STOCHASTIC AND STRAIN-WEIGHTED SIMULATIONS OF CANCELLOUS BONE REMODELLING: SIMULATION RULES AND PARAMETERS

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Abstract: Bone has well-defined structural and morphological properties, as well as cellular processes based on stimuli that control activity at microscopic level. Simulations that can take into account the above and can operate on real bone can be used to investigate scenarios such as normal age-related loss of bone, loss of bone due to disuse or osteoporosis or virtual drug treatment. The aim of this work is to define a set of simulation rules such that the cellular processes of bone can be modelled and used in scenarios that investigate bone remodelling and the effects on its mechanical properties.

Keywords: Simulation, cancellous bone, remodelling, stochastic, strain-weighted.

1. INTRODUCTION

Bone tissue consists of calcium hydroxyapatite mineral absorbed onto a collagen matrix. Throughout life there is a process of remodelling, where old bone is removed by osteoclast cells and new collagen fibres are laid down by osteoblast cells. This is under the control of physical activity and several hormones. There are two types of bone structure, cortical and cancellous. Cortical bone is predominantly solid and makes up the shafts of the long bones in the skeleton. Cancellous bone has a porous structure made up of an array of trabecular bone fibres interspersed with bone marrow, and is found near the joint surfaces of the long bones and within the individual vertebrae making up the spinal column. Bone grows under body forces and the trabecular fibres follow the principal lines of stress, as can be clearly seen, for example, in a cross-section of the hip.

2. BONE PATHOPHYSIOLOGY

The main responsibilities of bones are to withstand the mechanical forces exerted to them by muscles or gravity, protect the vital organs from possible damage, and provide a reserve of minerals such as calcium or phosphate to the body.

Most bones are composed of a dense outer shell of cortical bone surrounding the central porous cancellous (trabecular) bone. Cancellous bone can be considered to be a cellular structure, consisting of an interconnecting 3D network of thin bars (trabeculae) interspersed with marrow, connective tissue and blood vessels (Baron 1993), with the porosity of cancellous bone typically ranging from 30% up to 95% (Gibson and Ashby 1988).

From birth to maturity, healthy humans exhibit an increase in bone mass of about 40 times. The peak of bone mass as result of growth is reached between the ages 20-30, and bone mass starts decreasing around ages 30-40, while by the age of 70 more than 30% of the original peak bone mass is lost. This long-term bone loss is temporarily accelerated on women after menopause, but after a few years this acceleration stops. This process of old bone replaced by new one is also known as bone remodeling. The phases of the remodeling process are resorption, reversal, formation and quiescence, and last totally about 180-200 days.

The main two types of cells responsible for the remodeling process are osteoblasts and osteoclasts. Osteoblastic cells are responsible for the production of the material for reposition (e.g. collagen) and are not normally found alone, but in groups of about 100-400, forming a bone reposition site. On the other hand osteoclasts are responsible for the resorption of bone, and are usually found in groups of 1-2 or even 4-5 cells. Such a group of similar type of cells is also known as a BMU, or a basic multi-cellular unit.

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In bone remodeling, groups of osteoclasts firstly remove bone and after a reversal period, osteoblasts attempt to replace the same amount of bone that was resorbed. If less bone was reposited there is a negative BMU balance, and if more bone is reposited there is a positive BMU balance. If the same amount of bone lost is replaced, homeostasis is maintained, while the whole removal-reposition process occurs at the interface of bone with marrow. The acceleration of bone loss during menopause is accredited to osteoclasts digging larger holes at the surface of bone for longer time.

