Evaluating Daily Load Stimulus Formulas in Relating Bone Response to Exercise

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Abstract

Six formulas representing what is commonly referred to as "daily load stimulus" are identified, compared and tested in their ability to relate skeletal mechanical loading to bone maintenance and osteogenic response. Particular emphasis is placed on exercise- induced skeletal loading and whether or not the formulas can adequately capture the known experimental observations of saturation of continuous cyclic loading, rest insertion between repetitions (cycles), recovery of osteogenic potential following saturation, and multiple shorter bouts versus a single long bout of exercise. To evaluate the ability of the formulas to capture these characteristics, a set of exercise scenarios with type of exercise bout, specific duration, number of repetitions, and rest insertion between repetitions is defined. The daily load values obtained from the formulas for the loading conditions of the set of scenarios is illustrated. Not all of the formulas form estimates of daily load in units of stress or in terms of strain at a skeletal site due to the loading force from a specific exercise prescription. The comparative results show that none of the formulas are able to capture all of the experimentally observed characteristics of cyclic loading. However, the enhanced formula presented by Genc et al. does capture several characteristics of cyclic loading that the others do not, namely recovery of osteogenic potential and saturation. This could be a basis for further development of mathematical formulas that more adequately approximates the amount of daily stress at a skeletal site that contributes to bone adaptation.

Introduction

Quantifying the adaptive response of bones to loading in terms of a mechanical stimulus magnitude related to stress/strain from weight bearing activities is a modeling activity originated from studies by Carter et al. (1987) and Whalen et al. (1988). Commonly referred to as a Daily Load Stimulus (DLS), a stimulus expression was used in a computational simulation of a theory to determine the distribution of bone density in the adult proximal femur (Beaupre et al., 1990), and expressions were fit to experimental data in animal studies (Turner, 1998). Various versions have been developed and used for different research applications, such as the use of a stimulus magnitude formula to relate to the rate of fatigue damage accumulation and its influence on bone remodeling activation (Hazelwood et al. 2001, Nyman et al. 2004, and Hazelwood and Castillo 2007). Other examples include the use of a stimulus formula for estimating and comparing the osteogenic response of bone to different amounts of daily activity (Genc et al., 2009), as well as to estimate the effectiveness of daily exercise induced loading as countermeasure to spaceflight bone loss (Cavanagh et al., 2010). The latter application is used as a primary motivation for this perspective.

Under the conditions of microgravity, astronauts lose bone mass at a rate of 1 to 2 percent a month, particularly in the lower extremities such as the proximal femur (Lang et al., 2004, Buckley, 2006; LeBlanc et al., 2007). The most commonly used countermeasure against bone loss in microgravity has been a prescribed exercise regime (Layne and Forth, 2008). However, data has shown that existing measures of exercise do not completely eliminate bone loss in long duration, 4 to 6 months, spaceflight (Lang et al., 2004; LeBlanc et al., 2007; Keyak et al., 2009; LeBlanc et al., 2013). The introduction of the Advanced Resistive Exercise Device (ARED), coupled with improved nutrition, has further reduced the 4 to 6 month bone loss (Smith et al., 2012). But further work is needed to implement optimal exercise prescriptions since bone loss has not been completely eliminated, and future exploration class missions can only accommodate exercise devices that will be much smaller than the ARED. In this light, NASA's Digital Astronaut Project (DAP) is working with physiologists in the NASA Human Research Program to implement well-validated computational models to help predict and assess bone loss during spaceflight, and enhance exercise countermeasure development. More specifically, computational modeling is proposed as a way to augment bone research and exercise countermeasure development to specifically target weight-bearing skeletal sites that are most susceptible to bone loss in microgravity.

Several bone remodeling theories, a research area that has seen increased activity in the last decade, have been developed in an attempt to quantify the contribution of mechanical stimulus from daily loading to bone homeostasis via mechanotransduction (Hernandez et al., 2000, Garcia-Aznar et al., 2005). There have also been models that attempt to connect mechanical stimulus to cellular dynamics (Maldonado et al., 2007; Pennline, 2009). The major unit of the temporal scale in these modeling theories is typically a 24 hour day and the biological rate constants tend to be in units of 'per day'. For the model under development in the DAP, we are interested in establishing an expression that can approximate the amount of daily stress/strain at specific skeletal sites from exercise prescriptions, and in understanding how those stress/strain levels translate to maintenance of bone via bone remodeling, particularly in a weightless environment, in order to design optimal exercise prescriptions.

The purpose of this article is to identify the various DLS expressions that have been developed to date, conduct a perspective comparison, and test their abilities as appropriate tools to quantify stress/strain from exercise induced loading at specific skeletal sites. We describe a simple set of exercise scenarios and examine how the formulas carry out their evaluations in terms of the exercise performance logistics. Specific attention is given to their ability to capture the experimentally observed effects of cyclic loading. These include, for example, the diminishing effect of continuous repetitions, increased effect of rest insertion between repetitions of an exercise, and increased effect of rest insertion between entire bouts of an exercise.

Formulas and Explanation of Their Differences

Key experiments in the past have given insight into the dynamic nature of skeletal loading and helped to suggest the formulation of DLS expressions. The experimental study by Rubin and Lanyon (1985) on the isolated ulna of roosters demonstrated that newly formed bone area is proportional to applied strain while the same type of experiment (Rubin and Lanyon 1984) showed that increasing loading duration past 36 cycles per day caused little further increase in bone mass. Turner et al. (1994) showed that increasing the applied loading frequency of four-point bending significantly increased the mechanically induced bone formation rate on the endocortical surface of the rat tibia. In a similar experiment (Turner et al. 1995), mechanically induced bone formation rate was proportional to peak to peak loading magnitude at 2 Hz. Evidence of the diminishing effect of increasing loading duration was seen in an experiment by Umemura et al. (1997) which related increased bone mass to the number of jumps per day that rats were trained to perform.

