Effect of Stochastic Resonance on Bone Loss in Osteopenic Conditions

Marco Rusconi,[1,2] Alexey Zaikin,[1,3] Norbert Marwan,[1] and Jürgen Kurths[1]

[1]*Institute of Physics, University of Potsdam, 14415 Potsdam, Germany*

[2]*Max Planck Institute of Colloids and Interfaces, Dept. of Theory and Bio-Systems, Science Park Golm, 14424 Potsdam, Germany*

[3]*Departments of Mathematical & Biological sciences, University of Essex, CO4 3SQ Colchester, United Kingdom*

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We investigate the effect of noise on the remodelling process of the inner spongy part of the trabecular bone. Recently, a new noise-induced phenomenon in bone formation has been reported experimentally. We propose the first conceptual model for this finding, explained by the stochastic resonance effect, and provide a theoretical basis for the development of new countermeasures for bone degeneration in long space flights, which currently has dramatic consequences on return to standard gravity. These results may also be applicable on Earth for patients under osteopenic conditions.

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Bone is a continuously regenerated living tissue [1]. According to the Wolff law [2], the bone is cyclically resorbed and created to be rejuvinated and to achieve optimal adaptation to the external mechanical environment [3]. This evolution is the result of the balanced action between osteoblasts (formation cells) and osteoclasts (resorber cells). It has been suggested that while the osteoclasts remove material everywhere, the osteoblasts form new material only if the external stimulus is larger than some threshold [4]. Under microgravity conditions, the reduced mechanical load caused by hypodynamia (decreased forces) and hypokinesia (decreased mobility) results in an insufficient stimulus for initiating osteoblast activity. This leads to a dominant resorption and, hence, to a rapid bone loss [5]. For instance, without countermeasures during a 3 yr. long space flight, such as a Mars mission, an astronaut would lose as much as 50% of her or his preflight bone mass [6]. Recent experiments have demonstrated that the increase in bone creation rate due to the application of low frequency mechanical stimuli can be enhanced by additional noise application [7]. This has been attributed to the effect of stochastic resonance (SR) [8] on bone remodelling [7]. Because of its multidisciplinary applications, SR has attracted considerable attention in the last years. The main characteristic of SR is the optimization of weak signal processing in a nonlinear system by the action of an external noise with an appropriate amplitude. Such a behavior has been found in a large variety of biological systems: in human balance control [9], sensory systems [10], rat sensory neurons [11], cricket cercal sensory system [12], and in the human brain [13].

We now introduce a conceptual model showing that SR can optimize the bone remodelling process. For this goal, the mechanical noisy stimulus is related to the stochastic nature of the activation of osteoblasts and osteoclasts through the connection between bone remodelling and external mechanical stimuli (the Wolff law). We will show that there is a certain noise amplitude for which the bone adapts optimally to the external stimuli and for which, under microgravity conditions, a balanced action of osteoblasts and osteoclasts can be maintained.