3. BACKGROUND

Siffert *et al* (1996) developed a computational model at the tissue level to study the effects of short- and long-term periods of disuse osteopenia and repair to elucidate the interrelationships between bone mass, architecture, and strength. The model is based on the principle that osteoclastic thinning of trabeculae and osteoblastic thickening is a surface occurring phenomenon. The structure under consideration is a highly idealised rectangular mesh where half the horizontal trabeculae are thinner than the vertical ones. In the model it is assumed that the stimulus S for adaptation to the mechanical loading is the local mechanical strain rate, according to which the trabecular surfaces are differentially formed and resorbed. Typical levels of tissue modulus have been determined to be around 5-8 GPa, and the study considers 7 GPa, while the loading history of the bone was assumed to be that of normal walking, at a frequency of 1-2 Hz. The components of the model were:

- boundary element method (computationally evaluates the local stresses and strains at each point in trabecular surface, assuming that the trabecular bone material is linearly elastic and isotropic);
- the local adaptation criterion;
- initial trabecular structure;
- the applied loading regime (e.g. angular).

The criterion that deciding if a trabecula's width will increase, decrease or remain unchanged is given by the following step function:

$$U = \begin{cases} K_1\left(S - S_{o-}\right), S < S_{o-} \\ 0, S_{o-} < S < S_{o+} \\ K_2\left(S - S_{o+}\right), S_{o+} < S \end{cases} \quad (1)$$

The *short-term* loading regime was simulated by a short period of disuse and the reapplication of loading before any horizontal trabeculae were lost. Recovery was simulated by reapplying the loads until a new adaptation equilibrium was achieved.

The *long-term* loading regime was simulated after a long enough period of disuse such that some of the horizontal trabeculae were lost, and the reapplication of loading until new adaptation equilibrium was achieved.

t was observed that there was a significant change in the volume ratio of –12% for short-term and –20% for long-term disuse. For the horizontal direction, the Young's modulus decreased 36% and 62% for short and long term disuse, respectively. The shear modulus reduced by 57% and 85%, and the Young's modulus change in the vertical direction was negligible, around 2% and 3% respectively.

The results of the simulation suggest that when the local strain rates are below resorption limits, trabeculae are thinned and the disuse process stops before trabeculae are lost, the structure remodels to a new equilibrium stage. The longer the disuse period (>12 weeks for short-term and >20 weeks for long-term) the more trabeculae are lost, and when the loading is reapplied, vertical trabeculae are selectively thickened than horizontal. Additionally, bone growth is observed at pre-existing trabeculae, and as such the behaviour of the model is in agreement with clinical studies which show that the effects of long-term disuse cannot be fully reversed. Consequently, there is a disproportional decrease in the mechanical competence of long-term disused bone compared to short-term disused bone.

The model developed by Lacy *et al* (1994) extended Reeve's model (Reeve 1986), simulating changes in trabecular thickness and hence in bone volume, considering resorption and formation over a large number of remodeling sites.

The model depends on a large number of hypothetical trabeculae subject to bone loss or formation. A BMU (basic multi-cellular unit) may initiate bone turnover at either of the two opposing sites of a trabecula. During the simulation the thickness can decrease, remain unchanged or increase, according to what point it is at in the simulation, until the trabecula perforates (thickness becomes 0) or the simulation finishes.

During the simulation there is a random chance for a trabecula to be initiated, based on the activation frequency. Each activated BMU remodels bone according to a series of steps, the parameters of which are drawn randomly from statistical distributions in accordance with clinical data.

The parameters controlling the model are taken or derived from static and dynamic histomorphometric studies and are:

- activation frequency;
- final resorption depth;

- resorption period;
- formation period;
- BMU balance (formation / resorption);
- initial trabecular thickness;

The trabecular thickness is drawn from a random number distribution, and is in agreement with Recker *et al* (1988), at 134±34.4 (SD) μm for normal females from 55 to 64. The authors validate their model using clinical data from two histomorphometric studies (using Dual-energy Photon Absorptiometry) lasting 60 and 120 weeks predicting well the results of the biopsies with their model on both placebo and etidronate group.

The simulation involved 10 runs of 1000 trabeculae each (hence 2000 remodeling sites). The two most important simulation parameters are the activation frequency (increases likelihood of coincident activation) and resorption depth (increases likelihood of penetration). The main remodeling phases considered were bone resorption and formation. The reversal step between these two phases was not considered and justified by the unavailability of experimental data for representing reversal time.

