A MODEL OF BONE LOSS DYNAMICS DUE TO DISUSE AND OVERLOAD

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ABSTRACT

Osteoporosis is a skeletal disorder which is common especially among women after menopause. Decreased estrogen level, altered physical activity and insufficient dietary calcium supplementation are the basic causes of the disease. In this study, a dynamic simulation model is built to demonstrate dynamics of bone mass homeostasis with specific focus on long term osteoporosis disease. In the scenario analysis, several experiments are conducted for prevention of bone loss for both premenopausal and postmenopausal women. In post-menopausal women, bone loss can be slowed down or prevented by exercise plus calcium supplementation or estrogen replacement therapy. In pre-menopausal women, weight bearing exercise can promote bone gain with sufficient calcium supplementation. Moreover, a period of reduced weight bearing or accumulated damage due to pathologic overload can cause a considerable amount of bone loss. This model serves as an experimental tool to study the mechanical loading conditions as well as some therapeutic interventions to prevent bone loss after menopause.

1 INTRODUCTION

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” (1). According to WHO, 30% of postmenopausal and 70% of over 80 aged women are affected by osteoporosis (2). 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 (3). 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. (4)

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 (5). 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 ~3-4 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 a given of time, there are 2x106 BMUs act in the whole skeleton and 6x106 BMUs completed annually (6). The goals of the 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 (7).

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 loss of sex hormones, second phase is more slow and related to aging. At menopause, over about a decade, women lost 20-30% of their cancellous bone and 5-10% of their cortical bone in the rapid phase. 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 (8). 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 has an effect on bone cells and suppress their actions thus balances bone formation and bone resorption. When this effect is lost with the decrease of the hormone level, these events increases and leads to increased rates of bone loss from the skeleton. The imbalance between formation and resorption occurred by menopause is 25% based on a published data (9). On the other hand, effect of estrogen is explained by the role of the hormone in mechanical properties of the bone. With the decrease of the estrogen level, it is seen a decrease trend in bone mass same 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 (1999) hypothesized that when estrogen level decreases, the threshold value increases and bone perceives a spurious disuse and accelerates bone loss in order to adapt to the new state (10). The second slow phase is attributed to the age related changes in human body. With aging, the absorption of calcium from the gut decreases and leads hyperparathyroidism. 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 thorough 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 and provide 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, requirement for calcium is decreased. Depending on the individual changes among people, average recommended calcium intake for adult human is 1000 mg/day for a healthy skeleton. During lactation, pregnancy and after menopause, this value can increase. (11) On the other hand, it has been observed that body can adjust itself to the calcium intake as small as 200mg/day. Despite the recommended calcium intake levels, in most of the 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 (12). This process 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 (13). Loading history of bone is the main determinant of its health. When peak bone strains are below some threshold value (100 microstrain), bone undergoes remodeling and decreases its mass. When the strains are above some threshold value (3000 microstrain), microdamage accumulates in bone matrix and this time remodeling increases in order to remove damage to 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 calceneus showed 100% of gain (14).

Accordingly, weight bearing activities also provide alterations in 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 (15). However, depending on the calcium supplement and 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 is accumulated in bone matrix in the form of microcrack (16). Bone removes these microdamages 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 bone. Bone can collapse in the extreme cases.

There are many modeling studies in the field of bone mass homeostasis and osteoporosis researches. 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 bone resulted from bone remodeling stimulated by disuse and damage. (17) 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, a while after activation frequency returns to normal levels but porosity remains. With the increasing damage rate, bone renews itself by remodeling however, when bone is loaded too much, activation frequency and porosity increases rapidly and until a fracture occurs. Other modeling studies are devoted to the interactions between osteoblasts and osteoclasts and their population dynamics and simulate over a very short period of time. There are also studies that discuss the bone's adaptation mechanism as a dynamic stochastic and optimal control problem (18), (19). Most of these studies, simulation duration is over a short or relatively short period of time and do not allow to observe the long term dynamics of the human skeleton.

The purpose of this study is to develop a dynamic model which would demonstrate 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 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 effects of several treatment procedures and protective actions on the disease.

Causal-loop diagram of the model is given below:

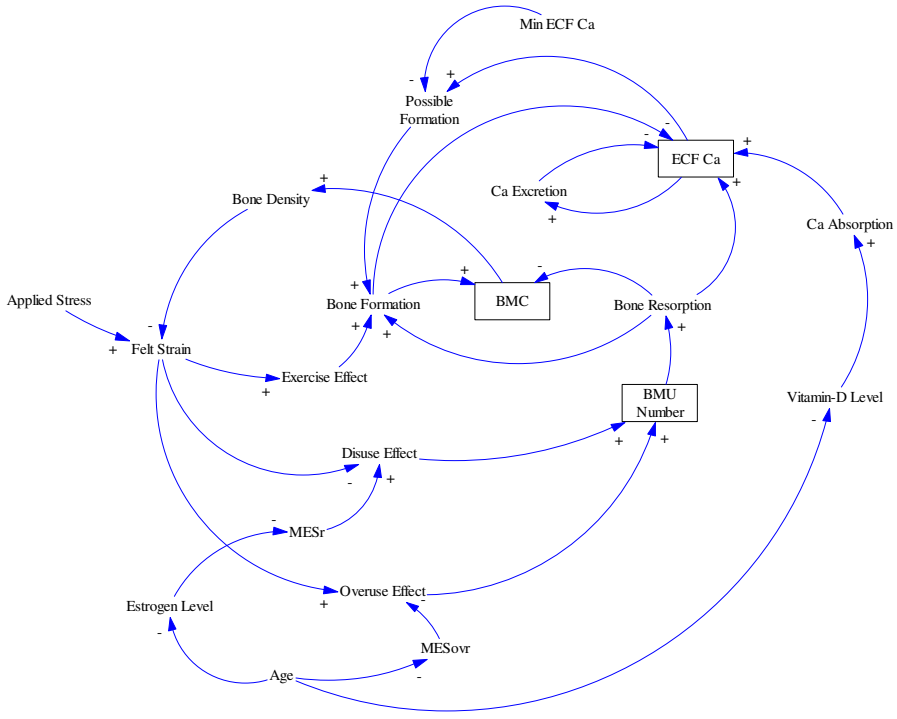


Figure 1 Causal-loop diagram of the model

2 DESCRIPTION OF THE MODEL

2.1 Bone Mass Sector

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. In the model, normal value for activation frequency is taken and set as Normal Birth Rate. Bone Surface Area refers to the area of bone affected by remodeling. BMU

Birth Rate is affected by changes of mechanical strain felt in bone tissue. In disuse and overload, BMU Birth Rate is increased in different amounts. BMU Death Rate is formulated by BMU Number divided by Lifetime of BMU.

BMU_Birth_Rate=Normal_Birth_Rate*Area_of_Bone_Surface*E_of_Disuse_on_BR*E_of_Overuse_on_BR 1

BMU_Death_Rate = BMU_Number/Lifetime_of_BMU 2

Bone Mineral Content changes by Formation and Resorption. In a remodeling cycle, OCs first appear on the remodeling site 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 2 weeks. OBs refill the resorption cavities and remodeling cycle is completed. Thus, the changes in the BMU Number first affect the resorption rate. Resorption rate is formulated by the Average Resorption Rate per BMU times BMU Number. After growth of mature skeleton, formation is generally completed with a slight deficient in adult human. The percent of average deficient per remodeling period is set to 0.06. This leads to a regular small decrease in bone mass throughout the 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 strain felt by bone falls between 2000-3000 microstrain, bone formation occurs without resorption. 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 effect of exercise on bone formation. Formation depends on the Calcium level available for mineralization in the body. If there is a lack of calcium in the body or ECF needs an urgent calcium supply, formation is not fulfilled or partially fulfilled. This is modeled with a Possible Formation variable that represents the available amount of calcium at that time. Thus, Formation is equal to the effect of Possible Formation multiplied by Possible Formation itself.