The remodelling process we propose involves the following assumptions: (1) The bone is considered to be a dynamical system responding to external mechanical stimuli. As demonstrated in previous works [14–16], two signals with a characteristic time scale are measured during normal daily activity: a low frequency large amplitude, $L(t)$, and a broad band signal, $\mathbf{H}(t)$. Because of the broad band nature of $\mathbf{H}(t)$, we regard it as white [7] or pink [16] noise $\xi_{ij}(t)$ (e.g., generated by random muscle contractions) while $L(t)$ is presumably connected to the gravitational field representing load bearing [15]. (2) During remodelling, according to the Wolff law, the trabecular bone evolves in order to achieve an optimal microarchitecture, given by the matrix $\mathbf{X}^{\rm opt}(t)$. Only under well-known fixed-load conditions it is possible to predict a general shape of $\mathbf{X}^{\rm opt}(t)$ [17]: trabeculae of longitudinal axis parallel to the direction of the applied load are thicker than perpendicular ones. In this sense, if the bone has not yet achieved $\mathbf{X}^{\rm opt}(t)$, it locally adapts by creating new material in the parallel trabeculae and removing material from the orthogonal trabeculae. Since we are interested in proposing a general model for SR in bone remodelling and not in investigating the relations between external conditions and optimal structure, we assume here that $\mathbf{X}^{\rm opt}(t)$ is a predefined function of $L(t)$: given load conditions correspond to specific $\mathbf{X}^{\rm opt}(t)$. This assumption allows us to consider more general aspects of bone remodelling. On one hand, $\mathbf{X}^{\rm opt}$ can represent the optimal bone local structure. On the other hand, it can describe, e.g., the complete set of optimal biochemical conditions that the bone fulfills in order to adapt itself to the local environment. In this sense, we propose a very general interpretation of the Wolff law. (3) The local processes of bone creation and resorption are stochastic with probabilities $F_{\rm cr}$, $F_{\rm r}$ and an activation threshold $T_{\rm cr}$. The new bone formation can start with probability $F_{\rm cr}$ only if the external mechanical stimulus exceeds the fixed $T_{\rm cr}$ [18]. In contrast, the resorption does not depend on the external stimulus, and it proceeds with probability F_r, which in general is different from F_{cr} [19].

We apply a 2D version of the model to a regular structure representing a typical configuration in the trabecular bone (Fig. 1). An extension to 3D as well as the application to modern high-resolution 3D computer tomography scans can be treated in the same manner. Following these assumptions, the evolution of the local (2D) structure matrix $X_{ij}(t)$ can be expressed as

$$X_{ij}(t+\Delta t) = f[X_{ij}(t), X_{ij}^{\mathrm{opt}}(t), H_{ij}(t), F_{\mathrm{cr}}, F_{\mathrm{r}}] \quad (1)$$

$$X_{ij}(t=0) = X_{ij}^{0} \quad (2)$$

where i, j are spatial coordinates, $\mathbf{X}^{\mathrm{opt}}(t)$ and $\mathbf{H}(t)$ stand for the external stimuli, and $f(\cdot)$ is a function defined below. For simplicity, in our modelling approach, we choose $X_{ij}(t)$ to be binary: the values 0 (black) and 1 (white) represent marrow and bone, respectively (Fig. 1). The Wolff law, i.e., the evolution of the bone toward the optimal structure, is represented for all i and j by the condition of the formation $S_{ij} = \beta\Theta[X_{ij}^{\mathrm{opt}}(t) - X_{ij}(t)] > T_{\mathrm{cr}}$, where $\Theta(\cdot)$ is the Heaviside function $[\Theta(x \le 0) = 0$ and $\Theta(x > 0) = 1]$. Note that the argument of the Θ-function can be only ± 1 or 0, with $+1$ corresponding to the necessity of formation. The coefficient β selects the standard or microgravity environment: $\beta = 1$ corresponds to standard gravity on Earth, while $\beta < 1$ corresponds to microgravity. To include the influence of $\mathbf{H}(t)$ on the bone dynamics, this condition is modified as $S_{ij} + H_{ij}(t) > T_{\mathrm{cr}}$.

The external low frequency stimulus determines the evolution of $\mathbf{X}^{\mathrm{opt}}(t)$. This structure can be found by using finite-element methods [20] or force flow algorithms [21] and is considered here to be a predefined function of $L(t)$. Possible transformations that can occur to $\mathbf{X}^{\mathrm{opt}}(t)$ include rotation, expansion-contraction, and translation.

