A REGULATORY MODEL FOR CONTROL OF BONE HOMEOSTASIS BY MECHANICAL FACTORS.

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Introduction: Rodan [1] speculated that "Bone homeostasis is controlled by mechanical factors in a hormonal environment." Earlier studies have shown that control of trabecular morphogenesis and adaptation by mechanical factors are feasible propositions from a regulatory point of view, when assuming a mechanosensory role for osteocytes [2,3]. In this study we investigated the hypothesis that the same is true for bone turnover and homeostasis. For that purpose we developed a regulatory model, based on the following assumptions: (i) osteoclasts resorb bone in a spatially random manner; (ii) resorption lacunae (and increases in external loads) produce local strain-energy density elevations, sensed by osteocytes which, as an effect, distribute a biochemical signal to the trabecular surface; (iii) the biochemical signal recruits osteoblasts which locally form bone as long as the signal is produced [4]. In this way, it is implied that coupling between osteoclasts and osteoblasts occurs indirectly, through mechanical factors [5]. This regulatory model was investigated with computer simulation, using FEA. For the hypothesis to be feasible, the regulatory process must be able to explain trabecular morphogenesis, turnover (maintenance) and adaptation as effects of only osteoclast resorption and changes in external loads as perturbations (Fig. 1).

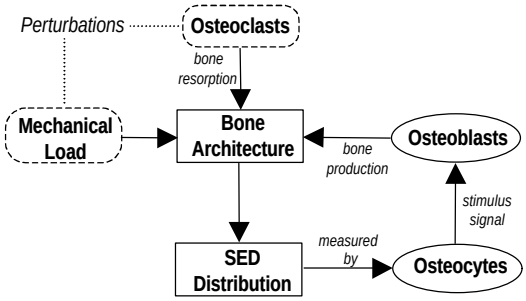

figure 1: *Diagram of the turnover and remodeling process*

Methods: Osteoclast resorption sites were selected with a Monte Carlo generator, in such a way that a fixed amount of bone is removed per time unit and per volume considered in the analysis, according to

$$\frac{dm_{oc}}{dt} = -R_{oc} \qquad \text{(eqn 1).}$$

Every osteoclast was assumed to remove a constant amount of bone.
Based on the local SED value S_i , computed by FEA, each osteocyte in the mesh produces a biochemical signal p_i

$$p_i(t) = s_i S_i(t) \qquad \text{(eqn 2),}$$

where σ_i is the osteocyte mechanosensitivity. The distribution of the osteocyte signals to the surfaces is governed by a spatial decay function, so that each surface site receives

$$P(\underline{x},t) = \sum_{i=1}^{n} p_i(t) \cdot e^{-d_i(\underline{x})/D} \qquad \text{(eqn 3),}$$

where D is the characteristic influence-distance parameter of the decay function and d_i is the distance between osteocyte and the surface site. The local amount of bone-matrix production by osteoblasts is governed by the local signal value, according to:

$$\frac{dm_{ob}}{dt} = C\{P(\underline{x},t) - k_{tr}\} \qquad \text{for } P(\underline{x},t) > k_{tr} \qquad \text{(eqn 4),}$$

where C is a rate constant and k_{tr} a signal threshold value. The equations were transformed to numerical algorithms and applied in a 2-D FEA model of 2x2 mm, divided in 80x80 elements. The simulation was run from several initial architectures, with constant and re-oriented external loads.

Results: From several arbitrary initial conditions the process developed trabecular-like architectures, with trabeculae aligned according to the applied external loads (Fig. 2). For different initial conditions, the eventual architectures were similar (morphogenesis). When the load was increased or reduced in value, bone mass was increased and reduced accordingly (adaptation). When the external load was rotated, trabecular orientation rotated accordingly (adaptation). When continuing the simulation long after the architecture had acquired a stable configuration at the apparent level (from 1000 to 3000 iterations), the architecture remained stable, despite continuing resorption/formation, whereby osteoclast lacunae were just filled with new bone, without changes in net bone mass (homeostasis and maintenance).

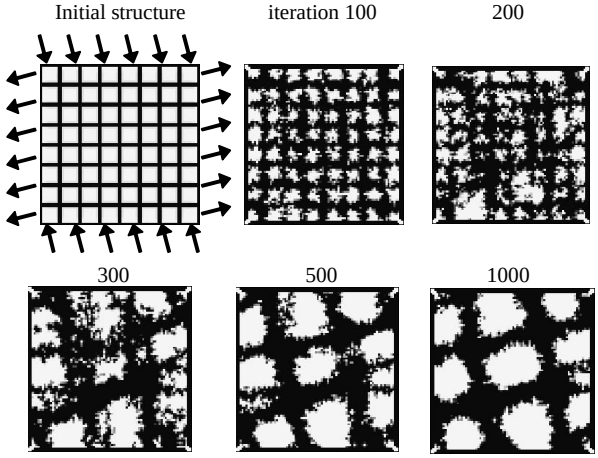

figure 2: *The initial, intermediate, and final stable morphology at the apparent level. The applied stress was 4 Mpa.*

Discussion: It is remarkable that such a stochastic (and maybe chaotic) process produces and maintains a 'homeostatic' architecture, purely under the influence of load. This implies that the proposed regulatory model is feasible in principle. This does not imply that all the assumptions underlying the model are true. The model is attractive, because it is inherently simple. The number of parameters on which the model is based is limited, and they are all measurable quantities in principle: osteocyte density, rate of bone resorption per apparent volume, maximal lacunar depth, osteocyte mechanosensitivity, osteocyte influence reach, an osteoblast formation rate constant, and a recruitment threshold. Stochastic osteoclast resorption could be based on several mechanisms, such as removal of dead bone, repair of microdamage or systemic calcium requirement, assuming that their sites are distributed randomly. The mechanosensory role of osteocytes has been made plausible, and signalling of osteoblasts by osteocytes seems reasonable, as they have the same lineage.
We conclude that the assumptions of random osteoclast resorption and indirect osteoclast-osteoblast coupling through mechanical factors, governed by osteocytes, can relate trabecular morphogenesis and adaptation to bone turnover

References

[1] *Rodan G.A., Bone Vol. 20, nr. 1, p1-4,* 1997.
[2] *Mullender M. et.al., J. of Orthopaedic Research 13, p503-512,* 1995.
[3] *Mullender M. et.al., Bone vol. 22 No. 2, p125-131,* 1998.
[4] *Cowin S.C. et.al., J. Biomech. Eng. 113: p191-197,* 1991.
[5] *Rodan G.A., in Marcus R. et.al., J., Eds., Osteoporosis, p289-299,* 1996.

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