Desired_Formation = Perceived_Resorption * (1-Formation_Deficient) +
(E_of_Exercise_on_Bone_Formation-1) * Normal_Formation 3

Perceived_Resorption = DELAY3(Desired_Resorption,Transition_Time) 4

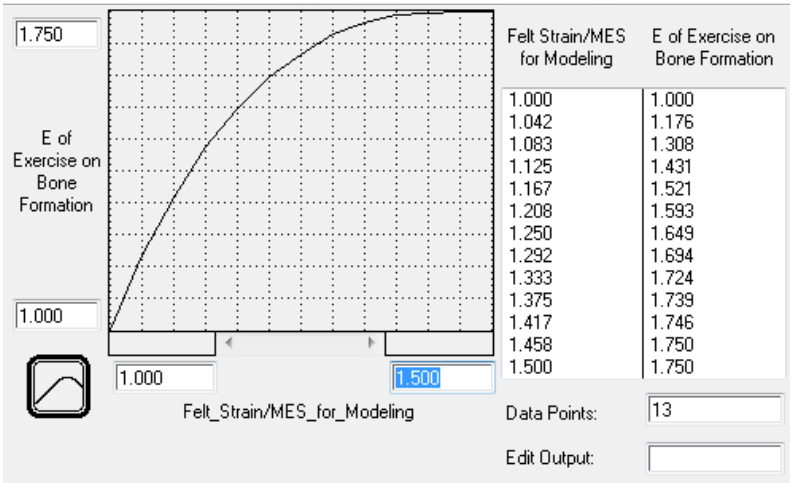


Figure 2 Effect of Exercise on Bone Formation

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 following formula:

Elastic Modulus= Stress/Strain

Strain=ΔL/L0

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, Keaveny et.al's findings are used to formulate the relationship between bone density and modulus.

Bone Modulus = 2.1*Bone Density-0.08

Bone density is a simple volumetric density of bone.

Bone Density= (Bone Mineral Content/Bone Volume)/mg to g convert

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

Unit of modulus in the model is in GPa. 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 producing 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 exceeds the threshold value for disuse.

This threshold value is determined as 100 microstrain and called as Minimum Effective Strain for remodeling (MESr). Below MESr, BMU Number is increased and resorption is stimulated by BMUs. Between 100-2000 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 delayed formation onset. These effects are given below:

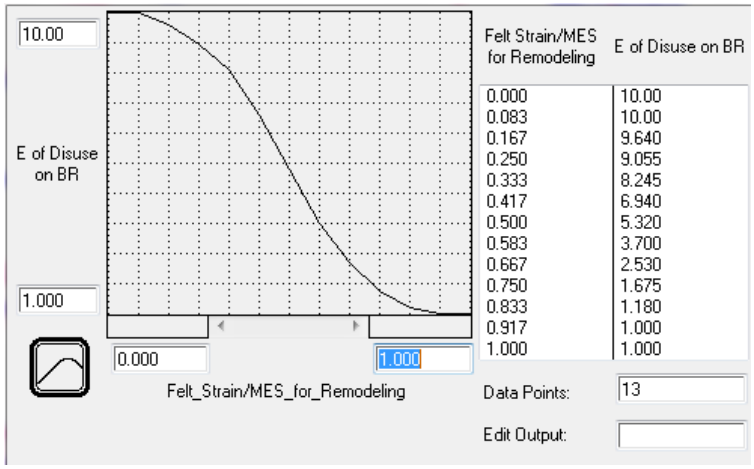


Figure 3 Effect of Disuse on Birth Rate

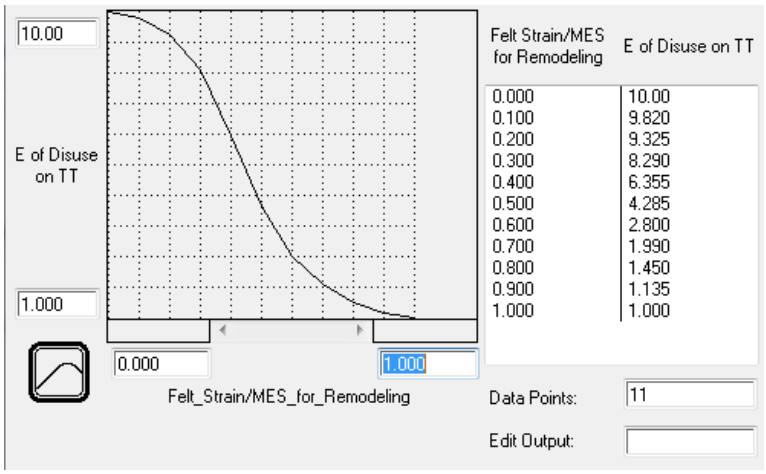


Figure 4 Effect of Disuse on Transition Time

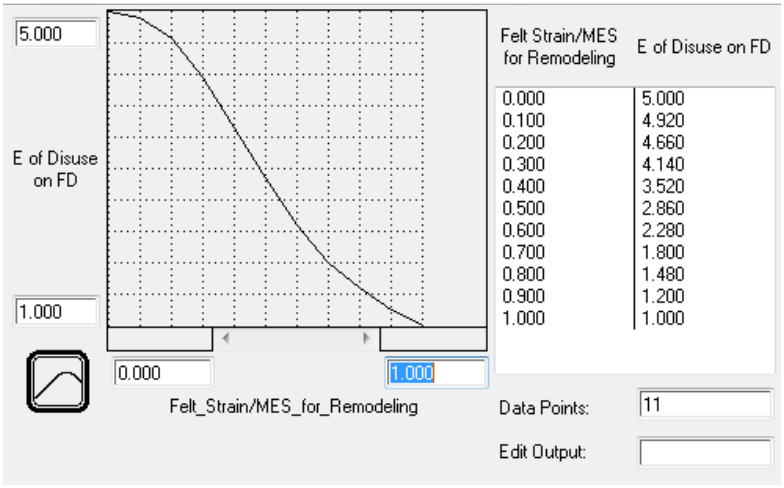


Figure 5 Effect of Disuse on Formation Deficient

Another factor that affects BMU number and stimulates resorption is overuse. When Felt Strain exceeds a threshold value, more microdamage accumulates in bone and this increases the resorption rate in order to remove the damaged bone as quickly as possible. Bone pulls the strains below this threshold by reducing bone density. This threshold level is called MES for overuse and set to 3000 microstrain.

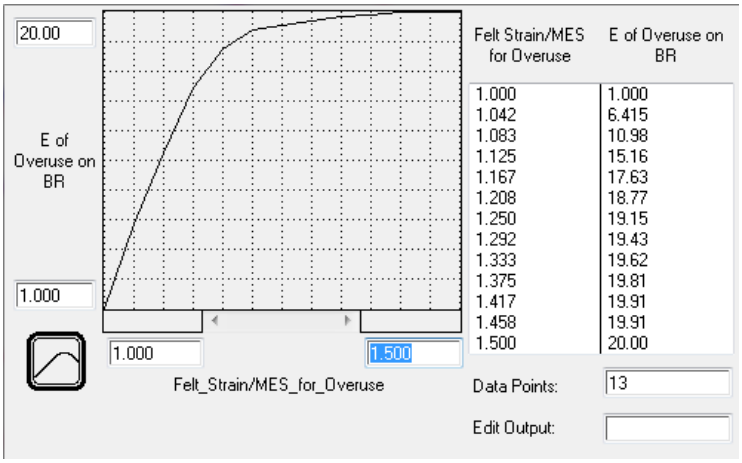


Figure 6 Effect of Overuse on Birth Rate

In this sector, Age and Estrogen Level has effects on MES values. Estrogen Level is a function of Age. With the onset of menopause in women, estrogen level decreases to 20% of premenopausal levels. Estrogen has suppressing effects on remodeling. When estrogen decreases, this effect is lost and remodeling increases. This is explained by the elevated MESr value by

Frost. 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.