In an article that cites these experiments, Turner (1998) translated the observations into rules for bone adaptation to mechanical stimuli. One rule states that bone adapts to dynamic skeletal loading, i.e., strain stimulus increases with increasing magnitude or frequency of the dynamic loading, and strain stimulus is

enhanced by increasing strain rate. Another rule is that continuous loading duration has a diminishing effect on bone formation response. Based on these rules, he discussed mathematical formulas that can be related to a DLS. One expression, which he credits to Carter et al. (1987), that emphasizes the effect of load magnitude and load frequency is given as:

$$S \propto \left[\sum_{j=1}^{k} N_j \sigma_j^m \right]^{1/m} \tag{1}$$

The quantities that the symbols represent are:

S Stimulus
k Number of loading conditions/activities (can be thought of as number of exercises per day)
N_j Number of loading cycles per loading condition (or number of repetitions per exercise)
σ_j Effective stress (or strain) per loading condition
m Weighting factor (experimentally determined)

Beaupre et al. (1990) assumed a value of $m = 4$ based on correlation with available experimental data by Whalen et al. (1988) and a study of experimental data of Rubin and Lanyon (1984), while Turner estimated a value of 3.5 based on the data of Umemura et al. (1997). Note that the expression represents a quantity that is proportional to what could be interpreted as a stimulus to bone that affected bone formation rate or an increase in bone mass.

The work of Carter et al. (1987) involved more specific relations to bone properties than what is indicated by Equation (1). They defined a quantity S^* as the constant daily stimulus that keeps a region of bone from experiencing neither a net loss nor gain of bone apparent density. Assuming a relation to a linear superposition of stimuli for all loading activities in a day it was expressed as:

$$S^* \propto \sum_{j=1}^{k} N_j \cdot (\sigma_j / \sigma_{ult})^m \quad \text{per day} \tag{2}$$

where σ_{ult} is the ultimate effective stress. Subsequently, assuming that the bone maintenance stimulus is constant everywhere, the ultimate stress is factored out of the summation and solved for σ_{ult} to obtain the following relation,

$$\sigma_{ult} \propto \left(\sum_{j=1}^{k} N_j \sigma_j^m \right)^{1/m} \tag{3}$$

Referring to the work of Carter and Hayes (1977), which showed the bone strength σ_{ult} for a single loading to failure to be approximately proportional to the square of the apparent density ρ (i.e., $\rho \propto (\sigma_{ult})^{1/2}$), Carter et al. assumed the following approximation for the apparent density for multiple loading conditions,

$$\rho \propto \left(\sum_{j=1}^{k} N_j \sigma_j^m \right)^{1/2m} \tag{4}$$

In addition to the daily loading history based on stress and bone strength, Carter et al. also formulated one based on fatigue damage accumulation, and another based on bone strain energy density.

Genc et al. (2009) used expression (4) to begin their development of an activity determination algorithm based on entire days of in-shoe-forces such as those resulting from typical weight bearing locomotion activities like walking, running, and standing.

$$\text{DLS} = \left(\sum_{j=1}^{k} N_j (Gz_j)^m \right)_{\text{per day}}^{\frac{1}{2m}} \tag{5}$$

Here, the effective stresses, σ_j, have been replaced with peak ground reaction force (GRF) magnitudes, Gz_j, in the late stance phase for each loading cycle. The term in-shoe force refers to data collected by an ambulatory biomechanical data collection system for use in space (Cavanagh et al., 2009). The goal of the whole effort was to have a daily load model that could be used in measuring the daily load impacted to the musculoskeletal system of an astronaut during a typical day on earth (Cavanagh et al., 2010). The earth DLS would serve as a target for prescribing a similar dose through exercises during spaceflight. Note that the exponent is different from the exponent in the expression of Equations (1) and (3). From the outline of the stress analysis (Eqs. (2) to (4)), it is clear that the DLS expression of Genc et al. is directly related to bone apparent density, whereas Turner's DLS expression relates to bone strength.

From Equation (5), an enhanced DLS (EDLS) was developed which, when applied to an entire day of loading activities, takes into account,

- Saturation of osteogenic response of bone cells to continuous cyclic loading,
- Mechanosensitivity recover time between repeated cyclic bouts, and
- Contribution of low microstrain loads (e.g., standing postural shifts),

$$\text{EDLS} = \left(\sum_{j=1}^{k} N_j (Gz_j)^m + AL \right)_{\text{per day}}^{\frac{1}{2m}} \tag{6a}$$

$$AL = (23.0)(\text{Standing time}) \tag{6b}$$

The additional term AL represents accumulated load from standing which was derived from an assumption that AL from 1 min of standing equals 25 percent of the AL from 1 min of slow walking. The idea of replacing the effective stresses by GRF was credited to a study by Whalen et al. (1988) in which the resulting DLS expression was used to study the effects of locomotion activities on calcaneal bone maintenance. However, that study did not take into account the effects of saturation, recovery time, and low microstrain.

Note that saturation and recovery parameters do not explicitly appear in the formula, Equation (6). Instead, a 5 min saturation limit for running and a 20 min limit for walking were identified in experimental results from animal studies (Robling et al., 2002). Also, a recovery factor based on a fit to animal data (Robling et al. 2001) was used and is given by:

$$\left(1 - e^{-t/2} \right) \tag{7}$$

where t is the time in hours since the end of the previously saturated period. Then, an algorithmic flow chart for calculating the EDLS was outlined. It included decision branches that tested whether or not each

cycle from a continuous load exceeded the limits. The 5 and 20 min limits for continuous running and walking in a single bout are implemented by excluding any GRF in the summation part of the formula that occurs after the limits. To implement the recovery, subsequent ground reaction peaks during periods of running or walking after saturation are multiplied by their recovery factor.