The model developed by Thomsen *et al* (1994) was based on Reeve's model, mainly considering horizontal trabeculae, while attempting to be a treatment extension to Lacy's model. The model extends the treatment regimes, including a second anti-resorptive agent, estrogen, along with an anabolic agent, fluoride. The thickness of each trabecula is taken from histomorphometric studies and set to approximately 135±24 μm, and totalling to about 600-630. The model is based on variation of the activation frequency and resorption depth, and describes the variation in the bone mass, the average trabecular thickness and the number of perforations over an extended period of time. The remodelling phases are in agreement with Frost and Eriksen, and are resorption, reversal, formation and quiescence.

The parameters that control the model are
- resorption period (σ_r);
- reversal period (σ_o);
- formation period (σ_f);
- initial trabecular thickness (w);
- resorption depth (d);
- critical trabecular thickness (w_c);
- "static" formation balance ΔB.BMU (b);
- activation frequency (μ);
- number of trabeculae – the only parameter fixed to 628 (N)

Given μ to be the activation frequency, the probability of starting remodelling on a trabecula under quiescence is given by uniformly distributed η:

$$\eta = \frac{1}{\frac{1}{\mu} - \left(\sigma_r + \sigma_o + \sigma_f\right)} \qquad (2)$$

Consequently, the number of trabeculae undergoing remodelling are given by

$$N_r = N \cdot \eta \cdot \left(\sigma_r + \sigma_o + \sigma_f\right) \qquad (3)$$

and under equilibrium, it should hold that:

$$N \cdot \eta = \frac{N_r}{\sigma_r + \sigma_o + \sigma_f} \qquad (4)$$

The model simulates the remodelling process (mostly loss of bone) of horizontal trabecular struts in human vertebral body. Linearity in time is assumed during the resorption and formation phases, and the thickness of each trabecula is drawn from a Gaussian random number generator (RNG) with a mean and variance being in accordance to clinical results. Lastly, an even distribution is assumed when selecting trabeculae for remodelling.

Events such as menopause are represented by substituting certain parameters with newer ones and replacing them with original values after the end of the event. Since such events do not occur from one day to another, the whole event is modelled as smaller scale events over the transition period.

The remodelling process is initiated by assigning the resorption depth for trabeculae from a Gaussian RNG, and the time is also selected by a similar RNG. The possibility of disconnected trabeculae under remodelling increases when the bone becomes thinner than the critical trabecular thickness. The later is in agreement with clinical studies which show that trabeculae with thickness under a certain level do not exist.

Kinney and Ladd (1998) developed a finite element based model to examine the relationship between connectivity density and elastic modulus of trabecular bone, using cubic specimens prepared from human distal radii and L1 vertebrae using synchrotron microtomography. The 3D images were reconstructed into binary volumes of mineralised bone and soft tissue. Despite the instrument's maximum spatial resolution, the data were reconstructed into cubic elements of average edge 20 μm, while the true dimensions were 17.7 and 23.4 μm for the radii and the vertebrae, respectively. The final data sets used were cubic structures of about 3.5 and 4.5 mm having 7.7 and 7.1 million elements, respectively.

Connectivity scaling was explored by thinning and thickening the trabecular bone in each volume set by removing or adding one element each time (≈20 μm).

Two methods were utilised to simulate bone atrophy or recovery. The first method involved the identification and subsequent thinning (atrophy) or thickening (recovery) of all surface elements, without regard to the connectivity of the trabecular network. With this method trabecular connections could be formed or destroyed, and plates could be fenestrated or filled. In the second method all the surface elements were removed or added subject to the condition that the connectivity of trabecular structure did not change. With the second method bone mass could be removed or reposited without destroying or forming trabecular connections or fenestrating plates. Each specimen was thinned three times with each method, and additional data was prepared by thickening each specimen for five times from its fully atrophied condition. Finally, the original unthinned volumes were thickened twice to establish connectivity and modulus values that could be used in interpolating the results.

