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Review Article

Hylonome

One mechanostat or many? Modifications of the site-specific response of bone to mechanical loading by nature and nurture

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Abstract

The concept of the mechanostat was not new in 1983, when Harold Frost coined the term to describe a mechanism by which bone responded to habitual exercise and changes in loading with structurally appropriate alterations in bone architecture. However, the word "mechanostat" has a meaning that is immediately apparent, and its adoption has led to a much wider appreciation of the process of functional adaptation by other scientists than those whose primary research focus is in the biology of adaptation. One problem exists though: it is widely thought that in a single individual, there is a setting for the mechanostat, just as a single thermostat might set the temperature for a whole house, and this is reflected in the idea that bones throughout the skeleton require a specific strain magnitude for maintenance. Increases in loading above that threshold are expected to induce bone formation and a stiffer structure that then experiences again the habitual strain magnitude. Reductions in strain magnitude supposedly induce resorption to reduce tissue mass and architectural properties so that the lower loading restores habitual strain magnitude. That widely held belief of a single unifying number of strain is fundamentally flawed. The purpose of this article is to explain the real basis of the mechanostat; that the skeleton responds to a complex strain stimulus, made up of numerous different parameters, of which peak magnitude is only one, and that the strain stimulus is different in different parts of the skeleton, so there is no universal number to describe a tissue strain magnitude that underlies the mechanostat's setting. Furthermore, males and females have different responses to loading, and those responses change in response to many factors including genetic constitution, age, concomitant disease, nutrient availability, and exposure to drugs or biochemicals. In summary then, there is not a single mechanostat controlling the skeleton of each of us. At a fundamental tissue level, small functional units of bone each have their own multifactorial threshold target strain stimuli for a given set of dynamic modifying influences. Understanding the biology behind the way that each of these mechanostats functions independently is likely to have pervasive consequences on our ability to control bone mass by manipulation of loading, either directly through different exercise regimens, or in a targeted manner using tailored site and individual specific pharmaceuticals.

Keywords: Bone, Loading, Exercise, Strain, Osteoporosis

While the bones of the skeleton have had many functions ascribed to them, it is unarguable that the one that dominates their size, shape, structure and material properties is the need to support loads. The mechanical function of the skeleton provides support and protection for the vital soft tissues essential for the immediate maintenance of life (the central nervous and cardiovascular systems), and a rigid structure that allows the contractile properties of muscle to act and result in locomotion for food gathering, reproduction and other less pressing requirements of life.

Since the mechanical needs of locomotion and weight-bearing differ in different individuals, it is not surprising that the mass of bone and its organisation differs in individuals with different activities[1-3]. However, since it is not known at the time of intrauterine development or even growth and adult life what activities the skeleton of any individual will be required to perform in the future, it is also not surprising to find that there is a dynamic regulatory system in bone that

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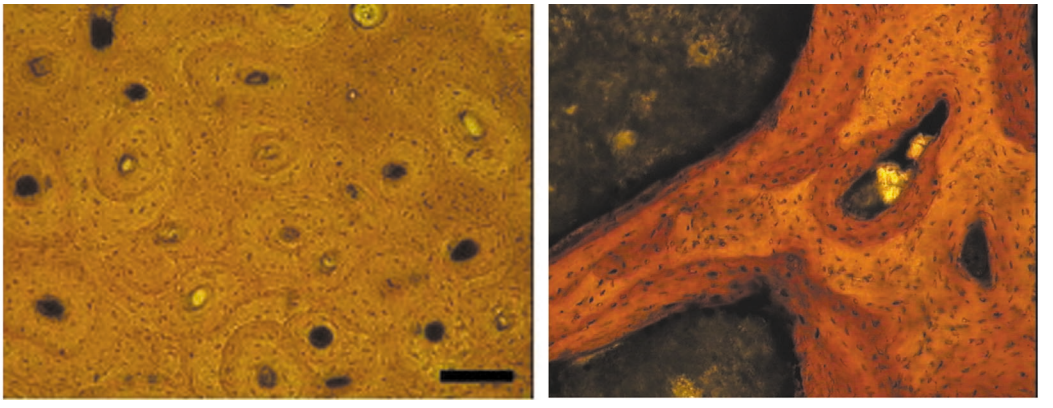

Figure 1. Sections of the tibial cortex (left) and metaphyseal trabeculae (right) of a mezozoic dinosaur (the iguanodon) approximately 170M years old. Recognisable features highly reminiscent of the adaptive response of modern bone to mechanical loading include the clear evidence of Haversian remodelling of the cortex, (left) and reversal lines in the trabeculae (right). (Scale bars 100 micrometres).

tunes its strength by alterations in the amount and orientation of bone present at each location in the skeleton.