Referring again to the work of Turner (1998), more variations in the DLS expression are formulated. He observed that the diminishing effect of continuous loading duration from the studies of Rubin and Lanyon (1984) and Umemura et al. (1997) could be mathematically modeled with a logarithmic function. Combining these observations with observations that both magnitude and strain rate can play a role in determining bone adaptation (Turner et al., 1995; Rubin and McLeod, 1994), the following alternate DLS expression is suggested:

$$S \propto \sum_{j=1}^{k} \log(1 + N_j) E_j \qquad (8)$$

The quantities k and N_j have the same definition as Equation (1). The new quantity E_j is intended to take into account a strain rate contribution to the DLS, and is defined as

$$E_j = \sum_{i=1}^{n} \varepsilon_{ji} f_{ji} \qquad (9)$$

where the variables are defined as follows:

n Number of frequency components for each loading cycle within a loading condition

f_{ji} Frequency component i for each cycle waveform in loading condition or exercise, j

ε_{ji} Peak to peak strain for strain component waveform i for each cycle N_j.

An application of formula (8) was used to quantify the load from a single bout of continuous bilateral jumping performed by human subjects (Ratalainen et al., 2009).

In addition to Equation (8), Turner (1998) replaced the stress factor in Equation (1) by the strain factor of Equation (9) obtaining another DLS version:

$$S \propto \left[\sum_{j=1}^{k} N_j E_j^m \right]^{1/m} \qquad (10)$$

Turner argued that, in the case of a long bone subjected to a periodic cyclic load represented by a single sinusoidal wave term with a frequency f, the strain rate is proportional to $\in f$ where $\in$ is the peak to peak dynamic strain, which is proportional to twice the amplitude of the sinusoidal wave. Note that this holds for a cyclic load represented by a single sinusoidal wave. The suggestion was made that the strain from a cyclic load represented by a general loading wave form, e.g., an exercise, could be expanded in a Fourier series consisting of sinusoidal waves at different amplitudes and frequencies. The derivative of the Fourier series, strain rate, would eliminate the static term and leave an infinite series of sinusoidal terms. This lead to the assumption that the strain stimulus could be proportionally represented as

$$E \propto \sum_{i=1}^{\infty} \in_i f_i \qquad (11)$$

where $\in_i$ is the strain magnitude related to the amplitude of term i in the expansion and f_i is the frequency of term i. Since the daily load consists of k activities or loading conditions, Equation (9) becomes the

strain stimulus as a factor in the overall mechanical stimulus expression of Equation (8) or (10). Unfortunately, it turns out that an infinite series formed as in Equation (11) may diverge. In such cases the series cannot possibly represent the strain stimulus in a proportional sense.

Mathematical models of bone adaptation seen in the first decade of this century have also used versions of a daily load. Because of the similarity to Equations (1) and (3), the versions used by Hazelwood et al. (2001) and Hazelwood and Castillo (2007) are mentioned here. Referencing Carter et al. (1987), Hazelwood et al. (2001) used the formula given by:

$$\Phi = \sum_{i=1}^{n} s_i^m R_{L_i} \tag{12}$$

where the following definitions apply:

n Number of loading conditions (or exercises),

s_i Strain range for each loading condition i,

R_{L_i} Cycles per day for each loading condition i

This expression appears to be more closely related to the daily loading history based on fatigue damage accumulation (Carter et al., 1987) where cyclic stress range is used explicitly in place of strain range. Equation (12) was treated as a loading potential proportional to fatigue micro damage rate in a study of bone remodeling due to overload. Similar to previous studies already mentioned, the value of m was chosen as 4 but other values (1, 6, and 8) were also examined.

For simplicity, cyclic loading of only one magnitude was applied ($n = 1$) and s was assumed to represent the principle compressive strain which returns to zero at the end of each cycle. Hazelwood and Castillo (2007) also used Equation (12) with $m = 4$ as the local stimulus for bone remodeling in a mechanistic model integrated with a finite element model of the femur. Specifically, they studied the effects of loading characteristic of marathon training on bone density, remodeling, and microdamage of the femur. In this case s was assumed to be the principle strain component with the largest magnitude.

The DLS expressions discussed above are summarized in Table 1.

TABLE 1.—SUMMARY OF DLS EXPRESSIONS

DLS	Expression	Reference
I	$\left[\sum_{j=1}^{k} N_j \sigma_j^m \right]^{1/m}$	Carter et al. (1987)
II	$\left(\sum_{j=1}^{k} N_j \sigma_j^m \right)^{\frac{1}{2m}}_{\text{per day}}$.	Carter et al. (1987) Whalen et al. (1988)
III	$\left(\sum_{j=1}^{k} N_j (Gz_j)^m + AL \right)^{\frac{1}{2m}}_{\text{per day}}$	Genc et al. (2009) Cavanagh et al. (2010)
IV	$\sum_{j=1}^{k} \log(1 + N_j) E_j$	Turner et al. (1998)
V	$\left(\sum_{j=1}^{k} N_j E_j^m \right)^{1/m}$	Turner et al. (1998)
VI	$\sum_{i=1}^{n} s_i^m R_{L_i}$	Hazelwood et al. (2001) Hazelwood & Castillo (2007)

In addition to the works mentioned above, a number of experimental studies have revealed additional insight into the nature of dynamic loading. Umemura et al. (2002) conducted a study with rats trained to perform a jumping exercise in three different formats:

(a) a single bout of 20 continuous jumps separated by 3 sec interval between jumps,
(b) a single bout of 20 jumps separated by 30 sec interval between jumps, and
(c) 2 bouts of 10 continuous jumps separated by 6 hr.

The results of this study revealed that the rats in all three groups had greater bone masses per body weight of the femur and tibia than rats in the control group which were allowed normal cage activity. However, those values in groups (b) and (c), although similar to one another, were greater than in group (a). A more recent experiment in which mice were subjected to cyclic loading using a noninvasive murine tibia loading device revealed that periosteal bone formation rate was significantly increased with 10 sec rest at zero load between each load cycle compared with continuous cyclic loading (Srinivasan et al., 2007). Results of these experiments suggest the assumption that rest inserted loading at more than a few seconds between cycles in a single bout of loading is more beneficial than continuous cyclic loading. Also, multiple shorter bouts of an exercise in a day, separated by sufficient time to reinitiate osteogenic sensitivity, are more beneficial than one long bout.