The authors note that a close inspection on the date sets prepared by the non connectivity-preserving algorithm shown several small plate perforations after a single thinning operation, clearly indicating that several plates were <40 μm thick. Without connectivity preservation, the atrophy model led to an increase in the connectivity with decreasing trabecular density. It was also observed that upon recovery plate fenestrations were removed while severely resorbed rods were not reconnected.

Both thinning methods resulted in a decrease in elastic modulus with trabecular bone density. In samples where lost connectivity was not restored, the original modulus for the equivalent trabecular bone density was also not restored. The results have also shown that due to the fact that connectivity is not dependent of the contact area, whereas mechanical load transfer is, there is no functional relationship between connectivity and elastic modulus. More importantly, a global measure of connectivity does not discriminate between trabeculae-like connections and fenestrated plates.

The authors conclude that irreversible connectivity reduction is one of the earliest manifestations of estrogen loss, and that early intervention to prevent possibly irreversible deterioration of the trabecular architecture after menopause is advised.

Silva and Gibson (1997) developed a two-dimensional model of human vertebral trabecular bone and investigated its mechanical behaviour using finite element analysis. Random reductions in the number and thickness of trabeculae were simulated.

The two-dimensional finite element model was generated using a technique based on Voronoi diagrams. A two-dimensional array of 20×20 points spaced 1×1 mm apart was generated. The co-ordinates of the points in the square array were perturbed in each direction by a random amount of the range -0.3 to 0.3 mm, based on a uniform distribution random number generator. To create a model with the appropriate bone volume and degree of anisotropy, the Voronoi diagram (trimmed to approximately 17×17 cells) was scaled by 2.33 times in the traverse direction and 3.5 times in the longitudinal direction. Each Voronoi diagram was then converted into a finite element mesh for its elastic and ultimate mechanical properties.

Three “intact” finite element meshes were first generated and analysed. Each mesh was generated using a unique list of random numbers to perturb the nucleation points. Values of 0.213 and 0.153 mm were assigned to the trabecular thickness in the longitudinal and transverse directions, respectively. The resulting bone volume for each intact mesh was 0.134.

The sensitivity of modulus and strength to changes in trabecular microstructure was investigated independently reducing the thickness and number of trabeculae in each of the two directions. Each of the four parameters (longitudinal thickness, longitudinal number, transverse thickness and transverse number) was by an amount necessary to produce reductions in bone volume of 5%, 10% and 15%, while holding the other tree parameters at their intact values. Trabecular thicknesses were reduced uniformly, whereas the numbers of trabeculae were reduced by randomly removing trabeculae from the intact meshes.

Two additional analyses were performed, one to simulate aging and one to simulate a possible scenario for restoration of bone mass following the treatment of aged bone. To simulate the aging process, concurrent changes in the number and thickness of both longitudinal and transverse trabeculae were made to an intact mesh. The resulting mesh, with its random defects, qualitatively resembled the appearance of thin section of vertebral trabecular bone taken from old donors. The authors then simulated a scenario for the restoration of bone mass following drug treatment of aged bone, in which trabecular thickness increases without changes in the number of trabeculae. In this mesh of “treated” bone, the authors increased the thicknesses of the longitudinal and transverse trabeculae to restore bone volume to its intact value, while holding the number of trabeculae fixed at their aged values.

The authors concluded that the modulus and strength of the model were at least twice as sensitive to random reductions in the number of trabeculae as compared to bone volume-equivalent, uniform reductions in the thickness of trabeculae. For a case

simulating aged bone, in which the thickness and number of trabeculae were reduced concurrently, the modulus and strength were approximately 20% of their values for the intact (young) case. When a treatment that restores bone mass was simulated by increasing the thickness but not the number of trabeculae, the modulus and strength were increased by 60% and 75% respectively, compared to the aged case, but were still less than 40% of the values for the intact case.

