Osteoporoz, düşük kemik kütlesi ve artan kırılma riski ile ortaya çıkan bir iskelet hastalığıdır. Her iki cinsiyette de görülmesine rağmen, hastalık kadınlar arasında menopoz sonrasında oldukça sık görülmektedir. Hastalığın temel sebepleri arasında azalan östrojen seviyesi, değişen fiziksel aktivite alışkanlıkları ve yetersiz kalsiyum alımı sayılabilir. Postmenopoz kadınların ve seksen yaşını geçmiş kadınların önemli bir oranı osteoporozdan etkilenmektedir. Osteoporotik kırılmalarla ilişkin artan bir ölüm oranı gözlenmektedir. Bu tezin amacı, postmenopozla ilişkili kemik kaybının uzun dönemli davranışını gerçekçi bir şekilde üreten bir dinamik benzetim modeli kurmaktır. Bu amaçla, kemiğin mekanik özellikleri ve kandaki kalsiyum dengesiyle ilişkileri üzerine odaklanmış bir sistem dinamiği modeli kurulmuştur. Elde edilen tıbbi verilerle yapılan karşılaştırmalar göstermektedir ki model, kadınlarda hem postmenopoz hem de menopoz haricindeki sebeplerle oluşan kemik kaybının davranışını gerçekçi bir şekilde üretmektedir. Model ile yapılan deneyler kemik sağlığı açısından kemik dokusundaki gerilmelerin belli bir eşik değerin üzerinde tutulmasının çok önemli olduğunu göstermektedir. Medikal ve medikal olmayan müdahalelerle menopoz sonrası kemik kaybını iyileştirmek mümkündür ancak osteoporoz tedavisinde en etkili yöntemler ilaç ve hormon tedavileri olarak öne çıkmaktadır. Benzetim deneyleri, menopoz dışı kemik kaybını önleyebilmek için, hem menopoz öncesi hem de sonrası kalsiyum alımının önemine işaret etmektedir.

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LIST OF ACRONYMS/ABBREVIATIONS

ALN	Alendronate
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMU	Basic Multicellular Unit
BR	Birth Rate
ECF	Extra Cellular Fluid
FD	Formation Deficient
FDA	Food and Drug Administration
HRT	Hormone Replacement Therapy
OB	Osteoblast
OC	Osteoclast
PTH	Parathyroid Hormone
SD	Standard Deviation
SCI	Spinal Cord Injury
TT	Transition Time
WHO	World Health Organization

1. INTRODUCTION

Bone is a living dynamic tissue that renews itself via remodeling throughout adult human life. After the construction of mature skeleton, there is always a loss even in small degrees in every person. This is because of the negative bone balance left after remodeling process. Indeed, every person is likely to develop osteoporosis due to this loss, if given a sufficiently long life span. Osteoporosis is a skeletal disease. It reveals with low bone mass and increased risk of fractures in the progressive years. Although, the disease is seen in both sexes, it is more prevalent in women because of the hormonal changes encountered with the onset of menopause. Besides the effect of reducing life quality in older ages, the increased expenditures related to treatment and management of osteoporosis oriented the involved parties to take preventive actions for the disease. There are several procedures for both prevention and treatment of osteoporosis. Nutrition, exercise, drug and hormone therapies are the principal interventions in the literature.

Men and women have different bone loss dynamics. Women have a rapid bone loss after menopause because of the increasing remodeling rate stimulated by the reduced estrogen level. A considerable amount of bone is lost in this phase. After this rapid phase, a slow and continuous phase starts and it lasts to the end of life. This slow phase is related to aging effects on bone mass. Men face only this slow phase in their life. Osteoporosis mostly shows itself with a fracture. One third of the osteoporotic fractures end up with death in the following years.

The principal regulator of bone mass homeostasis is the strain magnitude that is felt by bone tissue. Special bone cells receive external signals and restructure bone tissue. When peak bone strains fall below a threshold value, bone perceives disuse and acts so as to increase the peak strains above the threshold again. On the other hand, if peak strains exceed a threshold, microdamage accumulates in the bone and this time bone acts for removing them. The first process is governed by a negative feedback mechanism while the second one constitutes a positive feedback loop. Estrogen drop in menopause produces the same effect as disuse.

Calcium and bone mass homeostasis are intertwined mechanisms in the body. Bone needs calcium for renewing or building itself and the blood needs to keep calcium level in between some strict levels. In this relationship, calcium homeostasis has priority over the bone mass homeostasis because calcium is very crucial for the vital activites. Thus, when calcium is scarce in the body, it is removed from bone in the expense of bone loss.

In this study, both mechanical regulations in bone tissue and calcium homeostasis are considered in a single model. The aim of study is to construct a dynamic model in order to observe the long term behavior of bone mass and to test some interventions for prevention or treatment of post-menopausal bone loss in women.

In the following section, a review of bone mass regulation in the body and mechanisms of osteoporosis will be provided. Next, the system dynamics model will be presented that comprises both calcium and bone tissue structures. In the following sections, base behavior of the complete model and validation of the behaviours will be demonstrated. In the scenario analysis section, principal interventions for both premenopausal and postmenopausal women will be tested and findings will be summarized in the conclusion chapter.

2. LITERATURE SURVEY ON BONE MASS HOMEOSTASIS AND OSTEOPOROSIS

Osteoporosis can be defined as "a systemic skeletal disorder specified by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture" (Cooper, 1999). According to WHO, 30% of postmenopausal women and 70% of women aged over 80 are affected by osteoporosis (Fazzalari, 2008). In the US, every year at about 1.3 billion fractures have been associated with osteoporosis. It is estimated that 40% of women in US will have at least one fragility fracture in their lifetime. 14.5% of women will have repeated hip fractures and 25% will have vertebral fractures. In a population based study held in Turkey, the prevalence rate of osteoporosis was found to be 14.2% in rural and 15.2% in urban region (Arslantas *et al.*, 2008). 24000 hip fractures are estimated in Turkey in 2009 and 73% of which are found in women. In 2035, the number is expected as 64000 (Tuzun *et al.*, 2011).

Bone Mineral Density (BMD) is a widely used measurement for the diagnosis of the disease. Bone density can be expressed as standard deviations according to a reference population because of its normally distributed nature, irrespective of the measurement technique. According to BMD analysis, t-score with 2.5 SD or more below of the young healthy women mean is accepted as osteoporosis (Kanis *et al.*, 2008). In healthy human, BMD of the skeleton increases during growth by modeling and at about age 20, it peaks and stops growing. After maturity, bone tends to conserve its mass and starts to renew itself via remodeling different from modeling. Remodeling is a coupled process of bone resorption and bone formation. This is a complex process which involves a variety of biochemical and mechanical factors. Failure in these processes results in common diseases, such as osteoporosis.

Remodeling is achieved by a group of bone cells known as Basic Multicellular Unit (BMU). Old bone is removed by osteoclasts (Resorption) and then refilled with newly formed bone by osteoblasts (Formation). This sequence of events requires about three or four months to be completed at each remodeling location and typically leaves a slight formation deficient behind. Bone loss occurs throughout adult human life at least in small

degrees. At any moment, $2x10^6$ BMUs act in the whole skeleton and $6x10^6$ BMUs become completed annually (Frost, 1990). The goals of remodeling are; serving as a mineral reservoir in the extracellular fluid (ECF) by participating in plasma calcium homeostasis, repairing bone by removing damage occurred by successive mechanical loading and finally preserving bone's mechanical integrity in order to provide a rigid skeleton to the body (Burr, 2002).

Although osteoporosis is seen in both sexes, it is more frequent among women. Women experience two phases of osteoporosis. First phase is rapid and transient and accounted for the loss of sex hormones, second phase is more slow and related to aging. Women lost 20-30% of their cancellous bone and 5-10% of their cortical bone in the rapid phase. This rapid phase lasts about a decade. According to the differences among women, sometimes bone loss precedes menopause. At the end of the rapid phase, bone loss slows down and merges with the slow phase asymptotically (Riggs *et al*., 1998). This second slow phase continues throughout human life. These two phases are also named as Type I and Type II osteoporosis respectively. The early rapid phase is commonly attributed to the decrease of sex hormones with the onset of menopause in women. Estrogen is believed to have an effect on bone cells and suppress their actions thus it balances bone formation and bone resorption. When this effect is lost with the decrease of the hormone level, remodeling is stimulated and bone loss occurs. Menopause causes an imbalance of 25% between formation and resorption (Heshmati *et al.*, 2002). The effect of estrogen is explained by the role of the hormone in mechanical properties of the bone. With the decrease of the estrogen level, bone mass decreases as in the weightlessness state.

Bone adjusts itself in response to changing mechanical environment in order to maintain its integrity. When mechanical stimulus is below some threshold value, bone removes the excess bone tissue and manages to increase the peak strain above this threshold value. Depending on the strain rate, a considerable amount of bone loss occurs. Estrogen loss follows this pattern too. Frost hypothesized that when estrogen level decreases, the threshold value increases and bone perceives a spurious disuse and bone loss is accelerated in order to adapt to the new state (Frost, 1999). The second slow phase is attributed to the age related changes in human body. With aging, the absorption of calcium from the gut decreases. Parathyroid hormone is responsible for the maintenance of calcium

level in Extra Cellular Fluid (ECF) in calcium homeostasis. When calcium is scarce, secretion of PTH is stimulated. PTH increases Calcium level through its effects on kidney, bone and gut. In kidney, it increases the reabsorption of calcium ions and decreases calcium lost. In bone, it increases calcium release from bone and provides a calcium supply to the ECF. In gut, it stimulates the hydroxylation of calcitriol hormone which is a vitamin D metabolite, and increases the absorption of calcium from the gut by increasing the level of calcitriol.

Dietary calcium intake is an essential component of bone health. Calcium provides mechanical rigidity and strength to the bones and teeth and 99% of bodily calcium is stored in the skeleton. Remaining 1% of body calcium is in ECF and the ECF calcium level is under strict control of several hormones in the body because of its importance in metabolic events. Bone serves as a mineral reservoir for ECF and when the obligatory calcium losses exceed calcium absorption from gut, bone releases calcium into ECF until absorption returns back to normal levels. During growth, calcium requirement of the body is maximum. After skeletal maturation, the calcium requirement decreases. Depending on the individual changes among people, average recommended calcium intake for adult human is 1000 mg/day for the maintenance of healthy skeleton. During lactation, pregnancy and after menopause, this value can increase (Murray, 1996). On the other hand, it has been observed that body can adjust itself to the calcium intake levels as small as 200 mg/day. Despite the recommended calcium intake levels, in the most of countries, dietary calcium is not close to this value.

Mechanical forces also affect bone health. Bone's ability to adapt its mechanical properties in response to altered loading conditions is crucial for its integrity. Bone adapts itself to its mechanically changing environment by increasing or decreasing its density through modeling and remodeling respectively. It has been postulated that bone cells (known as osteocytes) are able to sense the mechanical loadings and take action when these loadings fall outside of some threshold values (Martin, 2000). This process is termed as bone's adaptation. Frost defines bone's adaptation by "mechanical usage windows" and states that bone can adapt to underloading as well as overloading (Frost, 1992). Loading history of bone is the main determinant of its health. When the peak bone strains are below some threshold value (100 microstrain), bone undergoes remodeling and decreases its

mass. When the peak strains are above some threshold value (3000 microstrain), microdamage accumulates in bone matrix and this time remodeling increases in order to remove damage and prevent loss of stiffness. Between these thresholds, remodeling conserves bone tissue. There are several studies that observe the effects of weightlessness on bone density. Space flight, post SCI (spinal cord injury) and bed rest cause significant bone losses in adult human. In a 17 weeks of bed rest, 10.4% and 3.9% of bone losses observed in calcaneus and spine respectively. During the 6-month re-ambulation period, BMD increased towards the pre-bed rest levels, however only some parts of the skeleton showed 100% of gain (Leblanc *et al.*, 1990).

Accordingly, weight bearing activities also provide alterations in the bone mass even after growth. In a 12-month weight lifting exercise study, mean change in vertebral bone density is 0.89% in premenopausal women (Gleeson *et al.*, 1990). However, depending on the calcium supplementation and the loading history of the subjects, bone gain levels differ among individuals and among pre and post-menopausal women.

As a result of every day activity, microdamage accumulates in the bone matrix in the form of microcrack (Zioupos, 2000). Bone removes these microcracks by remodeling. With the increasing age, micodamage density in the bone increases and alters the rate of remodeling. As remodeling spaces increase, bone loses its stiffness and this results even more loads on the bone tissue. Bone can collapse in the extreme cases.

There are many modeling studies in the field of bone mass homeostasis and osteoporosis research. Most of them do not consider bone-blood calcium exchange mechanisms. In the study of Hazelwood et.al, a simulation model is built that shows the changes in the porosity and activation frequency of the bone resulted from bone remodeling stimulated by disuse and damage (Hazelwood *et al.*, 2001). Activation frequency (number of BMUs reaching a remodeling site in a given period of time in a unit of bone surface) is formulated by a function of disuse and damage separately. In disuse, both activation frequency and porosity increase, and after a while activation frequency returns to normal levels, but porosity remains high. With the increasing damage rate, bone renews itself by remodeling, however, when bone is loaded too much, activation frequency and porosity increase rapidly until a fracture occurs. Other modeling studies are devoted to

the interactions between osteoblasts and osteoclasts and their population dynamics and simulate over very short periods of time. There are also studies that discuss the bone's adaptation mechanism as a dynamic stochastic and optimal control problem (Langton *et al.*, 1998 and Lekszycki, 2005). Most of these studies do not observe the long term dynamics of bone mass homeostasis.

3. RESEARCH OBJECTIVES AND OVERVIEW OF THE MODEL

The purpose of this study is to develop a dynamic model which would describe the long term dynamics of bone mass homeostasis with specific focus on osteoporosis disease. Although osteoporosis is diagnosed in both men and women, the model will be constructed for an adult woman physiology because of the severity of the disease among women. In the context of disease literature, there are several conflicting recommendations for preventing the disease or reducing the risks of it. By this study, it has been aimed to find out the relative effectiveness of several treatment procedures and protective actions on the disease.

System Dynamics modeling and simulation methodolody is used in this study (Sterman, 2000). The focus of System Dynamics method is to anticipate the dynamic behaviours of a system by applying alternative policies. Systems approach of system dynamics methodology is suitable for modeling physiological systems, because controling physiological system depends on a good interpretetation of the whole physiology, and a prospect of the overall system response to a series of interventions (Karanfil, 2005).

The focus of the model is the bone's mechanical properties. Bone is a dynamic tissue that adjusts itself to its mechanically changing environment. Normal adult human's mechanical usage falls between some limits. When mechanical strains fall below this limit, bone perceives disuse. Disuse is defined by a too low stress level that a person is exposed to. Disuse accelerates the activation of bone cells and bone loss continues until a new steady state occurs. After the felt strain exceeds the threshold level, bone loss decreases. Similarly, in overuse, microdamage accumulates in the bone and the activation of bone cells is stimulated in order to remove damaged bone part and form a new one.

The main contributor of the osteoporosis disease is the decrease in the estrogen level after menopause. Bone tissue perceives a spurious disuse when estrogen level decreases. Thus, with the onset of menopause, bone undergoes an accelerated bone loss that saturates to a new steady state in several years. This is the first rapid phase of the disease and dependent on the estrogen level. The second phase is slower and continues for lifetime. Aging effects have the main role in this slow phase.

Bone is one of the organs that are involved in Calcium homeostasis. 99% of the calcium is stored in the skeleton. Therefore, when calcium is scarce in the body, bone releases calcium into the extracellular fluid and helps to maintain calcium concentration in between the set levels. If the release continues for a long period of time, a considerable amount of bone is lost. Vitamin-D level is effective in calcium absorption from the intestine and is affected by estrogen level in body. When estrogen level decreases with advancing age, vitamin D level decreases and there will be calcium lost from the intestine.

The above dynamic hypothesis in terms of a broad causal-loop diagram is given in Figure 3.1:

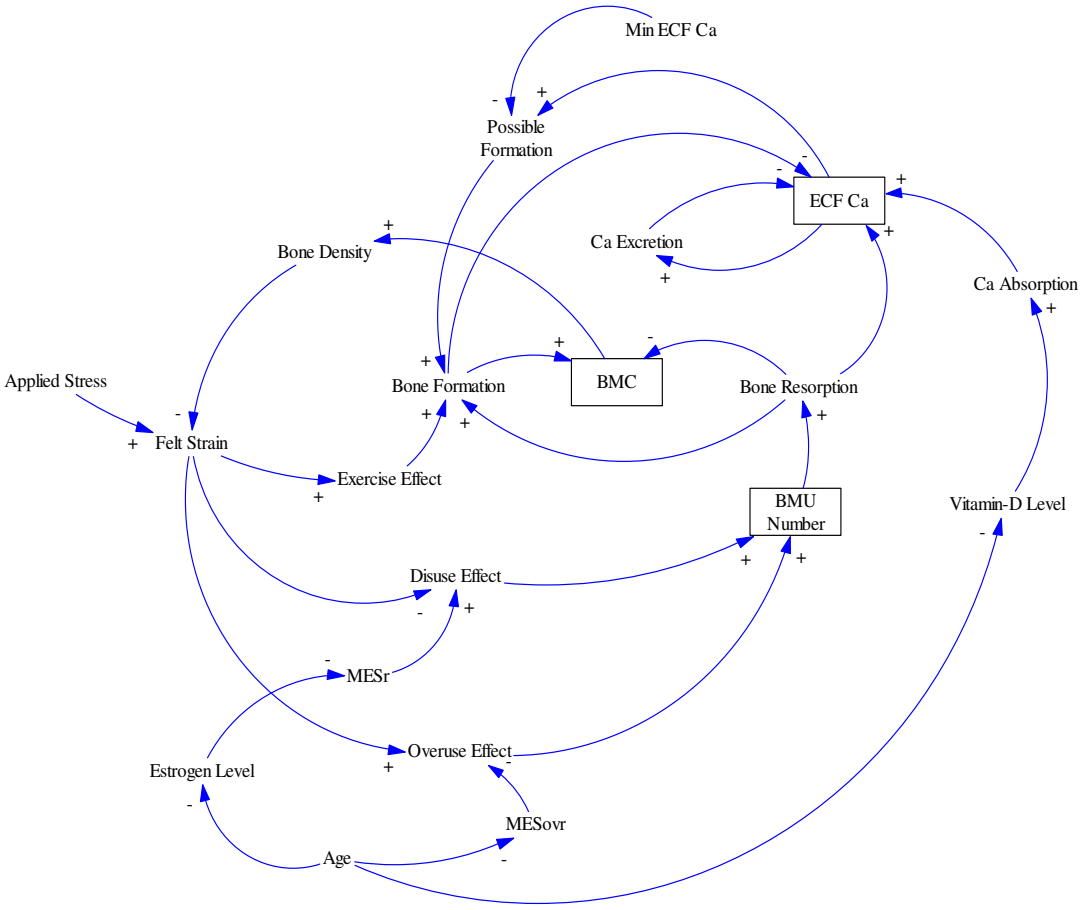

Figure 3.1. A Causal-Loop Diagram Depicting the Major Loops and Variables.

4. DESCRIPTION OF THE MODEL

4.1. Bone Mass Sector

4.1.1. Background Information

BMC refers to Bone Mineral Content of third lumbar vertebrae of human spine in this model. Bone is mostly comprised of calcium minerals, thus BMC is considered by total calcium content of the bone. Desired BMC is the desired level of mineral content which is regulated by Resorption and Desired Formation. In the low levels of calcium content in the body, calcium is removed from bone to blood, thus formation is delayed until the calcium content of the body returns to normal. BMU refers to Basic Multicellular Unit which is composed of bone resorbing and forming cells namely; osteoclasts (OC) and osteoblasts (OB). Remodeling refers to the combination of bone formation and bone resorption processes. As a result of remodeling, bone mass decreases or does not change but never increases. However, in modeling, bone mass increases or does not change but never decreases.

4.1.2. Fundamental Approach and Assumptions

Osteoporosis is diagnosed by bone mineral density measurement of several parts of the skeleton. Most of these skeletal parts are femur, tibia and vertebrae. Because of the osteoporosis fractures are common in vertebrae; lumbar spine of human vertebrae is modeled in this study. While a small portion of the skeleton is modeled in this sector, the flows between this sector and calcium sector are multiplied with a fraction to represent the whole skeleton.

Formation and Resorption are the processes that are achieved by bone cells and constitute a number of events including releasing Ca from bone and taking calcium from ECF. In the context of this model, these processes are the names of the calcium exchange with ECF. Resorption refers to the amount of calcium released to ECF and formation refers to the amount of calcium that is taken from ECF in a remodeling cycle. These two events

are different from the other calcium exchange mechanisms that are not cellular events but physio-chemical reactions.

Bone is composed of cancellous (trabecular) and cortical surfaces. Trabecular bone has a porous structure and forms the inner sides of the long bones and small bones. Cortical bone is rigid and constitutes the outer surface of the bones. Bone loss dynamics for these two bone types are different from each other. Because of the lumbar spine is mostly composed of trabecular bone, reference values for lumbar vertebrae are selected according to trabecular bone structure.

Applied stress is assumed as the peak bone strain that bone perceives in one week in its mechanical environment. The influences of body fluids flow are ignored in this study. In steady state level, stress is occurred because of the daily activities of human. In everyday activities, bone strains never exceed the threshold level for bone modeling.

After completion of bone formation, 80% of bone mineralization is occurred. Remaining mineral requirement is fulfilled during a long period of time. Therefore, Desired BMC is modeled as the ideal bone mineral content level that the bone desires to reach.

Variables and constants that are used in the bone mass sector are given in Table 4.1 and Table 4.2.

Table 4.1. Variables and Initial Values in Bone Mass Sector.

Variable Name	**Initial Value**	**Unit**
Bone Mineral Content	9436	mg
BMU Population	786.7944	BMU Number
Applied Stress	0.05	MPa
Normal Estrogen Level	1	Unitless
Normal MESr	100	Microstrain
Desired BMC	9436	BMU Number

Table 4.2. Constants Used in Bone Mass Sector.

Constant Name	Value	Unit
Normal Formation	4.3929	mg/week
Normal Transition Time	2	Week
Normal Formation Deficient	10	%
Bone Volume	52.51	cm^3
Average Resorption per BMU	0.005583	mg/week/BMU
Normal BMU Birth Rate	0.0469	BMU/week
Area of Bone Surface	1398	mm^2
Lifetime of BMU	12	week
Microstrain Converter	1000000	unitless
Normal MES Modeling	1000	Microstrain
Normal MES Overuse	3000	Microstrain
BMC Adjustment Time	520	week
Conversion Coefficient	100	unitless

4.1.3. Description of the Bone Mass Sector Structure

This sector has two stocks; BMU Number and Bone Mineral Content. BMU Number is changed with its flows BMU Birth Rate and BMU Death Rate. BMU Birth Rate does not have the same meaning with population birth rate. In the context of the bone mass homeostasis, "Activation Frequency" is used to explain the number of BMUs that reach the remodeling space per mm^2 per day. BMUs are composed of the OBs and OCs. The population dynamics of these cells are more complex and include many biochemical and physiochemical reactions. These mechanisms are beyond the boundary of this model. Thus, BMU Birth Rate is mainly determined by the activation frequency of bone cells. In the model, normal value for activation frequency is set as Normal BMU Birth Rate. Bone Surface Area refers to the area of bone affected by remodeling. BMU Birth Rate is affected by the changes of the felt mechanical strain in bone tissue. In disuse and overload, BMU Birth Rate is increased by different rates. BMU Death Rate is formulated by BMU Population divided by Lifetime of BMU.

$$BMU\_Death\_Rate = BMU\_Population/Lifetime\_of\_BMU \quad (1)$$

BMU Birth Rate=Normal BMU Birth Rate x Area of Bone Surface x E of Disuse on BR x E of Overuse on BR (2)

Bone Mineral Content is changed by Formation and Resorption. In a remodeling cycle, OCs appear on the remodeling site at first and remove bone tissue. After they disappear, there is a Transition Time until OBs appear on the remodeling site. Normal value of Transition Time is about two weeks. OBs refill the resorption cavities and the remodeling cycle is completed. Thus, the changes in the BMU Population first affect the resorption rate. Resorption rate is formulated by the Average Resorption Rate per BMU times BMU Population.

Resorption = BMU_Population x Avrg_Resorption_per_BMU (3)

Perceived_Resorption = DELAY3(Desired_Resorption,Transition_Time) (4)

After growth of mature skeleton, formation is generally completed with a slight deficient in adult human. The average value of this formation deficient per remodeling period is set to 6%. This leads to a regular small decrease in bone mass throughout adult human life. Formation is also affected by exercise. It is possible to increase bone mass in a limited degree with training weight bearing activities. When the bone's peak felt strain falls between 2000-3000 microstrain, bone formation occurs without resorption. (In this model, formation threshold is set to 1000 microstrain because of the formulating difficulties met in the model.) The effect of exercise is multiplied with a variable called Normal Formation. Normal Formation is taken as the formation rate that would occur if there is not a deficient following resorption in a normal strain condition. Thus, Desired Formation is equal to the delayed resorption rate with a small deficient plus the effect of exercise on bone formation. The graphical function of *Effect of Exercise on Bone Formation* is given in Figure 4.1

Desired_Formation = Perceived_Resorption x (1-Formation_Deficient) + (E_of_Exercise_on_Bone_Formation-1) x Normal_Formation (5)

Formation rate depends on the available calcium level in the ECF. If there is a lack of calcium in the body or ECF needs an urgent calcium supply, formation is not fulfilled or is partially fulfilled. The amount of Calcium that is released to bone for bone formation is modeled as *Ca_Release_Formation* and *Formation* is equal to this variable divided by conversion coefficient.

$$Ca\_Release\_Formation = Available\_Ca \times E\_of\_Available\_Ca \quad (6)$$

$$Formation = Ca\_Release\_Formation/conversion\_coeff \quad (7)$$

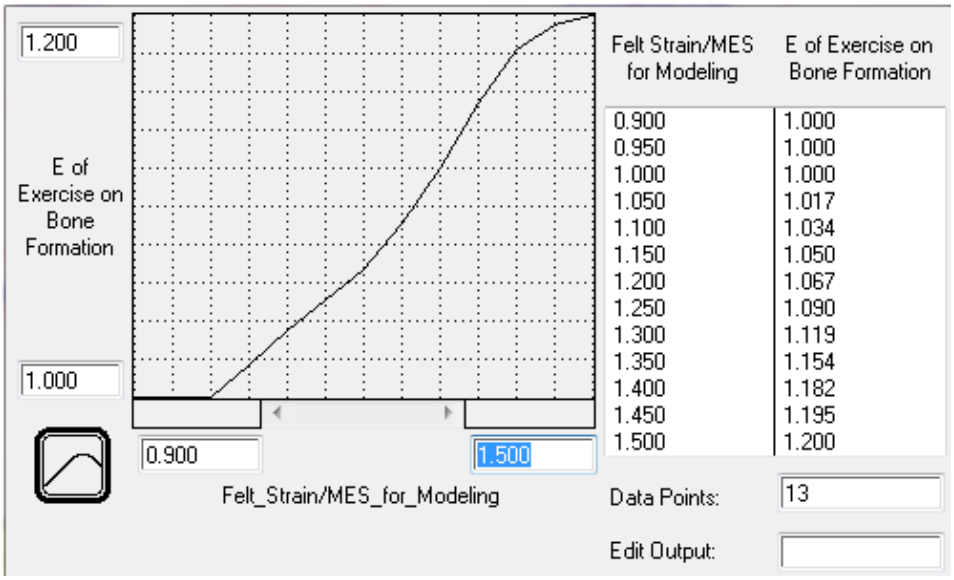

Figure 4.1. Effect of Exercise on Bone Formation.

When ECF Ca is not in its set value, an amount of calcium equal to the difference is removed from bone. Ca Release ECF refers to this flow and formulated as in Equation 8.

$$Ca\_Release\_ECF = Ca\_Uptake\_Bone/conversion\_coeff \quad (8)$$

Moreover, bone can adjust its mass by taking Ca when there is surplus in ECF. This adjustment is accounted for the mineralization of bone after formation. Bone is not fully mineralized after formation and a considerable amount of mineralization occurs after the formation is completed and lasts for several years. For this purpose, a Desired BMC stock variable is formulated and desired calcium uptake from ECF is modeled as in Equation 9.

$$Desired\_Ca\_Uptake\_ECF = ((Desired\_BMC - Bone\_Mineral\_Content)/BMC\_Adj\_time) \times conversion\_coeff \quad (9)$$

$$Change\_in\_Des\_BMC = Desired\_Formation - Resorption \quad (10)$$

Ca_Release_Adjustment is the flow of ECF Ca stock and formulated with available calcium level in the ECF and desired calcium uptake of bone from the ECF. The details of this flow variable are given in Calcium Sector chapter. Thus, Calcium_Uptake_ECF is equal to Ca_Release_Adjustment divided by conversion coefficient.

$$Ca\_Uptake\_ECF = Ca\_Release\_Adjustment/conversion\_coeff \quad (11)$$

Bone's Elastic Modulus is the maximum stress level that bone can stand without a fracture. In mechanics, elastic modulus of a material is given by the Equation 12.

$$Elastic\ Modulus = Stress/Strain \quad (12)$$

In this model, Felt Strain refers to the strain occurred in the bone by stress applied from the outside environment. Blood flow and other fluid flows also constitute a strain in bones however, in the context of this model, these effects are excluded. Applied Stress is modeled as an exogenous variable reflecting the weekly stress level that bone exposed to. There are many studies that construct a relation between bone density and its modulus. In this study, Kopperdahl and Keaveny's findings are used to formulate the relationship between bone density and modulus (Kopperdahl and Keaveny, 1998). This formula is given in Equation 13.

$$Bone\ Modulus = 2.1 \times Bone\ Density - 0.08 \quad (13)$$

Bone density is a simple volumetric density of bone. A converter is used to convert mg to g in the Equation 14.

$$Bone\ Density = (Bone\ Mineral\ Content/Bone\ Volume)/mg\ to\ g\ convert \quad (14)$$

Felt Strain= (Applied Stress x MPa to GPa Converter)/Bone Modulus) x Strain Converter (15)

Unit of modulus in the model is in GPa (gigapascal). A converter is used to convert it to MPa. Felt Strain is unitless and shows the deformation of a material caused by stress. In order to measure strain, microstrain is used in material science. One microstrain is the strain level that produces a deformation of one part per million (10^{-6}). Strain Converter in the model converts the result of the equation into microstrain unit.