Results of Application to Exercise

Based on the results of the experimental studies mentioned above, the following assumptions regarding cyclic loading are suggested:

A. Bone adaptation and maintenance are functions of dynamic loading (Turner et al., 1998).
B. Osteogenic potential decreases with increasing repetitions and eventually saturates (Rubin and Lanyon, 1984; Robling et al., 2002).
C. Once osteogenic potential has significantly diminished or saturated, a minimum time is required for recovery of full cellular sensitivity (Robling et al., 2001).
D. Multiple shorter bouts of an exercise are more beneficial than one long bout, if there is sufficient time for recovery of cell sensitivity between bouts (Umemura et al., 2002).
E. Within a weight bearing exercise, rest insertion of possibly 10 to 30 sec between repetitions is more beneficial than continuous repetitions (Srinivasan et al., 2007).

To test how well each DLS expression captures the characteristics of cyclic loading listed in the assumptions, we consider the following test set of exercise schemes and examine how the DLS expressions compute.

(1) Running on a treadmill for 18 min (Fig. 1.)
(2) A single bout of 20 squats with 3 sec pause between repetitions (Fig. 2)
(3) Two bouts of 10 squats separated by 6 hr., with 3 sec pause between repetitions
(4) A single bout of 20 squats with 10 sec rest insertion between squats
(5) One bout of 10 squats followed by another bout of 10 squats 1 hr later

Each scheme is assumed to be the only activity performed in a single day. The same subject is assumed to perform the exercises, thus keeping the influence of the anthropometrics consistent. For each single bout of squats, the individual is assumed to be under the maximum possible load that avoids muscle failure. The skeletal site of interest can be assumed to be the calcaneus of one foot for exercise scenario (1) while the site of interest can be taken as the proximal femur or just the femoral neck for exercise scenarios (2) to (5).

TABLE 2.—EVALUATIONS OF THE EXERCISE SCENARIOS FOR EACH OF THE DLS EXPRESSIONS

DLS	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
I	$\left(1200 \cdot \sigma_r^m\right)^{1/m}$	$\left(20 \cdot \sigma_s^m\right)^{1/m}$	$\left(20 \cdot \sigma_s^m\right)^{1/m}$	$\left(20 \cdot \sigma_s^m\right)^{1/m}$	$\left(20 \cdot \sigma_s^m\right)^{1/m}$
II	$\left(1200 \cdot \sigma_r^m\right)^{1/(2m)}$	$\left(20 \cdot \sigma_s^m\right)^{1/(2m)}$	$\left(20 \cdot \sigma_s^m\right)^{1/(2m)}$	$\left(20 \cdot \sigma_s^m\right)^{1/(2m)}$	$\left(20 \cdot \sigma_s^m\right)^{1/(2m)}$
III	$\left(333 \cdot (Gz)_r^m\right)^{\frac{1}{2m}}$	$\left(20 \cdot (Gz)_s^m\right)^{\frac{1}{2m}}$	$\left(19.5 \cdot (Gz)_s^m\right)^{\frac{1}{2m}}$	$\left(20 \cdot (Gz)_s^m\right)^{\frac{1}{2m}}$	$\left(14 \cdot (Gz)_s^m\right)^{\frac{1}{2m}}$
IV	$\log(1201) \cdot E_{(1)}$	$\log(21) \cdot E_{(2)}$	$\log(121) \cdot E_{(3)}$	$\log(21) \cdot E_{(4)}$	$\log(121) \cdot E_{(3)}$
V	$\left(1200 \cdot E_{(1)}^m\right)^{1/m}$	$\left(20 \cdot E_{(2)}^m\right)^{1/m}$	$\left(20 \cdot E_{(3)}^m\right)^{1/m}$	$\left(20 \cdot E_{(4)}^m\right)^{1/m}$	$\left(20 \cdot E_{(5)}^m\right)^{1/m}$
VI	$s_r^m \cdot 1200$	$s_s^m \cdot 20$	$2 \cdot s_s^m \cdot 10$	$s_s^m \cdot 20$	$2 \cdot s_s^m \cdot 10$

Table 2 shows how each DLS expression would form its numerical value based on the logistics of each exercise scheme. Each value in the table has the unit of per day as defined by the DLS expressions. The following notation can be matched to the variables in the summary of the expressions:

σ_r Effective stress on bone in the calcaneus from GRF of each impact during running

σ_s Effective stress on bone in the proximal femur from each squat

Gz_r Peak GRF during running

Gz_s Peak GRF from the squat exercise

s_r Maximum principle strain in the calcaneus during running

s_s Maximum principle strain in the proximal femur from a squat

Column 1 shows the DLS evaluations for the running exercise. Referring to Figure 1, the stride period is about 0.9 sec. In 18 min, the number of impacts (cycles) per foot amounts to 1200 cycles. For DLS III, the implemented algorithm eliminates the contribution from any impact occurring after 5 min which limits the number of cycles from this exercise bout to about 333. For DLS IV and V, the symbol $E_{(1)}$ represents the sum of a finite number of products of amplitude and frequency, Equation (11), from the Fourier expansion of one cycle which, for the left foot, is illustrated by the cycle beginning at about 0.14 and ending at 1.04 sec.

Column 2 shows the DLS evaluations for a single bout of 20 squats performed continuously. In this case, the symbol $E_{(2)}$ in IV and V represents the sum of a finite number of terms, Equation (11), formed from the products of amplitude and frequency in the Fourier expansion of a strain waveform of one squat. Figure 2 shows the magnitude of the resultant force at the hip joint for one repetition or one squat assuming a load on the individual that results in a joint force at the hip equal to about body weight prior to beginning the squat. It was produced relative to the data from Bergmann et al. (2001) showing the joint contact force at the hip from an individual performing a knee bend while presumably unloaded. A finite element model of the proximal femur could use the force vector to compute effective stress and maximum principle strain.

