



Published in final edited form as:

Exerc Sport Sci Rev. 2004 January ; 32(1): 9–13.

Why Rest Stimulates Bone Formation: A Hypothesis Based on Complex Adaptive Phenomenon

Ted S. Gross, Sandra L. Poliachik, Brandon J. Ausk, David A. Sanford, Blair A. Becker, and Sundar Srinivasan

Orthopaedic Science Laboratories, Department of Orthopaedics and Sports Medicine, University of Washington, Seattle

Abstract

Moderate exercise is an ineffective strategy to build bone mass. The authors present data demonstrating that allowing bone to rest between each load cycle transforms low- and moderate-magnitude mechanical loading into a signal that potently induces bone accretion. They hypothesize that the osteogenic nature of rest-inserted loading arises by enabling osteocytes to communicate as a small world network.

Keywords

bone; exercise; mechanical loading; mechanotransduction; rest-insertion; small world network

INTRODUCTION

Regardless of one's predilection for exercise, bone mass increases through the third decade of life, at which time both cortical and trabecular bone volume begin to decline. Beginning near age 40, bone loss has been estimated to total 0.3% to 0.5% per year. Postmenopausal bone loss occurs within the decade after menopause and temporarily elevates annual bone loss to 2% to 3% (7). Based on these estimates, the average 70-year-old woman can anticipate a decline of approximately 25% to 40% in bone mass from her maximal levels, whereas a like-aged man can anticipate a 10% to 15% decline.

Mechanical loading of bone through exercise has been investigated thoroughly for its potential to counter this bone loss. One of the most dramatic examples of the bone-building potential of exercise is the substantially enhanced bone mass (10% to 15% increases) found in the playing arms of competitive racquet sport athletes, particularly of those who begin the sport in childhood (*e.g.*, (4)). In general, exercise trials incorporating low- or moderate-magnitude repetitive loading activities (such as walking, jogging, or swimming) have demonstrated an inability to increase bone mass (6), whereas high-magnitude, high-impact loading induces modest bone mass increases (1% to 2% over a 9-month trial (15)). However, the elderly, who are most in need of enhanced bone mass, are unable to sustain impact-loading regimens without high risk of injury. Further, compliance with high-impact loading regimens is extremely challenging within a society in which physical activity is falling to all-time lows. As a means of overcoming these limitations, our recent work has focused on identifying how to modify low-magnitude loading (*e.g.*, walking) so that it becomes highly osteogenic.

USING REST TO TRANSFORM LOW- AND MODERATE-MAGNITUDE LOADING

In a recent analytical model of fluid flow in bone (10), we observed that canalicular fluid flows induced by cyclic loading exhibit a transient maxima during the first load cycle, with markedly reduced steady-state flow rates during subsequent load cycles. Physically, this phenomenon is related to the forced flow of viscous fluids within the lacunocanalicular porosity in bone and the related fluid flow inertia. Based on considerations of how osteocytes (the likely mechanotransducer within bone) may be stimulated by this fluid flow, we therefore hypothesized that inserting a nonloaded rest interval between each load cycle of a repetitive cyclic loading regimen would enable reproduction of the maximal transient flow for every load cycle and thereby significantly enhance the osteogenic potential of that regimen (11). In essence, by resting the tissue between each load cycle, we anticipated that bone would become more responsive to a given magnitude mechanical stimulus. Initially, we assessed whether insertion of rest between load cycles would influence a low magnitude cyclic regimen that was normally capable of only minimally activating osteoblasts (the bone-forming cell). We compared turkey ulnae loaded with 100 cycles/d for 5 d with ulnae loaded with 100 cycles/d for 5 d for the same low-magnitude loading (inducing bone strains equivalent to slow walking), but with 10 s of rest inserted between each load cycle (Fig. 1). Although repetitive cyclic loading resulted in a small but significant increase in the percentage of the periosteum activated by loading compared with intact bones (3.8 ± 1.5 vs. $1.6 \pm 1.5\%$; $P = 0.03$), insertion of rest resulted in a nearly 14-fold increase in compared with control bones ($21.9 \pm 4.5\%$; $P = 0.03$). Insertion of a rest interval between each load cycle effected a nearly sixfold increase in the percentage of osteoblasts activated by loading.