Following the recent ideas of evolutionary adaptation of biological self-organization to a noisy environment [22], we can assume that, generally, bone structure optimally adapts to these external periodic and noisy signals. In a

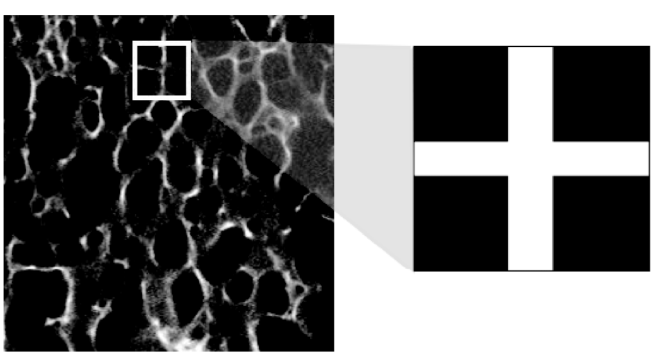

FIG. 1. Detail of human vertebral trabecular bone (left) and simplified structure as used in our model (right); $\Delta x \simeq 11$ μm corresponding to a trabecular diameter of 200 μm [30].

microgravity environment, however, the superposition of $L(t)$ and $\mathbf{H}(t)$ gives a combined stimulus below the threshold needed to activate the bone creation $S_{ij} + H_{ij}(t) < T_{\mathrm{cr}}$. As a consequence, the inactivity of the osteoblasts leads to resorption dominance and hence to increased bone loss (Fig. 2). A promising strategy to stimulate bone creation lies in increasing the noise amplitude α so that $H_{ij} = \alpha\xi_{ij}(t)$, where ξ_{ij} is white noise in space and time or white noise in space and pink noise in time. In this way, the externally modified stimulus will exceed the threshold and in a similar manner as found in experiments, the creation of new bone is activated [7]. To test our model, we introduce a cellular automatonlike algorithm (CA) [23] in which geometric, mechanical, and stochastic conditions are implemented. The stochastic condition, the main difference between our model and the standard CA, assures that the remodelling occurs only with certain activation frequencies (F_r and F_{cr}), in general different for resorption and formation. In order to have only remodelling of the bone surface, two geometric conditions are chosen. On one hand, a bone pixel $[X_{ij}(t) = 1]$ is eligible for resorption only if at least three connected surrounding pixels are marrow. On the other hand, a marrow pixel $[X_{ij}(t) = 0]$ can be a site of formation if at least two connected surrounding pixels are bone. Different geometric conditions were tested and the SR effect does not substantially depend on the choice made. Once fixed, the initial matrices $\mathbf{X}(0)$, $\mathbf{X}^{\mathrm{opt}}(0)$ (Fig. 1), the activation frequencies and the threshold T_{cr}, $\mathbf{X}(t)$ is iteratively remodeled. At each time step, the geometric, stochastic, and mechanical conditions are evaluated, and if each of them is fulfilled, the remodelling takes place.

In our simulations, the bone mass adaptation during an initial period of standard gravity ($\beta = 1$) is followed by three years of microgravity in which the noise amplitude can be modified. In order to mimic the microgravity environment, the dynamics of the optimal structure $\mathbf{X}^{\mathrm{opt}}$ is not changed, and only the stimulus is reduced (white noise: $\beta = 0.2$; pink noise: $\beta = 0.3$). The transformations analyzed are: (a) a rotation around the center of the structure with an angle given by $\theta(t) = A\sin(\frac{2\pi}{T}t + \phi_0)$ where $T = 5$ years corresponding to the suggested turnover time for bone remodelling [24]. A time step Δt is approximately equal to 1 d, $A = 90°$ and $\phi_0 = -25°$; (b) a translation along the horizontal axis by the same factor θ; and (c) a periodic expansion-contraction around the vertical axis again by the same factor θ. The first two transformations model a periodic variation of the direction of the load applied to the whole structure while the last one corresponds to a variation of the load intensity. For the rather low frequencies considered, the influence of the initial conditions is negligible. We emphasize that for SR, the periodicity of the signal is not required. As demonstrated, e.g., in [25], aperiodic stochastic resonance can be found with a signal of any form. Our choice of a periodic stimulus is motivated by the more physiological nature of such a stimulus [7,14–16].