The single activity in scenarios 1 and 2 reduce the expressions in Table 1 to a single term, $k = 1$. In the case of scenario 3, $k = 2$, and the bouts, although identical, are counted as two individual activities which is reflected in the evaluations in column 3 of Table 2. Note that DLS III multiplies the second bout of 10 squats by the osteogenic recovery factor $(1-\exp(-3))$, Equation (7). Expression IV shows the additive properties of the log function when combining two separate bouts of 10 squats. Note also that if squats are performed identically, $E_{(3)} = E_{(2)}$.

The forth squat exercise, although performed with a 10 sec rest insertion between repetitions, is treated as a single activity ($k = 1$ in the expressions). The results turn out to be identical to the evaluations for scenario 2 (column 2). However, the summation $E_{(4)}$ may be different from $E_{(2)}$.

Since the second exercise bout in scenario 5 is performed 1 hr after the first bout, the DLS expressions treat this as two loading conditions ($k = 2$). The contribution to the DLS from all loading cycles in DLS III is only 14. The reason for the difference is because the cycles from the second bout of squats are multiplied by the osteogenic recovery factor $(1 - \exp(-0.5))$. The summation $E_{(5)}$ should be the same as $E_{(2)}$ since the squats are performed identically with no rest insertion.

Gait Parameters
Running Data
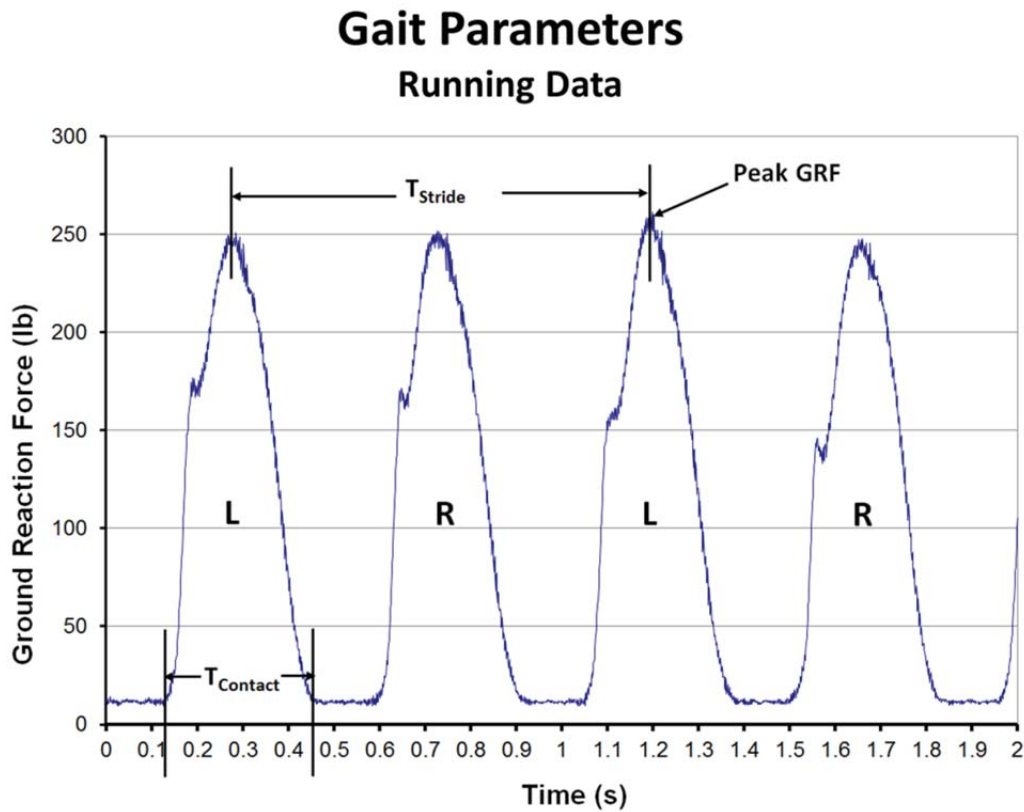
$$f_{stride} = \frac{1}{T_{stride}} \qquad Stride\ Length = (Treadmill\ Speed)(T_{stride})$$