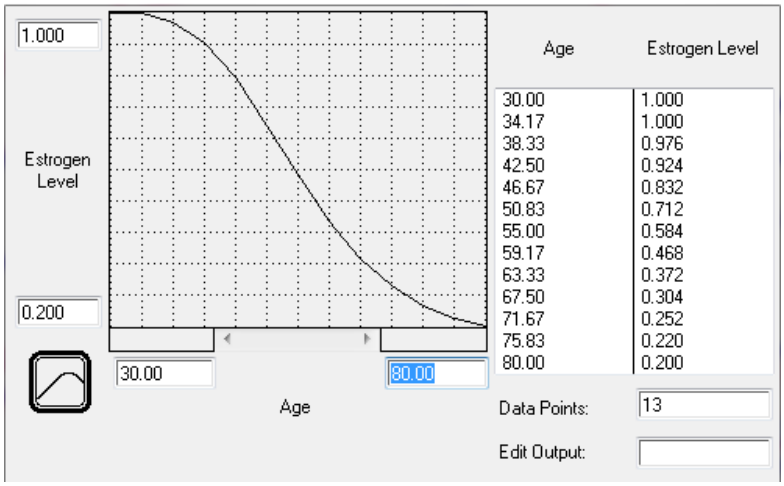


Figure 7 Estrogen Level as a Function of Age

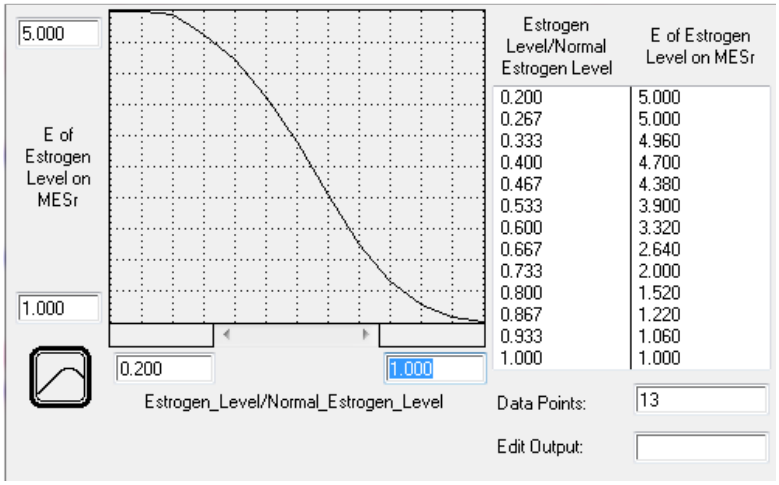


Figure 8 Effect of Estrogen Level on MES for Remodeling

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. The effect of age appears at age 60.

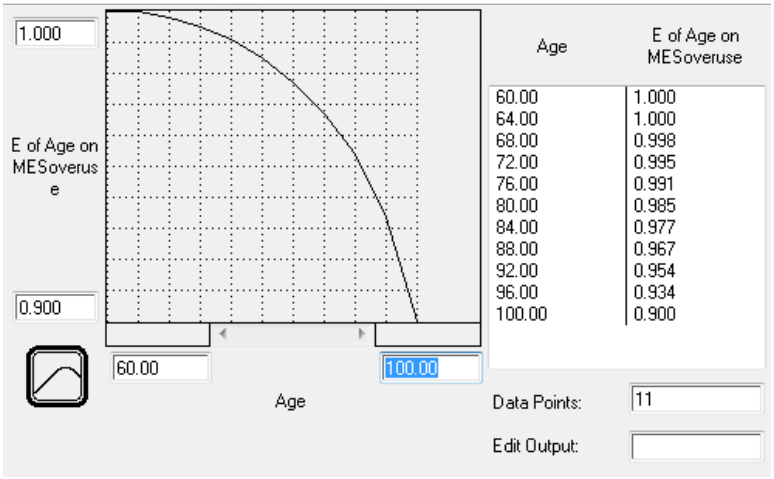


Figure 9 Effect of Age on MES for Overload

2.2 Calcium Sector

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 is summarized in an effect function in this sector. 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 value that is recommended by WHO for a healthy bone and metabolism. Vitamin D is also necessary for a healthy Ca metabolism. Vitamin D is not necessary 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 is decreased, thus it decreases the absorption indirectly.

Absorption = Ca_Intake*E_of_Ca_Intake_on_Absorption*E_of_VitD_Level_on_Absorption

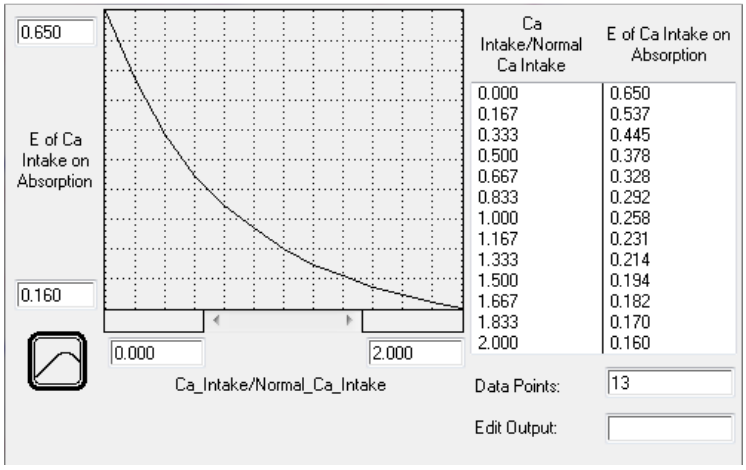


Figure 10 Effect of Calcium Intake on Absorption

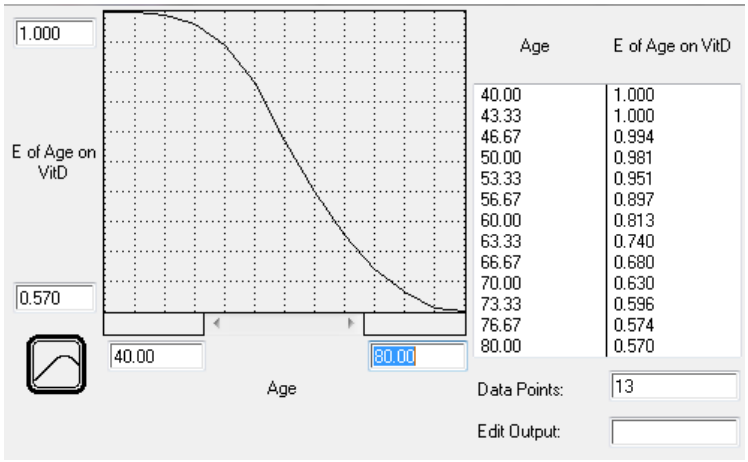


Figure 11 Effect of Age on Vitamin-D status

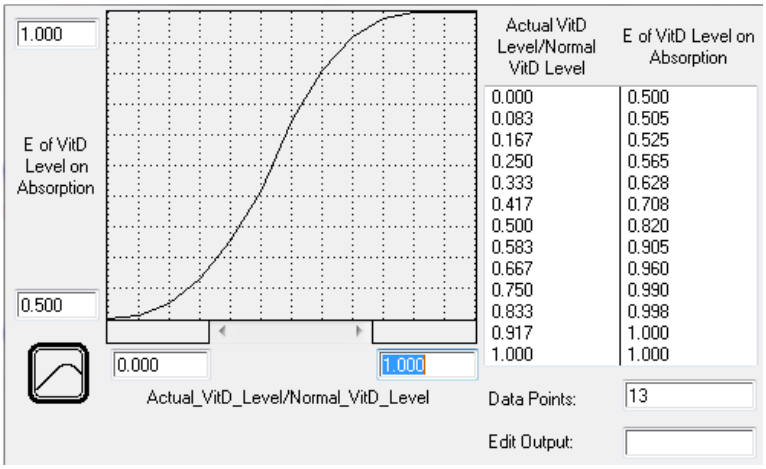


Figure 12 Effect of Vitamin-D Level on Absorption

Actual_VitD_Level = VitD_Level*E_of_Age_on_VitD

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 the model. If there are any deviations from the level of the ECF Ca for the body, ECF Ca Goal, Desired Excretion changes by an amount equal to the deviation from the set value plus any other inflow from bone. The max formulation guarantees that Desired Excretion never falls below the obligatory loss.