The strengths of the model of Silva and Gibson (1997) are the accurate replication of the important microstructural features of vertebral trabecular bone. Also, vertebral trabecular bone was modeled in a generic fashion, rather than modeling the specific microstructure of individual specimens of bone. Furthermore, in this model the trabecular microstructure can be varied in a controlled fashion, and thus the effects of independent variations in microstructure on mechanical properties were investigated.

On the downside, the authors assumed a uniform thickness of trabeculae, with one value for all longitudinal trabeculae and a second value for all transverse trabeculae, not accounting for the natural variance in trabecular vertebral bone. Additionally, had the authors reduced trabecular thickness non-uniformly, they would probably have observed a greater decrease in strength for a given decrease in bone volume. Furthermore, trabeculae were reduced randomly rather than based on any initial state of stress or strain or based on any initial distribution of trabeculae thickness. As a result they might have overestimated the effects of trabecular removal on mechanical properties if resorption preferentially removes thinner and/or less heavily loaded trabeculae. Finally, the two dimensional nature of the model did not allow direct comparisons made between absolute values of modulus or strength predicted using their model and those measured on bone specimens experimentally.

4. SIMULATION RULES AND PARAMETERS

The aim of our work was to define and develop a set of simulation rules and parameters that allow the cellular processes of bone to be modelled and used in scenarios that investigate bone remodelling and the effects on its mechanical properties. The simulations are based on the concept of a basic multi-cellular unit (BMU). Models are represented by a regular 2D or 3D matrix of BMUs that correspond to either bone or marrow. A set of rules controls the activity of BMUs, such as the type of activity (resorption or reposition), amount of turnover, activity based on external stimuli and cell mobility.

The simulation ruleset operates at the microscopic level and is independent of the trabecular nature of bone. Consequently simulations do not only consider uniform thinning or thickening of an artificially defined set of trabeculae, whilst bone activity and turnover is based on external mechanical stimuli. The parameters that control the amount of bone that can be resorbed or deposited are independent from each other and can be used to simulate natural bone loss, loss due disease or activity resulting from drug/hormone therapies.

4.1 Bone Remodelling Phases

Remodelling occurs on the surface of trabeculae (Frost 1997) with a three-stage cycle: activation, resorption and formation, such that the total cycle has a period of approximately 180-200 days. During remodelling, osteoclasts are responsible for the resorption of bone, forming a resorption pit that is subsequently filled with new collagen by osteoblasts. Typically, an osteoclast will remove the collagen to a depth of about 50 μm. The activity of osteoblasts is not always equal to that of osteoclasts and an imbalance in the osteoclastic and osteoblastic activity causes a net gain (+ΔB.BMU) or loss of bone (-ΔB.BMU). In osteoporosis, there is a negative imbalance (-ΔB.BMU) in remodelling usually caused by both increased osteoclast resorption and decreased osteoblast formation.

Each element in our simulations is represented by a square or cube of approximately 20μm. In osteoporosis the actual size of -ΔB.BMU is about 4 to 5 μm. Although the minimum size of ΔB.BMU in the simulation is 20 μm, having a larger sized bone element reduces the computational requirements by a factor of 25 for 2D and 125 for 3D simulations, without unduly affecting the validity of the model (Fagan *et al* 1999). In the simulator, bone remodelling activity also occurs at the interface between bone and marrow.

4.2 BMU Activation Algorithms

The simulations start by identifying a set of elements to initiate resorptive or repository activity. The algorithm for this stage of the simulation determines the maximum number of elements to be probed in the model matrix using an activation frequency (*activation frequency* $F \in [0,1]$) and the total number of elements of the model. Each element that is randomly probed using a uniform deviation generator (Press *et al* 1996) is automatically activated, provided it is situated at the interface between bone and marrow.