This regulatory system provides the mechanism for functional adaptation in the skeleton, so that the mass of load-bearing tissue we carry around is not so excessive as to waste energy in growth, maintenance and use. However, it must be sufficiently strong to provide a safety margin that protects against fracture in response to unlikely but occasional high loading events such as those experienced in falls and impacts[4]. It is possible to hypothesise that the adaptive mechanism arose as a result of evolutionary pressures in very distant times, when there were animals with genetically massive skeletons, resistant to all but the most extreme traumatic insults, but unable to evade more nimble predators or to capture prey. The development of animals with optimal (i.e., not excessively massive) skeletons would permit better survival for the species even if the individual's resistance to trauma were reduced. It seems likely that this evolutionary process was advanced at early stages of vertebrate evolution. In sections of fossil dinosaur bones from over 100 million years ago, it is possible to recognise the same organised trabecular arcades that led to the foundation of understanding of functional adaptation – Wolff's Law[5]. High magnification pictures of dinosaur bone also reveal features such as targeted Haversian remodelling that are entirely consistent with the same highly orchestrated control of bone architecture that underlies the adaptive mechanism as we understand it today (Figure 1).

The full details of the events and discoveries that led to Wolff's Law are beyond the scope of this article. However, it is known that Galileo considered the relationship between bone dimensions and body size when he wrote in the early 15th century that animal's "bones must consequently also disproportionately increase in girth, adapting to load-bearing rather than mere size" (translation of Galileo[6]). It is not known whether Galileo believed that this adaptation was merely a scaling phenomenon, or whether it occurred during each individual's life. However, a major advance in understanding in the area occurred in the 18th century when von Meyer, an anatomist, and Culmann, an engineer, compared pictures of the trabecular arrangements in the human femur with calculated stress patterns in engineered structures. Their work came to the attention of Roux, who first used a term implying functional adaptation, before Wolff formulated his law linking form and function dynamically. This "law" translates as "Every change in the form and function of a bone or their function alone is followed by certain definite secondary alterations in their internal architecture, and equally definite secondary alterations in their external conformation in accordance with mathematical laws," and this could imply that bone form was related to function during development, but not as a dynamic self regulating system. However, the concept of functional adaptation, as first stated by Roux, became more associated with Wolff in later years. (The work of von Meyer, Culmann, Roux and Wolff is cited from the translation and review by Roesler[7]).

Wolff's "law" and the process of functional adaptation suggests responsiveness to increased loads with stronger, more mechanically competent bones, but its natural corollary is that reductions in loading or usage lead to bone loss. Without such a negative aspect to the feedback system, gains in bone that were no longer appropriate would not be reduced to a new optimal level for a lower level of habitual activity.

This dynamic balance between form and function raises a question – what is the variable to which the skeleton's bone forming and bone resorbing cells respond? This question is still the source of debate as strongly-held views exist over the role of interstitial fluid flow or direct cellular strain in controlling adaptive responses. However, that discussion is irrelevant here since those are the consequences of tissue deformation or strain, which is what occurs when bone is

loaded. Strain, or deformation, is the ratio of change in length divided by original length, and is therefore expressed in absolute terms with no units, or as a percentage (Figure 2). (It is important to stress that the widespread use of the Greek Epsilon to indicate strain x10^6 does not confer units onto strain).