Using a noninvasive murine model in which the tibia is loaded exogenously, we then found that low-magnitude cyclic loading did not alter periosteal bone formation, but that insertion of rest significantly increased bone formation (eightfold elevation vs. low-magnitude cyclic loading; Fig. 2). Doubling the magnitude of cyclic loading, as would be expected, also significantly increased periosteal bone formation. We found that this response was statistically equivalent to that generated by rest-inserted loading incorporating only 10% of the number of load cycles and 50% of the load magnitude. Because the duration of the protocols were nearly identical (100 vs. 110 s), we inferred that the potency of rest insertion observed in the initial study was not the result of increased loading duration.

To explore further the characteristics of rest-inserted loading, we have begun to assess how rest insertion alters the relation between load magnitude and cycle number and resulting bone formation. As others have noted, when the magnitude of cyclic loading is increased, a threshold response is observed with lamellar bone formation induced by loading above a given magnitude (13). As loading magnitude is increased further, this response plateaus. When load magnitude is held constant, but cycle number is increased, bone formation induced by cyclic loading is saturated rapidly (9). We have found that rest-inserted loading lowers the threshold at which lamellar bone formation is initiated and, at a given load magnitude, precipitates a significantly elevated response (Fig. 3A). Rest-inserted loading also greatly diminishes the number of cycles required to induce significant bone formation (Fig. 3B). Further, because the magnitude of the response at any given load cycle greatly exceeds that induced by a like number of repetitive load cycles, it appears that the resulting saturation associated with cyclic loading can be overcome (5). An analogous observation recently was reported at the cellular level, where the ability of osteoblasts to respond repeatedly to fluid flow via calcium influx was enhanced greatly when rest was inserted between bouts of fluid flow (1).

In addition to these studies, two independent groups recently reported investigations in which rest insertion was found to augment the response of bone to mechanical loading. Based on our

initial observations regarding 10 s of rest, the relative benefits of 3, 7, and 14 s of rest inserted between each load cycle were explored (8). Although 3 and 7 s did not alter bone adaptation compared with cyclic loading, 14 s of rest significantly increased bone accretion. In a similar context, regimens in which rats jumped 20 times per day were contrasted with either 3 s or 30 s of rest allowed between each jump (14). Although both protocols increased femoral and tibia bone mass and strength compared with nonloaded controls, the 30-s rest interval further increased femur and tibia breaking strength as compared with 3 s of rest.

In sum, these data indicate that insertion of a rest interval between loading events greatly amplifies how bone responds to cyclic mechanical loading. In a broad context, these data suggest that rest insertion holds potential to convert mild activities, such as walking or gardening, into a powerful stimulus for bone accretion. For example, the childhood game of hopscotch could be modified to incorporate a 10- to 15-s rest interval between each hop. Success in optimizing this strategy, however, ultimately will rely on discovering why rest insertion has such a profound effect on bone mechanotransduction.

COMPLEX ADAPTIVE SYSTEMS: THE SMALL WORLD NETWORK

The counterintuitive potency of rest-inserted loading exemplifies the lack of understanding of how mechanotransduction functions in bone. We therefore have turned to the study of complex adaptive systems, which permits examination of nonlinear emergent phenomena. The examination of such systems is based on the premise that complex interconnected processes (*e.g.*, neurons of the brain or an ecosystem) demonstrate similar richness of “behavior” regardless of the specific mechanisms governing individual interactions (*i.e.*, neurotransmitters or components of a food chain). By identifying commonalities in behavior, it becomes possible to better predict and assess consequences of a specific alteration within a complex system (*e.g.*, when a specific component of an ecosystem is eliminated). The small world network is a particular subset of complex adaptive system whose essence recently has been popularized by the six degrees of separation phenomenon (for general reference, see (2)). A singular feature of the small world network is that rapid communication between disparate portions of a complex system is achieved if short cuts can be created (Fig. 4). In contrast to requiring a system of millions of components to communicate serially with each adjacent neighbor to effect a response, a small world network holds the potential to speed or amplify signal transmission, or both, exponentially.