Desired_Excretion=(ECF_Ca-ECF_Ca_Goal)/Excretion_Adjustment_Time+Absorption
+Ca_Release_Resorption-Ca_Release_Bone

Excretion = MAX(Min_Obligatory_Loss, Max_Excretory_Capacity*E_of_Capacity)

Calcium exchange between ECF and bone is formulated by three flows in the model. Ca Release Bone is equal to the total Ca outflow from ECF to Bone both by formation and diffusion times a fraction that adjusts the Ca exchange to the total skeleton. Ca Release Resorption is equal to the amount resorbed by OCs. Ca Uptake Bone adjusts ECF Ca for any fluctuations from its set level.

Ca_Release_Bone = (Ca_Uptake_ECF+Formation)*Conversion_to_Total_Bone

Ca_Release_Resorption = Resorption*Conversion_to_Total_Bone

Ca_Uptake_Bone = (ECF_goal-ECF_Ca)/Ca_Uptake_Bone_Adj_Time

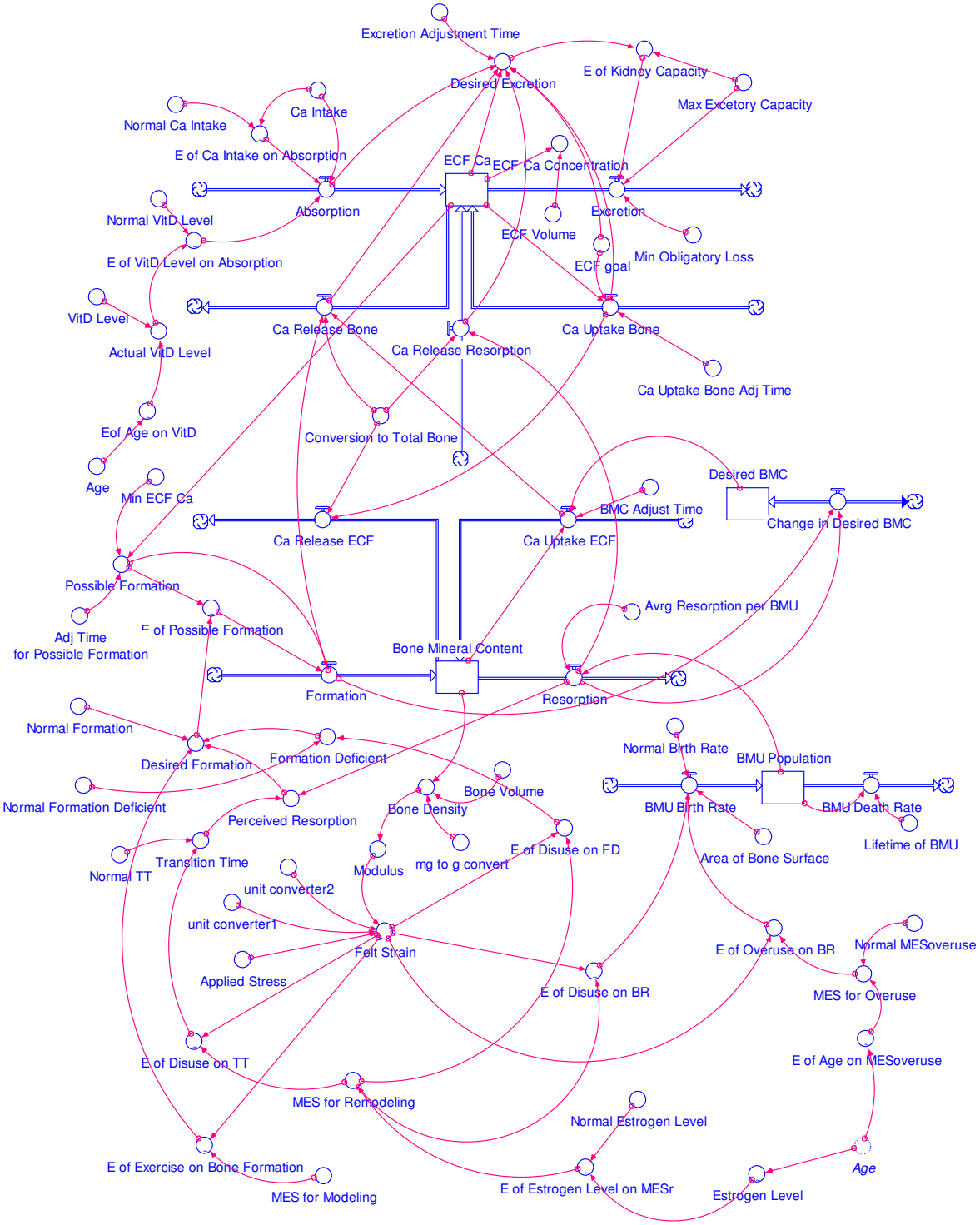


Figure 13 Stock-Flow Diagram of the Whole Model

3 BASE BEHAVIOUR OF THE 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 in order to observe the dynamics of aging. 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 occurs throughout human life. This means that, any individual would likely to develop the disease, given a sufficiently long lifespan (20). 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. 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 levels.

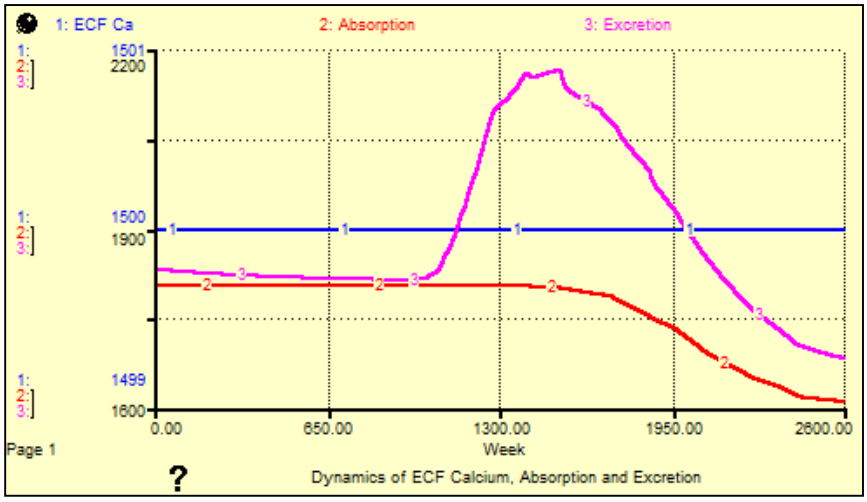


Figure 14 Base Dynamics of ECF Ca, Absorption and Excretion of Total Model

ECF Ca does not change in this run. Ca Excretion starts with a slightly higher than Ca Absorption and decreases slowly. This higher value is due to the Ca exchange with bone. When net influx to ECF from bone starts to decline, Ca Excretion decreases respectively. Ca Absorption decreases at about time 1500 because of the effects of aging on Vitamin-D. Ca Intake is enough for a healthy nutrition in this run. Therefore, ECF does not need to take Ca from bone by its mechanisms. Ca Release Bone is the net amount of Calcium that is needed for formation. It starts

with a lower value than Ca Release Resorption because of the formation deficient, and tries to reach Ca Release Resorption but will never catch it.