4.3 Probabilistic Resorption And Reposition

During a resorption activation, a number of continuous bone BMUs along a bone/marrow perimeter of a matrix of BMUs are resorbed and become marrow. The maximum number of bone

BMUs to be resorbed for a particular activation is determined by its resorption *activation length function* (Equation 5). In similar terms, Equation (5) is used for repository activity as well.

$$L = \lceil b + a \cdot random() \rceil \qquad (5)$$

A simulation run consists of a number of iterations N, where each iteration represents the remodelling that occurs over a period of time T. The *activation frequency* F defines the probability that a surface bone/marrow element will contain an activated BMU during the period T. For net resorption (net osteoclast activity), one or more bone elements become marrow, whereas for net formation (net osteoblast activity), one or more marrow elements are turned into bone. Net osteoclast activity is modelled as a resorption cavity that travels across the bone surface, whilst net osteoblast activity is modelled by a formation of collagen that travels along the bone surface. An activation consists of a channel of single elements that travels essentially in a straight line along a surface, whose length is controlled by Equation (5).

The ceiling function ($\lceil \ldots \rceil$) rounds the result of the enclosed expression to the nearest integer towards $+\infty$. The function $random()$ provides a normally distributed random number between $-\infty$ and $+\infty$ with mean 0 and variance 1 (Press *et al* 1996). For instance, constants a and b could be set to 1.8 and 6 respectively. Non-positive results of (5) are discarded, and since in 99.56% (Wonnacott and Wonnacott 1990) of cases $random() \in [-3,+3]$, L typically evaluates between 1 and 11. However, real study data (Eriksen *et al* 1990) report mean and standard deviation of bone turnover and can be used in relation to element or voxel size to determine appropriate values for a and b. Thus, constants a and b shift the probability distribution b units to the right or left and scale it by a (Law and Kelton 2000). By setting a to 0, L becomes deterministic in nature, allowing simulations to take place where the bone turnover is set at specific levels.

4.4 Cell Activity Control

Once an element is selected for resorption or reposition and the length of activity determined, the direction of an activation channel is chosen randomly. The four primary directions of travel are North, East, South and West (and Near and Far for 3D simulations). For an activated BMU, neighbouring elements to the N, S, E and W are checked. If only one of these is available the probability for the channel to go in that direction is 1.0. When two neighbours are available the probability of either direction to be chosen drops to 0.5, and decreases to 0.33 for three. Since an element is considered to be on the surface when there is an element of the opposite type anywhere on the N, S, E or W of it, it is impossible to have four possible main directions of travel (and hence a probability of 0.25). The BMU activity thus attempts to progress the net resorption or reposition channel in this primary direction by L steps. The direction taken at each step is either the primary direction or a direction that deviates ±45° from the primary direction, provided that the element in this direction is of the same type as the element that started the activity. If this is not possible, a step that is ±90° from the main direction is attempted. If this too fails, a step of ±135° is attempted and as a last resort, +180°. In general, when a step greater than ±45° is taken, the primary direction is also changed. This prevents a channel from moving backwards and forwards between two positions and creating a "deep pit" or a "high hill". The step direction is chosen randomly from all possible directions with equal probability.

At the end of an iteration any isolated marrow or bone islands are removed. This seems reasonable, as it is known that unattached trabeculae are resorbed. Once the primary direction of a net osteoclast or osteoblast activation has been determined, a step of an activation can only be taken if one of the candidate elements for the step is on a bone/marrow surface.

4.5 Relationship Of Strain And Remodelling

Since bone adapts to loading conditions, bone areas under low strain are also preferentially resorbed and areas of high strain reinforced by reposition of bone. Areas of bone under normal strain are mostly unaffected by remodelling processes. Support for strain-remodelling is achieved by associating strain with each element in the 2D/3D matrix and using that to initiate resorption or reposition of bone based on the value of strain for any particular element. Strain energy density values are obtained from linear finite element analyses. Low values of strain would primarily contribute to loss of bone (disuse) and high values to addition of bone (Wolff 1896).