Recent mathematical modeling of small world networks has enabled identification of characteristic behaviors of these systems (12). In particular, small world networks demonstrate three behaviors that are of potential relevance to the study of bone mechanotransduction. First, small world networks exhibit power law behavior, in which small magnitude events occur often, whereas large magnitude events occur infrequently (*e.g.*, the magnitude of earthquake tremors on a Richter scale). Second, small world networks demonstrate critical state, or threshold behavior. Until a threshold is reached, incrementally increased inputs elicit only a minimal system response. However, at the critical threshold, a single additional increment will result in a profound system response (*e.g.*, a light wind causing a subtle shift of surface snow and thereby precipitating an avalanche). Third, small world networks demonstrate enhanced capacity for entrainment or synchronization of component signaling units. Such synchronized signaling is then associated with greatly enhanced system response because of mechanisms such as resonance (*e.g.*, the rapid synchronization of clapping in an audience).

Osteocyte networks are acclimated to daily mechanical stimuli displaying a power law spectrum at the tissue level, in which high-magnitude strains occur rarely and low-magnitude signals occur much more often (3). Stimulation of bone via loading above this curve (*i.e.*, either more low-rate, high-magnitude loading or more high-rate, low-magnitude loading) results in

the formation of new bone via activation of signaling within the bone cell network. Threshold behavior is displayed at a variety of levels, ranging from calcium signaling in individual cells to bone formation at the tissue level. In each case, a minimal response is observed until a threshold is passed, whereupon a further stepwise increment in stimulus precipitates a nonlinear increase in response.

Evidence for synchronization or entrainment of bone cells in response to mechanical loading has, to our knowledge, not yet been obtained. We therefore recently began to explore this possibility by simulating the response of a population of osteocytic cells to both cyclic and rest-inserted loading using an agent-based modeling environment (NetLogo1.1; <http://ccl.northwestern.edu/netlogo>). The NetLogo modeling environment allows exploration of connections between the microlevel behavior of individuals and the macrolevel patterns that emerge from the interactions of many individuals. Within NetLogo, individual osteocytes were assigned localized sets of parametric rules (governing microlevel behavior) and were permitted to interact with a varying number of neighboring osteocytes. We then examined the response of population of osteocytes to the equivalent of either cyclic or rest-inserted loading. We found that when osteocytes, necessarily constrained by finite metabolic resources (*e.g.*, intracellular Ca^{2+} stores), were exposed to cyclic stimuli, cells demonstrated invariant levels of cellular coordination (*i.e.*, 50% of the osteocytes were active at any given point in time). Further, integrated signaling within the network was extremely inefficient. In contrast, osteocytes exposed to the equivalent of 10 to 15 s of rest-inserted loading displayed markedly enhanced cell signaling coordination (*i.e.*, up to 90% of osteocytes demonstrated synchronized activity; Fig. 5). As well, network signaling was enhanced (up to a 10-fold increase in integrated signals compared with cyclic stimuli). Interestingly, this preliminary analysis indicated that synchronization of the osteocytic network in response to rest-inserted (but not cyclic) stimuli was dependent strongly on the ability of a given osteocyte to communicate with its immediate neighbors and the ability of individual osteocytes to replenish metabolic resources.

SUMMARY AND HYPOTHESIS

In summary, inserting a rest interval between each cycle of repetitive loading transforms bone's perception of a mechanical stimulus otherwise dismissed as a metronomic background signal. With regard to how this intervention effects such a transformation, insertion of rest between each load cycle potentially enhances canalicular fluid flows and related stimulation of osteocytes. Such enhanced fluid flows may increase the "neighborhood" or communication range of typical osteocytes (*e.g.*, by allowing improved transport of signaling molecules between distant osteocytes). Additionally, rest-inserted loading may enable synchronized osteocytic activity. This ability to synchronize activity markedly amplifies and effectively expands the range of the integrated signals (*e.g.*, coherent or synchronous array of N cells would produce N^2 times as much power as asynchronous cells operating in distinct spatiotemporal patterns) (12). As such, we hypothesize that rest-inserted loading (via fluid flow, synchronized activation, or both) effectively may short-circuit signaling and may enable osteocytes to operate as a small world network.

We speculate that analyzing bone mechanotransduction as a complex adaptive process will enable unique insights into cellular mechanisms underlying its functioning in diverse systems, such as bones, plants, or *Caenorhabditis elegans*, that all fundamentally rely on mechanosensing for function or survival. Further, it is our belief that exercise strategies designed to take advantage of specific behaviors of small world networks ultimately will provide novel strategies to strengthen the skeleton to resist fracture.

Acknowledgements

Supported in part by the National Institutes of Health (grant no. AR 48102 [TSG]) and The Whitaker Foundation for Biomedical Engineering (SS).