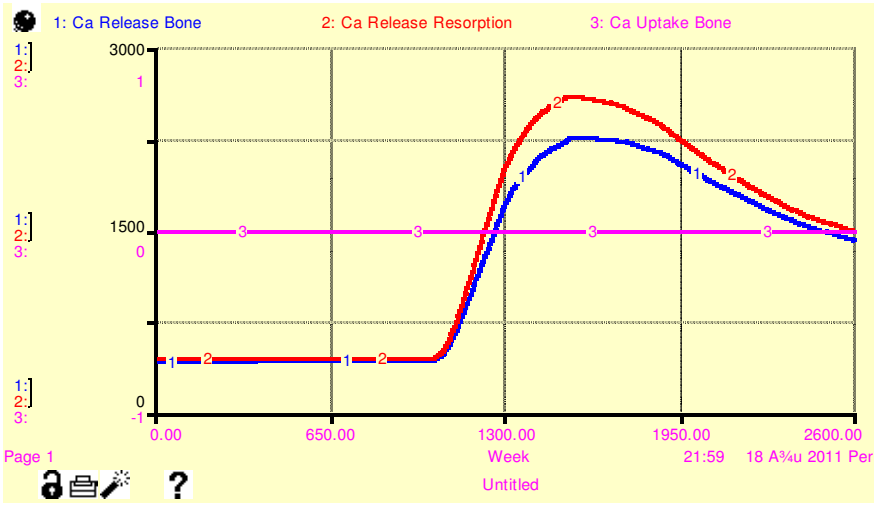


Figure 15 Base Dynamics of Ca Release Bone, Ca Release Resorption and Ca Uptake Bone

Bone Mineral Content decreases slightly while formation and resorption are constant between 0-1000. BMC always decrease even in small degrees because OBs always leave a small deficient behind after OCs remove bone. At ~1000, there is a rapid decrease in BMC because of start of estrogen decrease at that time. At ~1950, 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. Effects of disuse on formation deficient and transition time are effective through this time.

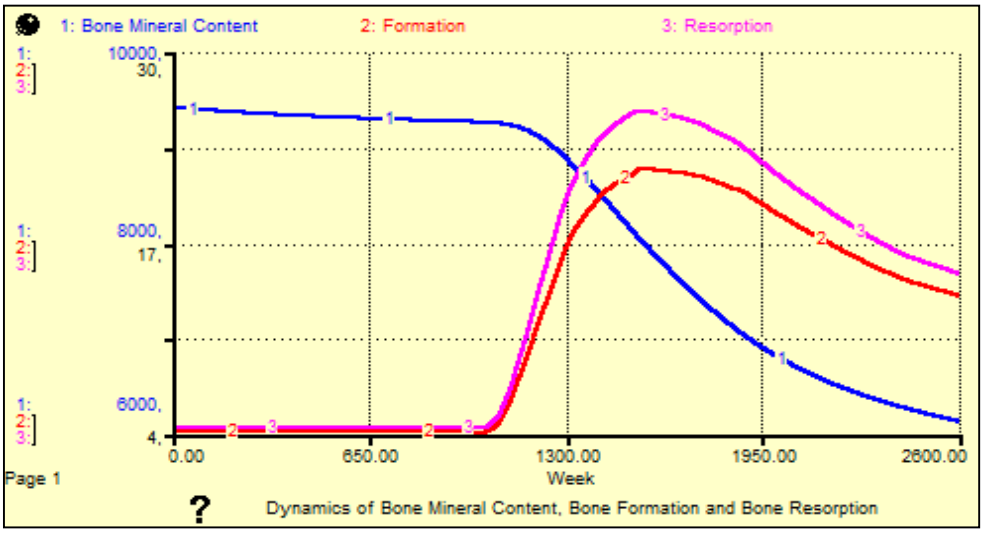


Figure 16 Base Dynamics of BMC, Formation and Resorption of the Total Model

BMU Population does not change because Felt Strain never falls below or above its normal values. However, because of the estrogen deficiency, disuse mode becomes active and BMU Population increases until the effect of disuse on birth rate decreases to normal.

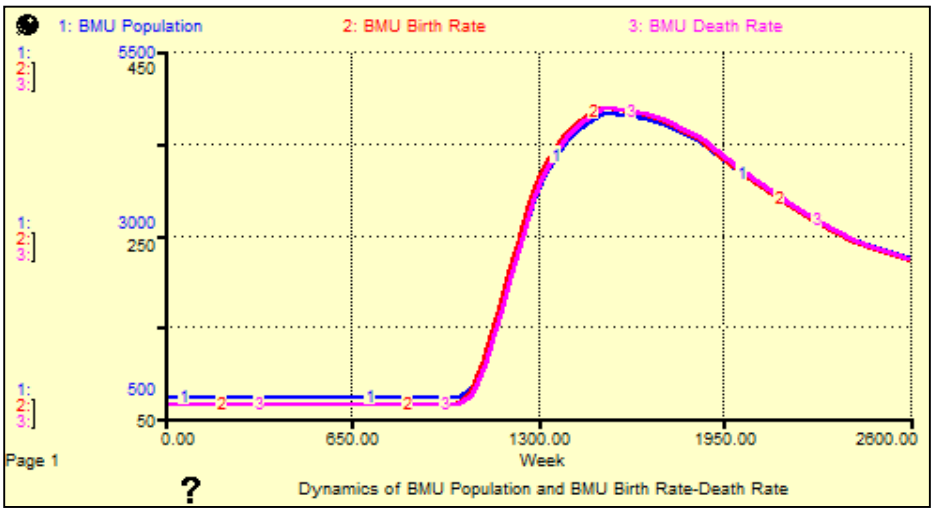


Figure 17 Base Dynamics of BMU Population, Birth Rate and Death Rate of the Total Model

Bone Density decreases because of the disuse mode generated by estrogen deficiency. Felt Strain is in normal levels at first but because the decrease in bone density, Felt Strain increases.

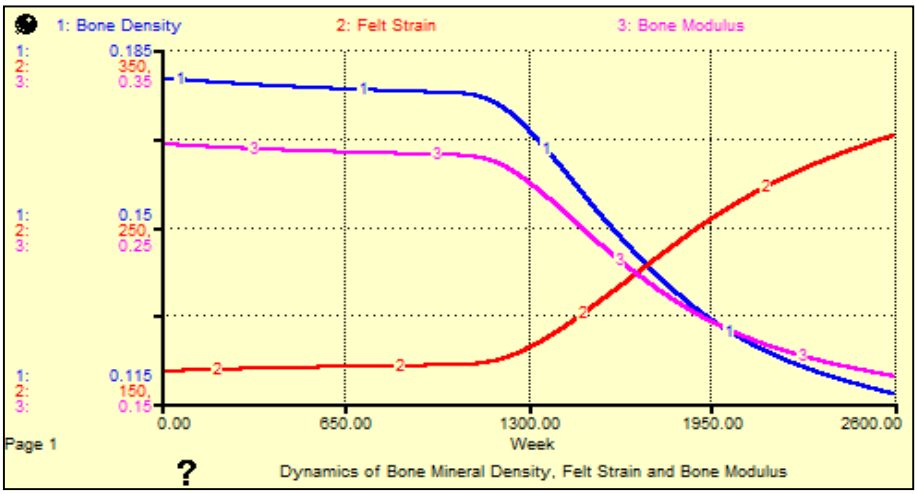


Figure 18 Base Dynamics of Bone Density, Felt Strain and Bone Modulus of Total Model

Estrogen Level decreases at about age 45 slowly at first and rapidly to 20% of its initial value.

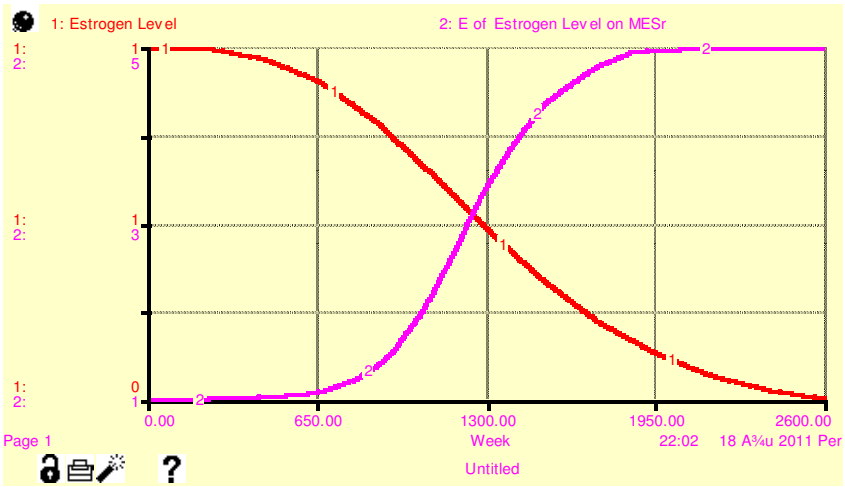


Figure 19 Base Dynamics of Estrogen Level and Effect of Estrogen on MESr

Effects of Disuse are 1 at the beginning, with the onset of estrogen deficiency; they increase to their max and then slowly decrease to normal values.