Two limits are associated with the above, where ε_1 and ε_2 are the strain-remodelling limits. Elements whose strain is less than ε_1 become potential candidates for resorption, whereas elements with strain above ε_2 become potential candidates for reposition of bone. The remaining elements whose strain is between ε_1 and ε_2 are not considered for any of the two types of activation.

$$StrainAdaptation(s,\varepsilon_1,\varepsilon_2)=\begin{cases} CL, s\in(-\infty,\varepsilon_1] \\ N, s\in(\varepsilon_1,\varepsilon_2) \\ BL, s\in[\varepsilon_2,+\infty) \end{cases} \quad (6)$$

Where s represents the strain-energy density associated with a probed element in the model matrix and ε_1 and ε_2 are strain-adaptation limits. Function (6) returns the type of activity to be initiated and can be osteoclastic (*CL*), none/no activity (*N* or neutral) and osteoblastic (*BL*).

5. VALIDATION AND VISUALISATION

5.1 Structural Morphology

The analysis of the morphology of the structures produced by our simulations (Fagan *et al* 1999, Langton *et al* 1998, Langton *et al* 2000) allows the indirect validation of the simulations by comparing the results with the literature, and facilitates the investigation of scenarios such as the effects of structural characteristics at the trabecular level to the structures' stiffness. Algorithms were defined that can compute morphological indices directly from 3D, offering a more accurate picture than current approaches where some metrics are calculated on a per voxel-plane basis (being effectively 2D). These algorithms have been incorporated into our simulations and are able to perform histomorphometric analyses on binary pixel and voxel maps without any user intervention (Sisias *et al* 2002).

The morphological indices computed are model independent and are derived directly in 3D using techniques such as volume ray-tracing. The first group involves indices such as mean trabecular thickness, mean trabecular separation (or spacing) and trabecular density (or number). The second group involves the computation of the star area and volume distribution of both bone and marrow elements. The third group considers simple indices such as bone and marrow fraction volume, surface roughness and perimeter/surface area. Other structural measurements involve the strain energy density distribution across all bone elements in a structure and the calculation of the structure's stiffness.

5.2 Interactive Visualisation

Three-dimensional visualisation of trabecular bone and its attributes is an essential tool in understanding this remodelling process for cancellous bone. It enables the bone researcher to quickly understand the dynamic behaviour of remodelling, the resulting geometry of the bone structure and it allows alternative remodelling scenarios to be compared. Phillips *et al* (2003) discuss stereoscopic visualization of bone structures using a volume rendering technique based on transparency of voxels integrated with a reflection model. The method the authors employ is more appropriate than surface rendering as it allows the inside of trabeculae to be viewed. The volume rendering implementation is based on texture mapping. It runs on a 1.1 GHz Athlon PC with 512 MB RAM and an NVIDIA GeForce 2 Ultra graphics card. The texture mapping technique used is preferred to ray-casting as it is less computationally intensive and it provides real-time interactive visualization on mainstream hardware.

6. APPLICATIONS

Langton *et al* (1998) developed and applied a stochastic simulation of cancellous bone resorption to the simple two-dimensional lattice structure representing vertebral bone. The study described a stochastic simulation of net bone resorption at a microscopic level, exhibiting both trabecular thinning and perforation. Finite element analysis was used to quantify the effects of resorption on the mechanical properties of bone after each simulation iteration. The structure after each step was analysed with FEA with a simple compressive load, to compute the nodal displacements. The relationship between relative stiffness and density as function of the simulation step was derived, along with the relationship between stiffness and bone porosity. In the simulations the structure began to suffer from loss of vertical trabecular connectivity from step 3 and started to collapse from step 4. By step 8 the structure totally lacked connectivity and mechanical integrity. Relative stiffness decreased more rapidly than density. Consequently the stiffness decreased faster than porosity for the first few steps and levelled to zero for the final steps as the structure lost connectivity and collapsed.

Fagan *et al* (1999) investigated the effects of mesh density and model size to the simulations of Langton *et al* (1998). Structures with 50% less and 50% more elements for both horizontal and vertical trabeculae than the structure of Langton *et al* (1998) were created. These were subsequently subjected to the same loading conditions as above and the results of their finite element analyses compared to those from the previous experiments. Furthermore the effect of model size was examined by setting the number of trabeculae to 3×3 and 9×9. As in the previous experiments, simulations were repeated five times with each of the models.