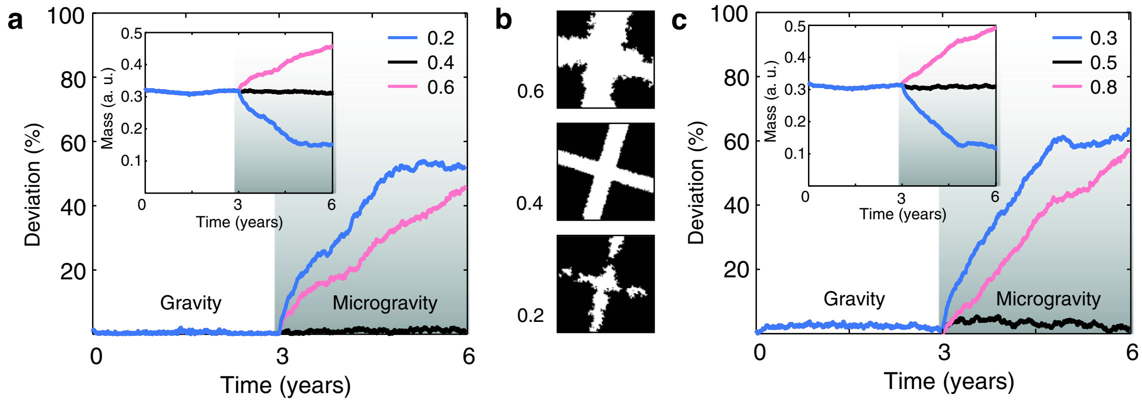

FIG. 2 (color online). (a) Time evolution of the mean deviation of the bone from the optimal structure $D(t)$ as well as bone mass density (inset) for white noise. Standard gravity is followed by three years of space flight (gray shading), during which the noise levels above ($\alpha_{max} = 0.6$ a.u.) or below ($\alpha_e = 0.2$ a.u., corresponding to earth conditions) the resonance amplitude ($\alpha_r = 0.4$ a.u.) cause higher deviations from optimal bone structure. For α_e, the mass decays to about 50% of its initial value, for α_r the mass is conserved, and for $\alpha > \alpha_r$, the noise level is so high that the system cannot follow the low amplitude signal and adapts through uncontrollable growth. (b) Trabecular structure snapshots at the end of the microgravity period, the value of α is shown. (c) Simulation results using pink noise. $\alpha_r = 0.5$ a.u. in this case. Threshold $T_{cr} = 1$ in all simulations.

We discuss the rotation case in details. The cases of translation and expansion reveal analogous results. For a given amplitude α, the bone adapts in different ways. During the period of microgravity, if α corresponds to the optimal noise amplitude on Earth α_e, the mass decays with a measured rate of 2.2–2.7% monthly [6], leading, during the three years of microgravity simulated, to a net loss around 50% of the total mass. Increasing the noise amplitude, for both cases white and pink, we observe a corresponding increase of bone mass gain (Fig. 2 insets). This behavior can be quantified by the standardized mean deviation $MD(\alpha)$ between the optimal and current structure

$$MD(\alpha) = \left\langle \frac{\langle | X_{ij}^{\mathrm{opt}}(t) - X_{ij}(t) | \rangle_{ij}}{\langle X_{ij}^{\mathrm{opt}}(t) \rangle_{ij}} \right\rangle_t \tag{3}$$