In a weightlessness state, bone adjusts itself to this new mechanical environment and reduces its mass by enhancing remodeling until strains exceed the threshold value for disuse. This threshold value is determined as 100 microstrains and called as Minimum Effective Strain for remodeling (MESr). Below MESr, BMU Number is increased and resorption is stimulated by BMUs. It has been assumed that people who practive exercise have higher MESr values. Between 100-1000 microstrain, bone is in steady state and there is not a significant loss in bone mass. In disuse, bone mass is reduced partly by forming less bone than resorbed, and partly by delaying the onset of formation. These effects are given in Figure 4.2, Figure 4.3 and Figure 4.4.

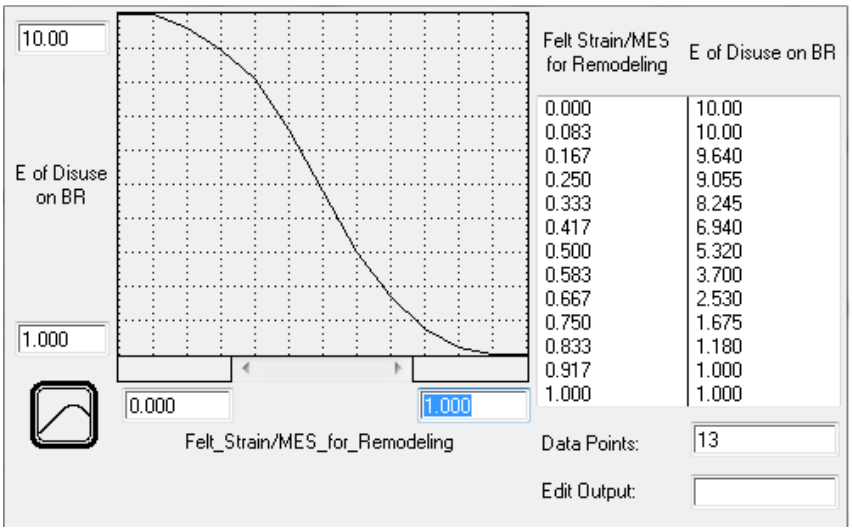

Figure 4.2. Effect of Disuse on BMU Birth Rate.

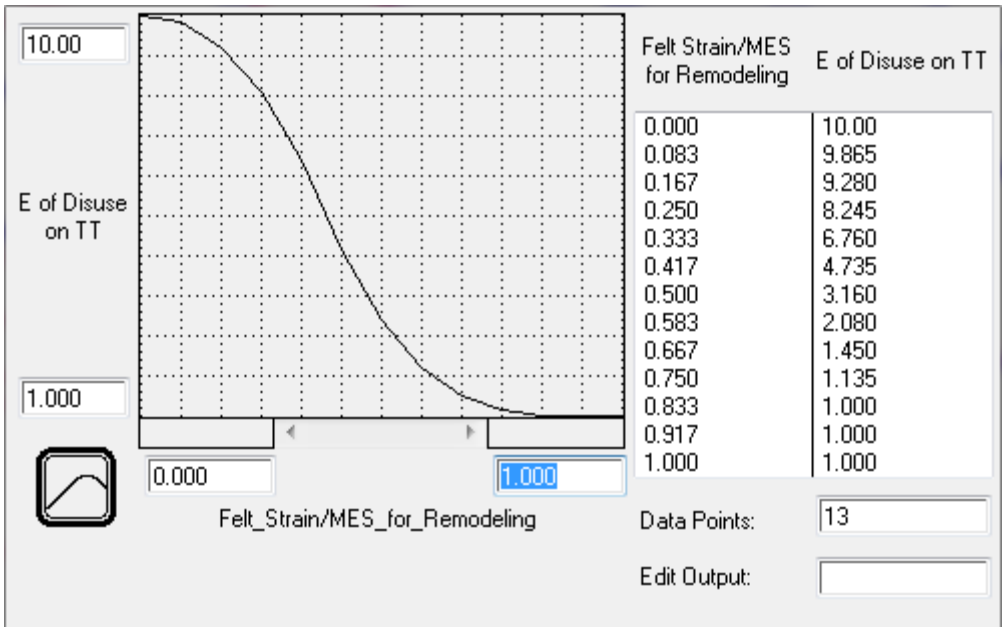

Figure 4.3. Effect of Disuse on Transition Time.

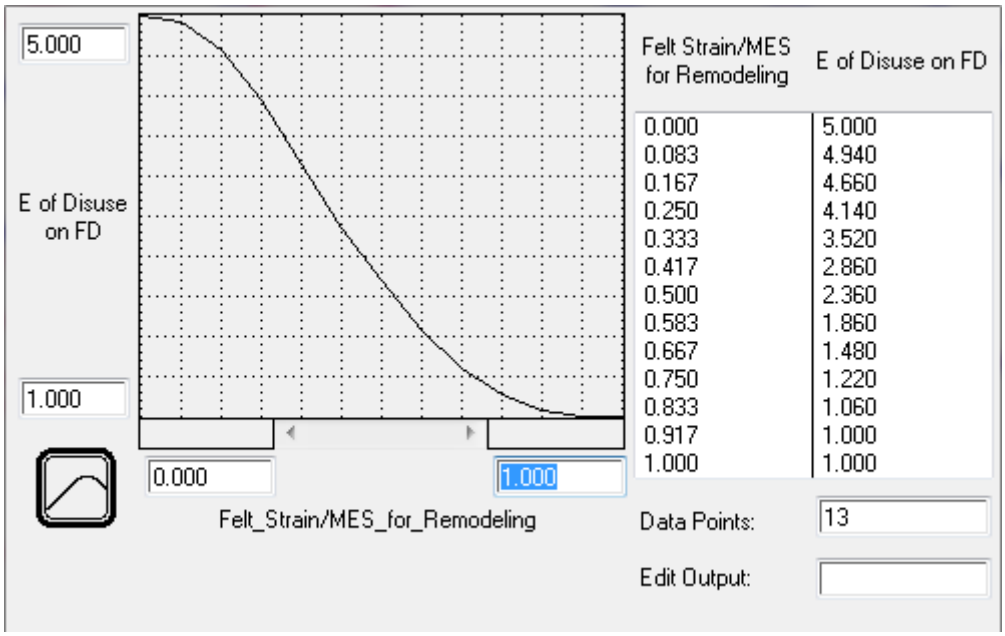

Figure 4.4. Effect of Disuse on Formation Deficient.

Another factor that affects BMU number and stimulates resorption is overuse. When Felt Strain exceeds a threshold value, more microdamage accumulates in the bone tissue and this increases the resorption rate in order to remove the damaged bone as soon as possible. This threshold level is called MES for overuse and set to 3000 microstrains (Figure 4.5).

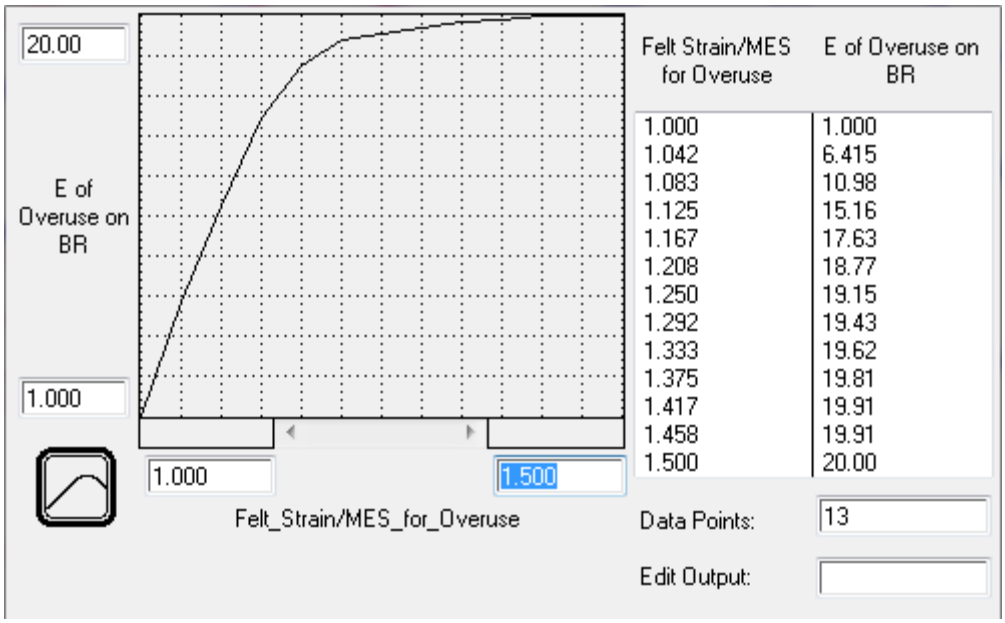

Figure 4.5. Effect of Overuse on BMU Birth Rate.

In this sector, Age and Estrogen Level have effects on MES values. Estrogen Level is a function of Age (Figure 4.6). With the onset of menopause in women, estrogen level decreases to 20% of premenopausal levels. Estrogen has suppressing effects on bone remodeling. When estrogen decreases, this effect is lost and remodeling increases. This is explained by the elevated MESr value by Frost (Frost, 1999). This increase depends on the strain history of women and differs among individuals. In this model, it is formulated by considering a reference subject whose strain levels fall between normal values (Figure 4.7).

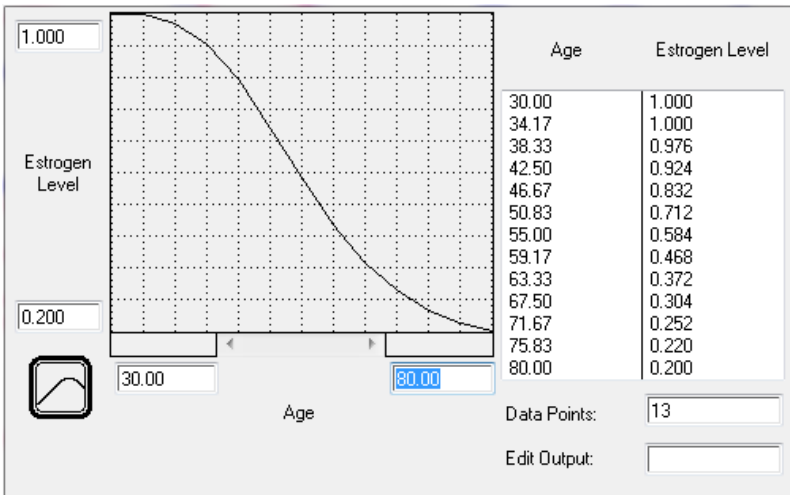

Figure 4.6. Estrogen Level as a Function of Age.

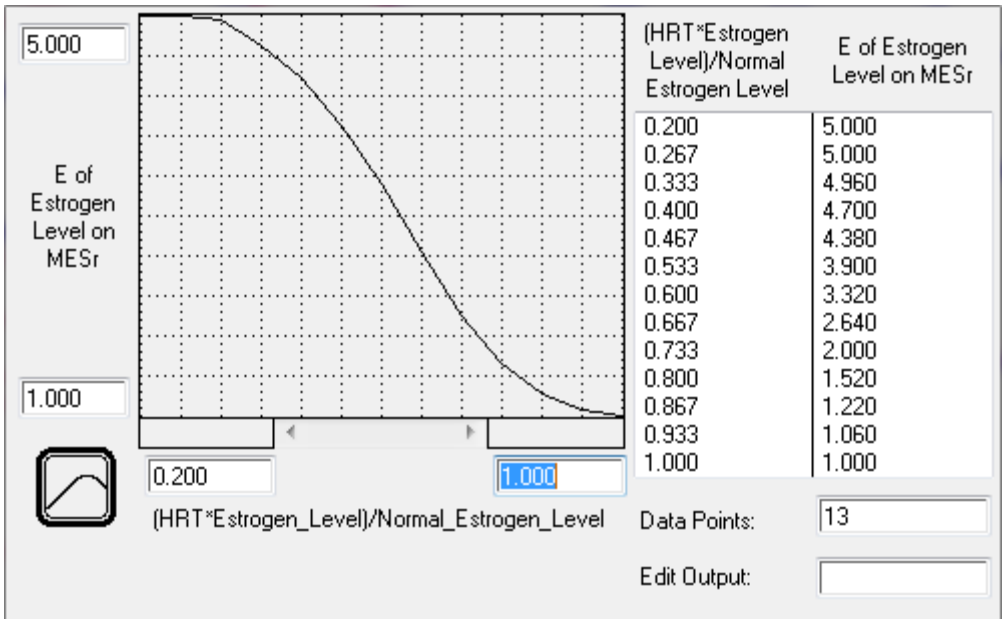

Figure 4.7. Effect of Estrogen Level on MES for Remodeling.

Moreover, with aging, bone is more vulnerable to the damage. This is due to the decreased strength of bone in aging people. Aging bone is more susceptible to fractures because of the increased amount of damage in bone. This effect is formulated by the decreased MESoverload value in the model (Figure 4.8.). The effect of age appears at age 60.

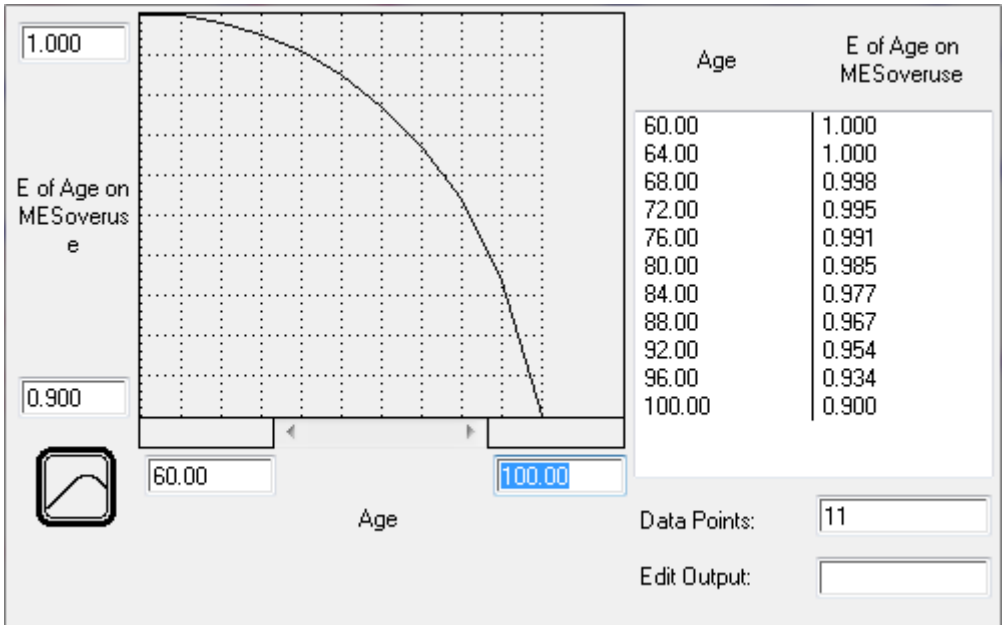

Figure 4.8. Effect of Age on MES for Overload.

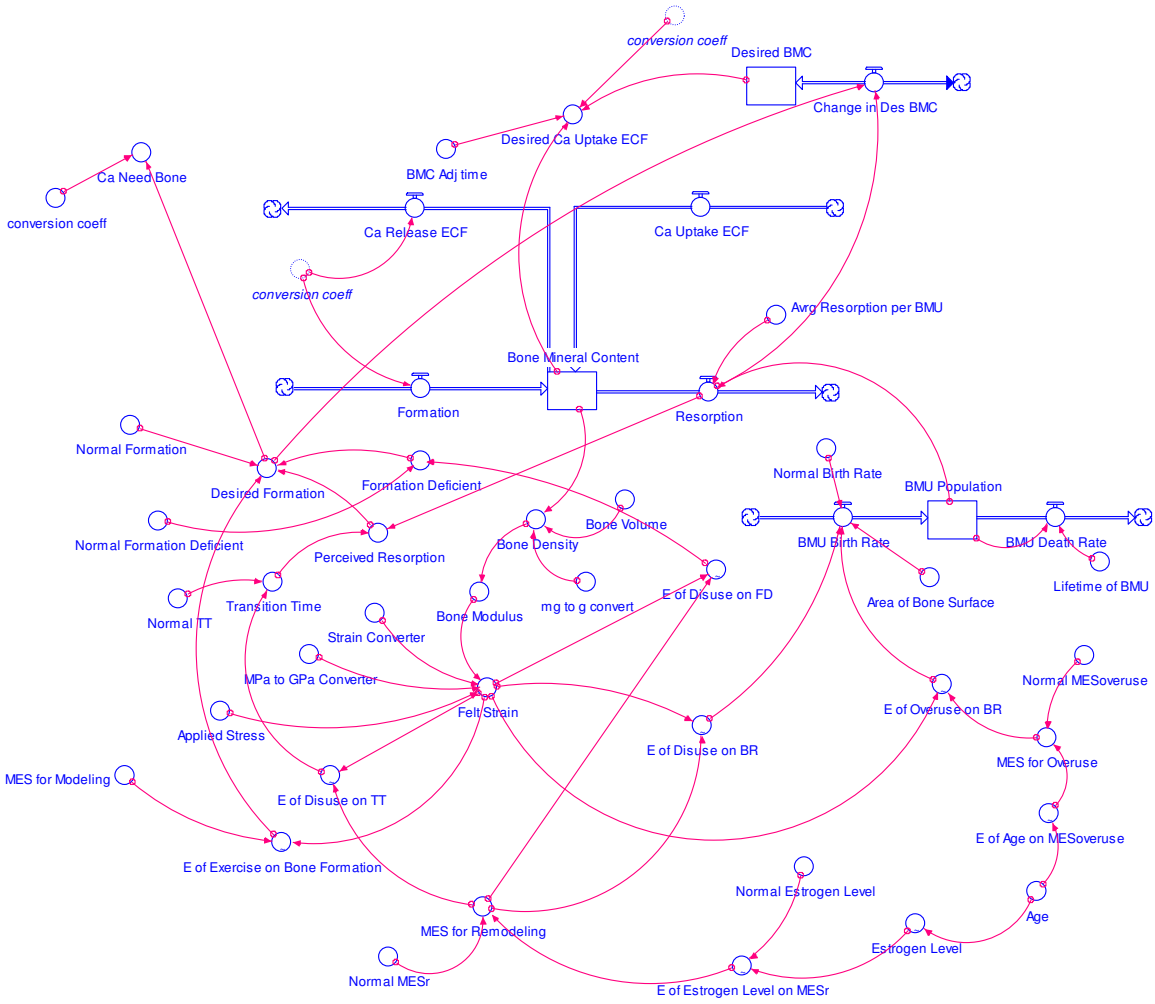

Figure 4.9. Stock-flow Diagram of the Bone Mass Sector.

4.1.4. Dynamics of Bone Mass Sector in Isolation

In this section, a number of tests will be conducted in order to verify that Bone Mass Sector works properly. In these experiments, calcium exchange with ECF is set to zero to observe the isolated dynamics of Bone Mass Sector. Thus, calcium requirement of bone is totally fulfilled without any limitations. In order to verify proper functioning of this sector, experiments with initial Applied Stress value and Disuse and Overuse conditions will be conducted. Behavior of the key variables such as Bone Mineral Content, BMU Number and Felt Strain will be demonstrated for a simulation period of 130 or 400 weeks.

In the first experiment, it will be tested whether BMU Population stays stable in the normal strain levels. The stimulator of the changes in BMU Population is the strain

magnitude felt by bone. If peak strains felt by bone stay between 100-1000 microstrain levels, there will be no change in BMU Population. The results demonstrate that when Felt Strain is between 100-1000 με, BMU Population does not change (Figure 4.10).

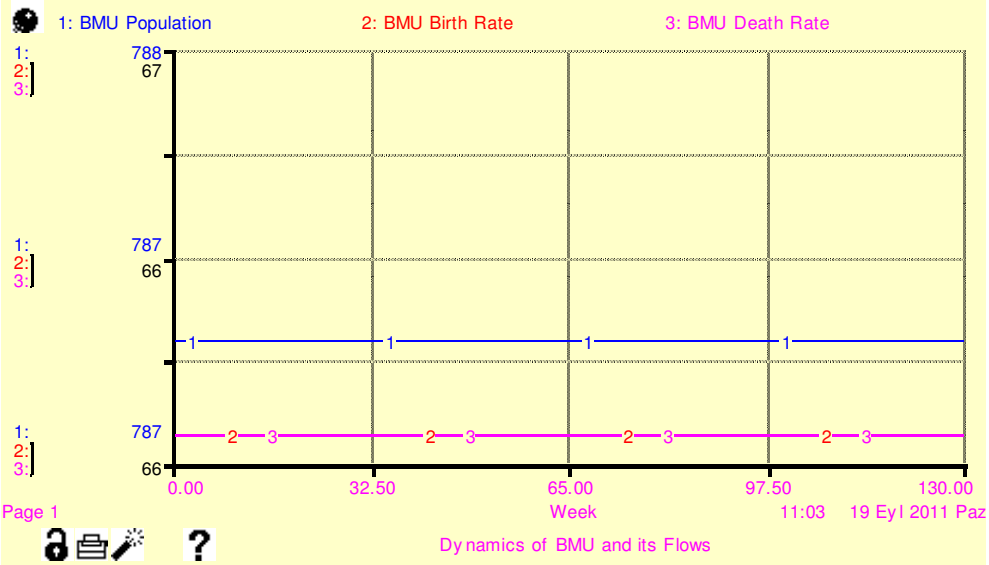

Figure 4.10. Dynamics of BMU Birth Rate, Death Rate and BMU Number.

Formation and Resorption are stable but resorption is higher than formation (Figure 4.11). This is because of the continuous formation deficient in a remodeling cycle after growth. This will cause a continuous bone loss throughout life. In the model dynamics, Bone Mineral Content is decreasing in small degrees.

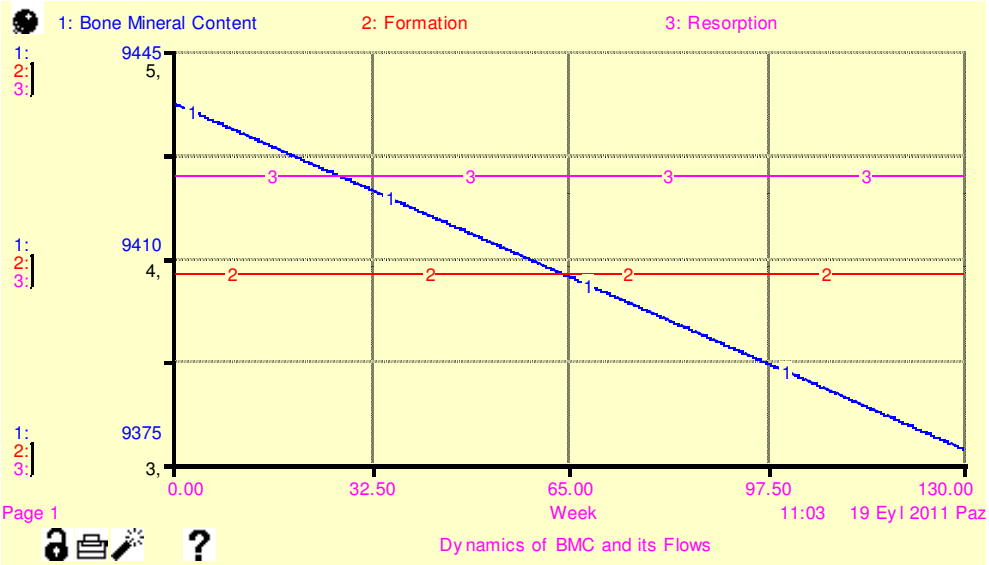

Figure 4.11. Dynamics of BMC, Resorption and Formation.

Although Applied Stress is increased to some degrees, BMU Birth Rate will not stimulated and BMU Population will be stable (Figure 4.12). Unless Felt Strain goes out of normal limits, BMU Birth Rate does not change.

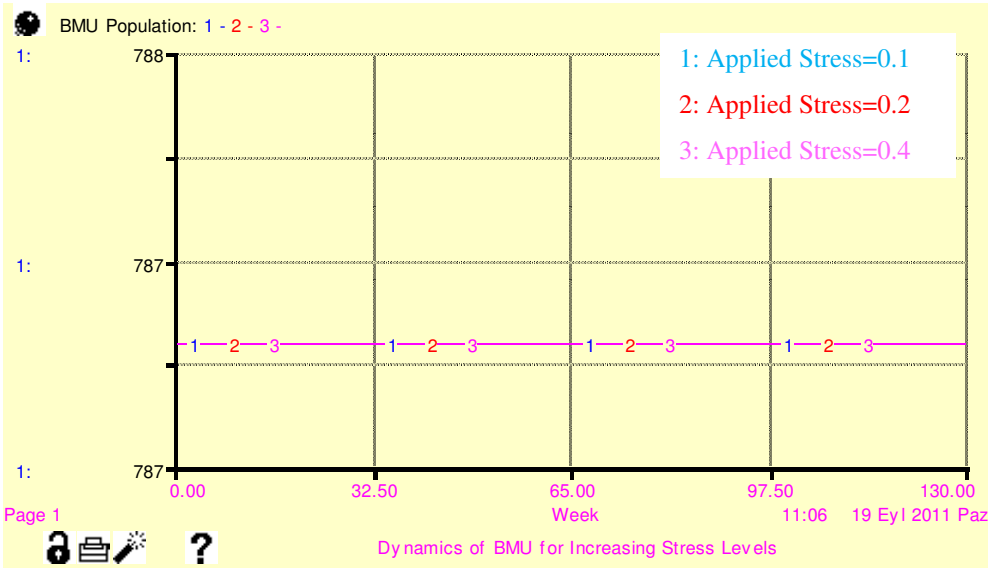

Figure 4.12. Dynamics of BMU Number for Changing Stress Levels.

The next experiment tests the response of BMC to the decreased Applied Stress. Stress Level is decreased to 0.01MPa at time 52. In a disuse state, remodeling rate increases more than normal. This leads to a higher rate of bone loss. Bone loss continues until peak strains exceed the disuse threshold again. During this period, BMC decreases and a while later it saturates. In Figure 4.13, BMC decreases more than normal decrease rate starting from week-52. Disuse stimulates formation and resorption both but Formation lags behind Resorption because of the increased Transition Time by disuse. Decreased Felt Strain also affects the amount of formation deficient and this constitutes a higher negative balance between resorption and formation. The effects of disuse on Birth Rate, Transition Time and Formation Deficient are seen in Figure 4.16.

In Figure 4.14, BMU Birth Rate suddenly increases with decreased Felt Strain. BMU Population increases with increasing Birth Rate. By the time Felt Strain exceeds disuse threshold and stays in normal limits, BMU Population starts to decline towards its normal value.

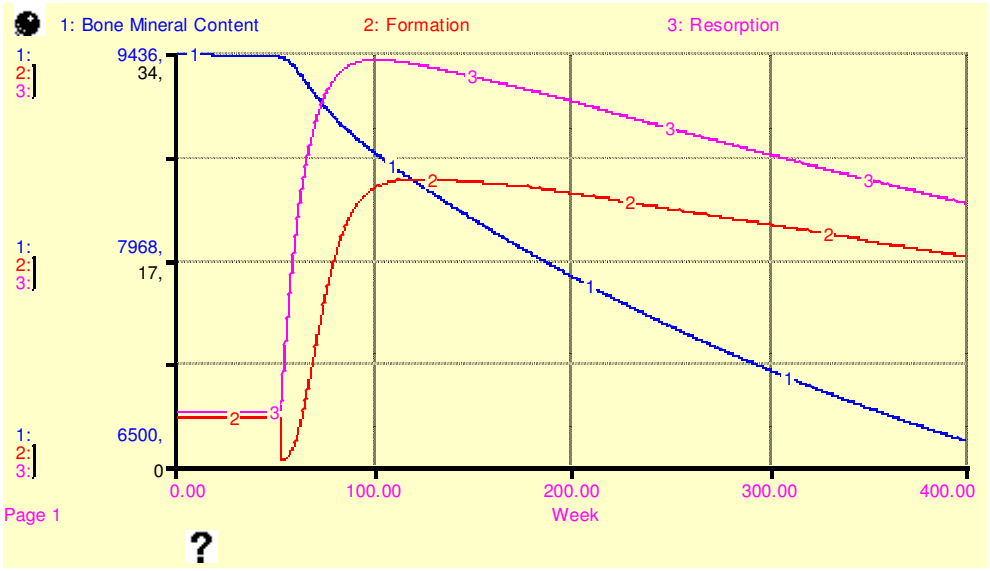

Figure 4.13. Dynamics of BMC, Formation and Resorption for Decreased Stress Level.