The role of tissue strain as a controlling influence in bone arose primarily from the work of Lanyon beginning in the 1970s, after the first pioneering but relatively unsophisticated *in vivo* bone strain gauge experiments of Gaynor Evans[8]. Lanyon and his co-workers made the first meaningful assessments of strain in bone *in vivo*[9-11] and as a result of the use of these techniques by others as well, it was soon discovered that the peak strain magnitudes in long bones were broadly similar in long bones of a wide range of species and in the range of 0.002 - 0.003[12]. This work led to the idea that strain magnitude was the target to which the adaptive response was aimed (Figure 3). While that is an oversimplification, the measurements of strain did show that bones did not remodel to minimise or abolish strains as previously thought[13]. In fact, it appears that bone curvature is induced and maintained not to minimise strain, but to allow activity to induce predictable strain directions in order to allow more strategic reinforcement of individual elements of the skeleton during adaptation than would be possible with a column of bone loaded purely in axial compression by usage[14-16].

The apparent universality of peak long bone strains has led to a widely held misconception that those strain magnitudes are the same in all bones, and further, that there is therefore the same strain numerical threshold for changes due to overload (>1500 microstrain) or disuse (<1000 microstrain) of any bone or bone cell. That seems to be very unlikely in that the strains experienced in different regions of a single bone vary considerably, and that there are more factors in a strain event that could be important to bone than merely the magnitude of the deformation. While there is no doubt that peak strain magnitude has a direct effect on the effectiveness of an exercise regimen in experimental animals[17] and humans[18] it is also clear that additional variables are important. The rate of strain change and its direction, as well as the number of cycles/the duration of loading, the frequency of repetition, the dwell times (hold or rest times during an individual cycle) all appear to have effects on the osteogenic nature of a loading[19-21].

Specifically, strains with high rates are profoundly more potent stimuli than low rate strains. Strains with rates of less that 4,000 microstrain per second have been shown experimentally to be ineffective at inducing formation, while those near to or above the high rate strains experienced during footfall at high speeds, or when landing from jumps (in the range around of 1-200,000 microstrain per second) are highly osteogenic regimen[22-24]. Interestingly, the direction of strain may be less important. In experimental animals, strain waveforms with high rate application of compressive strains (>100,000 microstrain per second) but slow release (4,000 microstrain per second) were associated with bone formation that was indistinguishable from animals loaded with the opposite waveform of slow rate load and high rate unloading[25]. The effect of frequency is harder to distinguish, as the experiments performed have for the most part failed to control for alteration of strain rates with higher frequency loading[24]. However, there appears to be an inverse relationship between strain frequency and magnitude as Rubin's work has shown that there are osteogenic effects of loading with peak strain magnitudes of single numbers of microstrain at frequencies above 30 Hz[26]. The effect of parameters other than peak strain magnitude may explain the observations that in humans, loading that induces unusual distributions of strain, even of a customarily experienced magnitude, alter bone mass.

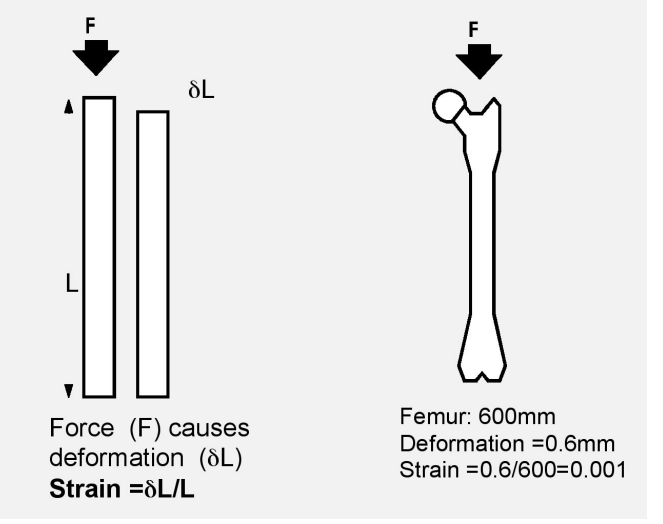

Figure 2. The effect of loading on bone is deformation or strain. As strain is a ratio, it has no units.