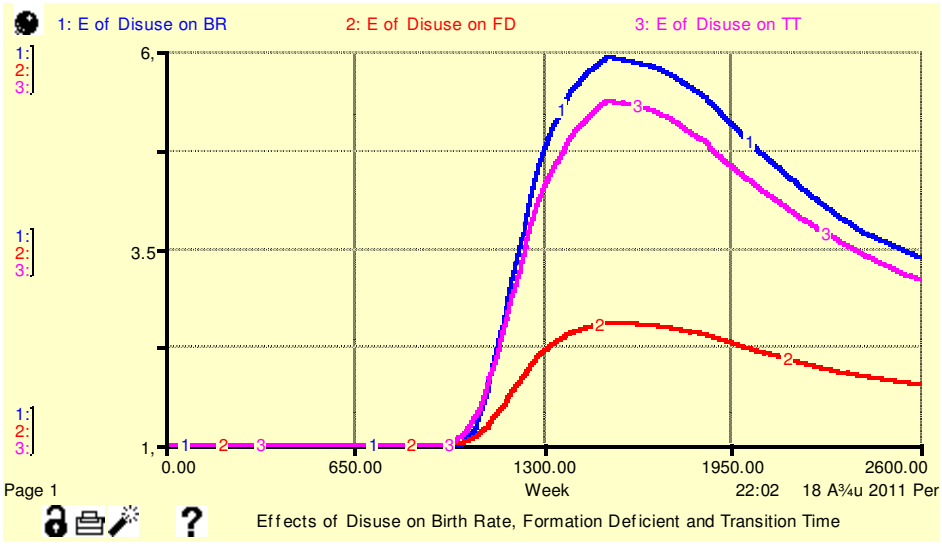


Figure 20 Base Dynamics of Effect of Disuse on Birth Rate, Formation Deficient and Transition Time

4 VALIDATION OF THE MODEL

Verification and validation was carried out on the model using the standard procedures. The estimation of most of the parameters is based on the published papers. The equations are tested according to their extreme conditions. Every variable in the model is checked for their dimensional consistency. There are no arbitrary or meaningless variable in the model. Behavior validity is established via comparisons of real data and model results for basic variables.

Following, there are comparisons of model results and real data.

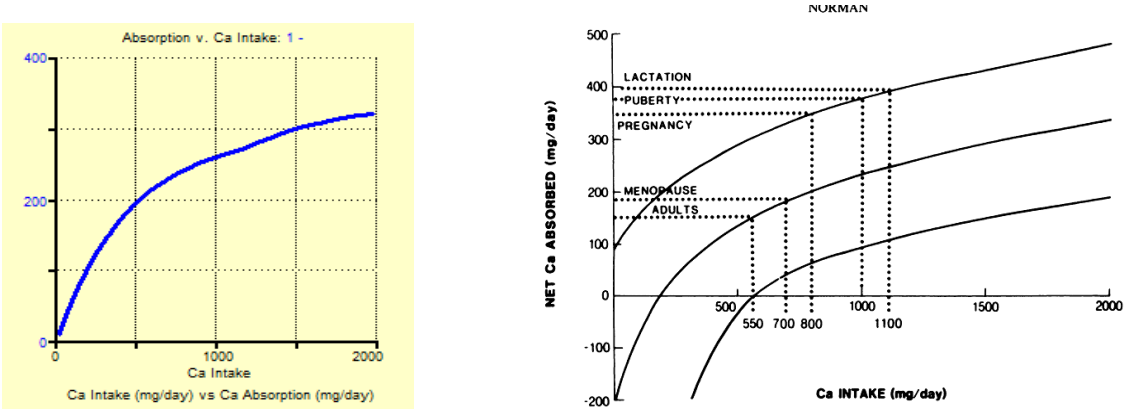
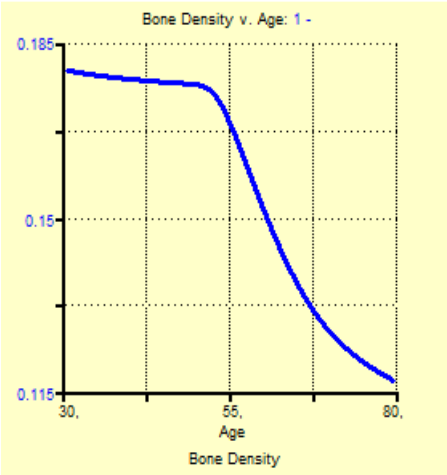


Figure 21 Model vs Real results for Ca Intake



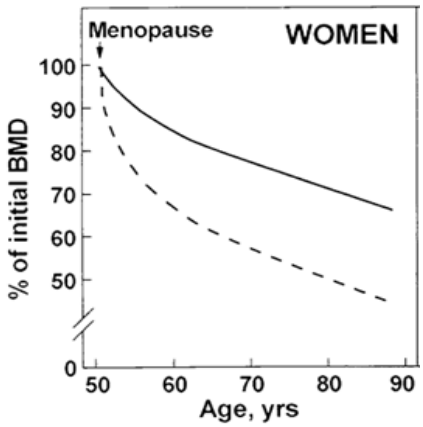


Figure 22 Model vs Real Results fo Bone Density after Menopause

5 SCENARIO ANALYSIS

5.1 Normal Subjects

5.1.1 Bed Rest History

In this scenario, a subject with a 1 year of bed rest is simulated. Starting from age 35, subject is exposed to 1 year of bed rest and then returns to pre-rest strain levels. A bed rest history before the onset of menopause made negative effects on bone loss however, the difference between normal and bed rest conditions are not too much at the end of age 80.

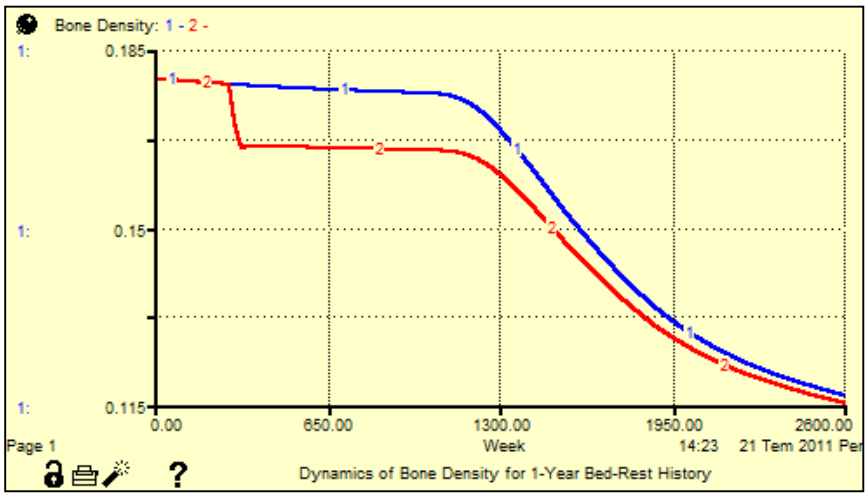


Figure 23 Dynamics of BMC for a 1-year Bed Rest Before Menopause

5.1.2 Exercise History

In this scenario, a subject with a history of weight bearing activities is simulated. The simulation starts with a high level exercise conditions after age 35, and then there comes a sedentary life period. This run aims to find out if there is a positive effect of exercise history on preventing osteoporosis. 1-year high impact exercise in pre-menopausal years has positive effects during menopausal years however; at the end of age-80 the end result does not change much.