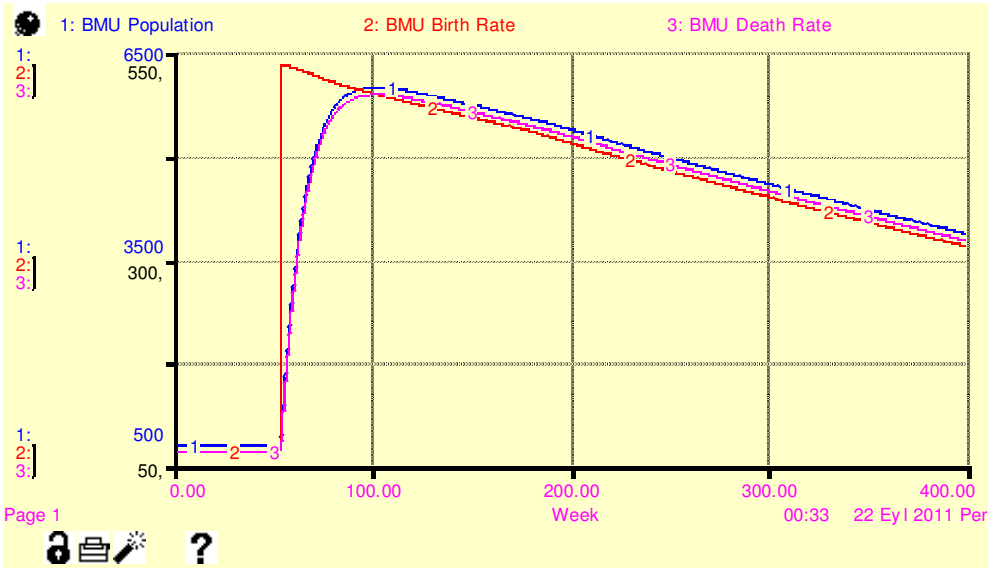

Figure 4.14. Dynamics of BMU Birth Rate, Death Rate and BMU Number for Decreased Stress Level.

Figure 4.15, Felt Strain decreases suddenly below MESr (100 microstrains). The stimulation of remodeling rate results in decreased bone density. There is an inverse relation between bone density and strain. The decreased bone density elevates the strain level over time.

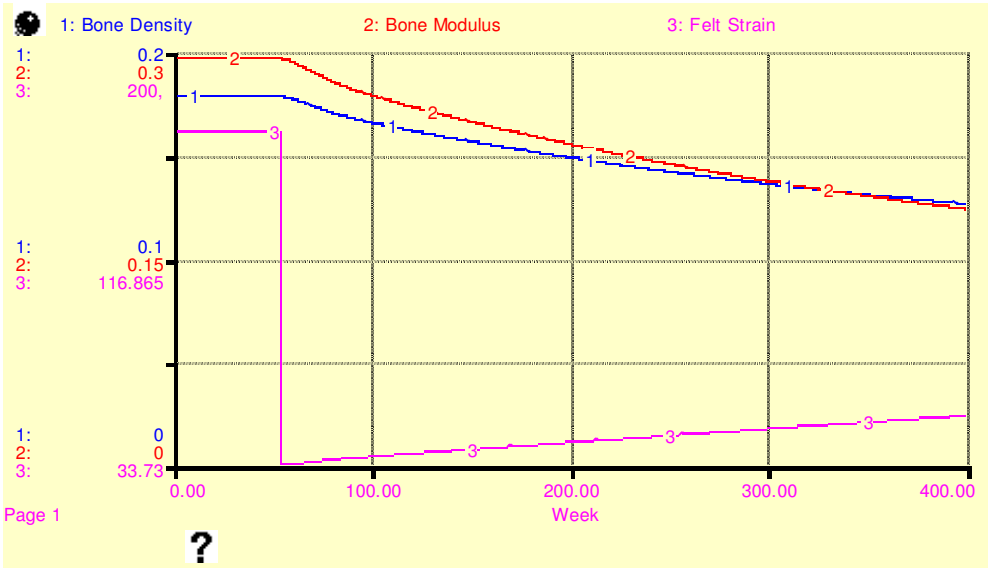

Figure 4.15. Dynamics of Bone Density, Modulus and Felt Strain for Decreased Stress Level.

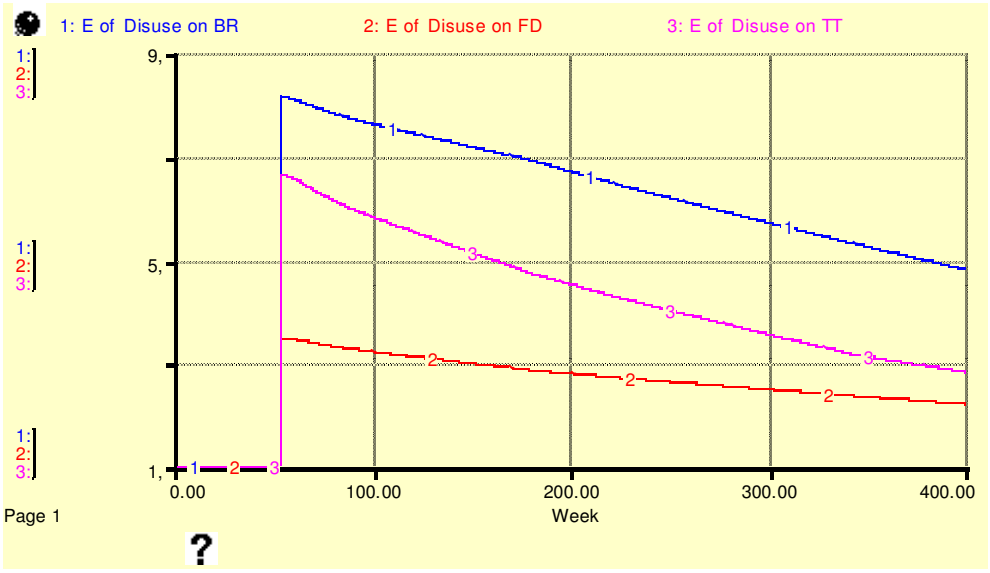

Figure 4.16. Dynamics of Effects of Disuse on Birth Rate, Formation Deficient and Transition Time.

In the third experiment, Bone Mass Sector's response to high Felt Strain level will be tested. Applied Stress is set to 0.8 MPa at week 52 in order to obtain a strain magnitude greater than 1000 με (threshold level for formation). BMU Population does not change because elevated strain level increases formation without changing remodeling rate. Thus, BMC increases without an increase in the BMU Number (Figure 4.17 and Figure 4.18).

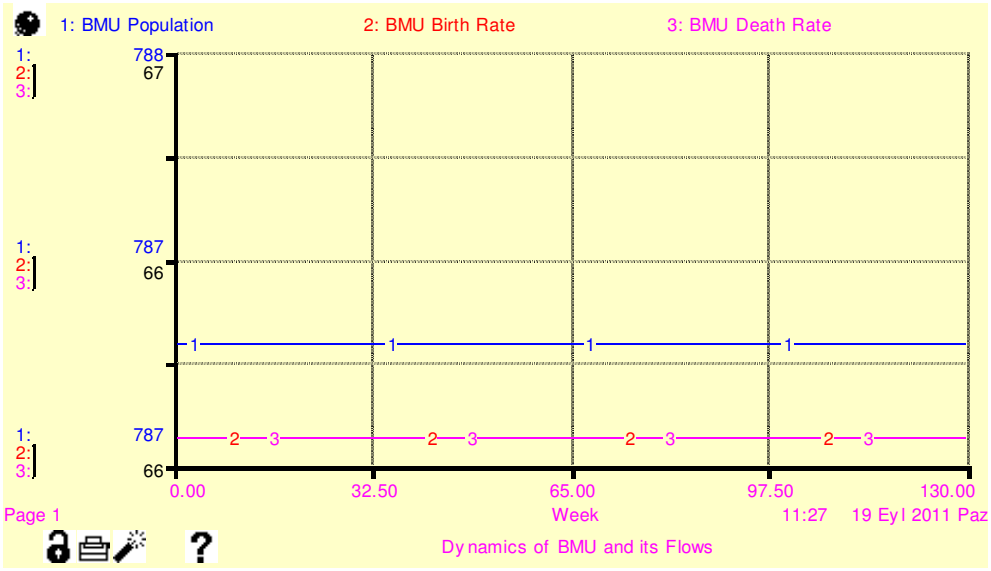

Figure 4.17. Dynamics of BMU Birth Rate, Death Rate and BMU Population for Increased Stress.

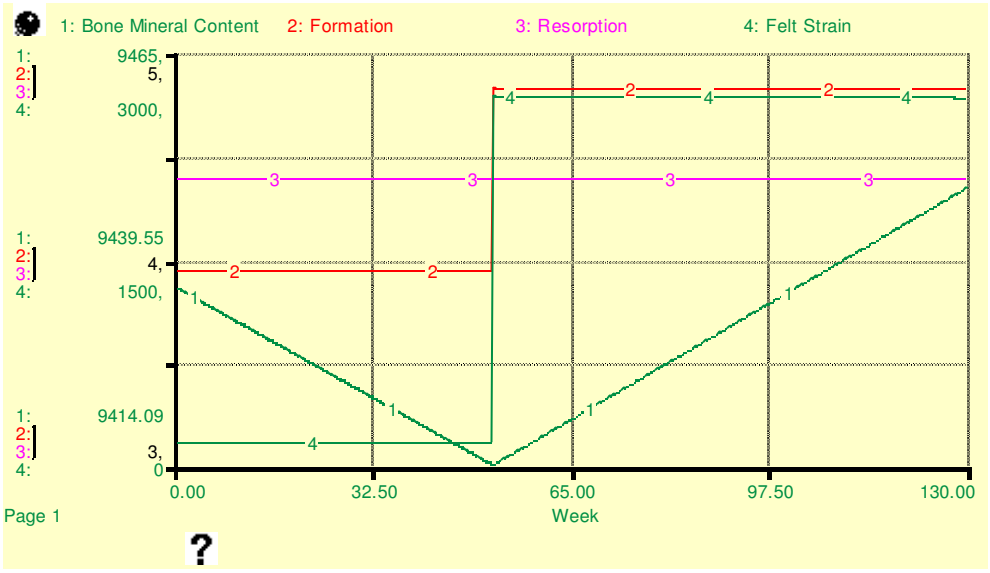

Figure 4.18. Dynamics of BMC, Formation, Resorption and Felt Strain for Increased Stress.

Felt Strain exceeds formation threshold suddenly because of the increased stress level. This leads to an increasing bone density and bone modulus. Felt strain starts to decline after the sudden increase at week-52 due to the increase in bone density.

In Figure 4.20, the effects of disuse do not change and are all equal to one. However, the effect of exercise (increase in stress) on formation increases suddenly at week 52 and follows a decreasing pattern with the increasing bone density.

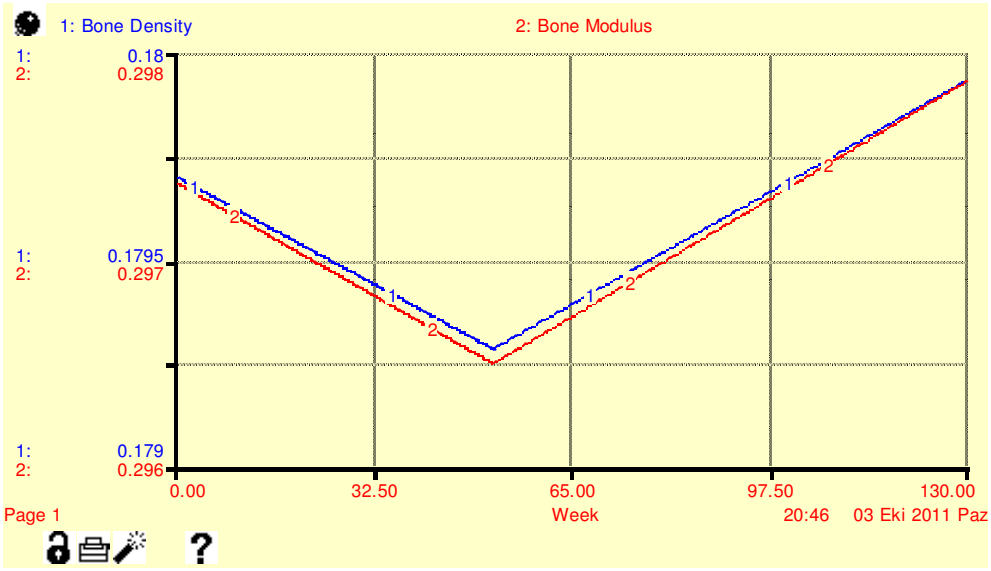

Figure 4.19. Dynamics of Felt Strain, Bone Density and Modulus for Increased Stress.

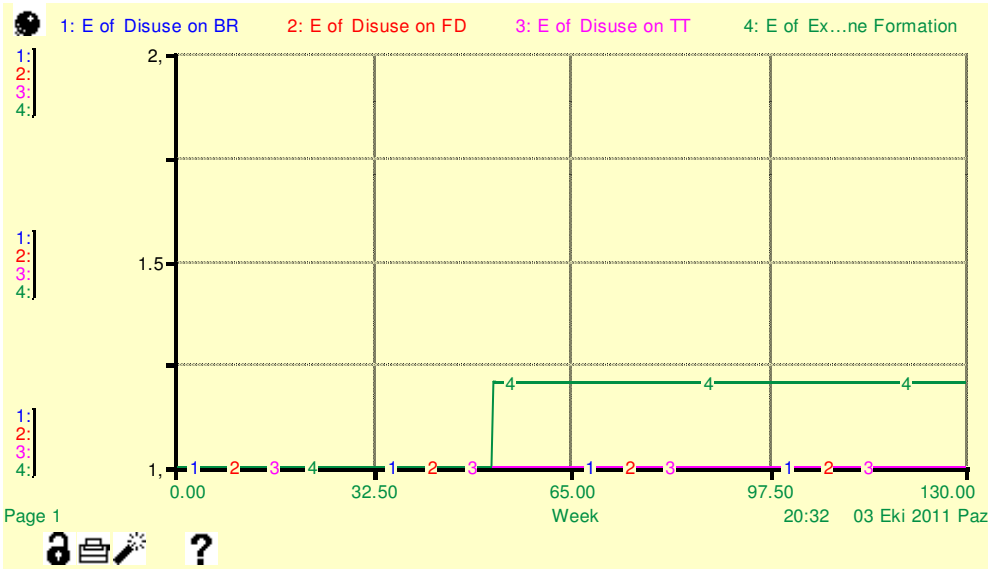

Figure 4.20. Dynamics of Effects of Disuse on Birth Rate, Formation Deficient and Transition Time and Effect of Exercise on Formation.

The last experiment will test the response of Bone Mass Sector to overload condition. Applied Stress is set to one megapascal at week 52 in order to obtain a strain level more than 3000 με. 3000 microstrain is the threshold for overuse and if the peak

strains increase 3000 microstrain, microdamage accumulates in bone and this stimulates remodeling rate in order to remove the damage. In Figure 4.21, BMU Birth Rate suddenly increases because of the effect of overuse on Birth Rate (Figure 4.24). BMU Population increases with increasing birth rate. The elevated remodeling rate causes a considerable amount of bone loss. Bone density decreases parallel to this bone loss. However, decreased bone density further increases felt strain (Figure 4.23) and this causes a continuous stimulation of bone remodeling and continuous bone loss. This positive feedback loop results in a catastrophic failure of bone unless felt strain returns to normal levels.

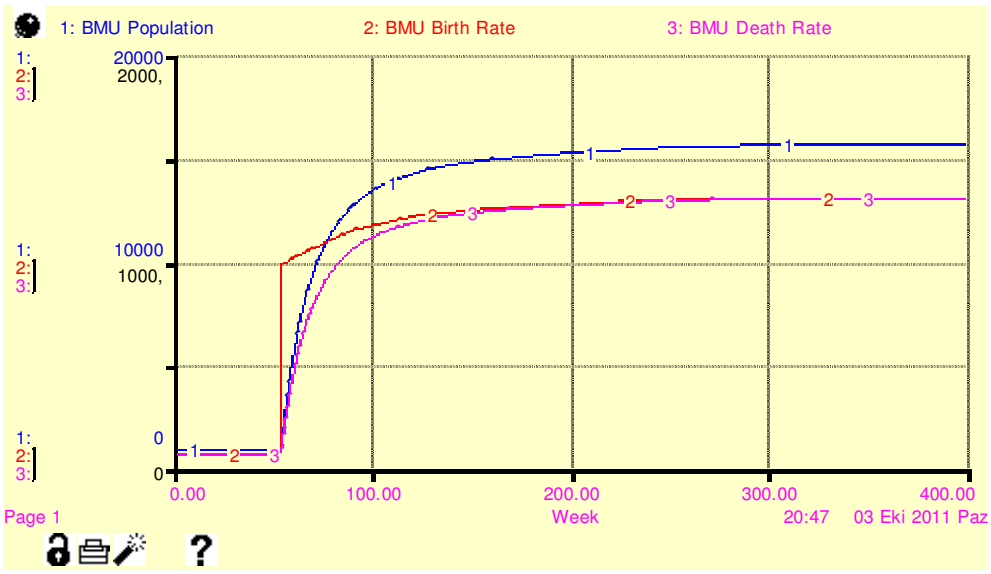

Figure 4.21. Dynamics of BMU Number, Birth Rate and Death Rate for Overuse.

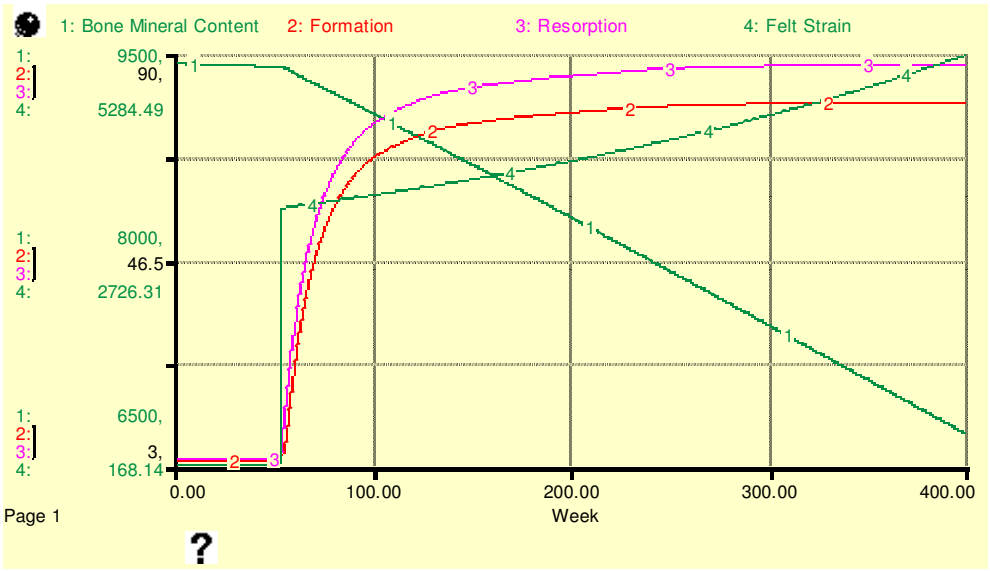

Figure 4.22. Dynamics of BMC, Formation, Resorption and Felt Strain for Overuse.

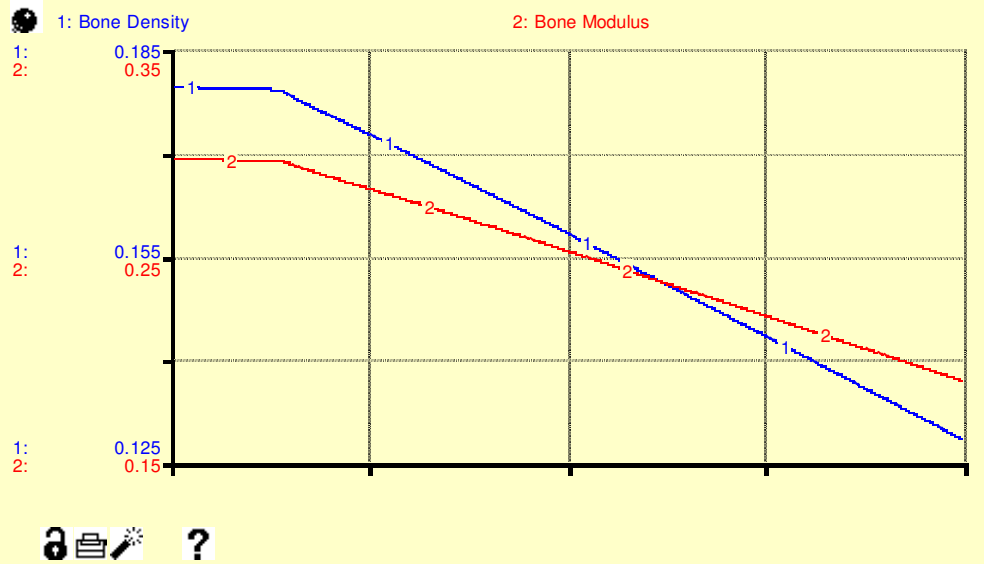

Figure 4.23. Dynamics of Bone Density and Bone Modulus for Overuse.

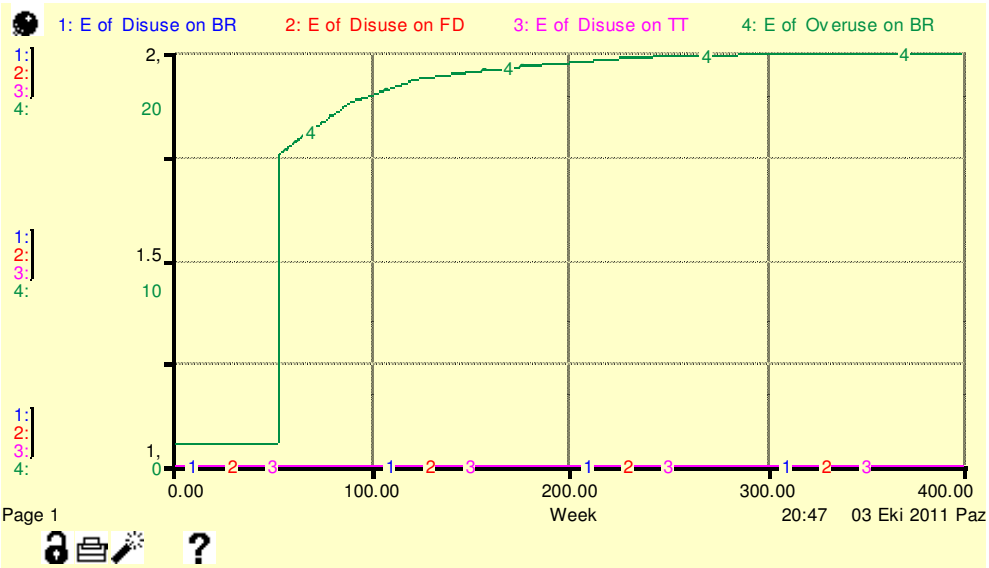

Figure 4.24. Dynamics of Effects of Disuse on Birth Rate, Formation Deficient and Transition Time and Effect of Overuse on Birth Rate.

4.2. Calcium Sector

4.2.1. Background Information

ECF Ca refers to the Calcium level in milligrams in the extracellular fluid. Absorption occurs in the gut and is the main Ca inflow into ECF. Excretion occurs in the kidney and is the main regulator of the calcium concentration of ECF. Ca Uptake

Resorption refers to the amount of calcium that is removed by OCs as a result of resorption period. Ca Uptake Bone refers to the amount of calcium that is taken by ECF from bone when there is a calcium need in ECF. Ca Release Formation refers to the amount of calcium that is taken by bone for formation and Ca Release Adjustment refers to the amount of calcium that is taken by bone for mineralization of bone. Ca Intake is the average calcium intake of an adult woman in a week.

4.2.2. Fundamental Approach and Assumptions

Calcium homeostasis is maintained by three organs in the body: bone, kidney and gut. In zero Ca balance, Ca input from gut is equal to the Ca output through kidney. In the fasting states or in severe depletion, Ca needed for metabolic activities is supplied from bone. Bone can release Ca into ECF in two ways: by cellular activity and ionic exchange. First one is achieved by resorption of bone and is not effective in short term control of ECF Ca. Second is a rapid response and amounts more than resorption per unit of time. This kind of calcium supplementation from bone happens quickly in real life. PTH is responsible for maintaining calcium level between set levels. When calcium falls below its set value, PTH secretion is stimulated. PTH increases reabsorption of calcium from kidney, stimulates the hydroxylation of calcitriol in kidney and therefore increases the absorption of calcium from the gut. The first action of PTH is rapid, completed in a few hours but the second is relatively slow, completed in a few days. However these two actions happen in a very short time according to the time unit of this model. This thesis tries to represent the long term dynamics of the human bone mass. Thus, calcium sector is modeled from a long term perspective and shows only the big fluctuations from the set value in a long period of time. Based on this assumption, the responses of ECF Ca Level to the changes of PTH level are ignored and the net result is modeled.

Ca is lost thorough several ways from the body; like urine, sweat, feces etc. However, in the context of this model, Ca losses other than urine are ignored.

In human body, Ca homeostasis is highly significant for the healthy progression of metabolic activities. Thus, in the scarce of Ca, it is released from bone at the expense of bone loss. When Ca intake turns back to normal, Ca loss from bone is replaced. ECF Ca

precedes bone and if there is not enough calcium in blood for the need of bone, bone cannot take and waits until there is a calcium surplus in ECF.

Absorption from intestine is regulated with a hormone called calcitriol, a Vitamin D metabolite. When there is excess calcium intake, PTH secretion decreases and calcitriol synthesis is slowed down. Thus, calcium absorption saturates with high intake of calcium. This result is believed to occur because of the decreased synthesis of calcitriol hormone however, in the model, the net effect is formulated as Effect of Calcium Intake on Absorption. In order to regulate calcitriol levels efficiently, a continuous Vitamin-D supply is needed. Without Vitamin-D, absorption does not stop but is not efficient as needed. In the model, these two effects of Vitamin-D are formulated separately and first effect is not associated with Vitamin D level.

Constants and variables that are used in the calcium sector are given in Table 4.3 and Table 4.4.

Table 4.3. Constants used in Calcium Sector.

Constant Name	**Value**	**Unit**
Normal Vitamin-D Level	35	pg/ml
Obligatory Loss	700	mg/week
Max Excretory Capacity	3500	mg/week
ECF Volume	15	liter
ECF Ca Concentration Goal	100	mg/liter
Conversion Coefficient	100	Unitless
Normal Ca Intake	4200	mg/week

Table 4.4. Basic Variables and Initial Values of Calcium sector.

Variable Name	**Initial Value**	**Unit**
Ca Intake	4200	mg/week
Vitamin-D Level	35	pg/ml
ECF Ca Level	1500	mg

4.2.3. Description of the Calcium Sector Structure

This sector has one stock. ECF Ca Level is mainly changed with its inflow Absorption and outflow Excretion. Absorption is a single rate constant changed with Ca Intake. Ca Intake is formulated as an exogenous variable. Effect of the PTH in absorption was summarized in an effect function in this sector (Figure 4.25). With the increasing level of the Ca Intake, absorption does not increase independently and a while later it saturates. In the scarce of Ca intake, Absorption increases in the gut. In this effect function, Ca Intake is normalized with Normal Ca Intake. Normal Ca Intake is taken as the average calcium consumption among healthy women and set to 600 mg/day (4200 mg/week). Vitamin D is also necessary for a healthy Ca metabolism. Vitamin D is not obligatory for absorption; however in the absence of enough Vitamin D, absorption efficiency is decreased. With the increasing age, Vitamin D related hormone-calcitriol synthesis in the body decreases and this causes a reduction in the absorption efficiency indirectly

$$Absorption = Ca\_Intake \times E\_of\_Ca\_Intake\_on\_Absorption \times E\_of\_VitD\_Level\_on\_Absorption \quad (16)$$

$$Actual\_VitD\_Level = VitD\_Level \times E\_of\_Age\_on\_VitD \quad (17)$$

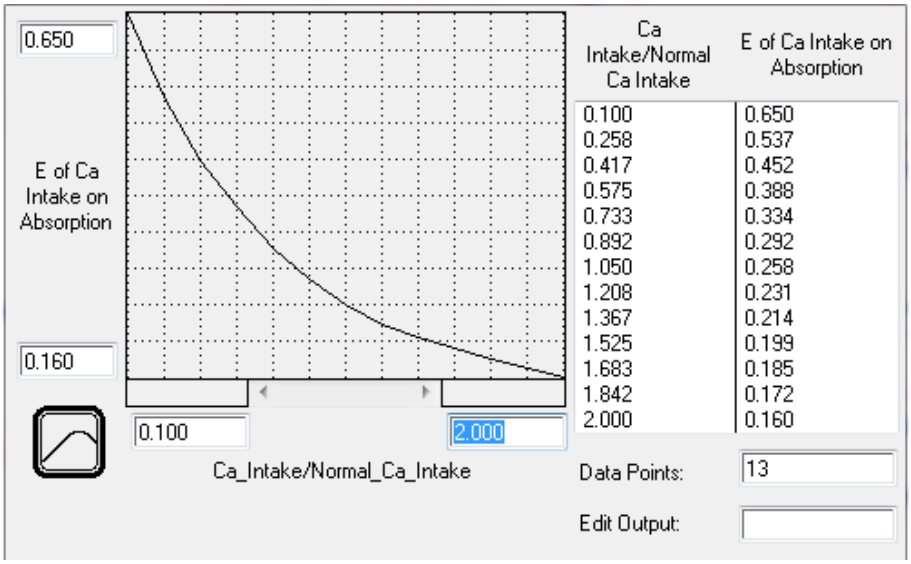

Figure 4.25. Effect of Calcium Intake on Absorption.