Langton *et al* (2000) used a simplistic symmetric lattice structure consisting of 5×5 trabeculae with constant width and intertrabecular spacing to stochastically resorb and rebuild bone until the structure's original stiffness was regained. The structure was resorbed using an activation frequency

of 0.05 (5%) and the activation length function L of Section 4. Constants a and b were set to 1.8 and 6, respectively. At the 95th percentile, L was 120±70.6 μm at 20 μm resolution. Resorptive activity was continued until nominal resorptions of approximately 10%, 15%, 20%, 25% and 30% below the original density were achieved. The simulation was then modified to create an anabolic effect (with the same parameters as above) where bone elements were added at the bone-marrow interface stochastically, providing a rate of net formation (+ΔB.BMU). The simulation of anabolic treatment was applied at the resorbed structures until the original stiffness had been regained. The simulations were repeated three times for each of the nominal resorptions. The simulations started with the intact structures, at a relative density and stiffness of 1.0. The stochastic simulation reduced density to the various levels. At that point anabolic treatment was simulated, until original density and stiffness were reached. Although original density was eventually reached, stiffness was not totally restored. Restoration of stiffness required density to increase to levels above 100%, especially for the most severely depleted structure (at 30%).

7. Discussion And Conclusions

The various models described address the issues of normal or hormonally affected bone growth, loss or adaptation from different and concentrated perspectives. Some models consider structural characteristics of cancellous bone such as trabecular network, whereas others target bone simulation at the microscopic level, such as multi-cellular units of a few μm in size. Models based on structural characteristics mainly tend to simulate the behaviour of large sections of bone, based on statistical data obtained from clinical studies. On the other hand models that operate on the microscopic level try to closely represent the small simulated structures and consider the activity of individual or groups of cells.

Model validations tend to present difficulties. The results obtained from statistically based simulations are compared to clinical studies, and mainly consider normal or hormonally affected bone loss or growth. Similarly the results obtained from microscopic simulations are related to real bone samples taken from biopsies of normal or osteoporotic patients of either sexes or women only when simulating the effects of menopause. Although the later simulations are generally aimed to be more accurate, they suffer from the fact that once bone is taken from a human, growth is non existent, either the sample was taken postmortem or growth stopped after the biopsy. Additionally, biopsies from live human give very small samples, are invasive and cannot supply a second sample from the same region as the original after the end of treatment or menopause. More importantly, mainly due to high radiation levels, samples might be impossible to take non-invasively from live subjects.

Microscopic simulations, although more accurate, tend to suffer from the high number of elements of the models and the cellular processes and finite element analyses considered on every element. Once technological restrictions relax, it should be possible to simulate the activity of cells on fine resolution voxel-based data sets, taking under consideration stochastic factors and bone adaptation. However, algorithmic efficiency in terms of storage and operations can play a decisive role in the size of structures and complexity of rules that can be employed. In terms of software development, though, more exotic solutions to projects pose restrictions in the availability of methods to be employed, particularly for finite element analyses.

The methods outlined are versatile in terms of the scenarios that can be investigated. As the scenarios increase in complexity and size, it becomes necessary to consider significant revisions of the underlying software to accommodate new modes of operation. As the software grows in size (presently the entire simulator suite is about 70 KLOC) alterations are more difficult to implement and test.

In comparison to the models reviews, the simulation ruleset outlined operates at the microscopic level and is independent of the trabecular nature of bone. Consequently simulations do not only consider uniform thinning or thickening of an artificially defined set of trabeculae, whilst bone activity and turnover is based on external mechanical stimuli. The parameters that control the amount of bone that can be resorbed or deposited are independent from each other and can be used to simulate natural bone loss, loss due disease or activity resulting from drug/hormone therapies. However, this versatility comes at a cost, as it is computationally expensive and causes the manifestation of the usual problems associated with microscopic simulations.

8. References

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