Figure 1.—This figure was plotted using, with permission, example ground reaction force data collected in the NASA Glenn Research Center enhanced Zero-gravity Locomotion Simulator during a study designed to assess harness comfort (Perusek et al. 2007). The following gait parameters are illustratively explained within the figure: peak ground reaction force (Peak GRF), contact time ($T_{contact}$) and stride time (T_{stride}). The alternating pulses represent contact by the left foot (L) and the right foot (R). Stride frequency (f_{stride}) is defined as the inverse of T_{stride} and the stride length is defined as the product of treadmill speed and T_{stride}.
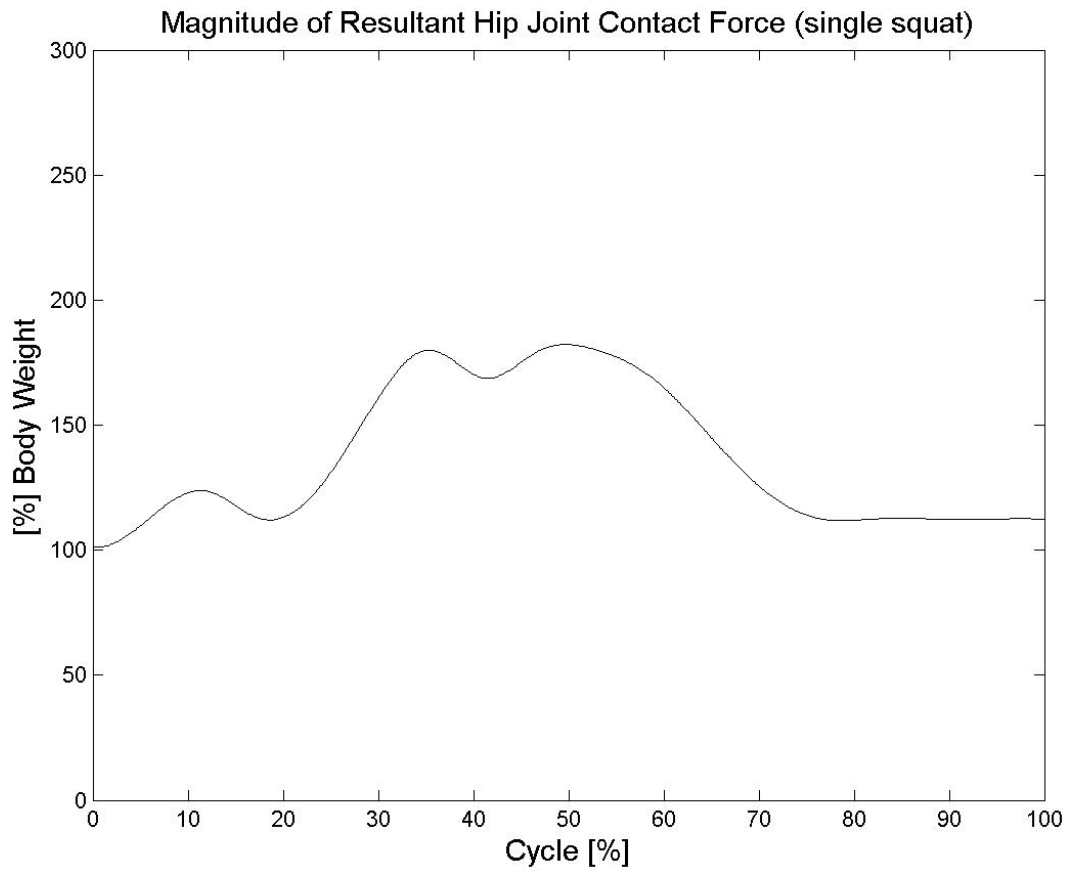
Figure 2.—Representative waveform of the resultant hip joint contact force during one squat. In a finite element model of the proximal femur, the force vector would relate to a comparative waveform for effective stress or maximum principle strain values in the hip. This figure was produced relative to a figure of the in vivo hip joint contact force measured with instrumented implants during a knee bend (Bergmann et al. 2001). The percent body weight increased uniformly across the cycle by a factor to adjust to approximate values for an adult who is moderately loaded while performing a squat.

Discussion

The DLS expressions differed in their applications. Expressions I and IV are the result of models fit to animal data. Expression III was used to quantify the amount of daily activity to maintain bone density, while VI was used to relate bone load from specific activities to the activity of remodeling units in a theoretical model of bone remodeling. The mathematical differences that appear in the DLS expressions are largely due to the use of the power function $N^{1/m}$ verses the $\log(1+N)$, and the role of stress, strain or GRF verses the role of strain rate in the form of the series expansion E. Since the quantifiable merits of the formulas would have to be based on more data, and in particular, human data, this discussion focuses more on the qualitative merits, and tries to answer the following questions:

(a) As a DLS formula is applied to each of the five exercise scenarios, does the formula demonstrate the ability to satisfy assumptions A to E?

(b) How well does the formula demonstrate the ability to satisfy assumptions A to E?

Row 1 of Table 2 shows the evaluations of DLS I. Referring to the curve $N^{1/4}$ in Figure 3; the expression shows the diminishing effect of the foot impacts from running (scenario 1) as the number increases up to 1200. However, compared to the diminishing effect of $\log(1+N)$ used by DLS IV, $N^{1/4}$ does not model saturation as well for large values of N such as those obtained from running. Numerically, $(1296)^{1/4}$ is two times $(81)^{1/4}$ whereas log (1000) is only one more than log (100). So, although Turner (1998) showed how well Carter's formula could fit to the data of Umemura et al. (1997) for values up to $N = 100$, it may not extend well to a larger range of values. The evaluations of DLS I for scenarios 2 to 5 give an identical result, and therefore do not capture the benefits of osteogenic recovery, multiple shorter bouts, and rest insertion stated in assumptions C, D, and E. Since the DLS expression II is the square root of DLS I, the same analysis applies, it may not work as well for large values of N, and fails to satisfy assumptions C, D, and E.
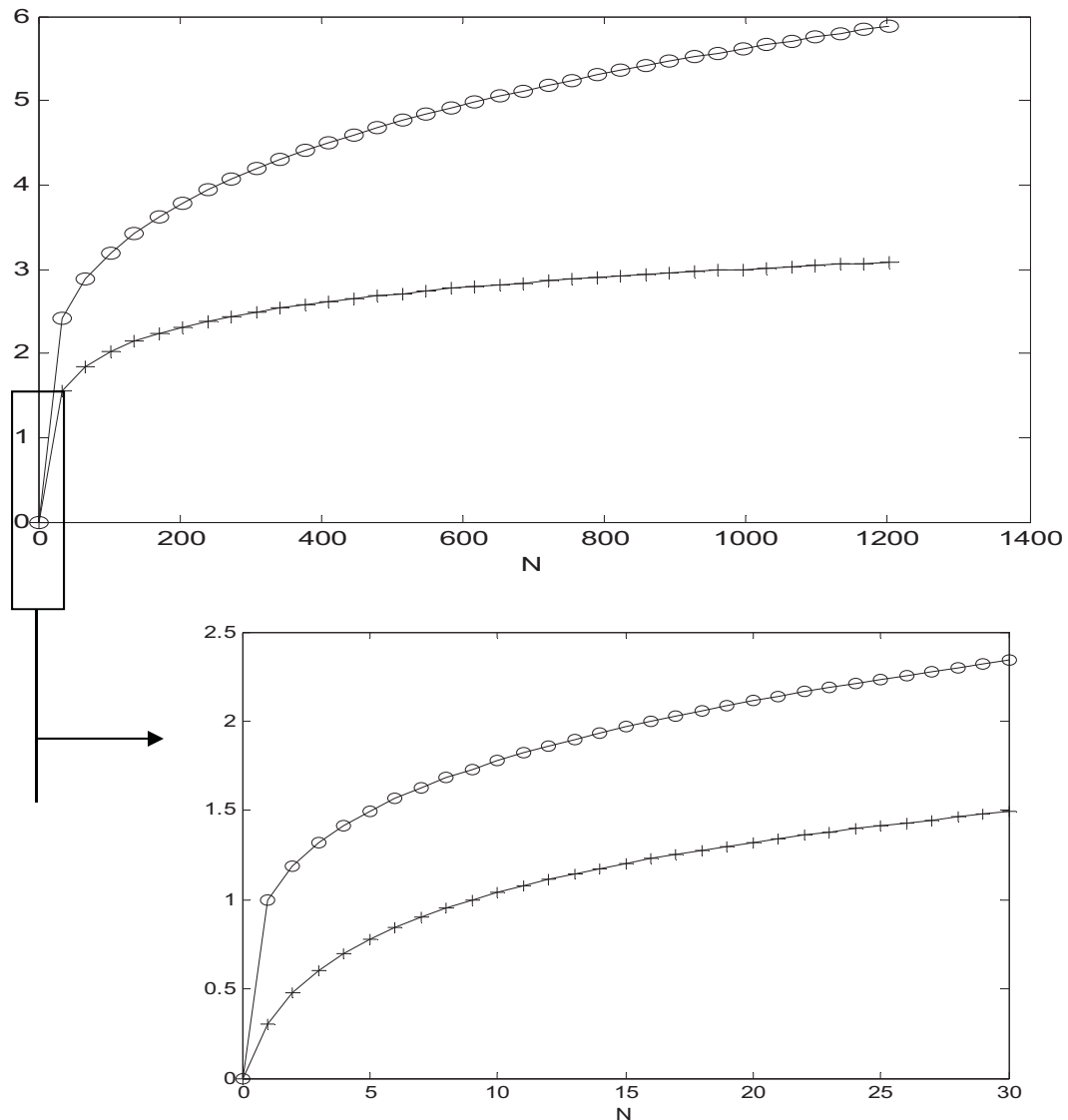