The graphical functions of Effect of Vitamin-D Level on Absorption and Effect of Age on Vitamin D are showed in Figure 4.26 and Figure 4.27.

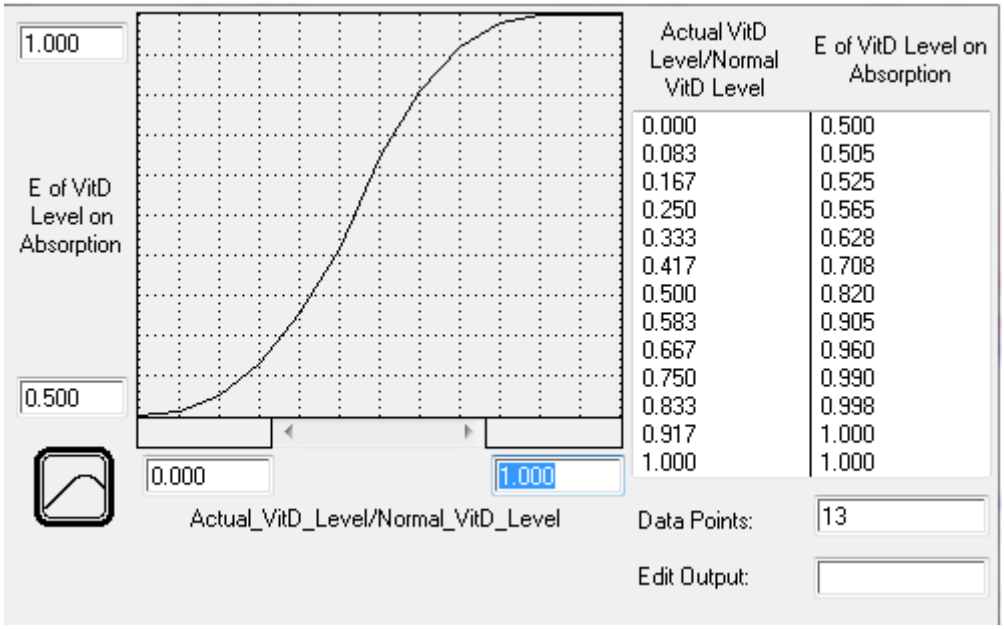

Figure 4.26. Effect of Vitamin-D Level on Absorption.

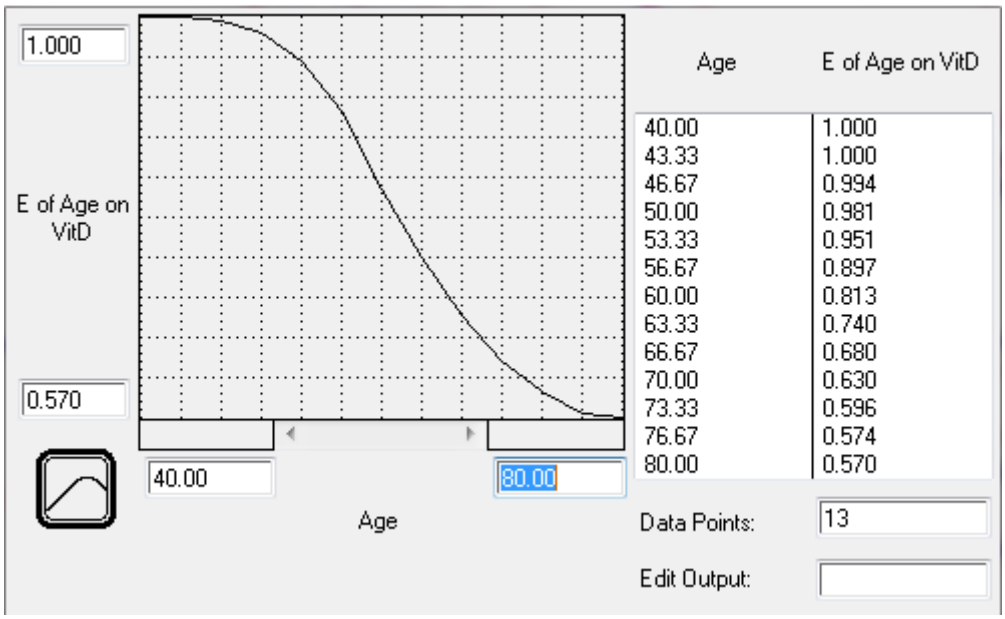

Figure 4.27. Effect of Age on Vitamin-D status.

Norman reports that intestinal calcium absorption is saturable and in the very high calcium diet there is an upper value for the amount of calcium absorbed (Norman, 1990). In Figure 4.28, there is a comparison of the calcium absorption between simulation results

and real data. Figure shows that *E of Calcium Intake on Absorption* creates similar results with field data for absorption.

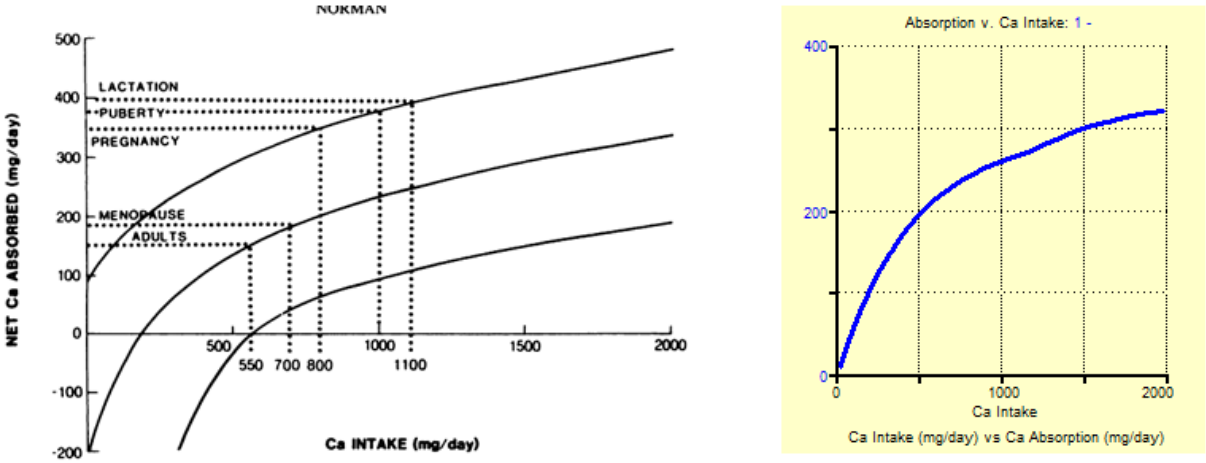

Figure 4.28. Comparison of field data (Norman, 1990) and model results for Calcium Absorption.

ECF Ca is formulated as a stock management problem in this model. Excretion is the main regulator of ECF Ca stock. In the zero Ca balance, absorption is equal to the excretion. Even Ca Absorption is zero; a minimum amount of Calcium is lost in the urine. This is formulated as Min Obligatory Loss in Equation 19. If there are any deviations from the level of the ECF Ca in the body (ECF Ca Goal), Desired Excretion changes by an amount equal to the deviation from the set value plus any other fluctuations. The maximum formulation guarantees that Desired Excretion never falls below the obligatory loss.

$$Desired\_Excretion=(ECF\_Ca\_Level-ECF\_Ca\_conc\_Goal \times ECF\_Volume) + (Absorption+Ca\_Uptake\_Resorption-Ca\_Release\_Formation - Ca\_Release\_Adjustment) \quad (18)$$

$$Excretion=MAX\ (Min\_Obligatory\_Loss, Max\_Excretory\_Capacity \times E\_of\_Capacity) \quad (19)$$

Calcium exchange between ECF and bone is formulated by three flows in the model. Ca Release Formation is the amount of total Ca outflow from ECF to Bone for bone formation. Depending on the available calcium level, Ca Release Formation flow changes. Effect of Available Calcium on Ca Release Formation is given in Figure 4.29. Available

calcium is equal to the amount of calcium absorbed minus minimum obligatory loss. The amount of calcium released to bone is limited to the available calcium in the ECF at that time. This is formulated with a capacity effect function. Ca Need Bone is a variable in the Bone Mass Sector and was explained in the previous chapter.

$$Ca\_Release\_Formation = Available\_Ca \times E\_of\_Available\_Ca \quad (20)$$

$$Available\_Ca = Absorption\text{-}Min\_Obligatory\_Loss \quad (21)$$

$$Ca\_Need\_Bone = Desired\_Formation \times conversion\_coeff \quad (22)$$

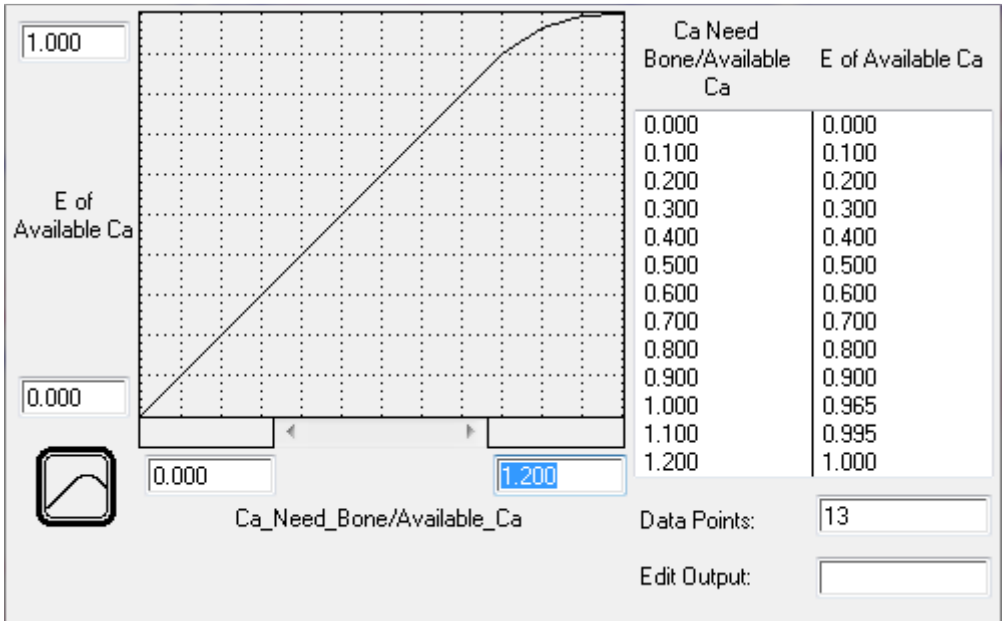

Figure 4.29. Effect of Available Calcium on Ca Release Formation.

Ca Release Adjustment is equal to the amount of calcium that bone takes from ECF different from formation. The amount of calcium released by this way depends on the desired calcium uptake of bone and available calcium efflux from ECF other than calcium released for formation. This is formulated as a capacity effect function (Figure 4.30). Desired Ca Uptake ECF is a variable of bone mass sector and the details were given in the previous chapter.

$$Ca\_Release\_Adjustment = Available\_Ca\_Efflux\_Bone \times E\_of\_Available\_Efflux \quad (23)$$

Available_Ca_Efflux_Bone =Available_Ca-Ca_Release_Formation (24)

Desired_Ca_Uptake_ECF=

((Desired_BMC-Bone_Mineral_Content/BMC_Adj_time) x conversion_coeff (25)

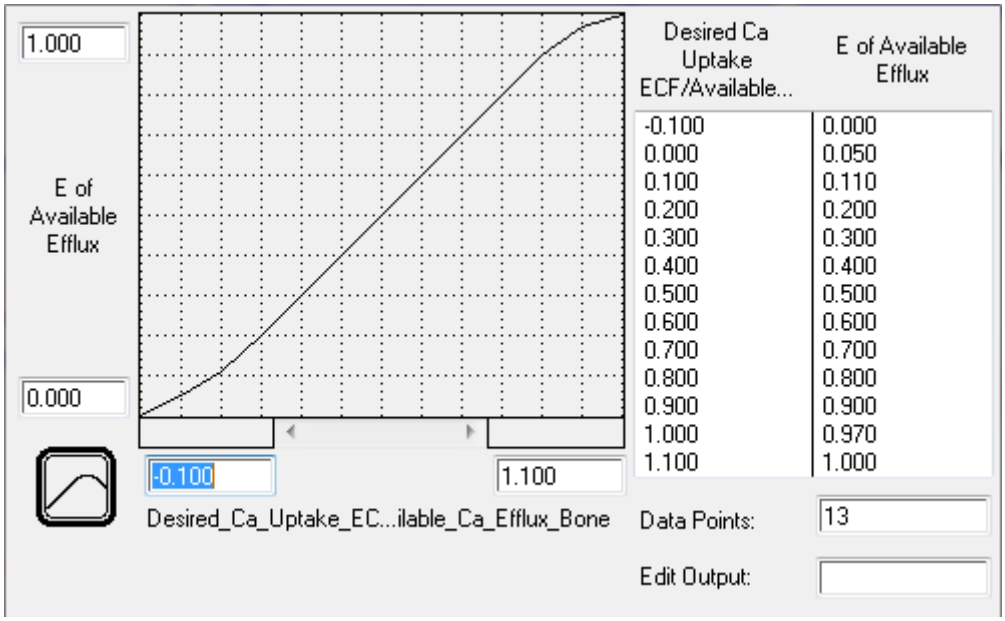

Figure 4.30. Effect of Available Ca Efflux on Ca Release Adjustment.

Ca Uptake Resorption is equal to the amount of calcium resorbed by OCs and formulated by multiplying resorption flow with the conversion coefficient.

Ca_Uptake_Resorption = Resorption x conversion_coeff (26)

Ca Uptake Bone adjusts ECF Ca for any fluctuations from its set level.

Ca_Uptake_Bone=IF ECF_Ca_conc<ECF_Ca_conc_Goal THEN

(ECF_Ca_conc_Goal- ECF_Ca_conc) x ECF_Volume ELSE 0 (27)

Stockflow diagram of the Calcium sector is shown in Figure 4.31.

4.2.4. Dynamics of Calcium Sector

In this section a number of experiments will be conducted on Calcium Sector dynamics. First experiment will be initialized with the following conditions: 1500 mg ECF Ca, 4200 mg/week Ca Intake which is equal to weekly normal intake and 35 pg/ml Vitamin-D. These values are the standard values for a normal healthy woman. Bone Sector variables are set to their normal values for all Calcium Sector experiments. Applied Stress is set to 0.05 MPa that provides a strain level between normal values. Only in the first run, the exchange of Calcium with bone is set to zero in order to see the dynamics of Calcium Sector in isolation. When there is zero calcium exchange with bone, Ca Excretion is equal to the Ca Absorption. ECF Ca does not fluctuate from its set level (Figure 4.32).

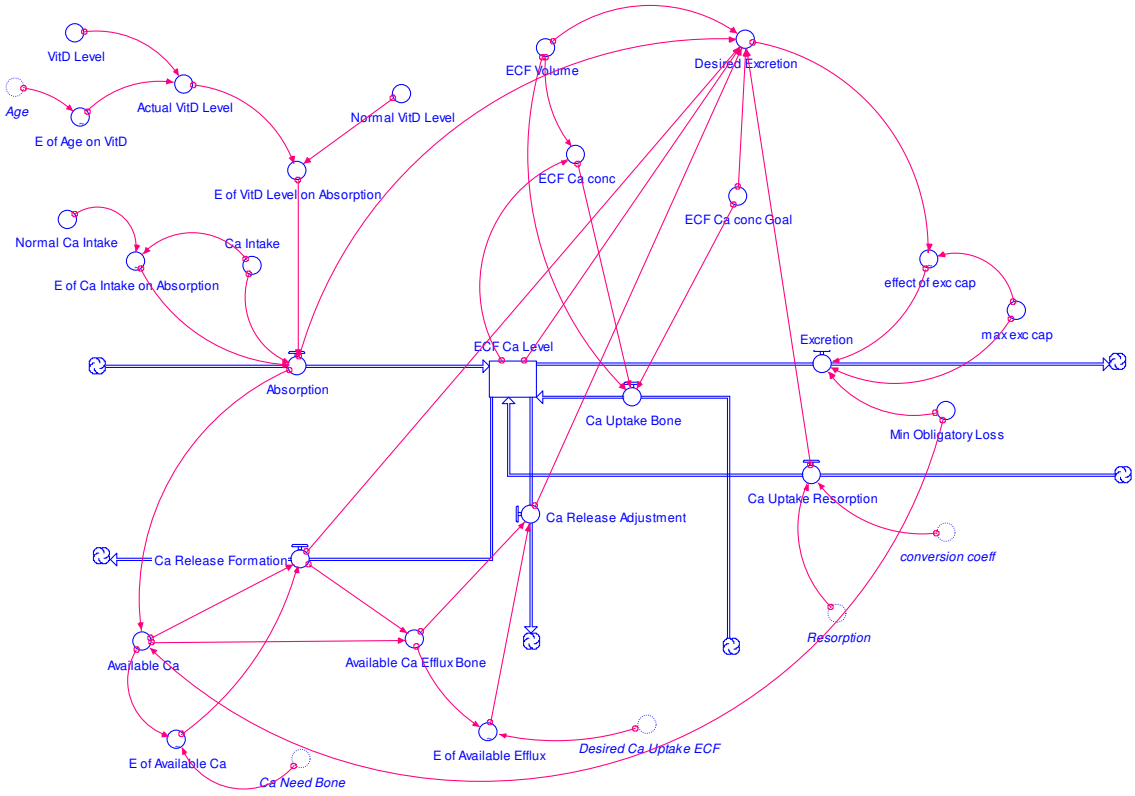

Figure 4.31. Stock-flow diagram of the Calcium Sector.

In the second run, calcium exchange with bone is allowed. The other conditions are same with the first experiment. ECF Ca did not change in this run too (Figure 4.33). Ca Excretion starts from a higher value and decreases with the increasing rates of calcium intake of bone from ECF. Ca Uptake Resorption and Ca Release Formation are constant

because of the stable BMU population. Ca Release Adjustment is increasing because of the formation deficient. Ca Uptake Bone is equal to zero because there is not a calcium deficiency in the body and ECF Ca Level is stable (Figure 4.34).

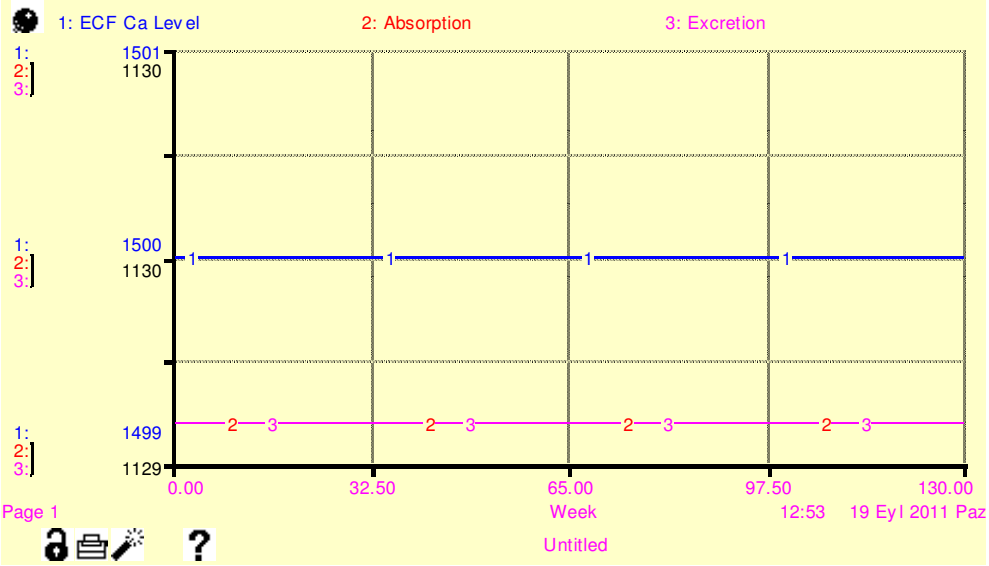

Figure 4.32. Dynamics of ECF Ca, Excretion and Absorption in Isolation.

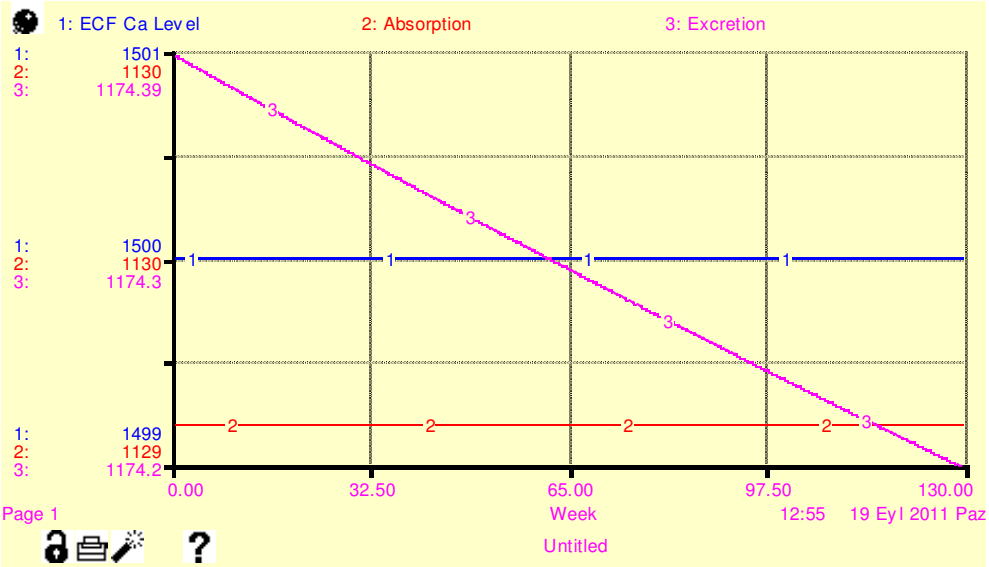

Figure 4.33. Dynamics of ECF Ca, Excretion and Absorption in Steady State.

Third experiment tests the response of Calcium Sector to low levels of Ca Intake. Ca Absorption changes with the changing levels of Ca Intake. Ca Excretion decreases with the decreasing Ca Absorption in Figure 4.35, however, when Absorption is very low, kidney

excretes an amount equal to minimum obligatory loss, and this leads to a decrease in ECF Ca (Figure 4.36).

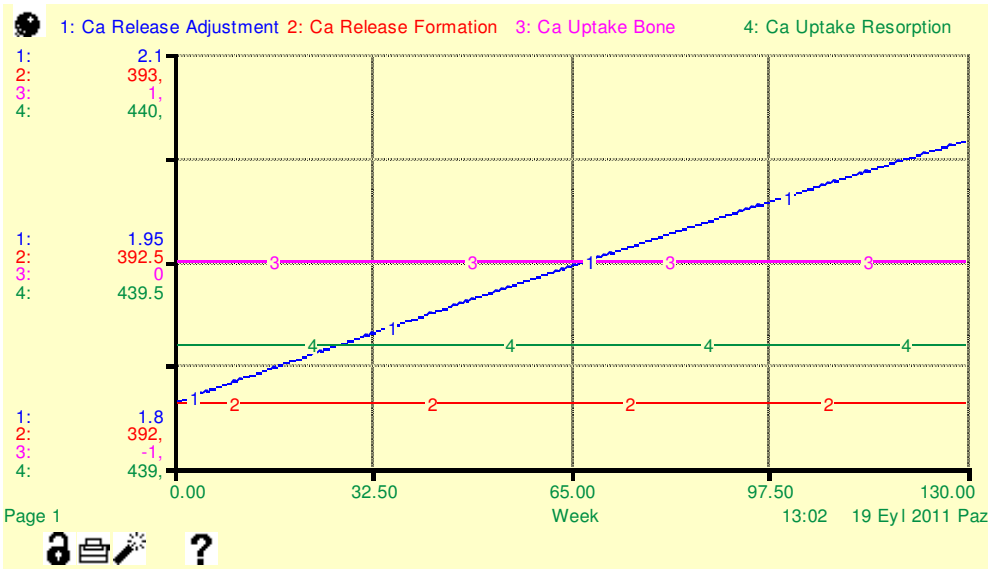

Figure 4.34. Dynamics of Ca Release Bone, Ca Uptake Bone and Ca Release Resorption in Steady State.

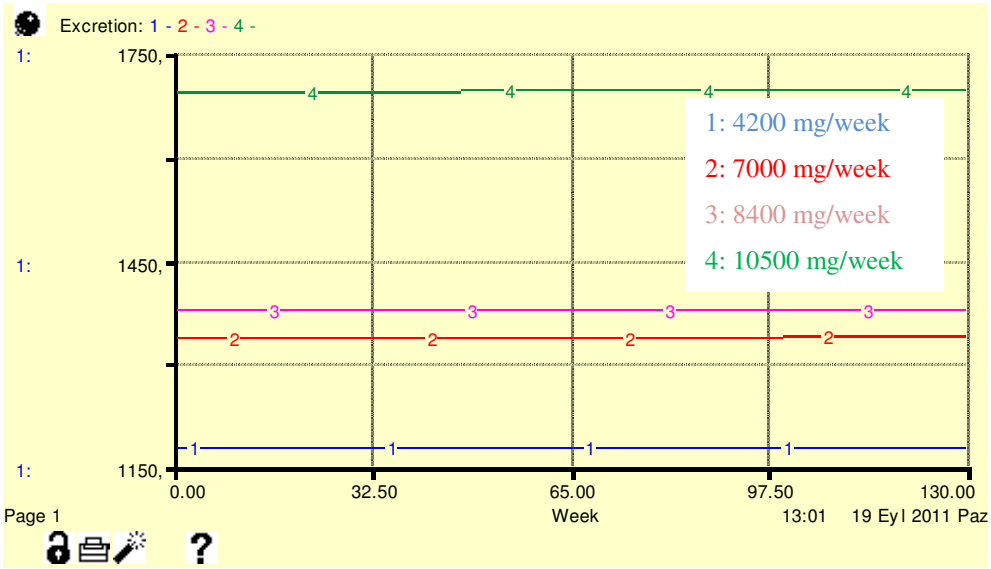

Figure 4.35. Dynamics of Ca Excretion for Different Levels of Calcium Intake.

The next experiment tests the response of Calcium sector to the changing initial values of ECF Ca. To do this, ECF Ca will be initialized with 1300-1500-1700 mg respectively. Other variables are set to their normal values. This experiment is run for a

short period of time in order to show the fast renewal of ECF Calcium level. ECF Ca reaches its set level very quickly (Figure 4.37).

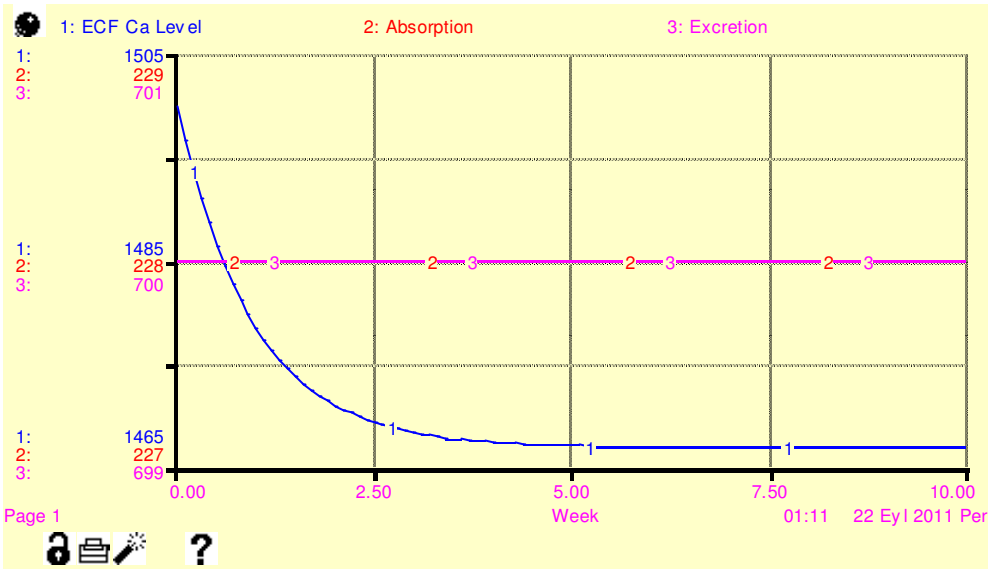

Figure 4.36. Dynamics of ECF Ca, Excretion and Absorption for Insufficient Calcium Intake.