References

1. Batra NN, Li YJ, Jacobs CR. Effect of short term recovery periods on fluid flow induced calcium oscillations in MC3T3-E1 osteoblastic cells (Abstract). *Trans 49th Orthop Res Soc* 2003;28:129.
2. Buchanan, M. *Nexus: Small Worlds and the Groundbreaking Science of Networks*. New York: W. W. Norton & Company, 2002.
3. Fritton SP, McLeod KJ, Rubin CT. Quantifying the strain history of bone: spatial uniformity and self-similarity of low-magnitude strains. *J Biomech* 2000;33:317–325. [PubMed: 10673115]
4. Haapasalo H, Kannus P, Sievanen H, Pasanen M, Uusi-Rasi K, Heinonen A, Oja P, Vuori I. Effect of long-term unilateral activity on bone mineral density of female junior tennis players. *J Bone Miner Res* 1998;13:310–319. [PubMed: 9495526]
5. Poliachick SL, Agans SC, King KA, Gross TS, Srinivasan S. Rest alleviates tissue saturation due to repetitive mechanical loading. *J Bone Min Res* 2003;18:73.
6. Pruitt LA, Taaffe DR, Marcus R. Effects of a one-year high-intensity versus low-intensity resistance training program on bone mineral density in older women. *J Bone Miner Res* 1995;10:1788–1795. [PubMed: 8592957]
7. Riggs BL, Melton LJ. Involutional osteoporosis. *N Engl J Med* 1986;314:1676–1686. [PubMed: 3520321]
8. Robling AG, Burr DB, Turner CH. Recovery periods restore mechanosensitivity to dynamically loaded bone. *J Exp Biol* 2001;204:3389–3399. [PubMed: 11606612]
9. Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. *J Bone Joint Surg [Am]* 1984;66:397–402.
10. Srinivasan S, Gross TS. Canalicular fluid flow induced by bending of a long bone. *Med Eng Phys* 2000;22:127–133. [PubMed: 10854966]
11. Srinivasan S, Weimer DA, Agans SC, Bain SD, Gross TS. Low-magnitude mechanical loading becomes osteogenic when rest is inserted between each load cycle. *J Bone Miner Res* 2002;17:1613–1620. [PubMed: 12211431]
12. Strogatz SH. Exploring complex networks. *Nature* 2001;410:268–276. [PubMed: 11258382]
13. Turner CH, Forwood MR, Rho JY, Yoshikawa T. Mechanical loading thresholds for lamellar and woven bone formation. *J Bone Miner Res* 1994;9:87–97. [PubMed: 8154314]
14. Umemura Y, Sogo N, Honda A. Effects of intervals between jumps or bouts on osteogenic response to loading. *J Appl Physiol* 2002;93:1345–1348. [PubMed: 12235034]
15. Witzke KA, Snow CM. Effects of plyometric jump training on bone mass in adolescent girls. *Med Sci Sports Exerc* 2000;32:1051–1057. [PubMed: 10862529]