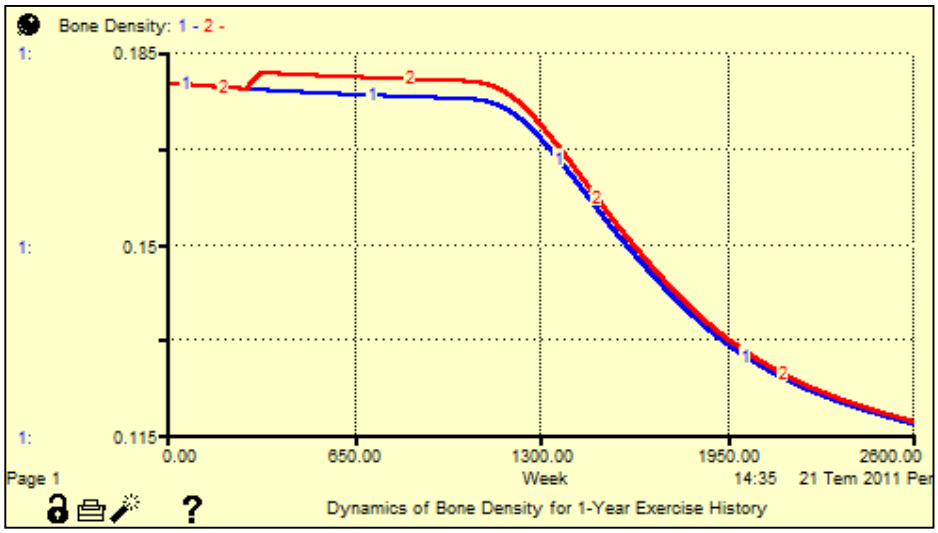


Figure 24 Dynamics of BMC with a Weight Bearing Exercise History

5.1.3 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?" During the exercise training time, Ca supplementation is important in order to increase bone mass as much as possible. If Calcium intake is low, exercise is not helpful in developing bone mass.

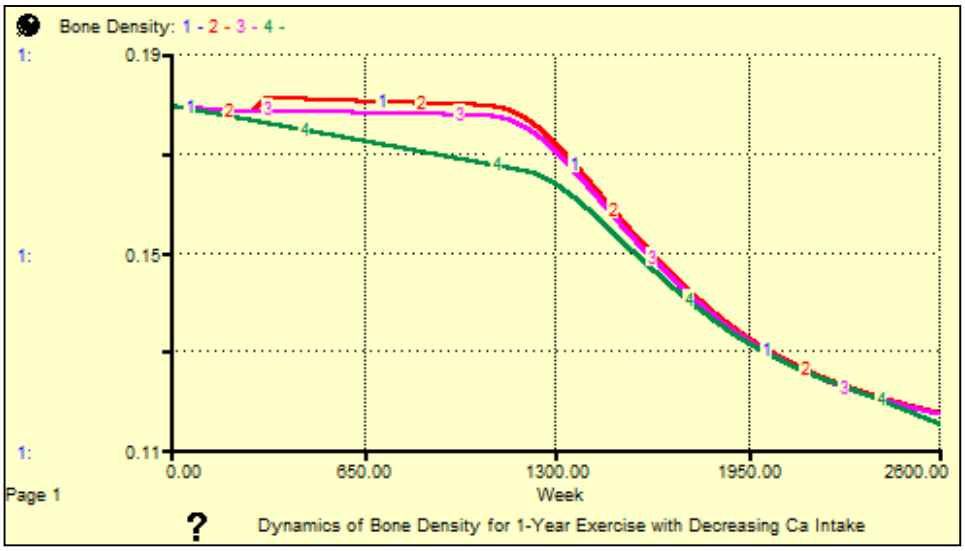


Figure 25 Dynamics of BMC for Decreasing Level of Calcium Intake with High Impact Exercise

5.1.4 Overload History

In this run, subject will expose to a 1 year overload history at age 35. Pathologic overload increases the amount of damage in bone and this stimulates remodeling rate on bone surface thus leads to bone loss.

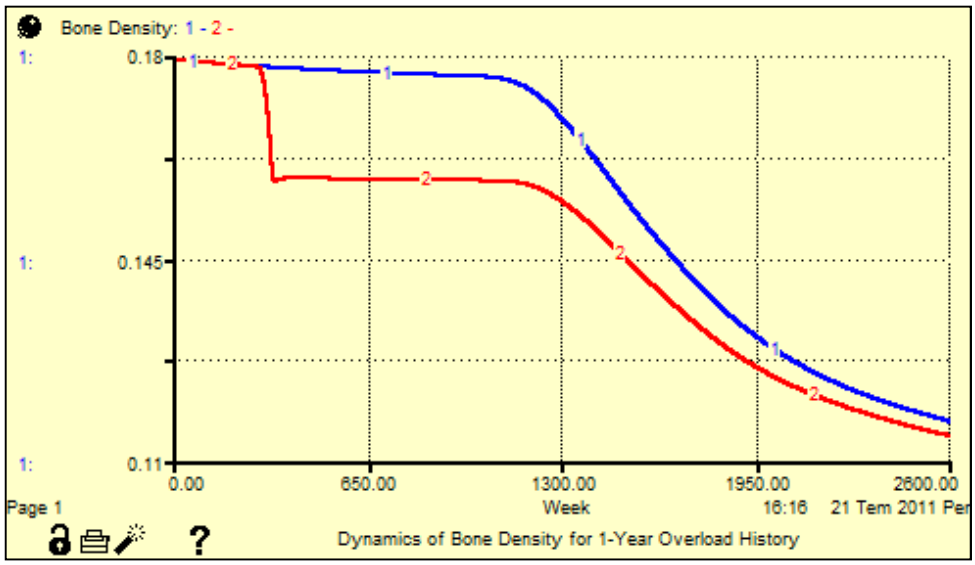


Figure 26 Dynamics of Bone Density for 1-Year Overload History

5.2 Osteoporotic Subjects

In this part, an osteoporotic subject will be simulated. Several interventions will be tried in order to observe their effects on managing the osteoporosis and preventing further loss. The trials will be started at time 1300 (age 55) that represents post-menopausal state.

5.2.1 Exercise

This run will test the effect of two year-exercise history on bone mass. There will be no increase in the Ca supplement. The amount of recovery from the initial conditions will be observed. Exercise has positive effects on bone loss prevention after menopause, but the necessary amount of stress for bone is less than for normal conditions. For normal people, while 0.8 MPa stress level is necessary to obtain bone mass increase, 0.4 MPa is enough for osteoporotic people.

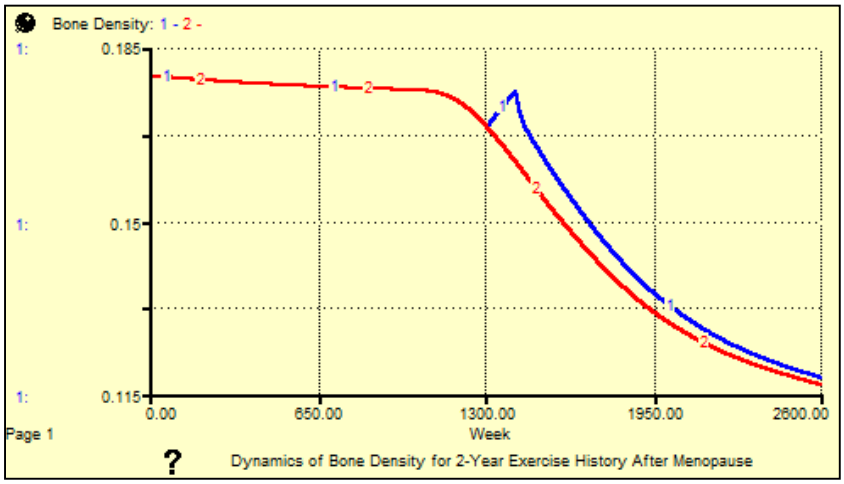


Figure 27 Dynamics of BMC for High Impact Exercise for Osteoporotic Person

5.2.2 Hormone Therapy

Osteoporotic patients generally receive ERT (Estrogen Replacement Therapy) in order to return the effects of decreased estrogen levels. In this scenario, with the onset of menopause, the subject is given an amount of estrogen equal to complete the present level to the pre-menopausal condition. The results show that estrogen therapy is effective in eliminating or reducing bone loss after menopause.