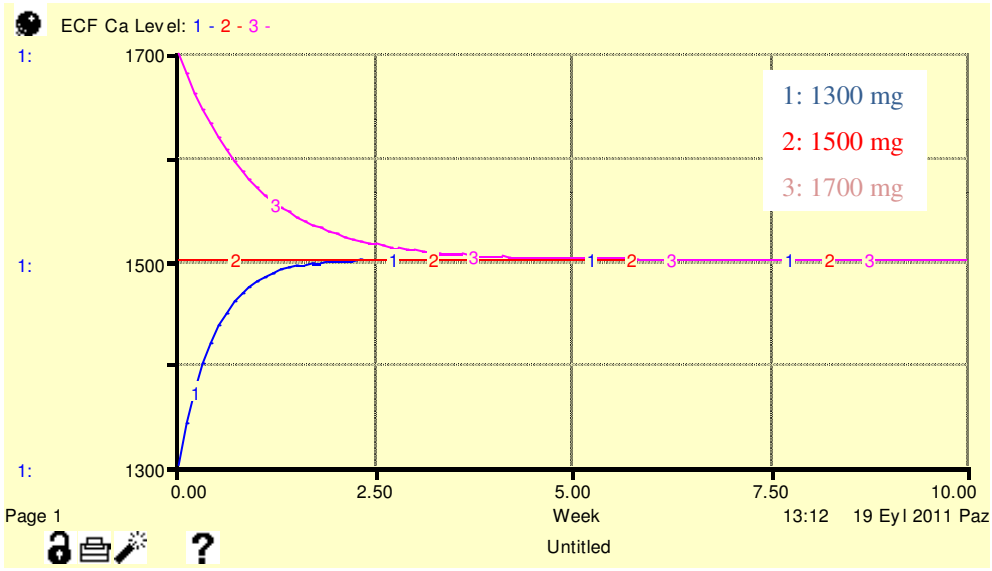

Figure 4.37. Dynamics of ECF Ca for Different Initial Values.

The next experiment tests the response of Absorption for the low levels of Vitamin-D with a normal Ca Intake. Ca Absorption takes a lower value with the low levels of Vitamin-D according to normal Vitamin-D level (Figure 4.38).

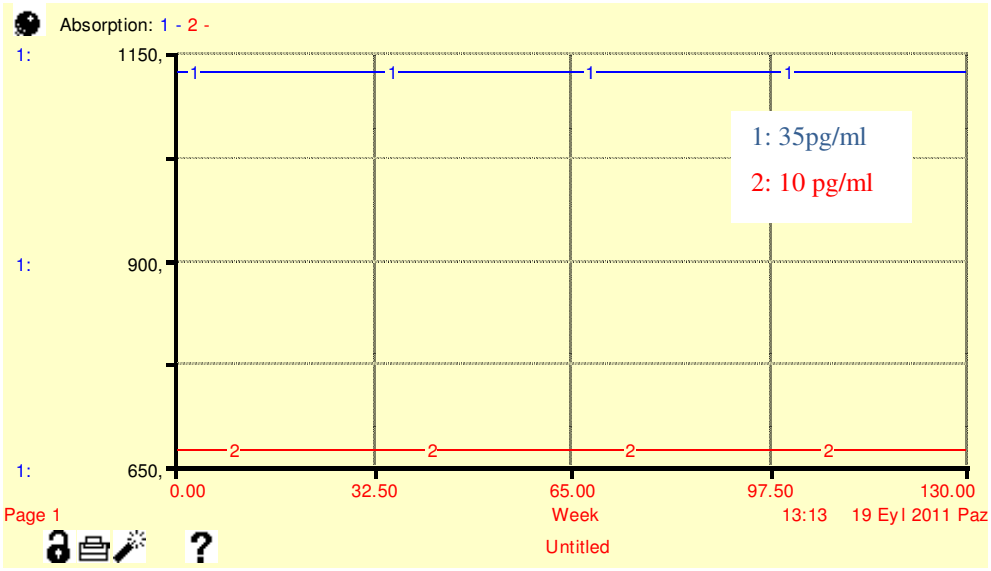

Figure 4.38. Dynamics of Absorption for Low Vitamin-D Level.

5. BASE BEHAVIOUR OF THE INTEGRATED MODEL

5.1. Structure of the Integrated Model

The complete stock flow diagram of the integrated model is given in Figure 5.1. *Ca Need Bone*, *Desired Ca Uptake ECF* and *Resorption* are the common variables that connect the two sectors. The values of these variables were not changed during simulation in Calcium Sector. In Bone Mass sector, in order to see isolated dynamics of bone mass, calcium exchange with ECF was not limited. Therefore, formation was set to desired formation, and Ca Need Bone variable was not used in Bone Mass Sector. Flow variables of Calcium Sector, *Ca Release ECF* and *Ca Uptake ECF,* are integrated with Bone Mass Sector by multiplying with a conversion coefficient.

5.2. Base Behaviour of the Complete Model

The start of the simulation for base runs, week zero, represents a 30 year old woman who is in her peak bone mass and has not experienced any bone loss related to any abnormalities. The simulation ends at age 80 to observe the effects of aging on bone mass. In adult human life, after maturation there is always a small bone loss due to the formation deficient. Indeed, most adults are in the process of developing osteoporosis because of the bone loss occuring throughout human life. This means that, any individual would likely to develop the disease, given a sufficiently long lifespan (Hernandez *et al.*, 2003). Mechanical strain is the most important variable of bone homeostasis. In the base run, Applied Stress is set to a level that keeps bone's Felt Strain in between normal levels (0.05MPa). Normal Felt Strain means no change in the remodeling rate. Dietary Calcium is also essential for a healthy bone. Ca Intake is also set to its normal level (4200 mg/week).

Estrogen Level decreases starting from age 45 slowly in Figure 5.2. At the end of the simulation, it decreases to 20% of the initial value. MESr increases with the decreasing estrogen level.

In Figure 5.3, there is a comparison of real data and model results of estrogen dynamics according to age. The model result shows a theoretical value for estrogen level. At the end, 80% of initial estrogen disappears. The real data show similar dynamics for bioavailable estrogen level in women (Riggs *et al.*, 2002).

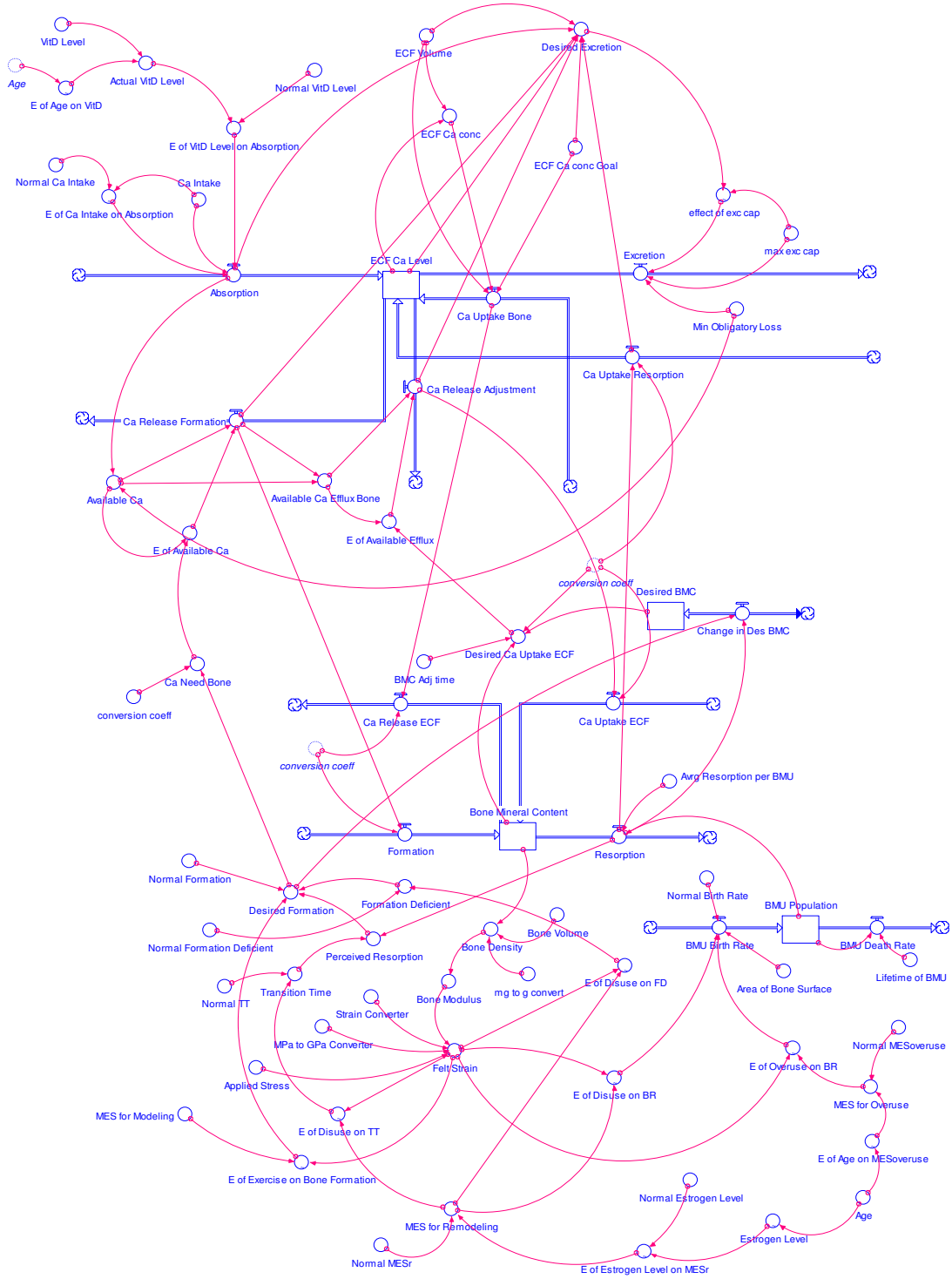

Figure 5.1. Stock-Flow Diagram of the Integrated Model.

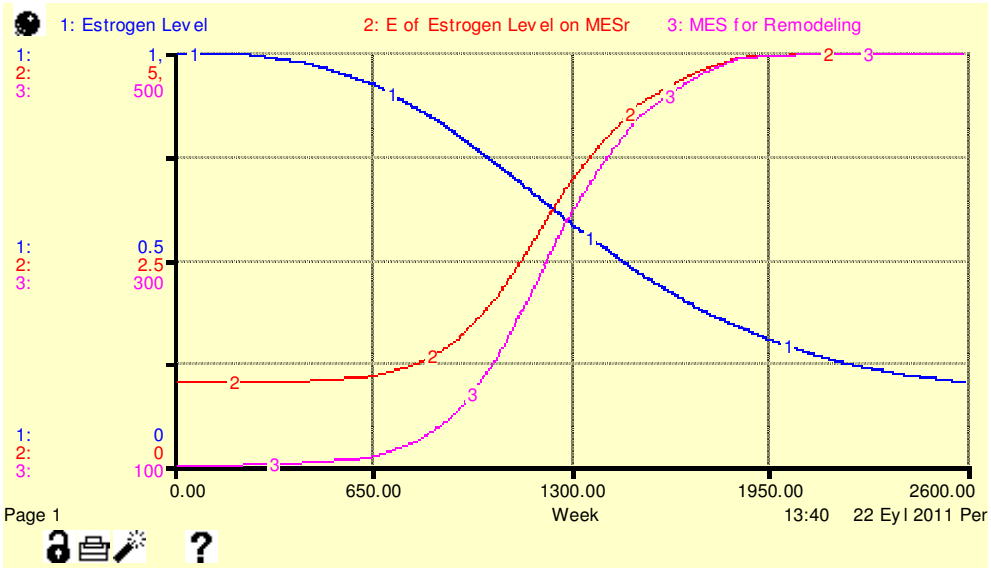

Figure 5.2. Base Dynamics of Estrogen Level and Effect of Estrogen on MESr in the Model.

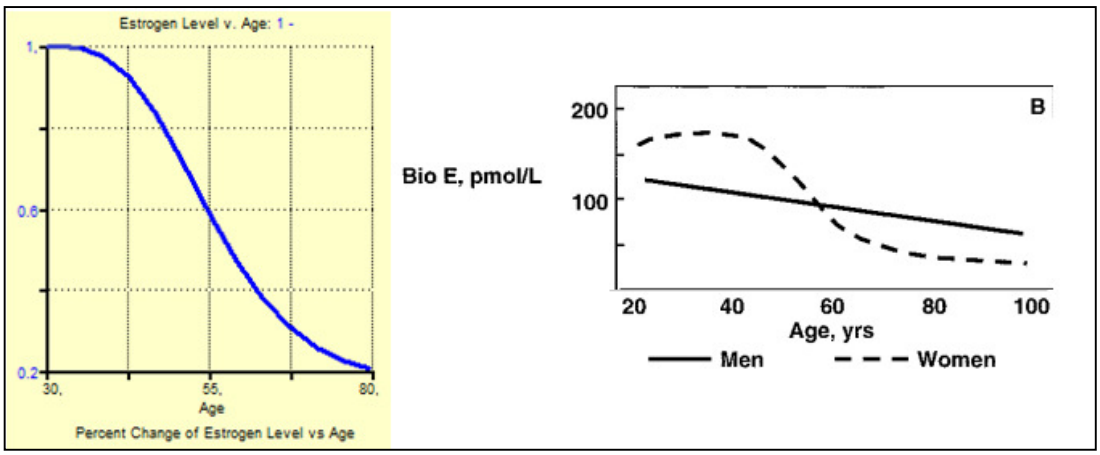

Figure 5.3. Comparison of Simulation Results and Real Data for Estrogen Level (Riggs *et al.*, 2002).

Effects of Disuse are all one at the beginning. By the onset of menopause, they increase and then slowly decrease to their normal values after menopause (Figure 5.4).

ECF Ca does not change in this run. In a day, ECF Ca is not exactly constant and oscillates over time because of calcium intake or fasting etc. However, this model is interested not in the short term dynamics of calcium homeostasis, but in the role of ECF calcium as a participant of bone mass homeostasis. Thus this model does not demonstrate significant deviation in the value of ECF Ca Level. Ca Excretion starts with a slightly

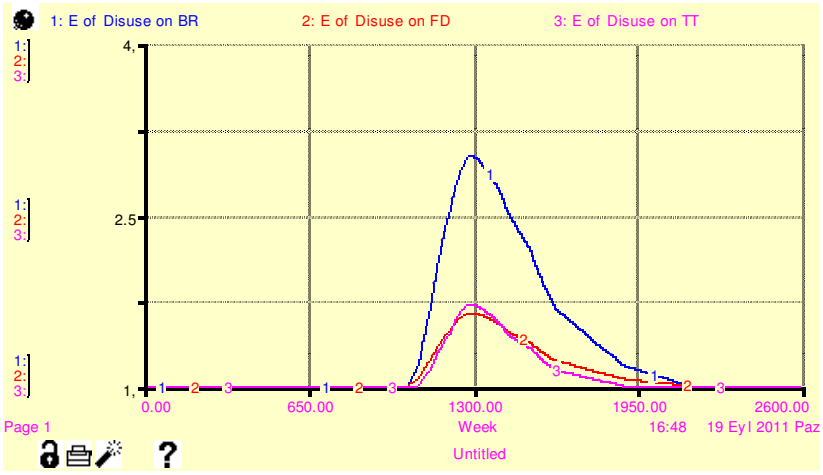

Figure 5.4. Dynamics of Effects of Disuse on Birth Rate, Formation Deficient and Transition Time in the Model.

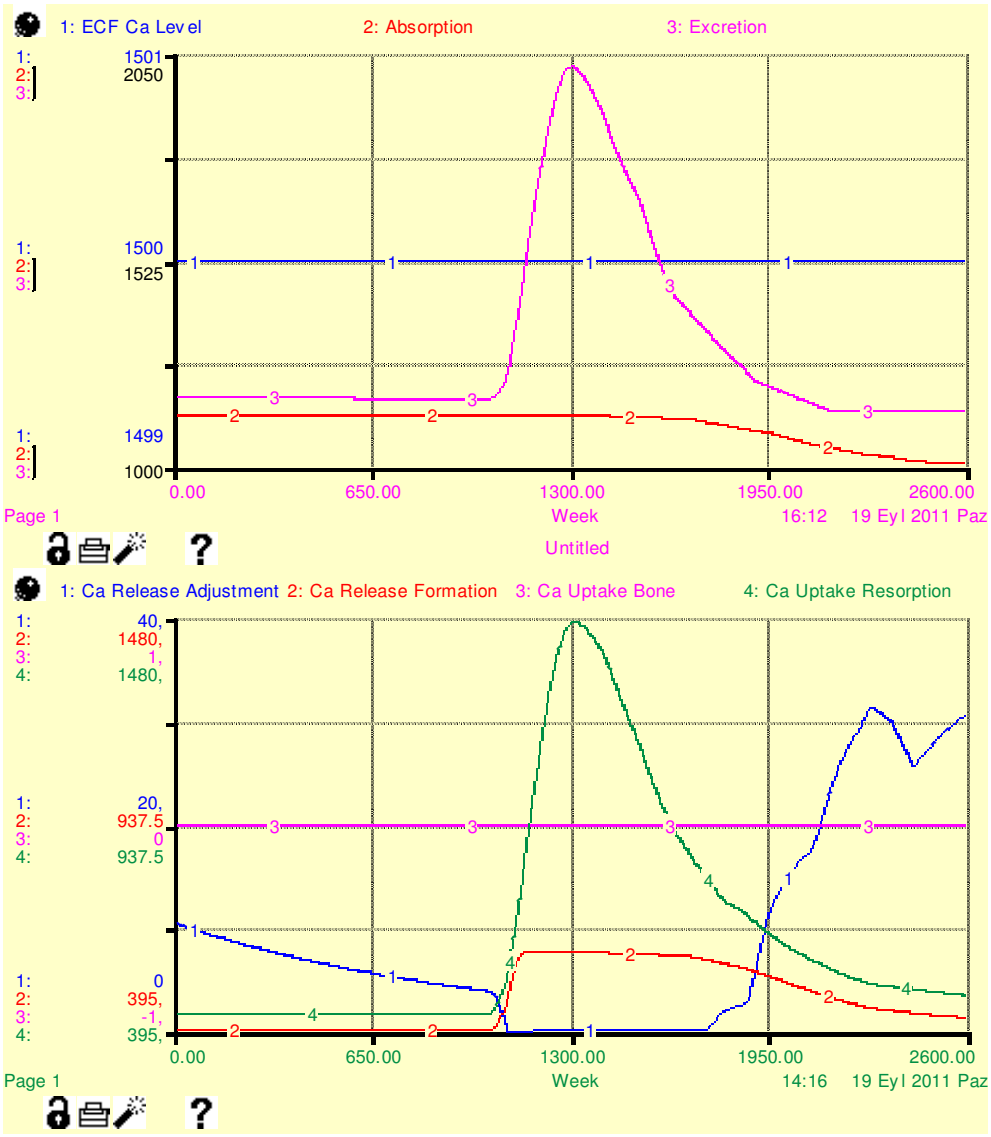

Figure 5.5. Base Dynamics of ECF Ca and its Flows in the Model.

higher value than Ca Absorption and decreases slowly. This higher value is due to net Ca input from bone as result of continuous Ca exchange between ECF and bone. Excretion suddenly increases because of the increased resorption level with the onset of menopause. When net influx to ECF from bone starts to decline, Ca Excretion decreases respectively. Ca Absorption is constant until time 1600 because of the constant calcium intake but it starts to decline due to the effects of aging on Vitamin-D. Vitamin-D is a stimulator on calcium absorption and when it is insufficient, absorption does not fully disappear but it decreases by a significant percent.

Ca Release Adjustment depends on the desired calcium uptake of bone and available calcium efflux from ECF (Figure 5.5). Therefore, it becomes zero in a certain interval and can make sharp increases and decreases through the simulation.

In this run, Ca Intake is enough for a healthy nutrition. Therefore, ECF does not need to take Ca from bone and Ca Uptake Bone is equal to zero (Figure 5.5). Ca Release Formation is the net amount of Calcium that is needed for bone formation. It starts with a lower value than Ca Release Resorption because of the formation deficient. Ca Release Formation does not increase as much as Ca Release Resorption because of the insufficient Calcium intake in order to refill the resorption cavities. Calcium Intake is sufficient for Ca homeostasis however for a healthy skeleton; it does not meet the expectations.

In Figure 5.7, Bone Mineral Content decreases slightly while formation and resorption are constant. BMC always decrease even in small degrees because OBs always leave a small deficient after OCs remove bone. Around week 1100, there is a rapid decrease in BMC because of the start of estrogen decline at that time. At about week 1600, the decrease slowdowns and continues throughout life. There is always a difference between resorption and formation however, this difference is bigger when estrogen level decreases because of the spurious disuse that bone perceives at that time. With the onset of disuse mode, transition time and formation deficient both increase and make Ca balance more negative (Figure 5.6).

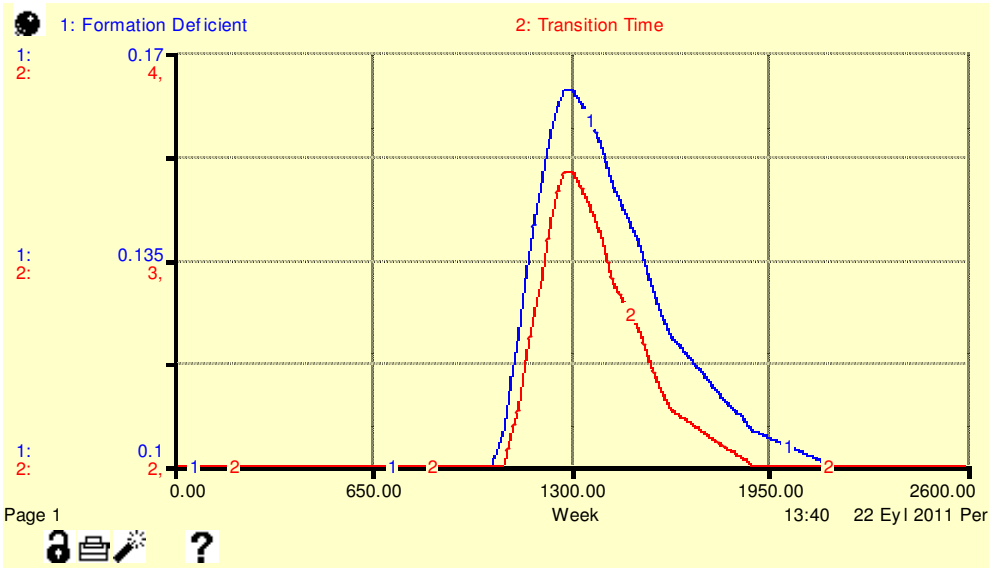

Figure 5.6. Base Dynamics of Formation Deficient and Transition Time in the Model.

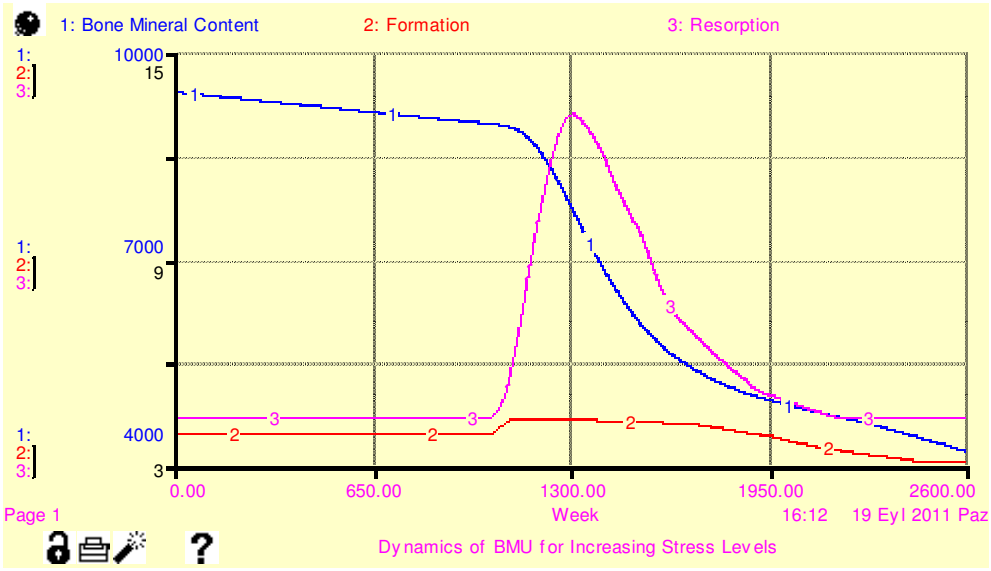

Figure 5.7. Base Dynamics of BMC, Formation and Resorption in the Model.

When estrogen level decreases, bone resorption increases rapidly. There is an imbalance between bone resorption and formation in this period with resorption exceeding formation. The result is accelerated post-menopausal bone loss (Christiansen, 1995). In Figure 5.8, there is a theoretical representation of this imbalance. The model dynamics also draw a similar imbalance between formation and resorption.

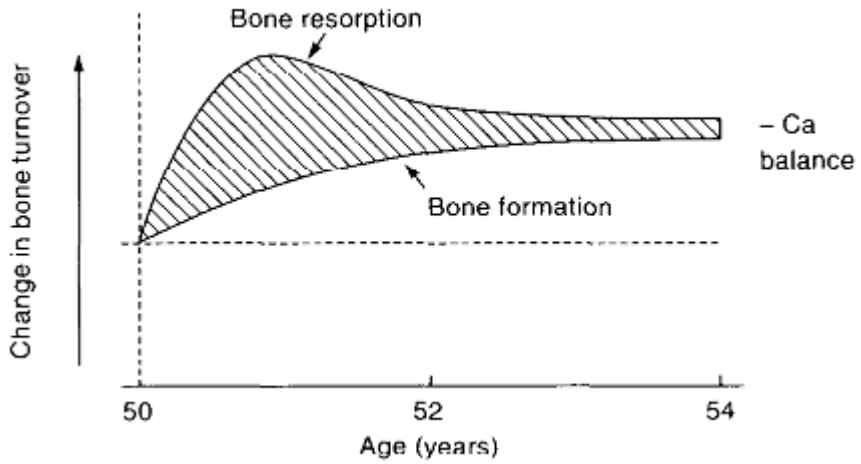

Figure 5.8. Theoretical Representation of Imbalance Betwen Bone Resorption and Formation (Christiansen, 1995).

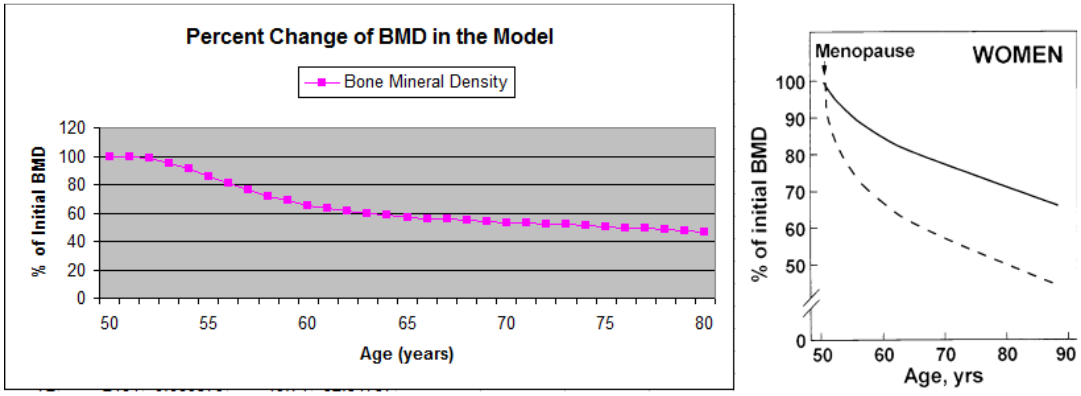

Figure 5.9. Comparison of the model result (left) and real data (right-dotted lines show trabecular bone) for Percent Change in BMD (Riggs *et al.*, 1998).

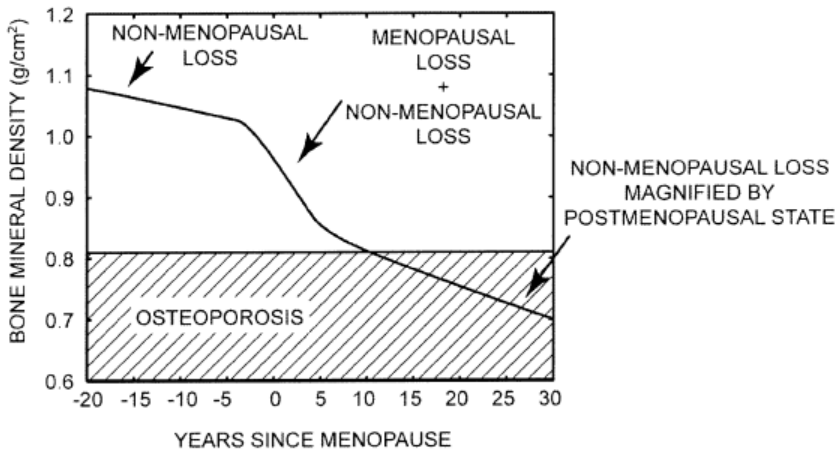

Figure 5.10. Theoretical Representation of Menopausal and Non-menopausal Bone Loss (Hernandez *et al.*, 2003).