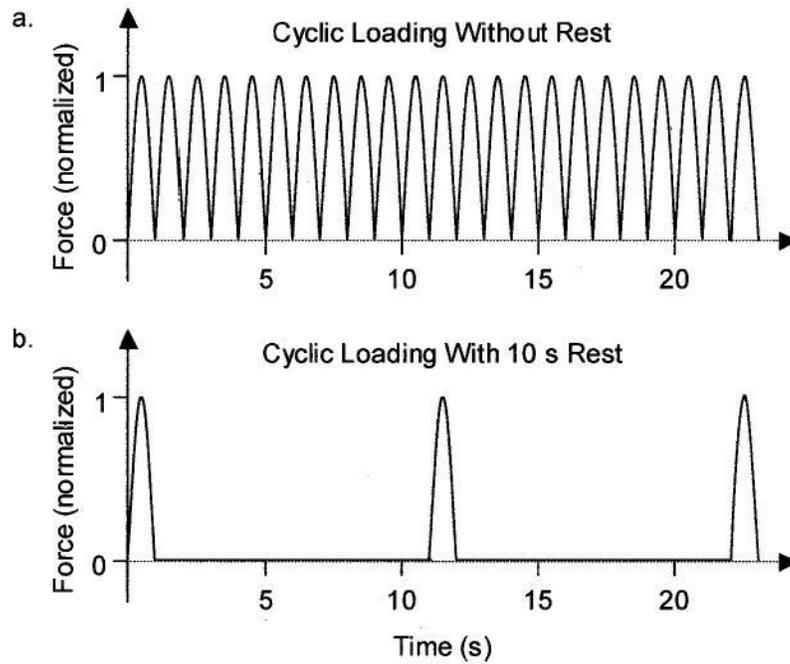


Figure 1. Schematic of cyclic and rest-inserted loading. Cyclic loading without rest at a 1-Hz frequency results in 23 load cycles within the first 23 s of the regimen. Inserting 10 s of rest between each load cycle results in three load cycles in the first 23 s. The load cycle is identical for both cyclic and rest-inserted loading.

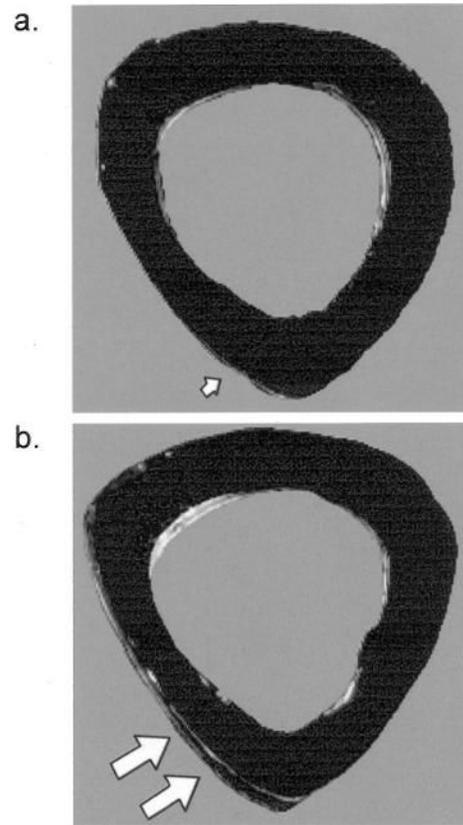


Figure 2.

Composite fluorescent micrographs of the mouse tibia mid-shaft illustrate (A) minimal periosteal response to a low-magnitude 3-wk cyclic loading regimen (100 cpd, 3 d-wk⁻¹; calcein label noted by arrow) and (B) substantial periosteal new bone formation induced by a 3-wk (3 d-wk⁻¹) regimen with 10 s of rest inserted between only 10 load cycles per day (arrows). (Reprinted from Srinivasan, S., D. A. Weimer, S. C. Agans, S. D. Bain, and T. S. Gross. Low-magnitude mechanical loading becomes osteogenic when rest is inserted between each load cycle. *J. Bone Miner. Res.* 17:1613–1620, 2002. Copyright © 2002 American Society for Bone and Mineral Research. Used with permission.)

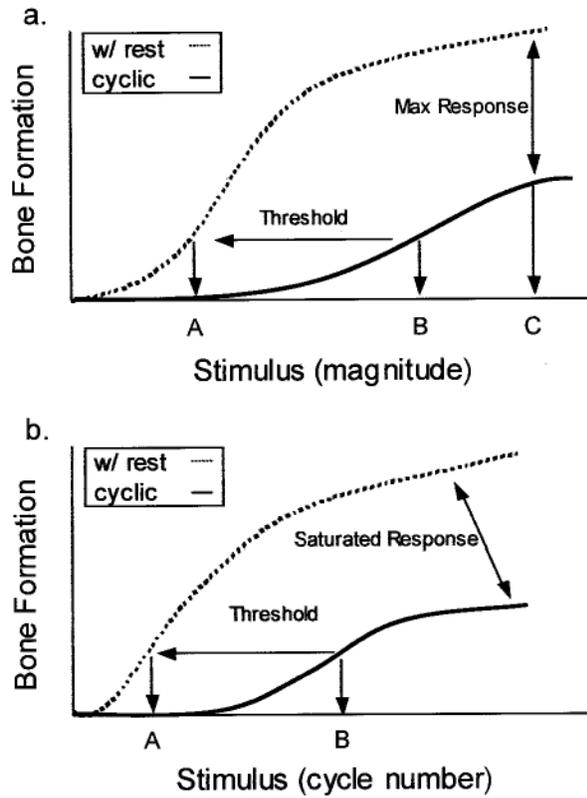


Figure 3.