where $\langle \cdot \rangle_t$ and $\langle \cdot \rangle_{ij}$ denote the time and space averages, respectively. This measure shows a minimum for the value $\alpha_r = 0.4$ a.u. [Fig. 3(a)], which clearly indicates the presence of a threshold SR effect: an appropriate amount of noise provides the most effective bone adaptation with respect to the given external conditions. For this value of α, the mean deviation $D(t) = \langle |X_{ij}^{\mathrm{opt}}(t) - X_{ij}(t)| \rangle_{ij}$ as a function of time is also minimal [Fig. 2(a)]. This behavior confirms the presence of SR in the system. Simulation snapshots of the bone structure show the bone adaptation after the microgravity period for three noise conditions: with the amplitude of optimal adaptation in standard gravity $\alpha = \alpha_e$, with the optimal amplitude in microgravity $\alpha = \alpha_r$ and too high noise level $\alpha \gg \alpha_r$ [Fig. 2(b)]. If α is equal to the optimal value for standard gravity, the bone is strongly resorbed in microgravity conditions. For values of α considerably exceeding the resonance level, the bone adapts through an uncontrollable growth. Only for values close to resonance a homeostatic equilibrium between resorption and creation can be obtained that maintains a roughly constant mass density. The results presented here are obtained with activation frequencies for creation and resorption, respectively, equal to 0.9 and 0.1 a.u., [20]. The range of activation frequencies between 0 and 1 is chosen to provide the realistic turnover time. Simulations with different values of F_r and F_{cr} and with the other two transformations have been performed as well. The results

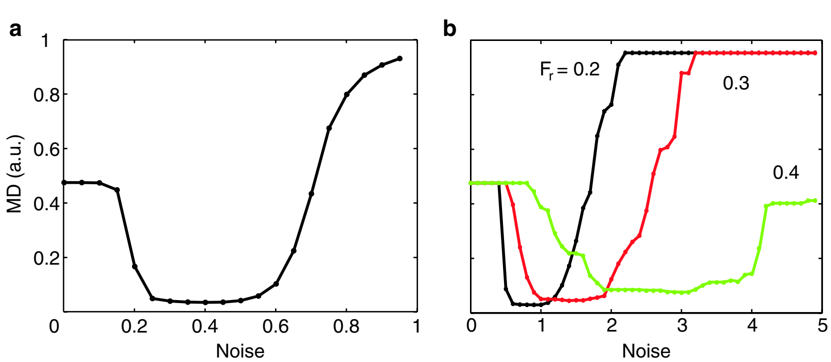

FIG. 3 (color online). (a) Standardized mean deviation $MD(\alpha)$ for white noise revealing an optimal adaptation only for a region around $\alpha_r = 0.4$ a.u., and, thus, indicating stochastic resonance. (b) Similar findings for pink noise; results for variation of the resorption probabilities F_r shown. Increase of F_r leads to a shift of α_r to larger values.

confirm the existence of SR in the model showing its robustness against the change of parameters. In [16], it was suggested that the oscillations in bone are better represented by pink noise. In [26], experimental data suggest that F_r increases during space flight. Our simulations show that the generalization to pink noise does not change substantially the effect of noise and in consequence, the optimal adaptation [Fig. 2(c)], whereas the increase of F_r leads only to a shift of α_r to larger values [Fig. 3(b)].

In conclusion, bone structure is the optimal adaptation to a mechanical noisy environment. A strategy to maintain a mass equilibrium and an optimal mechanical adaptation in "osteopenic conditions" is the modification of the external stimuli. We have shown how a superposition of external noise and periodic stimuli can mimic the Earth mechanical environment producing a constructive bone response and appreciably reducing the risk of crucial resorptive remodelling [27] and the resulting dramatic consequences [28]. The positive effect of noise can be useful for standard therapies of bone diseases based on the application of periodic vibrations [29]. The superposition of periodic and noisy stimulations with an appropriate amplitude may improve their efficiency, and supports, e.g., an increasing of the flight-time of astronauts or reducing the risk of more invasive therapies in osteoporotic patients on Earth. Any biological system has to coexist with noises of different nature (thermal, chemical, etc.). There are two fundamental strategies to achieve that aim: either the system acts to reduce the noise or to cooperate with it. SR is an example of making effective use of the noise presence. The findings of recent experiments provide evidence for such a bone adaptive response [7]. For these reasons, we emphasize the importance of including noise impact and SR in bone remodelling in order to obtain more realistic models.

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