Riggs *et al.* mentions that postmenopausal women experience two phases of bone loss; accelerated and slow phases (Riggs *et al.*, 1998). In the accelerated phase, 30% of initial bone mass is lost in the first decade of menopause. This is because of the loss of supressive effect of estrogen on formation and resorption. The second and slow phase is related to non-menopausal losses, like aging effects. Figure 5.9, model results show that there is about 35% of bone loss compared with the initial bone mass. After age 60, there is continuous bone loss related to aging and senescence. Model results show similar dynamics with the theoretical representation of bone mass in Figure 5.10.

BMU Population does not change because Felt Strain never falls below or above its normal values between weeks 0-1100. However, because of the estrogen deficiency, disuse mode becomes active at about week 1100 and BMU Population increases until the effect of disuse on birth rate decreases to normal. At the end of rapid bone loss period, BMU Number and its flows return to their initial normal values. This also shows that, after rapid bone loss, the remaining loss is not because of menopause. Aging is the secondary cause of this post-menopausal loss.

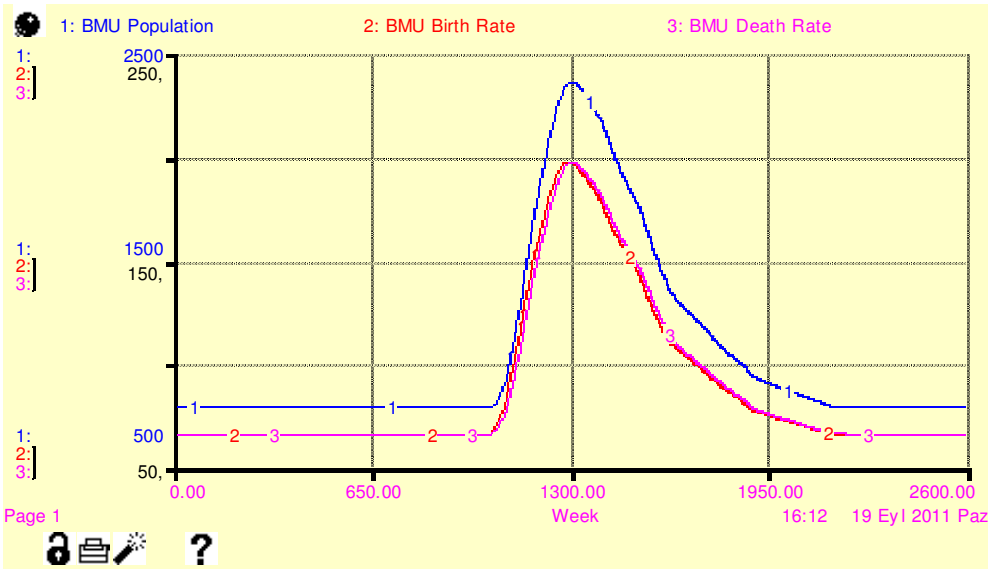

Figure 5.11. Base Dynamics of BMU Population, Birth Rate and Death Rate in the Model.

Bone Density decreases because of the decrease in Bone Mineral Content. Felt Strain is in normal levels at first but because of the decrease in bone density, it increases until the menopausal effects are lost. At about week 1950, Felt Strain goes into a saturation trend

however, because of the continuous bone loss related to senescence (aging); it starts to increase in an increasing fashion after that time.

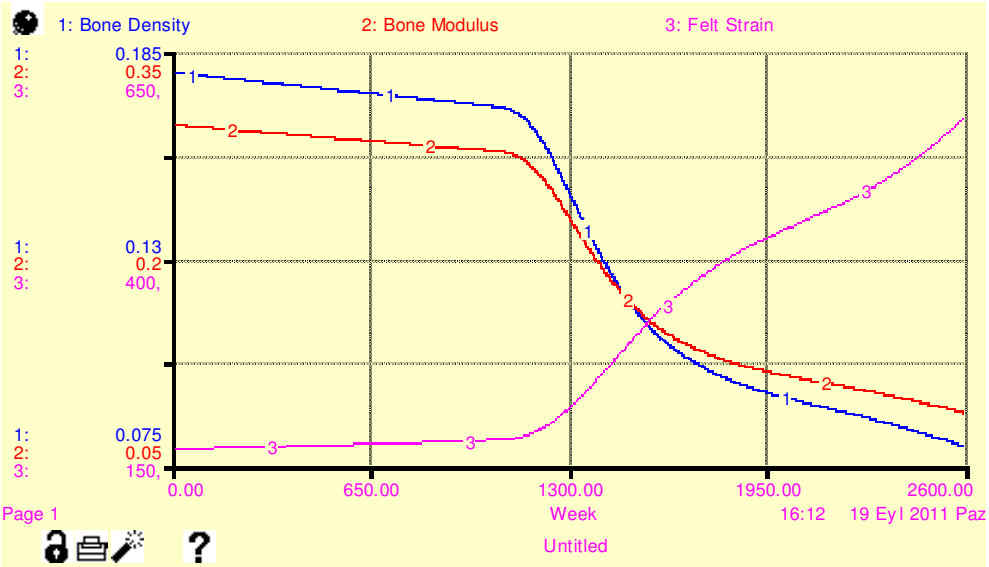

Figure 5.12. Base Dynamics of Bone Density, Felt Strain and Bone Modulus in the Model.

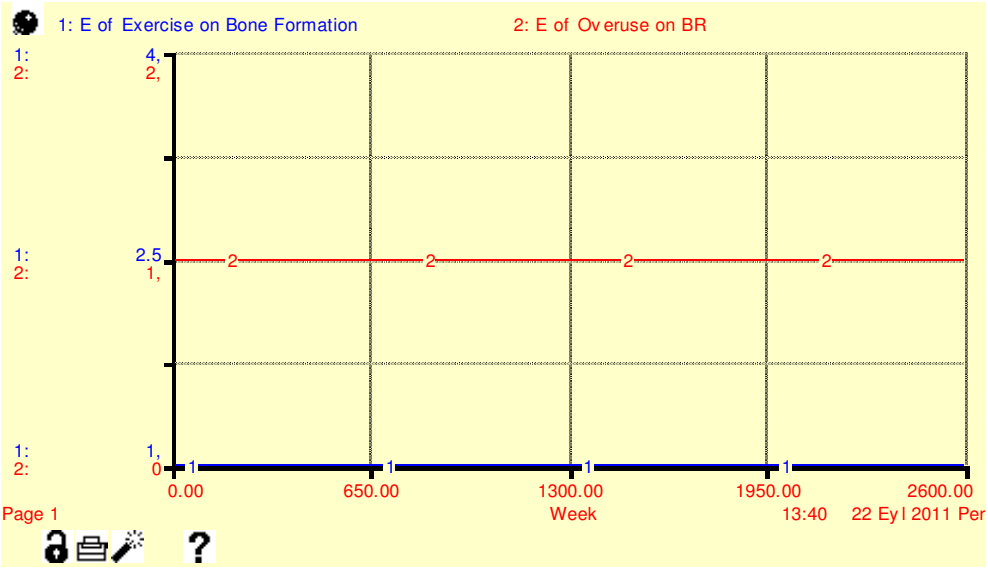

Figure 5.13. Base Dynamics of Effect of Exercise on Bone Formation and Effect of Overuse on BMU Birth Rate in the Model.

There is not a change in exercise level. Therefore the effects of exercise and overuse do not change (Figure 5.13). After a certain age, bone becomes more fragile and prone to be damaged. This is because of the decrease in MES for Overuse after age 60 (Figure 5.14).

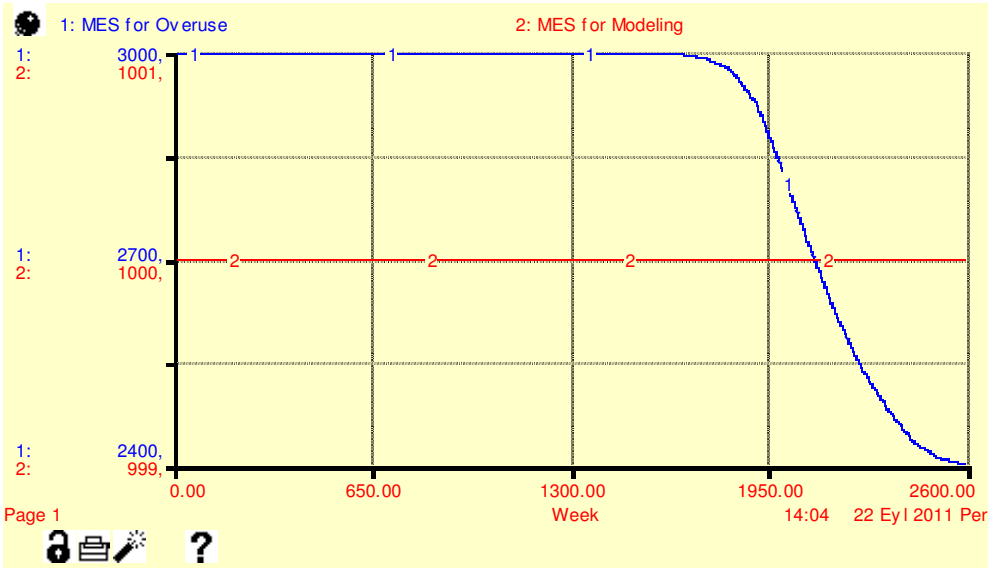

Figure 5.14. Dynamics of Minimum Effective Strain for Overuse and Modeling in the Model.

6. VALIDITY TESTS AND ANALYSIS OF THE MODEL

The aim of this chapter is to further demonstrate and analyze the validity of the model described and partially tested in the previous chapter. Validation of system dynamics models mainly concentrates on the internal structure of the model, and behavior validation is tested only after there is enough confidence in the underlying structure. Hence, a formal validation process is followed in order to detect structural flaws of the model (Barlas, 1996). The model is simulated via Stella Software and the simulation time unit is weeks. Simulation length is 2600 weeks, stands for an age interval between 30 and 80. A sufficiently small time step (1/10) is used for the simulation.

6.1. Calcium Supplementation

6.1.1. Premenopausal Women

The daily Calcium Intake is set as 600 mg/day in the base model. In order to see the effects of Calcium supplementation on Bone Mineral Content, Ca Intake is increased to 1000 mg/day that is recommended by WHO for women who have not experienced menopause. All other variables are set to their normal values. Welten et.al found that Calcium supplementation of about 1000 mg/day in premenopausal women can prevent bone loss by about 1% per year (Welten *et al.*, 1995). In the simulation results, bone loss is decreased by 0.04% per year, with 1000 mg/day Calcium intake (Figure 6.1).

6.1.2. Post-menopausal Women

The daily Calcium intake is set to 600 mg/day in the base run. In the treatment run, Calcium Intake is increased to 1500 mg/day after age 55 that is the recommended amount for postmenopausal women by WHO. All other variables are set to their normal values. A meta-analysis study that evaluates the effects of Calcium in post-menopausal found that Calcium is effective in reducing rates of bone loss after two or more years of treatment (Shea *et al.*, 2002). The percent change of bone loss with Calcium treatment is 1.66% per year in lumbar spine in this study. In the simulation results, bone loss is decreased by

1.87% per year in lumbar spine of post-menopausal women who receive 1500 mg/day Ca supplementation (Figure 6.2). Percentage difference is calculated by percent of bone loss in treatment group minus percent of bone loss in control group.

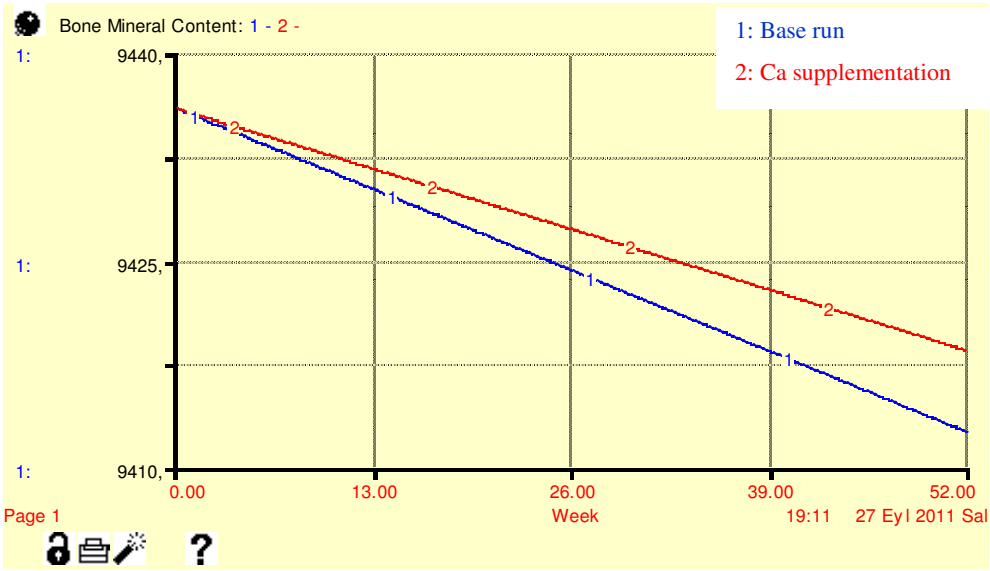

Figure 6.1. Effect of Calcium Supplementation on Premenopausal Women in the Model.

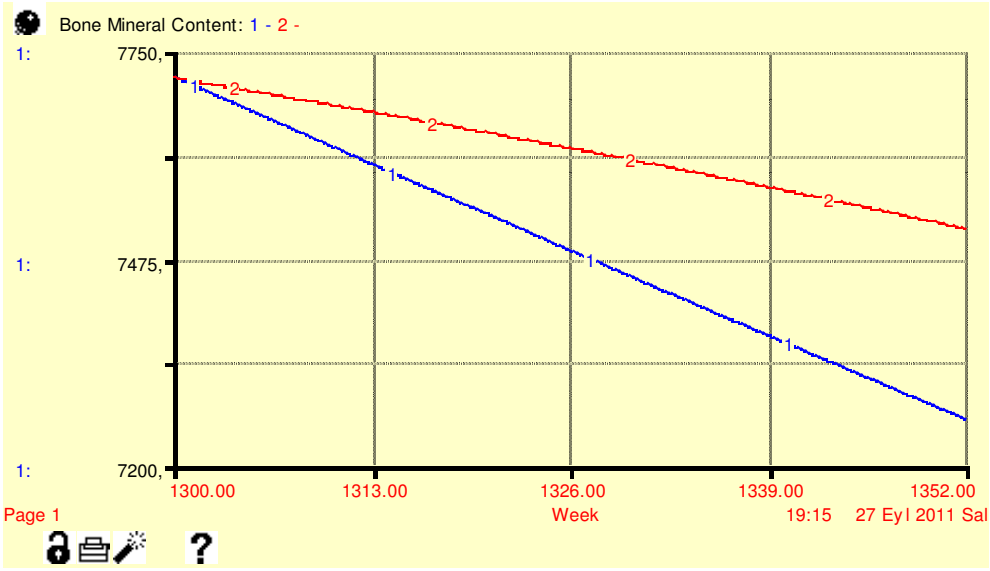

Figure 6.2. Effect of Calcium Supplementation on Post-menopausal Women in the Model.

6.2. Exercise

6.2.1. Pre-menopausal

In the base run, Stress Level that shows the exercise history of the subject is set to 0.05MPa. In the treatment run, Stress Level is increased to 0.4MPa that corresponds to a weight bearing activity like resistance weight training or weightlifting exercises. The simulation is run for two years starting from age 30. Winters-Stone and Snow found that premenopausal women who practive aerobics and weight training exercises for two years experience 0.8% change in bone mass than control group (Winters-Stone and Snow, 2006). In the simulation run, the percent difference between treatment and control is 0.68% at the end of two years (Figure 6.3). Percent difference is calculated by percent change in treatment group minus percent change in control group.

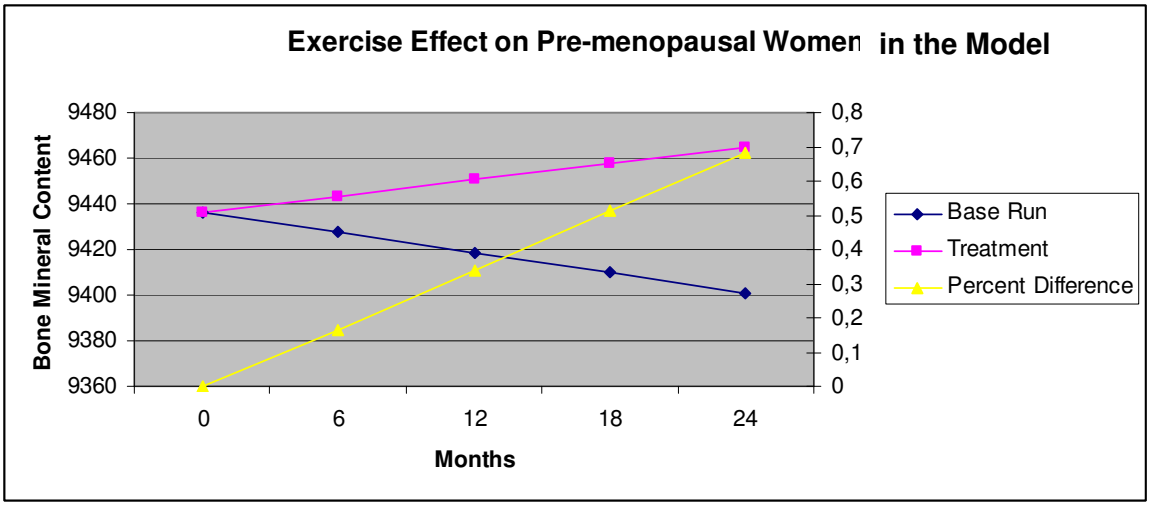

Figure 6.3. Effect of Exercise on Bone Mass in Pre-menopausal Women in the Model.

6.2.2. Post-menopausal

In this run, simulation starts with a Stress Level of 0.05MPa and at time 1560 (age 60), it is increased to 0.1 MPa that corresponds to light exercise regime for older people. The simulation is run for 12 months starting from age 60. The percent difference between treatment and control group is 2.24% in the simulation (Figure 6.4). In the study of Bravo *et al.*, the percent difference between control group and post-menopausal women who

practice moderate level exercise like walking, dancing, stepping up and down for 12 months was 1.8% in lumbar spine (Bravo *et al.*, 1996).

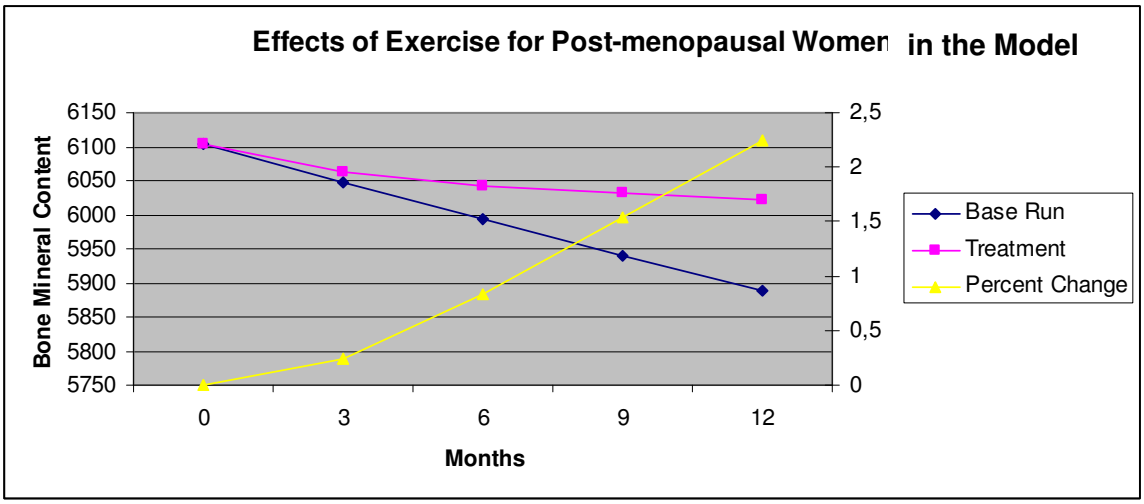

Figure 6.4. Effect of Exercise on Bone Mass for Post-Menopausal Women in the Model.

6.3. Hormone Replacement Therapy (HRT)

In this run, Hormone Replacement Therapy (HRT) intervention is tested. In the base run, there is no interference with estrogen level. In the treatment run, estrogen level is increased by 60% at time 1820 (age 65). Calcium intake is set to 1000 mg/day as its initial value. All other variables are set to their normal values. FDA recommends women to use HRT but in small amounts because of the risks of the drugs associated with breast cancer, heart attacks and strokes. In the simulation results, the percent change in the bone mineral content of HRT treatment group from baseline is 2.3% after three years (Figure 6.5). Greenspan *et al.* evaluated this value as 3% after three years of HRT use in post-menopausal women (Greenspan *et al.*, 2003).

6.4. Anti-resorptive Agents (Alendronate)

Alendronate is the most used drug for osteoporotic patients in order to decrease the increased resorption levels and so to prevent bone loss after menopause. Alendronate acts on bone resorbing cells, osteoclasts, and encourages them to undergo apoptosis, thereby slows bone loss. Thus, a variable named Antiresorptive Agent is formulated as an effect

variable on death rate of BMUs and is set to two to obtain same effect of 10 mg/d alendronate on bone mass. In the base run it is set to one. Calcium Intake is set to 1000 mg/day to promote normal bone formation. In the simulation results, percent change in bone mineral content is 3.65% after three years therapy (Figure 6.7). In Figure 6.6, Greenspan *et al.* evaluated this value as 4.2% (Greenspan *et al.*, 2003).

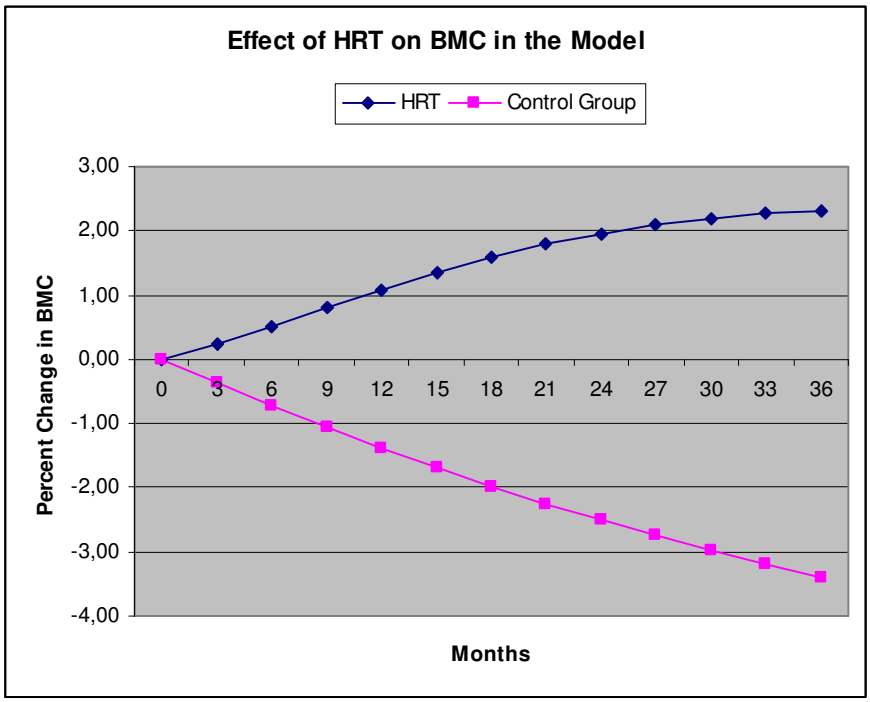

Figure 6.5. Effect of HRT on Bone Mass in the Model.

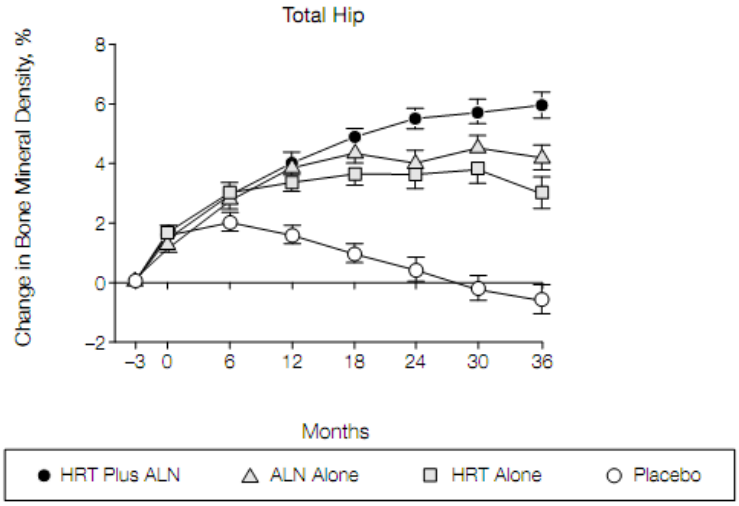

Figure 6.6. Experimental Data on the Effect of HRT on Bone Mass (Greenspan *et al.*, 2003).

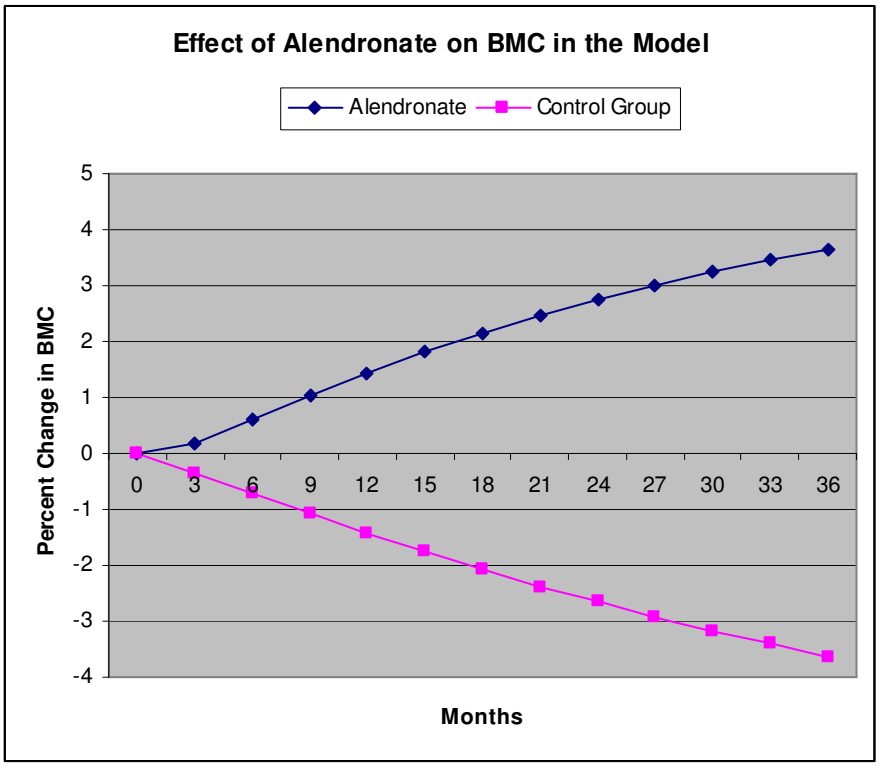

Figure 6.7. Effect of Anti-resorptive Agents (Alendronate) on Bone Mass in the Model.

7. SCENARIO ANALYSIS

7.1. Pre-menopausal Subjects

In this part, a woman who has not experience menopause will be tested. The simulation starts with a 30-year-old adult healthy woman. The interventions tested in this part are not for therapeutic purposes but for preventing regular bone loss in pre-menopause or increasing bone mass before menopause thereby protect bone against further losses after a certain age.

7.1.1. Onset of Menopause

The first scenario tests the effect of timing of menopause on the development of osteoporosis. The onset of menopause depends on the estrogen level. In the base model, the decrease in estrogen level starts at about age 40 and saturates towards the age 80. In this scenario the decrease will begin at age 45, 50 and 55. Other variables of the model are initialized from their normal levels. Bone Mineral Content decreases less than the base case when the onset of menopause is at a later time (Figure 7.1). Model results show similar dynamics with Figure 7.2.

Figure 7.1. Dynamics of BMC for Changing Levels of Onset of Menopause in the Model.

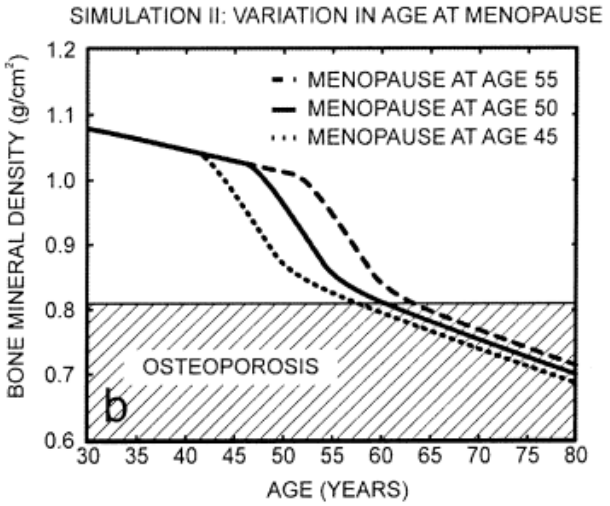

Figure 7.2. Simulation results for different ages of menopause (Hernandez *et al.*, 2003).