Schematic summarizing recent studies exploring the ability of rest to alter the response of bone (as measured by bone formation) to increased load magnitude (a) or cycle number (b). When rest is inserted between each load cycle, the magnitude of stimulus required to surpass the threshold for elevated bone formation is reduced greatly compared with a cyclic loading regimen (A; A vs. B). As well, at any magnitude of loading, insertion of rest increases the amount of bone formation (*e.g.*, C). Once a certain cycle number is surpassed, further loading cycles do not yield an appreciable increase in bone formation (*i.e.*, saturation has occurred). (B) When rest is inserted, substantially fewer load cycles are required to precipitate a significant bone formation response (A vs. B). As well, at cycle numbers associated with saturation with cyclic loading, the bone formation response is increased greatly by the same number of cycles of rest-inserted loading (C).

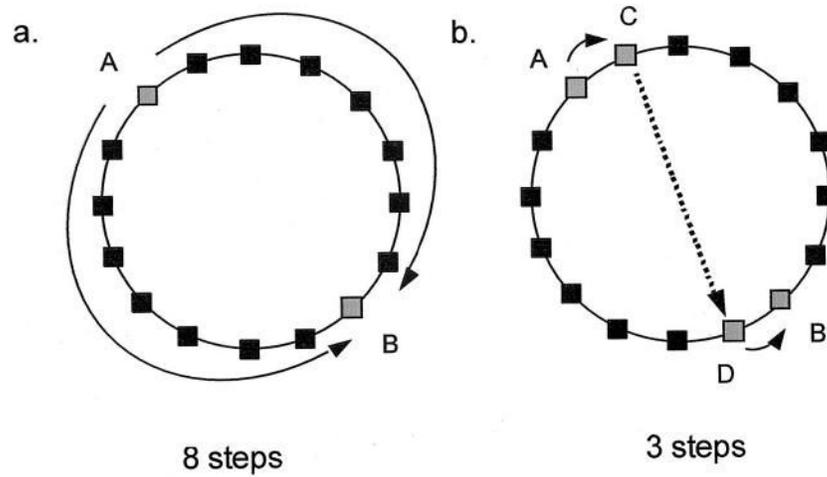


Figure 4. Schematic illustrating enhanced signaling of a small world network. In a nonsmall world network (a), a signal from point A to point B requires eight steps through adjacent neighbors. The addition of one small world network short cut (point C to point D) would enable communication to be reduced to three steps, thereby greatly improving signal transmission from point A to point B (b).

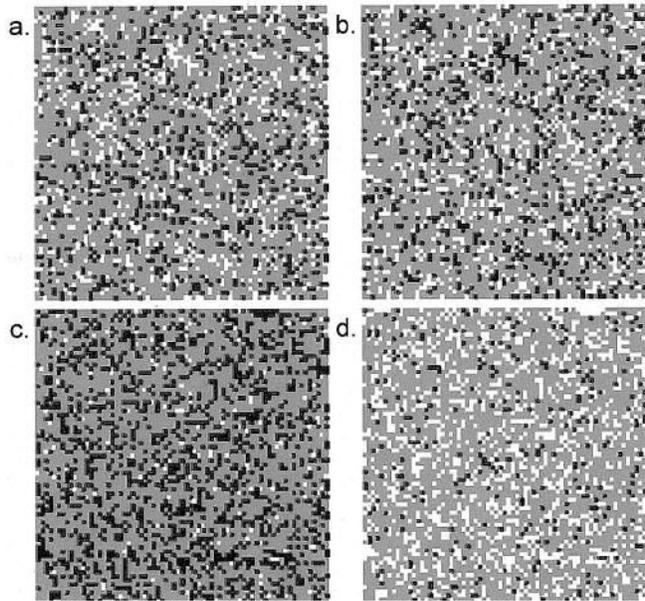


Figure 5.

Contrasting population dynamics of a group of 2000 osteocytes exposed to the equivalent of either cyclic loading (a and b) or rest-inserted loading (15 s rest; c and d). Active osteocytes are white; inactive osteocytes are black. Cyclic loading did not influence cell synchronization, because 50% of the population were either active or inactive at any one point in time. In contrast, exposure to rest-inserted loading rapidly synchronized cells, with up to 90% of osteocytes simultaneously active (or inactive) at any one point in time.