A PLATFORM FOR IN-SILICO EXPERIMENT OF BONE REMODELING FOR UNDERSTANDING ROLES OF MECHANO-CHEMICAL COUPLINGS

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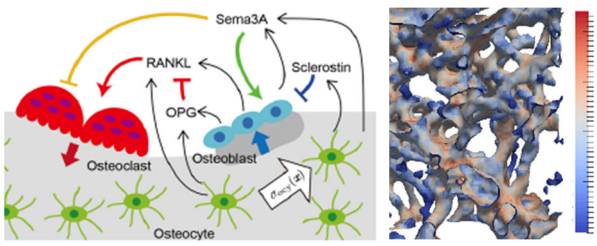
Introduction

Homeostasis of bone structure and function can be disrupted by an imbalance between osteoclastic resorption and osteoblastic formation of bone caused by disuse during prolonged bed rest and immobilization. Bone with a significant loss will be at high risk for developing osteoporosis and having a fracture [1]. To maintain bone health and to gain bone mass by drugs and weight-bearing exercise, effects of mechano-chemical couplings on bone remodeling needs to be understood. However, understanding and predicting the physiological or pathological processes of bone as a system remain difficult because of the complexity of relevant molecular and cellular behaviors. In this study, we propose a novel *in-silico* experimental platform that mathematically models bone remodeling by linking microscopic molecular and cellular interactions to macroscopic tissue/organ level behaviors.

Methods

In silico platform of bone remodeling, incorporating mechano-biochemical couplings (Fig. 1(a)), has been developed [2] by combining an image-based voxel finite element method (Fig. 1(b)) [3]. Important signaling molecules in bone remolding such as sclerostin, RANK/RANKL/OPG, and semaphorin 3A (Sema 3A) were involved in the platform with mechanical stimulus. To investigate the roles of essential signaling molecules in bone remodeling, as is often conducted *in vivo* experiment, the molecule of interest was perturbed *in silico* on the proposed platform. A case study was conducted to investigate the effect of Sema 3A, known as a bone-protective factor [4], on bone remodeling, in which Sema3A-deficient mice were modeled *in silico* by down-regulating its production rate in the platform.

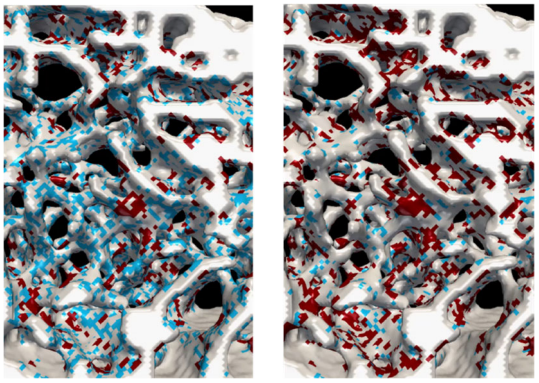


(a) Intracellular signaling *(b) FE analysis*

Figure 1: In-silico platform of bone remodeling. (a) Intracellular signaling for bone remodeling incorporated to the in-silico experimental platform [2]. (b) Mechanical signals sensed by osteocytes in response to mechanical loading, which was analyzed using an image-based FE model of mouse trabecular bone.

Results and Discussion

In silico perturbation experiment was performed for Sema 3A-deficient mice (Fig. 2). Trabecular surfaces under osteoclastic resorption/osteoblastic formation are indicated by red/blue colors, respectively. Comparing to the control model in Fig. 2(a), larger surface was occupied by osteoclasts resulting in osteoporotic bone with thin trabeculae and large pores, as shown in Fig. 2(b). Trabecular structure was qualitatively compared to *in- vivo* experiment (date not shown). Cancellous bone morphology in the Sema3A-deficient model was similar after 10 weeks of simulation to that obtained *in vivo* with BV/TV and trabecular number Tb.N significantly smaller than in the control model.



(a) Control *(b) Sema3A deficient*

Figure 2: In silico experiment of Sema 3A-deficient mice using an image-based FE model of cancellous bone.

By using the proposed platform as an *in-silico* experimental tool, perturbation analysis would make possible to explore efficiently the role of each signaling molecule in the complex bone remodeling system with biochemical and mechanical couplings. Furthermore, it would be a powerful tool to predict the effects of drugs on bone structural changes that is clinically important.

References

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