7.1.2. Bed Rest History

In this scenario, a subject with a 12-week bed-rest history will be simulated. Starting from age 35, subject is exposed to 12 weeks of bed rest and then returns to pre-rest strain levels. Zerwekh *et al.* found in an experimental study that 12-week of bed-rest resulted in 2.9% bone loss in lumbar spine (Zerwekh *et al.*, 1998). In the model, this value is 2.02% (Figure 7.3).

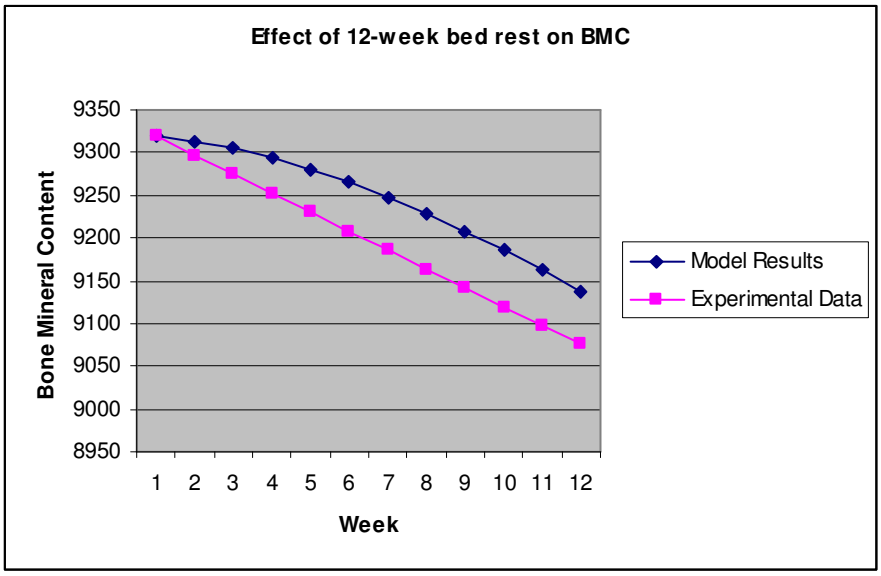

Figure 7.3. Comparison of model and real data (Zerwekh *et al.*, 1998) for 12-week Bed-Rest History.

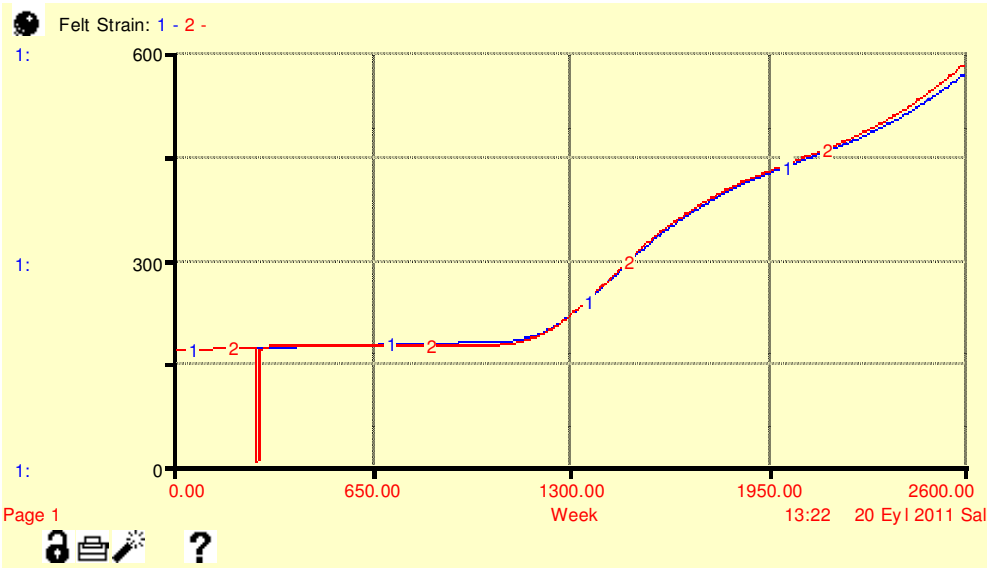

Figure 7.4. Felt Strain Level for Base Run and Disuse (Bed Rest) Experiment.

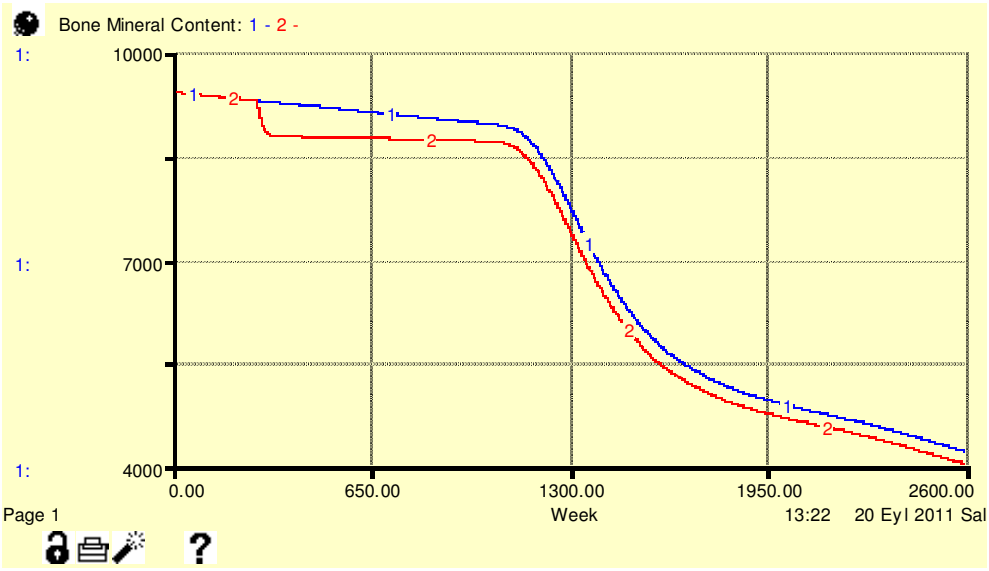

Figure 7.5. Dynamics of BMC for a 12-week Bed Rest before Menopause in the Model.

7.1.3. Exercise History

In this scenario, a subject with different exercise history will be simulated. Calcium Intake level is set to 1000 mg/day in this scenario not to suppress the effect of exercise. Applied stress levels are shown in the Figure 7.7. This run aims to find out if there is a positive effect of exercise history on preventing osteoporosis. First treatment is effective in menopausal years, not in the pre-menopausal phase. Applied Stress is not above the formation threshold. Second run is able to increase bone mass in pre-menopausal years and

preserves bone mass from higher menopausal losses and decreasing the risk of developing osteoporosis (Figure 7.6). Bone tissue becomes more fragile in post-menopausal women, so applied stress levels are set to lower values than in pre-menopausal women in the scenario runs of post-menopausal women.

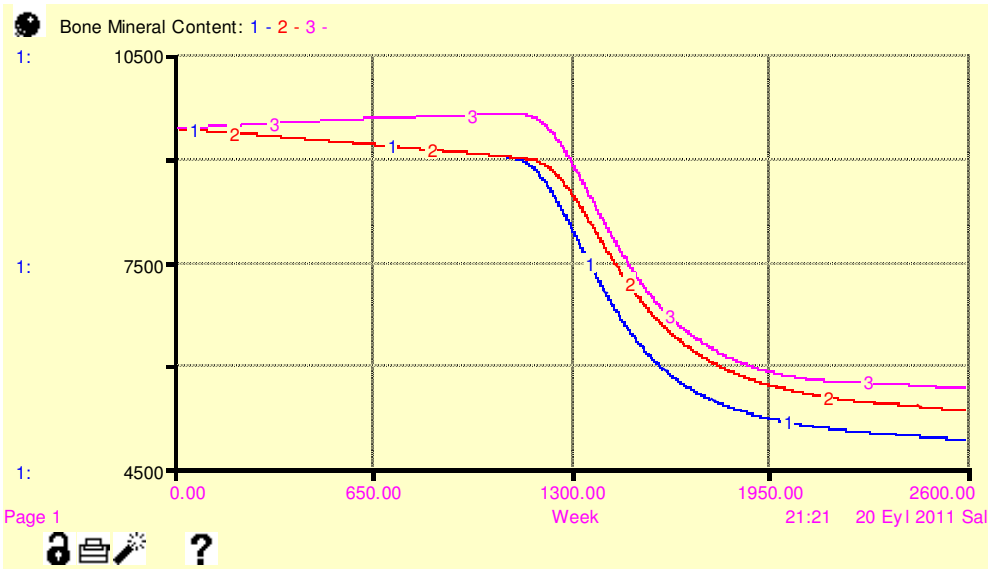

Figure 7.6. Dynamics of BMC with a Weight Bearing Exercise History in the Model.

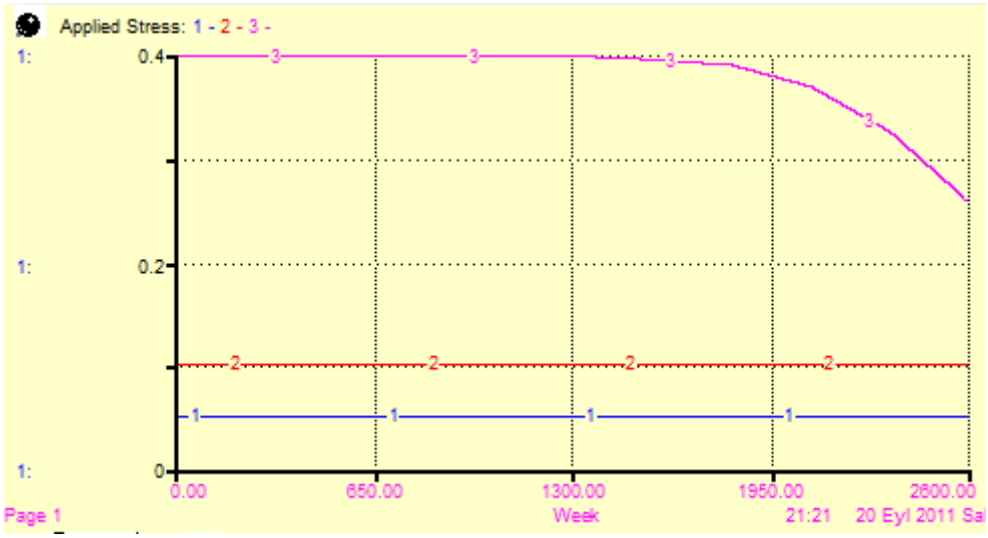

Figure 7.7. Applied Stress Levels in the Exercise Scenarios for Premenopausal Women.

7.1.4. Calcium Supplementation

In this scenario, the subject's Calcium Intake habits will be simulated. In sedentary subjects who are subjected to normal stress level, it will be tested whether Dietary Calcium intake makes a difference in development of osteoporosis after the maturation of adult human bone. Very high, normal and low values of Calcium Intake will be run. In the base run, Calcium Intake is set to 600 mg/day which is average daily intake of women. Recommended daily intake level is 1000 mg/day by WHO for premenopausal women. 1200 mg/day will also be tested whether increasing Calcium level is beneficial for bone health in premenopausal women. Calcium Intake can prevent bone loss before menopause to some degree (Figure 7.8). However, a more significant effect is seen in older ages. Aging has a reducing effect on the efficiency of Vitamin-D. This results as a lower Ca absorption rates in older ages. Therefore, Ca Intake should be increased to prevent further bone loss in older ages.

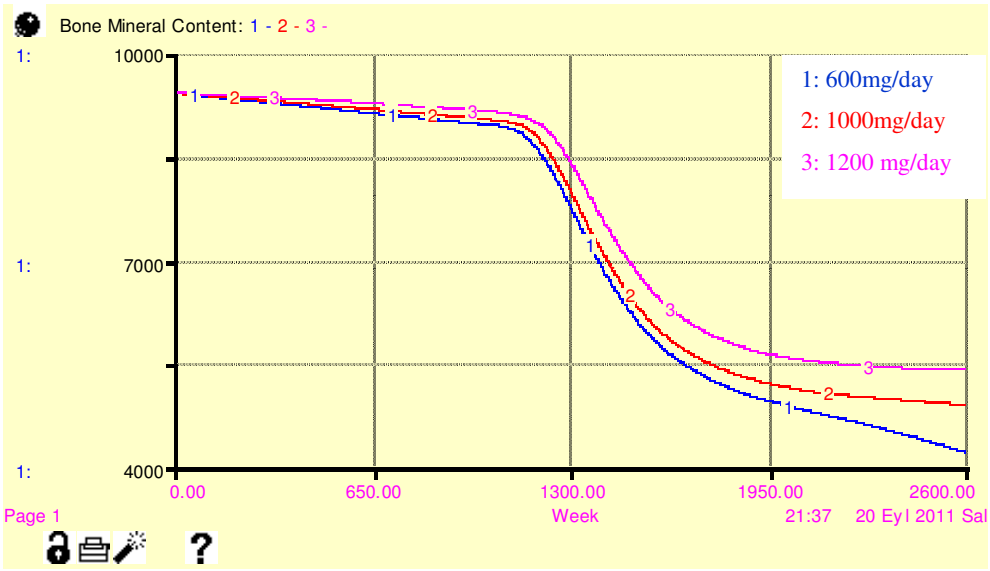

Figure 7.8. Dynamics of BMC for Different Levels of Ca Intake in the Model.

7.1.5. Nutrition and Exercise

In this scenario, the combined effect of high strain exercise and Dietary Calcium Intake is tested. The question is "Is exercise helpful in developing bone mass without Ca supplementation?" Calcium Intake will be set 600 mg/day, 1000 mg/day and 1500 mg/day

in each run respectively. Increasing Calcium Intake is crucial while conducting exercise in order to increase bone mass. Same level of exercise is most beneficial when calcium intake is enough in order to meet the calcium desire of bone stimulated by increased bone formation levels (Figure 7.9). If Calcium intake is low, exercise is not helpful in developing bone mass.

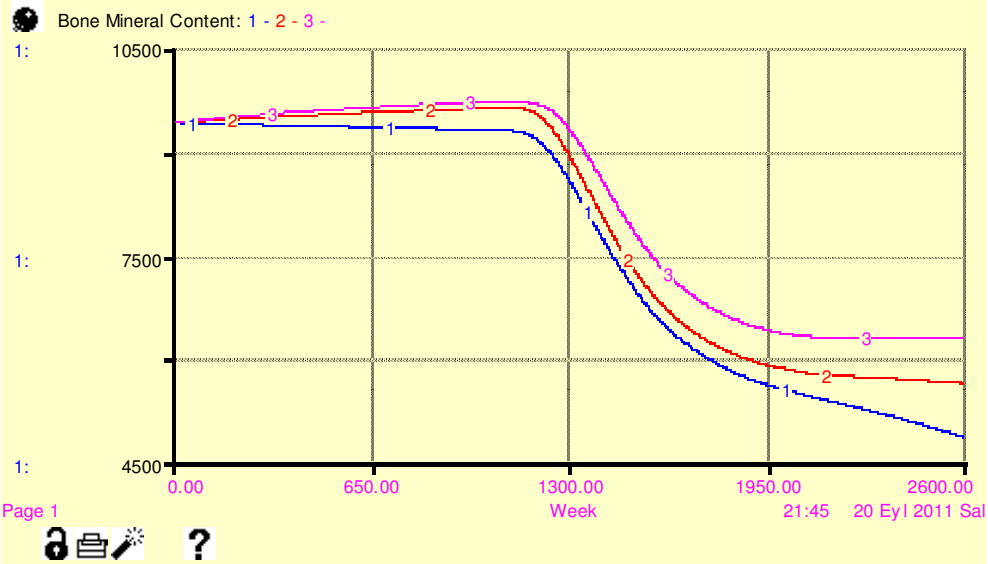

Figure 7.9. Dynamics of BMC for Decreasing Level of Calcium Intake with High Impact Exercise in the Model.

7.2. Post-menopausal Subjects

In this part, a post-menopausal woman will be simulated. Several interventions will be tested after the onset of menopause in order to observe their effects on preventing or treating bone loss. The simulation will start at time 1300 (age 55) that represents a post-menopausal state.

7.2.1. Nutrition

In this scenario, the effects of Calcium intake will be tested. The simulation will be started at age 55 and low, normal and high calcium intakes will be tested for the rest of the simulation time for a post-menopausal woman who has a sedentary lifestyle. Calcium Intake of 600 mg/day, 1000 mg/day and 1500 mg/day will be run respectively. The results show that calcium supplementation is a therapeutic intervention for the rapid bone loss

phase (Figure 7.10). Taking necessary amount of calcium is also important in order to prevent effects of aging on intestinal absorption.

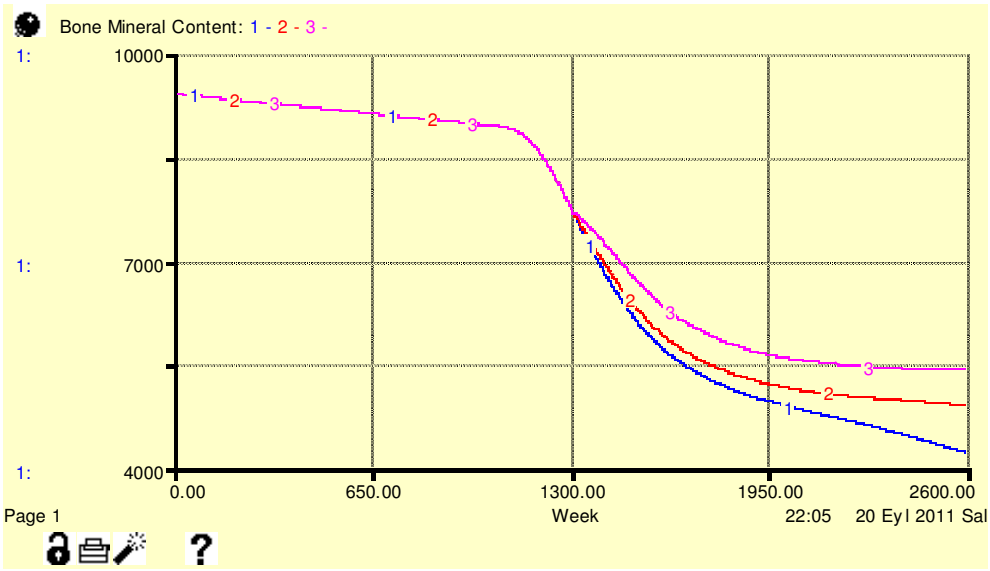

Figure 7.10. Dynamics of BMC for Changing Ca Intakes for Post-menopausal Women in the Model.

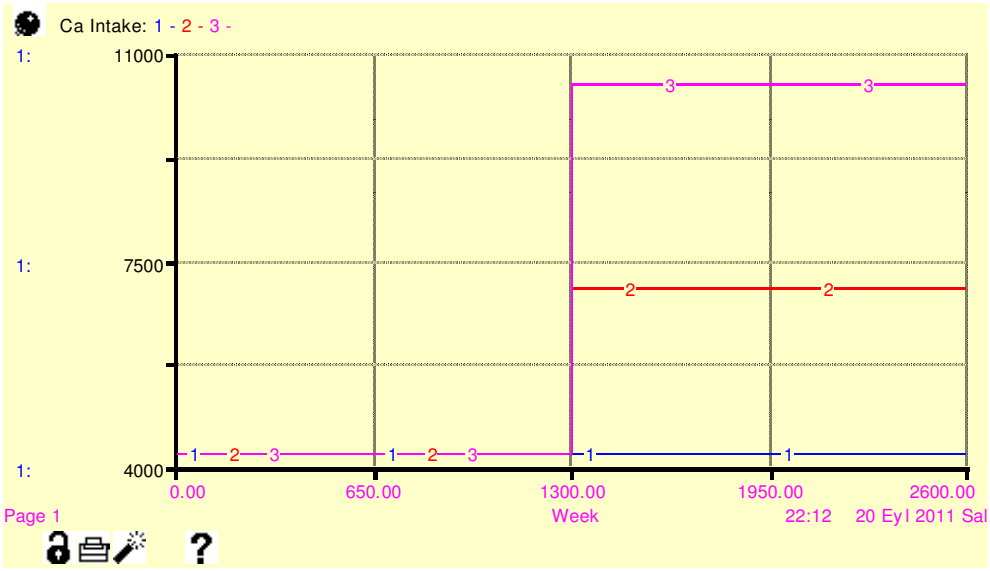

Figure 7.11. Calcium Intake Regimes in the Model.

7.2.2. Exercise

This scenario will test the effects of the exercise on bone mass. Subject will conduct several exercise levels after age 55. There will be no increase in the Ca supplementation.

The amount of recovery from the initial conditions will be observed. Exercise has positive effects on bone loss prevention after menopause (Figure 7.12). However, because of the decreased bone mass and increased strain levels, stress level can be increased to limited levels. With aging, bone becomes more fragile and the risk of fracture increases. Therefore, exercise intervention should be applied carefully and must be appropriate for the subject's bone strength characteristics.

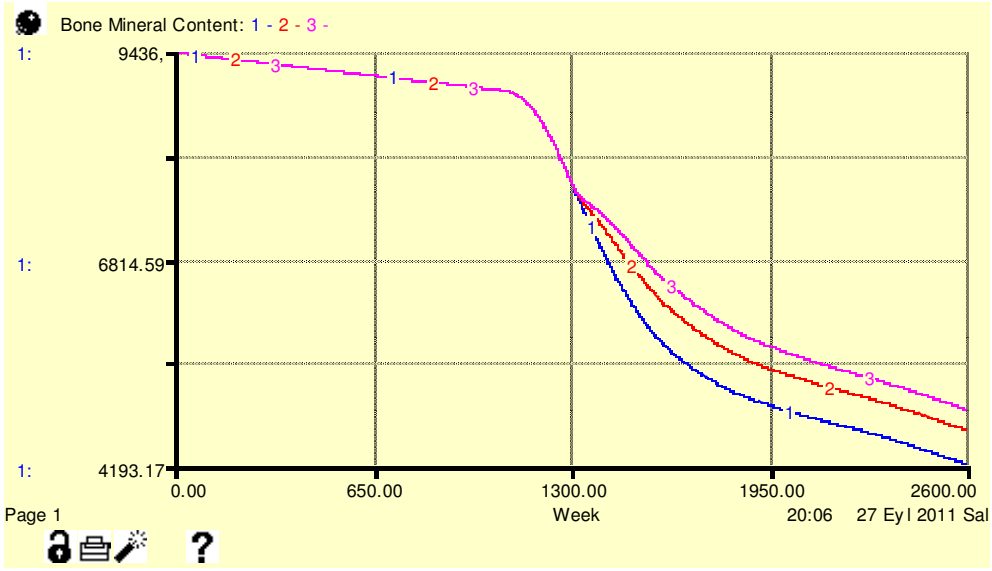

Figure 7.12. Dynamics of BMC for High Impact Exercise for Post-menopausal Women in the Model.

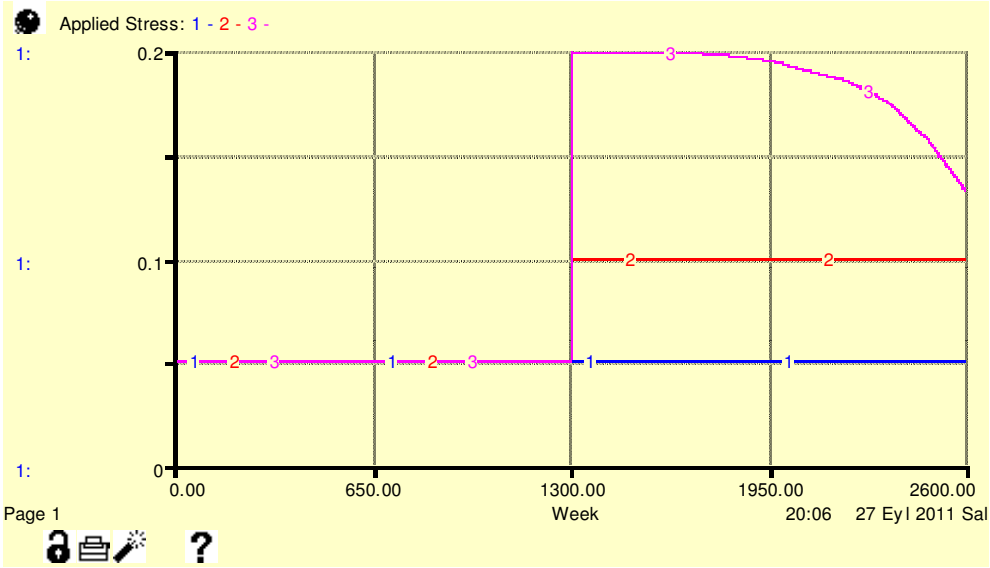

Figure 7.13. Applied Stress Levels in the Exercise Scenarios for Post-menopausal Women in the Model.

7.2.3. Exercise and Calcium

In this run, combined effect of exercise and calcium will be tested. In the first run, subject is exposed to a moderate exercise level (0.1MPa) without enough calcium intakes (600 mg/day). In the second run, 900 mg/day calcium supplement is taken to increase total level to 1500 mg/day. In the simulation results, it can be concluded that exercise without calcium is not much effective in increasing bone mass or preventing bone loss (Figure 7.14).

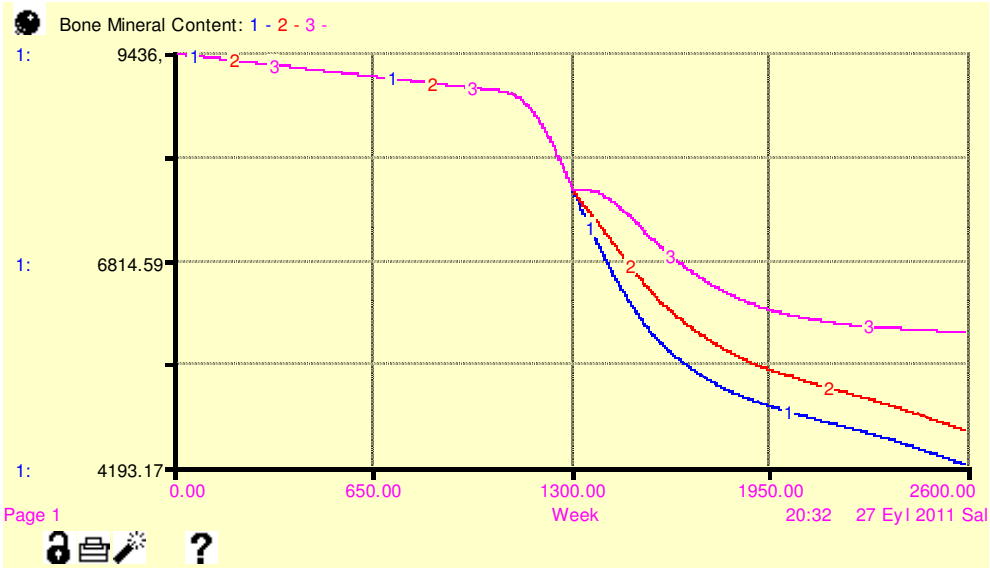

Figure 7.14. Combined Effect of Exercise Plus Calcium after Menopause in the Model.

7.2.4. Hormone Replacement Therapy

Osteoporotic patients generally receive HRT (Hormone Replacement Therapy) in order to reverse the effects of decreased estrogen level. FDA approves HRT for preventing bone loss in menopausal women however, because of the risk of HRT associated with breast cancer and hearth stroke, it must be taken in small degrees. In this scenario, a HRT effect variable is formulated that generates an effect 0.625 mg/day of HRT that is a recommended amount by most of the physicians. Applied Stress and Calcium Intake are set to their normal levels. HRT is applied at time 1300 (age 55) in this run. The results show that estrogen therapy is useful in preventing bone loss after menopause (Figure 7.15).

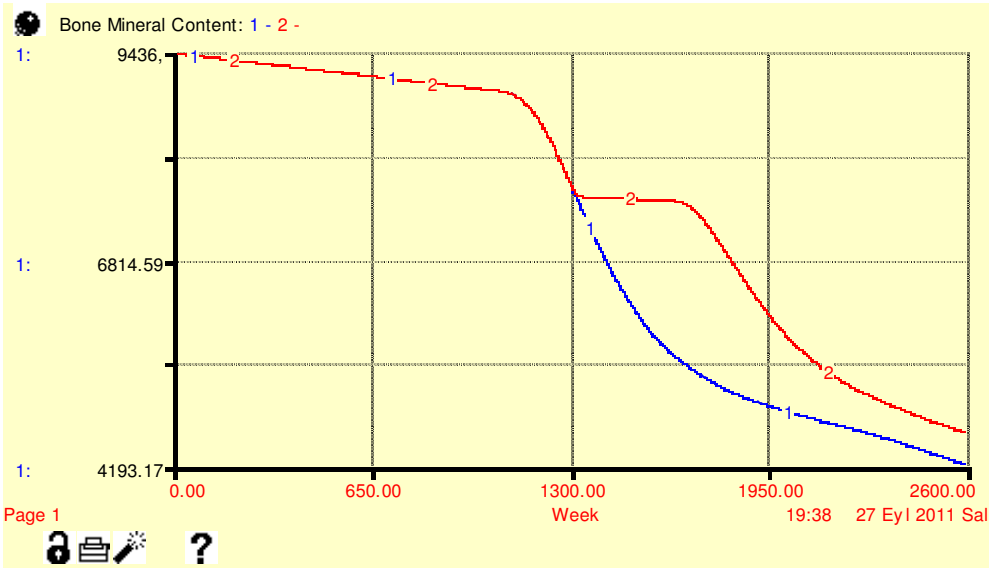

Figure 7.15. Dynamics of BMC for ERT in the Model.