Finally, there are three observations that are connected with the way that different forms of loading or exercise affect the skeleton. First, the number of cycles of loading applied to bones appears to be relatively unimportant once some threshold level has been reached. The first study to demonstrate this showed that in experimental animals, 36 cycles of loading per day (occupying ~2 minutes in each 24-hour period) induced bone formation that could not be increased by greater numbers of cycles of the same magnitude and waveform[27]. Secondly, additional osteogenic benefits can be gained by inserting rest periods between individual load cycles[21]. Rest periods of less than 9 seconds are not effective in rodents, and periods of over 15 seconds induce no greater benefit than 15 seconds. This is a phenomenon that is not currently fully explained, but it has been hypothesised that it may be due to a lag in the flow of fluid through the interstices of bone that is induced by loading and may play a role in the mechanotransduction process[28]. Finally, it has been shown that the division of a saturating number of load cycles (360)

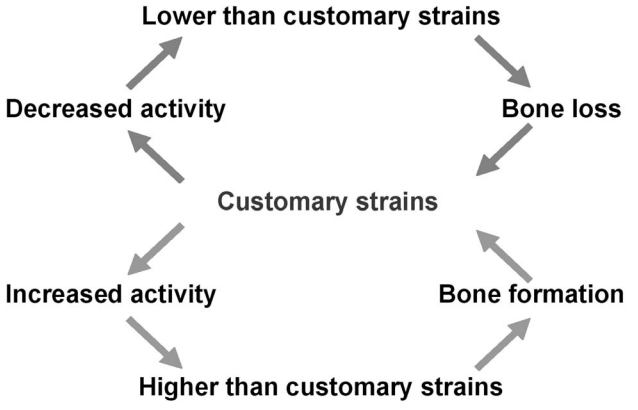

Figure 3. Putative regulation of bone mass/architecture by peak strain magnitude. In a given individual, habitual activity leads to customary strains, which are sufficient to resist the "resorptive" demands placed on the skeleton by systemic influences. Increased activity leads to greater deformation i.e., higher strains, engendering a drive to increase bone mass or adjust architecture to resist the new levels of load more optimally. These changes lead to the resumption of customary strains as a result of the higher levels of load. Reductions in activity reduce strains, and the effect of this is to permit bone loss or architectural modifications that lead to the reinstatement of customary strains by the effect of the reduced level of loading on the less massive structure.

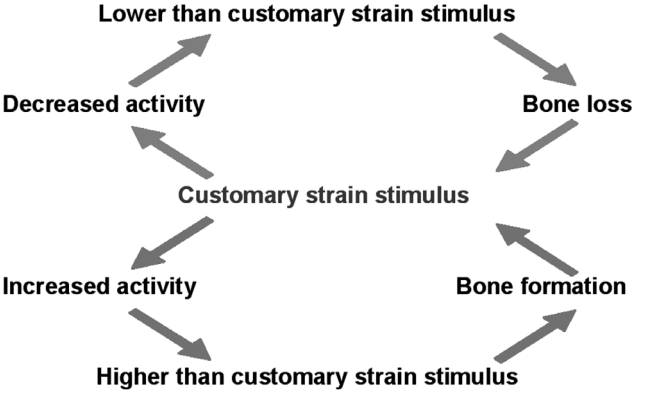

Figure 4. Modified schematic to illustrate the regulation of bone mass/architecture by strain. Instead of a numerical peak strain magnitude, the customary strain stimulus (CSS) comprises an appropriate match of magnitude, rate, frequency, duration rest periods and previous loading history. Mismatch between experienced strain stimulus (higher or lower) and CSS leads to adaptive changes in bone mass and architecture.

into several shorter bouts separated by rest periods (2x180, 3x120, 4x90) increases the bone formation response *in vivo*[20].

These findings have one unifying principle. Each suggests that at some level, bone retains the effect of loading events, and the information stored is used to modify subsequent events. Rapid repetition of single load cycles appears to cause desensitisation to immediate subsequent events (in the next 9 seconds), while once a saturating number of cycles has been applied, the "memory" system is not stimulated further within the same bout of loading. However, a rest period of 1-4 hours appears to allow for the resensitising of the sensing system to cause potentiated effects. Our discovery of synapse-like communication between bone cells, involving glutamate signalling[29,30], and a mechanism in osteoblasts with strong similarities to the Long-Term Potentiation (LTP) that underlies memory formation in the CNS may be linked to these phenomena[31].

However, the clear effects of different loading parameters than peak strain magnitude on bone lead to the concept that a better descriptor of the biological target of loading is not a customary bone strain (i.e., magnitude) but a customary bone strain stimulus (CSS), that encompasses not only magnitude, but also rate, frequency, rest periods, subsequent loading events, and to some extent duration or number of cycles of loading and their timing of application as one or more events per day (Figure 4).

