

## Author's Accepted Manuscript

Towards a cell-based mechanostat theory of bone:  
the need to account for osteocyte desensitisation  
and osteocyte replacement

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PII: S0021-9290(16)30579-6  
DOI: <http://dx.doi.org/10.1016/j.jbiomech.2016.05.012>  
Reference: BM7731

To appear in: *Journal of Biomechanics*

Received date: 20 December 2015  
Revised date: 13 April 2016  
Accepted date: 15 May 2016

Cite this article as: Chloé Lerebours and Pascal R. Buenzli, Towards a cell-based mechanostat theory of bone: the need to account for osteocyte desensitisation and osteocyte replacement, *Journal of Biomechanics* <http://dx.doi.org/10.1016/j.jbiomech.2016.05.012>

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1 Towards a cell-based mechanostat theory of bone: the need to account for  
2 osteocyte desensitisation and osteocyte replacement

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5 **Abstract**

Bone's mechanostat theory describes the adaptation of bone tissues to their mechanical environment. Many experiments have investigated and observed such structural adaptation. However, there is still much uncertainty about how to define the reference mechanical state at which bone structure is adapted and stable. Clinical and experimental observations show that this reference state varies both in space and in time, over a wide range of timescales. We propose here an osteocyte-based mechanostat theory that encodes the mechanical reference state in osteocyte properties. This theory assumes that osteocytes are initially formed adapted to their current local mechanical environment through modulation of their properties. We distinguish two main types of physiological processes by which osteocytes subsequently modify the reference mechanical state at different timescales. One is cell desensitisation, which occurs rapidly and reversibly during an osteocyte's lifetime. The other is the replacement of osteocytes during bone remodelling, which occurs over the long timescales of bone turnover. The novelty of this theory is to propose that long-lasting morphological and genotypic osteocyte properties provide a material basis for a long-term mechanical memory of bone that is gradually reset by bone remodelling. We test this theory by simulating long-term mechanical disuse (modelling spinal cord injury), and short-term mechanical loadings (modelling daily exercises) with a mathematical model. The consideration of osteocyte desensitisation and of osteocyte replacement by remodelling is able to capture a number of phenomena and timescales observed during the mechanical adaptation of bone tissues, lending support to this theory.

6 *Keywords:* Mechanobiology, Bone remodelling, Bone modelling, Mechanical adaptation, Cell  
7 adaptation

8 Word-count from Introduction to Discussion: 4329 words.

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