Figure 3.—Comparison of power function to log function.

$$-\!o\!- \quad N^{1/4}$$

$$-\!+\!- \quad \log(1+N)$$

In the evaluations of DLS III, note that the application of the algorithm forces complete saturation at about 333 impacts on the left or right foot. Although this is the only one of the six expressions that prevents any unrealistic contributions to bone response as N becomes increasingly large, it's unknown if saturation after 5 min of running is applicable to humans. The authors of expression III admit this to be a limitation in the formula. The evaluation of scenario 3, multiple shorter bouts, correctly applies the osteogenic recovery factor in the algorithm but the quantification is effectively the same as scenario 2, a single longer bout, thus excluding any benefit from multiple shorter bouts. Since the evaluation of scenario 4 is the same as scenario 2, the DLS expression fails to capture any benefit of short rest insertion, assumption E. Because of the application of the osteogenic recovery factor to the second bout of exercise of scenario 5, contribution to DLS from all loading cycles is only 14. Thus, expression III has the ability to distinguish the case when osteogenic potential has not fully recovered following a certain amount of saturation, assumption C, and is the only one in column 5 showing that ability.

The evaluations of DLS IV are the only ones that use $\log(1 + N)$ instead of N. As, indicated in Figure 1, the running scenario 1 will show a more asymptotic approach as N increases to 1200 and beyond with the log function. Also, DLS expression IV is able to capture the benefit of multiple shorter bouts as indicated by the scenario 3 evaluation. However, the benefit of short rest insertion, assumption E, of scenario 4, is not captured nor is insufficient osteogenic recovery, assumption C, accounted for by the scenario 5 evaluation. More importantly, the values $E_{(i)}$ consist of a finite sum of terms of the series formed by Equation (11), which can in certain cases have an infinite value. For example, consider the trapezoidal strain waveform that Turner (1998) uses to illustrate the formation of the series. The waveform is illustrated in Figure 4 and its functional representation is:

$$f(t) = A \begin{cases} 2t, & 0 \leq t \leq 0.5 \\ 1, & 0.5 \leq t \leq 1.5 \\ 4 - 2t, & 1.5 \leq t \leq 2 \end{cases} \tag{13}$$

In the caption of Turner's figure, a static loading component of about 0.75A is shown followed by increasing frequency components with progressively lower amplitudes, but the Fourier series is not displayed. The Fourier series expansion of Equation (13) is

$$f(t) = 0.75A - A \cdot \sum_{n=1}^{\infty} \frac{4}{(n\pi)^2} \cdot (1 - \cos(\frac{n\pi}{2})) \cdot \cos n\pi t \tag{14}$$