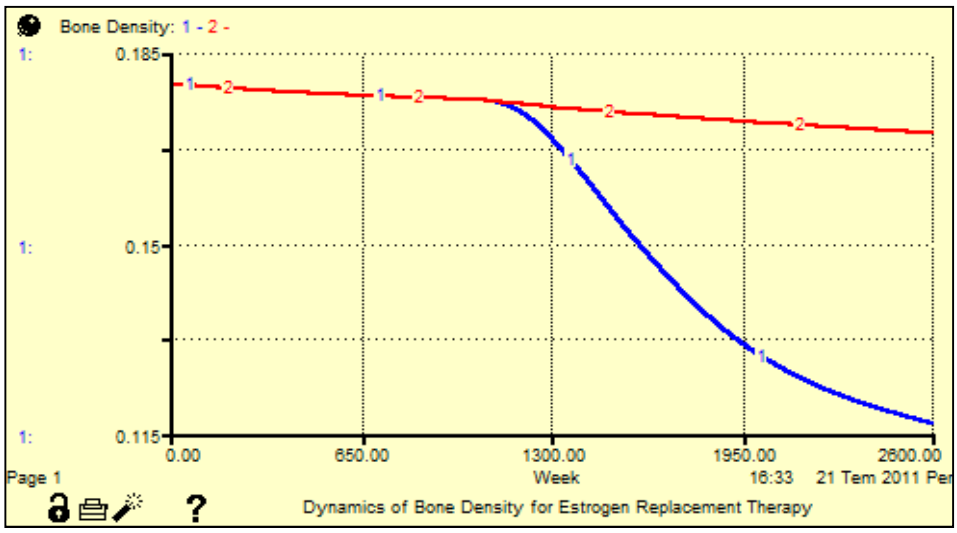


Figure 28 Dynamics of BMC for ERT

6 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 analysis for normal subjects are designed to find out 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 osteoporotic women evaluate the effects of some interventions that help to reverse the results of the disease. After the onset of menopause, nutrition does not affect bone mass however, at the progressing years, it is important to increase dietary calcium intake because of the decreased absorption of calcium from intestine. Exercise and ERT has positive effects on developing bone mass.

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.

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APPENDIX

Equations of the total model are given below:

Bone Mass Sector

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

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 = E_of_Possible_Ca_Release_for_formation*Possible_Ca_Release

Ca_Uptake_ECF = Possible_Ca_Release*E_of_Possible_Release_for_uptake

OUTFLOWS:

Resorption = BMU_Population*Avrg_Resorption_per_BMU

Ca_Release_ECF = Ca_Uptake_Bone/Conversion_to_Total_Bone

Desired_BMC(t) = Desired_BMC(t - dt) + (Change_in_Desired_BMC) * dt

INIT Desired_BMC = Bone_Mineral_Content

INFLOWS:

Change_in_Desired_BMC = 1.05*Formation-Resorption

Adj_Time__for_Possible_Ca_Release = 4*2

Applied_Stress = 0.05

Area_of_Bone_Surface = 1398

Avrg_Resorption_per_BMU = 0.01675/3

BMC_Adjust_Time = 260*2

Bone_Density = (Bone_Mineral_Content/Bone_Volume)/mg_to_g_convert

Bone_Modulus = 2.1*Bone_Density-0.08

Bone_Volume = 52.51

Desired_Ca_Uptake_ECF = (Desired_BMC-Bone_Mineral_Content)/BMC_Adjust_Time

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

Felt_Strain = ((Applied_Stress*MPa_to_GPa_Converter)/Bone_Modulus)*Strain_Converter

Formation_Deficient = E_of_Disuse_on_FD*Normal_Formation_Deficient

Lifetime_of_BMU = 6*2

MES_for_Modeling = 2000

MES_for_Overuse = Normal_MESoveruse*E_of_Age_on_MESoveruse

MES_for_Remodeling = 100*E_of_Estrogen_Level_on_MESr

mg_to_g_convert = 1000

Min_ECF_Ca = 1275

MPa_to_GPa_Converter = 1/1000

Normal_Birth_Rate = 0.0938/2

Normal_Estrogen_Level = 1

Normal_Formation = 8.785871/2

Normal_Formation_Deficient = 0.06

Normal_MESoveruse = 3000

Normal_TT = 1*2

Perceived_Resorption = DELAY3(Resorption,Transition_Time)

Possible_Ca_Release = (ECF_Ca-Min_ECF_Ca)/Adj_Time__for_Possible_Ca_Release

Strain_Converter = 1000000

Transition_Time = Normal_TT*E_of_Disuse_on_TT

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_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, 1.08), (0.917, 1.02), (1.00, 1.00)
E_of_Disuse_on_TT = GRAPH(Felt_Strain/MES_for_Remodeling)
(0.00, 10.0), (0.1, 9.87), (0.2, 9.28), (0.3, 8.25), (0.4, 6.76), (0.5, 4.73), (0.6, 3.16), (0.7, 2.08), (0.8, 1.45), (0.9, 1.14), (1, 1.00)
E_of_Estrogen_Level_on_MESr = GRAPH(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)
(1.00, 1.00), (1.04, 1.18), (1.08, 1.31), (1.13, 1.43), (1.17, 1.52), (1.21, 1.59), (1.25, 1.65), (1.29, 1.69), (1.33, 1.72), (1.38, 1.74), (1.42, 1.75), (1.46, 1.75), (1.50, 1.75)
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_Possible_Ca_Release_for_formation = GRAPH(Desired_Formation/Possible_Ca_Release)
(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, 0.97), (1.10, 0.99), (1.20, 1.00)
E_of_Possible_Release_for_uptake = GRAPH(Desired_Ca_Uptake_ECF/Possible_Ca_Release)
(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, 0.97), (1.10, 1.00), (1.20, 1.00)
Calcium Sector
ECF_Ca(t) = ECF_Ca(t - dt) + (Absorption + Ca_Uptake_Bone + Ca_Release_Resorption - Excretion - Ca_Release_Bone) * dt
INIT ECF_Ca = 1500
INFLOWS:
Absorption = Ca_Intake*E_of_Ca_Intake_on_Absorption*E_of_VitD_Level_on_Absorption
Ca_Uptake_Bone = (ECF_goal-ECF_Ca)/Ca_Uptake_Bone_Adj_Time
Ca_Release_Resorption = Resorption*Conversion_to_Total_Bone
OUTFLOWS:
Excretion = MAX(Min_Obligatory_Loss,E_of_Kidney_Capacity*Max_Excetory_Capacity)

Ca_Release_Bone = (Ca_Uptake_ECF+Formation)*Conversion_to_Total_Bone

Actual_VitD_Level = VitD_Level*E_of_Age_on_VitD

Age = 30+TIME/52

Ca_Intake = 7000

Ca_Uptake_Bone_Adj_Time = 2

Conversion_to_Total_Bone = 100

Desired_Excretion = (ECF_Ca-ECF_goal)/Excretion_Adjustment_Time+Absorption+Ca_Release_Resorption-Ca_Release_Bone

ECF_goal = 1500

Excretion_Adjustment_Time = 1

Max_Excetory_Capacity = 112000/2

Min_Obligatory_Loss = 1400/2

Normal_Ca_Intake = 7000

Normal_VitD_Level = 35

VitD_Level = 35

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_Ca_Intake_on_Absorption = GRAPH(Ca_Intake/Normal_Ca_Intake)

(0.00, 0.65), (0.167, 0.537), (0.333, 0.452), (0.5, 0.388), (0.667, 0.334), (0.833, 0.292), (1, 0.258), (1.17, 0.231), (1.33, 0.214), (1.50, 0.199), (1.67, 0.185), (1.83, 0.172), (2.00, 0.16)

E_of_Kidney_Capacity = GRAPH(Desired_Excretion/Max_Excetory_Capacity)

(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, 0.97), (1.10, 1.00), (1.20, 1.00)

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)