7.2.5. Hormone Replacement Therapy (HRT) and Calcium

In this scenario, combined effect of HRT and Calcium will be tested. Recommended HRT and Calcium levels will be applied in the simulation at age 55. All other variables are set to their normal. Calcium supplementation increases the effect of HRT in this run (Figure 7.16).

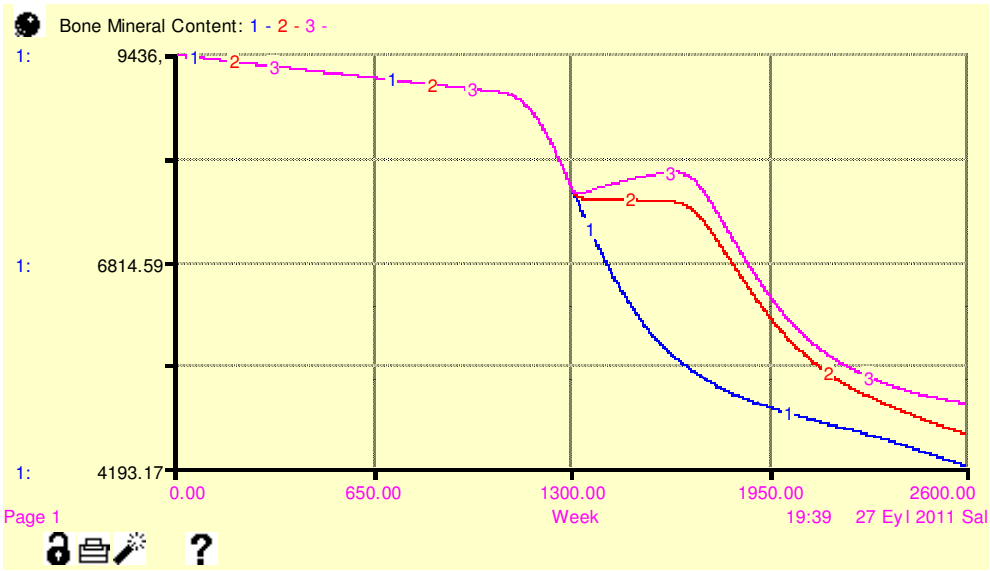

Figure 7.16. Combined Effect of HRT and Calcium on Bone Mass in the Model.

7.2.6. Antiresorptive Drug Therapy

In this run, antiresorptive drug therapy will be simulated. Antiresorptive agents like alendronate (ALN), are a kind of biphosphanate that suppress effects of resorbing cells by promoting cell death. In this run, a variable for Alendronate will be formulated and set to two to represent the effect of 10 mg/day intake of drug. Subject will be given the drug starting from age 55. All other variables are set to their normal values. The results show that drug therapy is an effective alternative for treating menopausal losses (Figure 7.17).

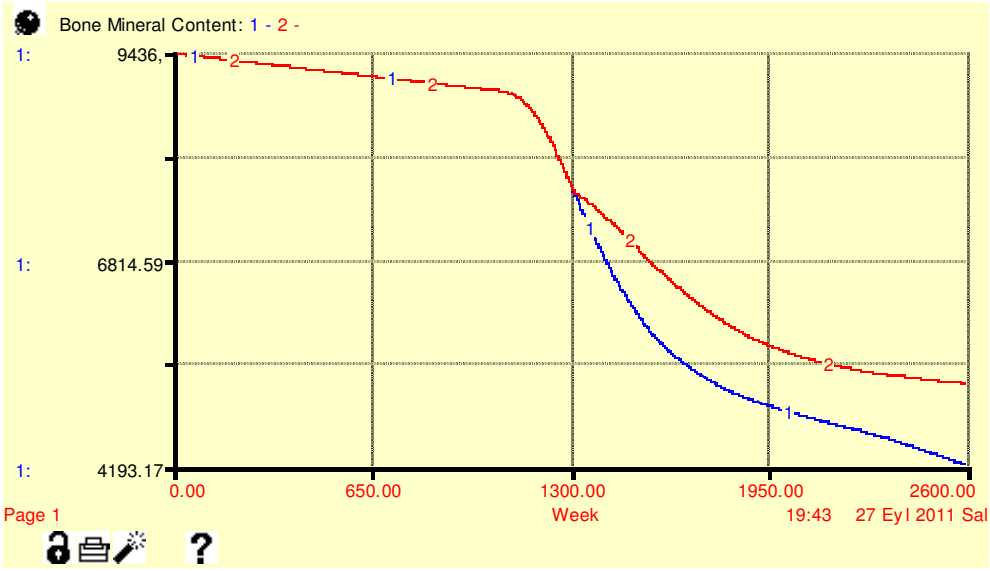

Figure 7.17. Effect of Drug Therapy on Bone Mineral Content in the Model.

7.2.7. Antiresorptive Drug Therapy and HRT Combination

In this run, combined effect of antiresorptive drug and HRT will be tested. Recommended uptakes for HRT and Alendronate are 0.635 mg/day and 10 mg/day respectively. These doses are applied in the simulation. The combination therapy is more effective than HRT or ALN alone (Figure 7.18).

7.2.8. Antiresorptive Drug and Calcium Combination Therapy

In this scenario, combined effect of ALN and calcium supplementation will be tested. In the first run drug is set to 10 mg/day and calcium intake is set to 600 mg/day. In

the second run, calcium intake increased to 1500 mg/day. Drug therapy with enough calcium intakes is more effective than drug therapy alone (Figure 7.19).

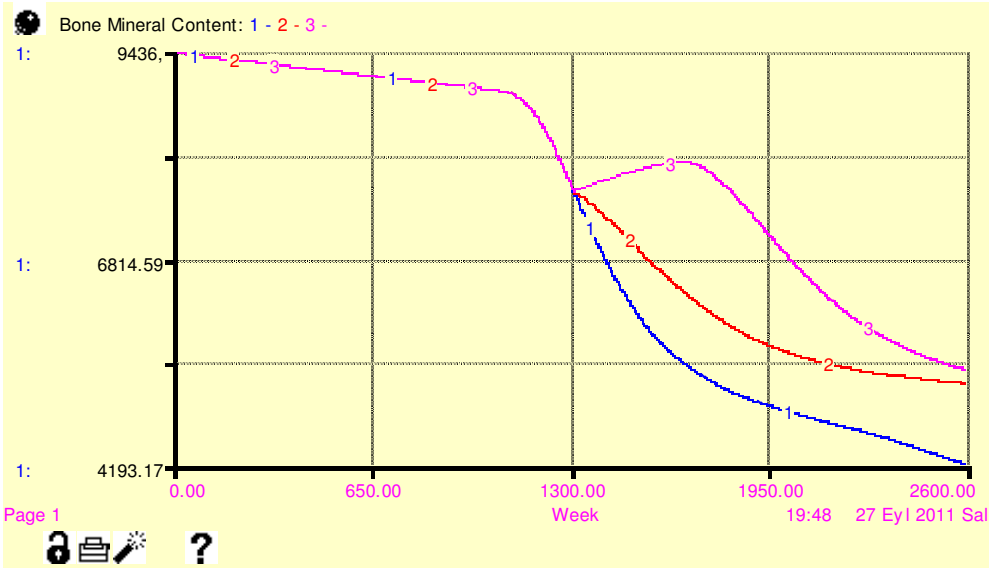

Figure 7.18. Combination effect of Antiresoprtive Drug and HRT in the Model.

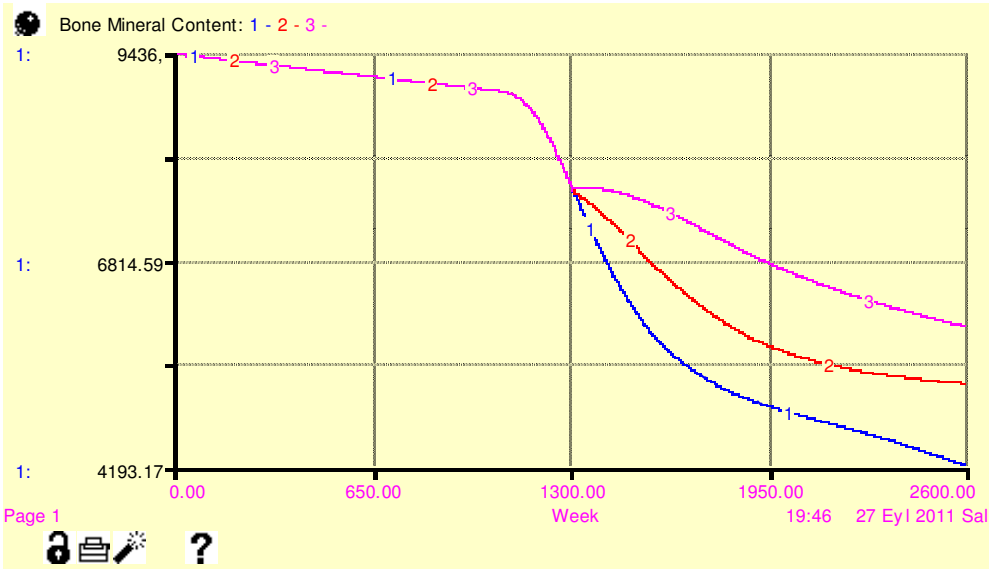

Figure 7.19. Combined Effect of Anti-resorptive Drug and Calcium in the Model.

7.2.9. Antiresorptive Drug, Calcium and HRT Combination

This scenario tests the combined effect of drug, calcium and HRT at the same time. Calcium level is set to 1500 mg/day. HRT is set to 0.625 mg/day and alendronate is set to

10 mg/day. This scenario results as the most protective action against post-menopausal losses over the treatments conducted in this study (Figure 7.20).

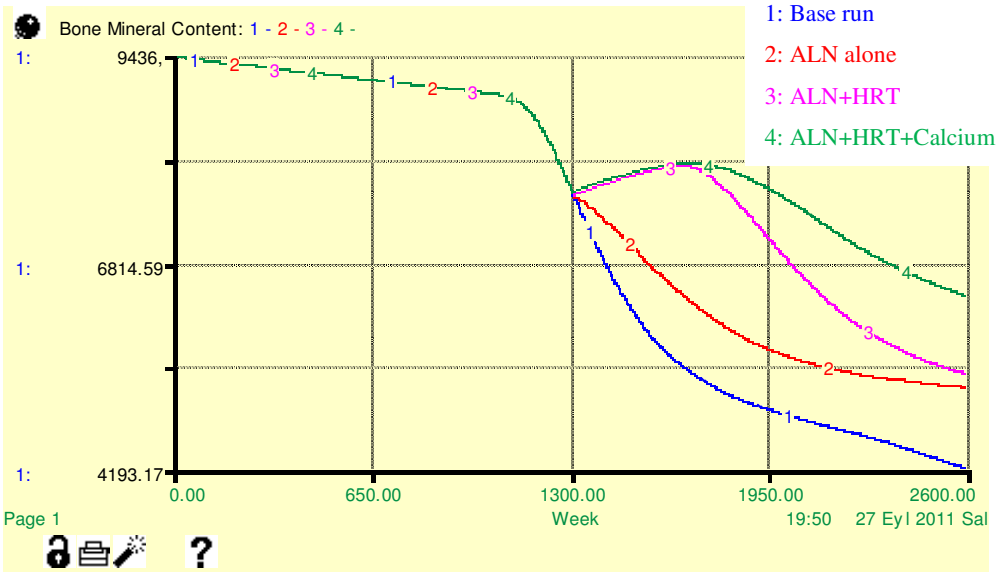

Figure 7.20. Combined Effect of Anti-resorptive Drug, Calcium and HRT on Bone Mass in the Model.

Several scenarios are tested in this section for preventing or treating bone loss after menopause. There is a comparison of the effects of these scenarios in Table 7.1 and Figure 7.21. The values indicate the percent changes in the bone mineral content from the baseline value.

Table 7.1. Comparison of the Effects of All Treatments for Post-Menopausal Women

Treatment\Duration	Year 1	Year 5	Year 10	Year 25
Control	-5,91*	-23,88	-33,50	-45,66
HRT	-1,42	-1,77	-11,64	-40,37
HRT+Calcium	-0,28	2,44	-7,41	-35,26
ALN	-2,25	-12,27	-22,71	-32,18
ALN+Calcium	0,15	-2,53	-9,16	-22,75
ALN+HRT	0,36	3,54	-0,45	-29,93
ALN+HRT+Calcium	1,00	4,02	3,59	-17,13
Exercise	-3,69	-17,13	-27,10	-40,02
Exercise+Calcium	-0,31	-8,27	-17,54	-23,66
Calcium	-2,61	-15,93	-24,94	-29,98

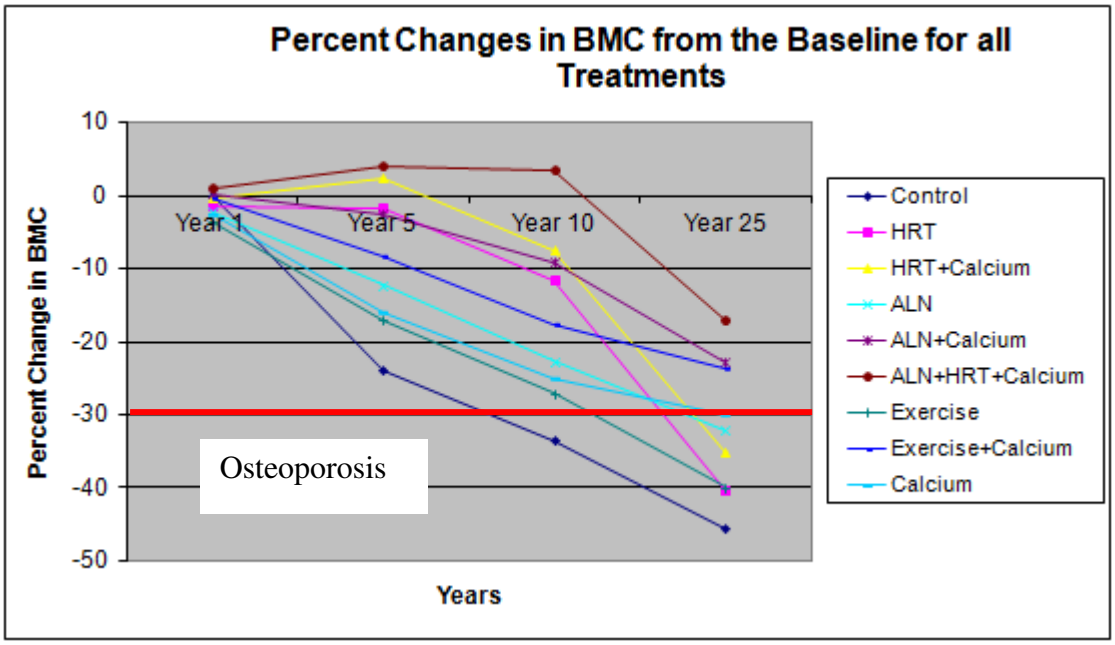

Figure 7.21. Percent Changes in BMC for all Treatments.

8. CONCLUSION AND FUTURE RESEARCH

There exist comprehensive dynamic simulation models on bone mass dynamics and osteoporosis. However, most of them deal with short term dynamics of the mechanical properties of bone and bone's cellular activities. There are also minimum numbers of studies that combine calcium dynamics in bone homeostasis. A long term dynamic model of mechanical and biologic changes in bone homeostasis could facilitate a framework to test many different interventions that prevent bone loss in osteoporosis.

In this model, both calcium dynamics of body and bone's mechanical and physiological environment are modeled from a long term perspective. In normal conditions, because of the continuous loss of bone throughout adult human life, every human is likely to develop osteoporosis if there is enough long period of time. Different from men, women are more prone to develop the disease because of the decreased level of estrogen hormone after a certain age. The main contributor of the disease in women is the hormone level. What makes difference among women in terms of developing osteoporosis is the age of onset of menopause and the degree of decrease in estrogen level.

The reference run of the model for normal subjects demonstrates a version of bone loss dynamics throughout adult life. Scenario analyses for pre-menopausal subjects are designed to find out if lifestyle factors before menopause are effective in developing the disease. It can be inferred from the results that the age of estrogen loss is more effective in preventing bone loss. Exercise is beneficial to protect bone heath but enough Ca supplementation is necessary to achieve good results.

Scenario analyses for post-menopausal women evaluate the effects of some interventions that help to reverse the results of the disease. The most effective treatment is evaluated as drug, HRT and Calcium therapy. After one year of treatment, ALN, HRT and Calcium combination therapy is the most effective way of preserving bone mass against menopausal losses. Both ALN and HRT treatments are more effective when applied with calcium. However, ALN and Calcium treatment is more beneficial than HRT and Calcium treatment at the end of the first year. Moreover, exercise is not effective without necessary

calcium supplementation. After 25 years of treatment, ALN, HRT and Calcium combination threrapy is still the most effective treatment. By taking the 30% bone loss level as suggested by Hernandez *et al.* as an indicator for the diagnosis of osteoporosis in Figure 7.21, it can be concluded that combination of HRT, ALN and Calcium can prevent osteoporosis at the end of year 25 after the treatment (Hernandez *et al.*, 2003). However, regular exercise practice with necessary amount of calcium supplementation is most beneficial treatment for preventing osteoporosis for women who reject to use HRT and drugs because of the side-effects of them.

The model is limited to the dynamics of human lumbar spine and its trabecular structure. A conversion fraction is used to represent the whole skeleton in the model. As a further study, both cortical and trabecular structures can be modeled and more parts of the skeleton can be included to the model.

APPENDIX A: EQUATIONS OF THE MODEL

Equations of the total model are given below:

BMU_Population(t) = BMU_Population(t - dt) + (BMU_Birth_Rate - BMU_Death_Rate) * dt
INIT BMU_Population = 786.7944
INFLOWS:
BMU_Birth_Rate = Normal_Birth_Rate*Area_of_Bone_Surface*E_of_Disuse_on_BR*E_of_Overuse_on_BR
OUTFLOWS:
BMU_Death_Rate = (BMU_Population/Lifetime_of_BMU)*Antiresorptive_Agent
Bone_Mineral_Content(t) = Bone_Mineral_Content(t - dt) + (Formation + Ca_Uptake_ECF - Resorption - Ca_Release_ECF) * dt
INIT Bone_Mineral_Content = 9436
INFLOWS:
Formation = Ca_Release_Formation/conversion_coeff
Ca_Uptake_ECF = Ca_Release_Adjustment/conversion_coeff
OUTFLOWS:
Resorption = BMU_Population*Avrg_Resorption_per_BMU
Ca_Release_ECF = Ca_Uptake_Bone/conversion_coeff
Desired_BMC(t) = Desired_BMC(t - dt) + (Change_in_Des_BMC) * dt
INIT Desired_BMC = Bone_Mineral_Content
INFLOWS:
Change_in_Des_BMC = Desired_Formation-Resorption
ECF_Ca_Level(t) = ECF_Ca_Level(t - dt) + (Absorption + Ca_Uptake_Bone + Ca_Uptake_Resorption - Excretion - Ca_Release_Formation - Ca_Release_Adjustment) * dt
INIT ECF_Ca_Level = 1500
INFLOWS:
Absorption = Ca_Intake*E_of_Ca_Intake_on_Absorption*E_of_VitD_Level_on_Absorption

Ca_Uptake_Bone = IF ECF_Ca_conc<ECF_Ca_conc_Goal THEN (ECF_Ca_conc_Goal-ECF_Ca_conc)*ECF_Volume ELSE 0

Ca_Uptake_Resorption = Resorption*conversion_coeff

OUTFLOWS:

Excretion = MAX(Min_Obligatory_Loss,effect_of_exc_cap*max_exc_cap)

Ca_Release_Formation = Available_Ca*E_of_Available_Ca

Ca_Release_Adjustment = Available_Ca_Efflux_Bone*E_of_Available_Efflux

Actual_VitD_Level = VitD_Level*E_of_Age_on_VitD

Age = 30+TIME/52

Antiresorptive_Agent = 1

Applied_Stress = 0.05

Area_of_Bone_Surface = 1398

Available_Ca = Absorption-Min_Obligatory_Loss

Available_Ca_Efflux_Bone = max(0.00001,Available_Ca-Ca_Release_Formation)

Avrg_Resorption_per_BMU = 0.01675/3

BMC_Adj_time = 520

Bone_Density = (Bone_Mineral_Content/Bone_Volume)/mg_to_g_convert

Bone_Modulus = 2.1*Bone_Density-0.08

Bone_Volume = 52.51

Ca_Intake = 10500

Ca_Need_Bone = Desired_Formation*conversion_coeff

conversion_coeff = 100

Desired_Ca_Uptake_ECF = ((Desired_BMC-Bone_Mineral_Content)/BMC_Adj_time)*conversion_coeff

Desired_Excretion = (ECF_Ca_Level-ECF_Ca_conc_Goal*ECF_Volume)+(Absorption+Ca_Uptake_Resorption-Ca_Release_Formation-Ca_Release_Adjustment)

Desired_Formation = Perceived_Resorption*(1-Formation_Deficient)+(E_of_Exercise_on_Bone_Formation-1)*Normal_Formation

ECF_Ca_conc = ECF_Ca_Level/ECF_Volume

ECF_Ca_conc_Goal = 100

ECF_Volume = 15

Felt_Strain =
((Applied_Stress*MPa_to_GPa_Converter)/Bone_Modulus)*Strain_Converter
Formation_Deficient = E_of_Disuse_on_FD*Normal_Formation_Deficient
HRT = 1
Lifetime_of_BMU = 6*2
max_exc_cap = 3500
MES_for_Modeling = 1000
MES_for_Overuse = Normal_MESoveruse*E_of_Age_on_MESoveruse
MES_for_Remodeling = E_of_Estrogen_Level_on_MESr*Normal_MESr
mg_to_g_convert = 1000
Min_Obligatory_Loss = 700
MPa_to_GPa_Converter = 1/1000
Normal_Birth_Rate = 0.0938/2
Normal_Ca_Intake = 4200
Normal_Estrogen_Level = 1
Normal_Formation = 8.785871/2
Normal_Formation_Deficient = 0.1
Normal_MESoveruse = 3000
Normal_MESr = 100*E_of_Stress_on_MESr
Normal_TT = 1*2
Normal_VitD_Level = 35
Perceived_Resorption = DELAY3(Resorption,Transition_Time)
Strain_Converter = 1000000
Transition_Time = Normal_TT*E_of_Disuse_on_TT
VitD_Level = 35
Applied_Stress1 = GRAPH(TIME)
(0.00, 0.05), (260, 0.05), (520, 0.05), (780, 0.05), (1040, 0.05), (1300, 0.05), (1560, 0.05),
(1820, 0.047), (2080, 0.0415), (2340, 0.036), (2600, 0.03)
Applied_Stress2 = GRAPH(TIME)
(0.00, 0.06), (260, 0.06), (520, 0.06), (780, 0.06), (1040, 0.06), (1300, 0.06), (1560, 0.06),
(1820, 0.056), (2080, 0.048), (2340, 0.042), (2600, 0.04)
effect_of_exc_cap = GRAPH(Desired_Excretion/max_exc_cap)

(0.00, 0.00), (0.1, 0.1), (0.2, 0.2), (0.3, 0.3), (0.4, 0.4), (0.5, 0.5), (0.6, 0.6), (0.7, 0.7), (0.8, 0.8), (0.9, 0.9), (1, 0.965), (1.10, 0.995), (1.20, 1.00)

Estrogen_Level = GRAPH(Age)

(30.0, 1.00), (34.2, 1.00), (38.3, 0.976), (42.5, 0.924), (46.7, 0.832), (50.8, 0.712), (55.0, 0.584), (59.2, 0.468), (63.3, 0.372), (67.5, 0.304), (71.7, 0.252), (75.8, 0.22), (80.0, 0.2)

E_of_Age_on_MESoveruse = GRAPH(Age)

(60.0, 1.00), (64.0, 1.00), (68.0, 0.998), (72.0, 0.995), (76.0, 0.991), (80.0, 0.985), (84.0, 0.977), (88.0, 0.967), (92.0, 0.954), (96.0, 0.934), (100, 0.9)

E_of_Age_on_VitD = GRAPH(Age)

(40.0, 1.00), (43.3, 1.00), (46.7, 0.994), (50.0, 0.981), (53.3, 0.951), (56.7, 0.897), (60.0, 0.813), (63.3, 0.74), (66.7, 0.68), (70.0, 0.63), (73.3, 0.596), (76.7, 0.574), (80.0, 0.57)

E_of_Available_Ca = GRAPH(Ca_Need_Bone/Available_Ca)

(0.00, 0.00), (0.1, 0.1), (0.2, 0.2), (0.3, 0.3), (0.4, 0.4), (0.5, 0.5), (0.6, 0.6), (0.7, 0.7), (0.8, 0.8), (0.9, 0.9), (1, 0.965), (1.10, 0.995), (1.20, 1.00)

E_of_Available_Efflux = GRAPH(Desired_Ca_Uptake_ECF/Available_Ca_Efflux_Bone)

(-0.1, 0.00), (1.39e-017, 0.05), (0.1, 0.11), (0.2, 0.2), (0.3, 0.3), (0.4, 0.4), (0.5, 0.5), (0.6, 0.6), (0.7, 0.7), (0.8, 0.8), (0.9, 0.9), (1.00, 0.97), (1.10, 1.00)

E_of_Ca_Intake_on_Absorption = GRAPH(Ca_Intake/Normal_Ca_Intake)

(0.1, 0.65), (0.258, 0.537), (0.417, 0.452), (0.575, 0.388), (0.733, 0.334), (0.892, 0.292), (1.05, 0.258), (1.21, 0.231), (1.37, 0.214), (1.52, 0.199), (1.68, 0.185), (1.84, 0.172), (2.00, 0.16)

E_of_Disuse_on_BR = GRAPH(Felt_Strain/MES_for_Remodeling)

(0.00, 10.0), (0.0833, 10.0), (0.167, 9.64), (0.25, 9.05), (0.333, 8.25), (0.417, 6.94), (0.5, 5.32), (0.583, 3.70), (0.667, 2.53), (0.75, 1.67), (0.833, 1.18), (0.917, 1.00), (1.00, 1.00)

E_of_Disuse_on_FD = GRAPH(Felt_Strain/MES_for_Remodeling)

(0.00, 5.00), (0.0833, 4.94), (0.167, 4.66), (0.25, 4.14), (0.333, 3.52), (0.417, 2.86), (0.5, 2.36), (0.583, 1.86), (0.667, 1.48), (0.75, 1.22), (0.833, 1.06), (0.917, 1.00), (1.00, 1.00)

E_of_Disuse_on_TT = GRAPH(Felt_Strain/MES_for_Remodeling)

(0.00, 10.0), (0.0833, 9.87), (0.167, 9.28), (0.25, 8.25), (0.333, 6.76), (0.417, 4.73), (0.5, 3.16), (0.583, 2.08), (0.667, 1.45), (0.75, 1.14), (0.833, 1.00), (0.917, 1.00), (1.00, 1.00)

E_of_Estrogen_Level_on_MESr = GRAPH((HRT*Estrogen_Level)/Normal_Estrogen_Level)

(0.2, 5.00), (0.267, 5.00), (0.333, 4.96), (0.4, 4.70), (0.467, 4.38), (0.533, 3.90), (0.6, 3.32), (0.667, 2.64), (0.733, 2.00), (0.8, 1.52), (0.867, 1.22), (0.933, 1.06), (1, 1.00)

E_of_Exercise_on_Bone_Formation = GRAPH(Felt_Strain/MES_for_Modeling)

(0.9, 1.00), (0.95, 1.00), (1.00, 1.01), (1.05, 1.02), (1.10, 1.03), (1.15, 1.05), (1.20, 1.07), (1.25, 1.09), (1.30, 1.12), (1.35, 1.15), (1.40, 1.18), (1.45, 1.19), (1.50, 1.20)

E_of_Overuse_on_BR = GRAPH(Felt_Strain/MES_for_Overuse)

(1.00, 1.00), (1.04, 6.42), (1.08, 11.0), (1.13, 15.2), (1.17, 17.6), (1.21, 18.8), (1.25, 19.1), (1.29, 19.4), (1.33, 19.6), (1.38, 19.8), (1.42, 19.9), (1.46, 19.9), (1.50, 20.0)

E_of_Stress_on_MESr = GRAPH(Applied_Stress)

(0.00, 1.00), (0.05, 1.00), (0.1, 1.75), (0.15, 2.50), (0.2, 3.25), (0.25, 4.00), (0.3, 4.75), (0.35, 5.55), (0.4, 6.75)

E_of_VitD_Level_on_Absorption = GRAPH(Actual_VitD_Level/Normal_VitD_Level)

(0.00, 0.5), (0.0833, 0.505), (0.167, 0.525), (0.25, 0.565), (0.333, 0.627), (0.417, 0.708), (0.5, 0.82), (0.583, 0.905), (0.667, 0.96), (0.75, 0.99), (0.833, 0.998), (0.917, 1.00), (1.00, 1.00)

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