However, even the idea of a CSS is a gross oversimplification. Different bones require different safety factors, so that the ratio of habitual to maximum strain before failure cannot be the same throughout the skeleton, whereas the breaking strain for almost all bones is in the vicinity of 8,000 microstrain. In the skull, peak strain magnitudes and rates are very low indeed, and never exceed 10% of those that are habitual in the tibia[32]. If the tibia was to experience regularly, only the peak magnitudes and rates of strain to which the skull was rarely exposed, then there would be profound bone loss due to disuse. It appears that between the strains in the skull and those in the long bones there is a continuum of different customary strain stimulus where, for example, strain magnitudes and rates in the ribs are lower than long bones, but higher than those in the skull (Skerry, unpublished data). This suggests that there is some form of positional cue that is responsible for the "set point" threshold for mechanical loading *at each location in the skeleton*, so that architecture is optimised to habitual strains experienced for each of those locations. That implies that a *site-specific* customary strain stimulus (SSCSS) exists for each site within the skeleton, and it is that combination of different strain parameters to which the modelling and remodelling processes are directed.

However, even SSCSS appears to become an oversimplification when the data on other influences on the response of bone to load are considered. It is known that responses in animals are greater during growth than in older individuals[33-34], and that males have greater responses to load than females[35]. As Harold Frost was a great creator of acronyms, it is tempting to use ARSSSCSS for Age Related Sex and Site Specific, Customary Strain Stimulus, but even this does not tell the whole story. Circulating and local biochemical influences such as estrogen, PTH, cytokines and their various inhibitors and soluble receptors have the ability to influence how bone responds to loading, as do pharmacological agents[36-37]. Final-

ly, it is clear that an individual's genotype influences bone strength, and this could be a direct effect on strain sensing mechanisms or by effects on other regulators of them[38,39]. This would lead to an acronym of GRPBMASSSCSS - Genetically Regulated Pharmacologically and Biochemically Modified Age, Sex and Site Specific Customary Strain Stimulus! It is likely that even Harold Frost would have objected to this, and perhaps instead of GRPBMASSSCSS it is more appropriate to think that this is really what the term "mechanostat" really means. In each one of us, at each location in the skeleton, subject to all local, systemic and external influences and those of age and genetics, our bones perceive their total mechanical environment and compare it with what is expected for the specific habitual circumstances in order to determine whether bone architecture is appropriate, and then initiate an adaptive response.

I have deliberately not included the effects of nutrients in this concept of the controlling influences on adaptation. That is because while it is necessary to have sufficient building materials to create bone, the fact that they are available does not *control* adaptation. Harold used the analogy that the amount of fuel in a car's tank influenced whether it could run, but had *no* influence on the direction of travel. Nutrition is a permissive influence for bone adaptation but not a controlling one.

From this it seems clear that there is not a single mechanostat even in each of us, but that our skeletons contain vast numbers of small units of bone, each of which has its own dynamically regulated mechanostat. In summary then, there is not one mechanostat in each of our skeletons but many of them.

Personal note

This article is part of a tribute to the life of Harold Frost, and I do have what I think is a unique personal memory of him that I would share even though it has more to do with Harold as a person than anything to do with his work.

Harold was an intimidating person and on several occasions I was exposed to the more forceful side of his personality. However, I do know that underneath all of the gruff self-confessed "feisty dinosaur" exterior, there was a charming, friendly and down-to-earth man.

In 1995, Harold made his first trip to the UK, and gave a seminar at the School of Veterinary Science at Bristol University. I invited him to stay with me for a few nights while he was in Bristol. Although my memories include several late nights discussing bone biology, the most memorable event for me was when I came downstairs one morning to find Harold deeply engrossed in discussions with my (then) 11-year-old son Giles. What was the topic – bones? Homework? Sport? None of these. As I came down, Harold was saying to Giles as they each held out a Swiss Army penknife, "No mine is better because it has two screwdrivers", to which Giles replied forcefully "But you don't have the spike for taking stones out of horses hooves". To see this eminent and until then, still occasionally intimidating person engaged in discussions of penknife blades with an 11-year-old boy changed my view of Harold for ever, and he was never intimidating again!

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