The infinite series formed from summing the products of strain amplitude and frequency in each term becomes

$$
\begin{aligned}
E &= A \cdot \frac{4}{\pi^2} \cdot \left\{ \frac{1}{1^2} \cdot 1 \cdot \frac{1}{2} + \frac{1}{2^2} \cdot 2 \cdot 1 + \frac{1}{3^2} \cdot 1 \cdot \frac{3}{2} + 0 + \frac{1}{5^2} \cdot 1 \cdot \frac{5}{2} + \frac{1}{6^2} \cdot 2 \cdot \frac{6}{2} + \frac{1}{7^2} \cdot 1 \cdot \frac{7}{2} + 0 + \cdots \right\} \\
&= A \cdot \frac{4}{2\pi^2} \cdot \left\{ 1 + \frac{1}{2} \cdot 2 + \frac{1}{3} + \frac{1}{5} + \frac{1}{6} \cdot 2 + \frac{1}{7} + \cdots \right\} \\
&> A \cdot \frac{4}{2\pi^2} \cdot \left\{ \frac{1}{3} + \frac{1}{5} + \frac{1}{7} + \cdots \right\} > A \cdot \frac{4}{2\pi^2} \cdot \frac{1}{4} \sum_{n=1}^{\infty} \frac{1}{n}
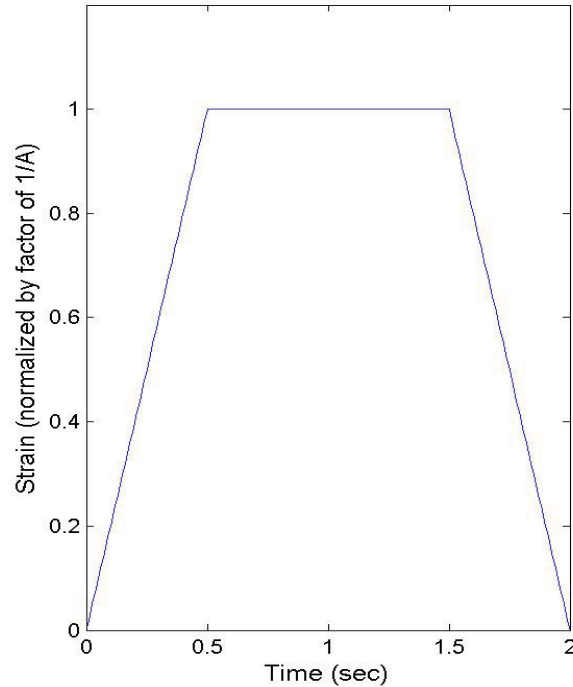\end{aligned} \tag{15}
$$

Figure 4.—Trapezoidal loading waveform.

Note that the series is greater than one fourth of the well-known harmonic series which is divergent, so by comparison, the entire series diverges. This suggests revisiting ways to relate bone response to multiple higher frequencies. Turner's cites strong evidence from experimental studies to justify the direct relation of a single term, consisting of the product of a peak-to-peak loading magnitude and a frequency, on bone formation. This appears true for a sinusoidal loading waveform. As he illustrates, you cannot keep loading frequency and strain rate constant while varying strain magnitude (wave height), assuming that the duration (wave width) of the strain magnitude remains constant. In Figure 4, if the strain magnitude is lowered while keeping the strain rate (slope) constant, the loading frequency will increase. So in case of non-sinusoidal loading waveforms, the loading frequency may need to be captured in a strain stimulus relation. In those cases, an expression like:

$$\varepsilon \cdot f_l$$

where ε is the peak strain magnitude and f_l is the true loading frequency, may serve as a generalization of the simple sinusoidal loading waveform.

As to row 5 of Table 2, DLS V fails to satisfy assumptions C, D, and E, and also uses the finite sum of terms of a potentially divergent series, Equation (11), for the values $E_{(i)}$. Lastly, the evaluations in row 6, scenarios 2 to 5, are identical and indicate that the use of DLS expression VI did not involve the consideration of saturation. None of the other effects of rest insertion or osteogenic recovery is able to be captured, so it can potentially fail all of the assumptions except A.

The DLS algorithm presented by Genc et al. (2009) appears to satisfy the most assumptions. Although it does not appear explicitly in the expression, it's the only one that has a temporal dependency. However, it does have limitations in applications to human models, as admitted by the authors. The numerical time limits for running and walking may not apply to humans. In the specific application (Cavanagh et al. 2010), the formula was used to estimate the amount of GRF from exercise prescriptions performed on orbit relative to the amount experienced by astronauts in a typical working day on Earth. The conclusion from the results was that duration and loading from current ISS exercise prescription do

not provide sufficient weight bearing stimulus required to prevent bone loss. It was not intended to predict the exact contribution of specific exercise induced stress at a specific skeletal site. However, the algorithmic scheme may form the basis for devising a formula suitable for estimating the average amount of daily stress/strain at a specific skeletal site due to exercise induced cyclic loading applicable to bone remodeling theories. If the GRF in the osteogenic index (OI) measure of exercise effectiveness (Turner and Robling 2003) is replaced by effective stress, a DLS can be defined by

$$S \propto \sum_{j=1}^{k} \ln(1 + N_j) \cdot \sigma_j \tag{16}$$

Use this expression in the algorithm of DLS III, including the limit on duration and the factor accounting for osteogenic recovery, and the results of the exercise scenarios become those in Table 3.

TABLE 3.—EVALUATIONS OF THE EXERCISE SCENARIOS FOR EXPRESSION (15)

Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
$\ln(1201) \cdot \sigma_r$	$\ln(21) \cdot \sigma_s$	$\ln(107.4) \cdot \sigma_s$	$\ln(21) \cdot \sigma_s$	$\ln(28) \cdot \sigma_s$

This shows a potential of satisfying all the assumptions except E. Stress values in a bone site could come from a finite element model with loading boundary conditions obtained from a commercially available or open source biomechanics modeling tool.

Conclusion

The results of Table 2 indicate that no single DLS expression in Table 1 appears able to satisfy all the assumptions A through E (in fact none seem to satisfy assumption E) regarding exercise induced cyclic loading. Although the algorithm presented by Genc et al. (2009) appears to satisfy the largest number of assumptions (A, B, and C), it does not provide results in units of stress or in terms of strain. Therefore it's unsuitable for direct utilization in the DAP bone adaptation model under development discussed in the Introduction. However, its algorithmic scheme may form the basis for devising a robust DLS formula in terms of stress or strain like measures as described in combination with an example expression like Equation (16). Another option is to combine Genc's algorithmic scheme with Carter's expression I in Table 2. Ultimately, DLS expressions will be tested in the computational development of the DAP model to determine if they adequately represent the osteogenic response of bone to exercise.

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