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MECHNO-REGULATION OF BONE REMODELLING AND THE TOPOLOGY OF OSTEOCYTE NETWORKS

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The structural adaptation of living bone is made possible by a continuous renewal process known as bone remodeling. During remodeling in trabecular bone osteoclasts resorb small bone packets from the surface, while osteoblasts deposit new bone. This process is at least partly mechanically controlled. It is thought that deposition occurs preferentially at locations of higher mechanical strains, and resorption where the local load is reduced. Responsible for the mechano-sensation seem to be the osteocytes. These cells are former osteoblasts, which have been walled in the bone during the remodeling process and differentiate to a new cell type thereby forming characteristic cell processes. The osteocytes connect with each other using a network-like system of small channels within the bone matrix, the canaliculi.

The many open questions concerning the cellular mechanobiology of bone remodeling are due to the extreme challenges to perform controlled in vivo experiments to learn about the cell response to mechanical stimulation. An alternative approach to bridge the gap between the control of remodeling on the cell level and the experimental data available at the tissue level is to use computer simulations. In a computer experiment different hypotheses about the mechanical control of remodeling can be implemented and the resulting bone structure can be compared with experimental data. Using this approach, simulations indicated the existence of a threshold of the mechanical stimulus, above which bone deposition by osteoblasts is strongly enhanced [1,2]. Addressing the question of how the signal sensed by the osteocytes is integrated by the cell network, simulations showed that a collective signal from many osteocytes is in better agreement with experimental observations than assuming the strongest signal of one osteocyte to dominate [3].

Recent advances in experimental methodology now allow to verify predictions from computer experiments. Using *in vivo* micro-computed tomography [4,5], the amount and specific site of remodeled bone can be determined in living small animals. Examples of concepts first used in the context of computer simulations and which are now “measurable” are (i) the remodeling rule [1,2], i.e. the probability of form/resorb bone as a function of the mechanical stimulus [4] and (ii) the mineralization law [6], which describes the temporal increase of mineral content from the initially unmineralized osteoid to fully mineralized bone [7].

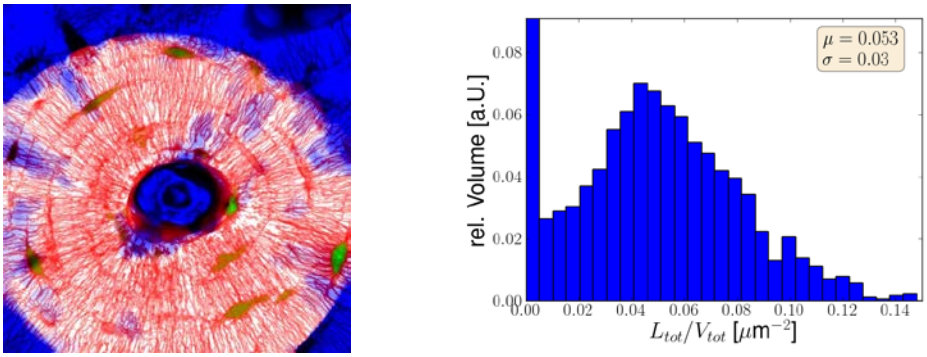

Figure 1: Left, projection of a stack of confocal microscopy images highlighting the different densities of the osteocyte lacuno-canalicular network within an osteon. Bluish regions within the osteon denote regions of low density. Right, frequency distribution of the network density within the same osteon revealing a strong variability in the density.

Recently we started efforts to shed light on the mechano-regulation of remodeling on the cellular level. A first step is here to characterize the topology of the network of osteocytes. Our focus is on the osteocyte lacuno-canalicular network (OLCN) within human osteons. Osteons are cylindrical structures formed during remodeling in cortical bone, where first osteoclasts dig a tunnel, which is then closed by osteoblasts leaving in the middle a Haversian canal free for blood vessels. Four samples from femora of middle-aged healthy women were stained using rhodamine and then for each sample 10 osteons were 3-dimensionally imaged by confocal laser microscopy [8]. The image data of the OLCN was skeletonized (Fig. 1, left) rendering the network topology. Evaluating the density of the network, i.e. the total length of all canaliculi per volume, we obtained an average value of around 0.05 $\mu m/\mu m^3$ with substantial variability (Fig. 1, right). The network density decreased from the Haversian canal moving outside. Furthermore the orientation of the canaliculi and the density with respect to the lamellar structure within the osteon were evaluated. The obtained topological results have to be interpreted in terms of the network function. Thereby it has to be kept in mind, that the OLCN has also a function in mineral homeostasis influencing the properties of the nanoscopic mineral particles depending on their distance from the network [8].

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