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A novel mathematical modeling to assess the bone mineral density under mechanical stimuli

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Abstract*— *Assessing the variation in bone mineral density (BMD) remains as a complex task, given the countless variables and parameters that constitute the boundary conditions. The present study aims to present a novel mathematical modeling to assess the BMD of maxilla and mandible through of bone remodeling under mechanical simulations. The behavior analyze of bone remodeling tissue will be verified by submitting to mechanical stimuli and application of stress on dental implants. The analyze process will use computational tools and mathematical modeling, which should provide the evolution of the density in the bone tissue in the time, considering different mechanical stimuli. The studies on bone remodeling are not specific for the bones that make up the maxilla and mandible. Thereby, the findings don't translate the specific behavior of increased bone density in these regions, reference values are used, however do not demonstrate correlations that are significant between the density of other areas studies with the maxilla or mandible, in view of the fact that bone density may reflect in the responses obtained in relation to orthodontic movements. This study allows determining the appropriate parameters and reference values that correspond to these evaluated regions, whose bone density is variable in the same element and have a great difference in density between the maxilla and the mandible. The use of such suitable reference values in the bone regions may provide a better understanding of the behavior of the bone tissue in the mandibular region as a function of time. The simulations pointed that the loadings can be applied with different types of stimulus. The modeling was able to measure stress loads, indicated to obtain a better response to dental treatments.

I. INTRODUCTION

The mechanical resistance of bone tissue is directly related to its mineral density. The behavior of this tissue in relation to its growth, remodeling and resorption, has been the subject of several studies due to its anisotropic characteristic [1]. For this, the study of bone remodeling is based on the Theory of Elasticity [2], for the analysis of structural behavior and variation in bone mineral density (BMD) as a function of mechanical stimuli [3]. Application of mechanical stimuli can induce the cellular activity, which causes the flow of interstitial fluid in the lacuno-canalicular network, and molecular production [4].

Advances in knowledge about bone mineral density associated with the analysis of its regeneration contribute to the implantology treatments [5], which aims to provide an improvement in the condition of oral functions. Nevertheless, the efficiency of an implant is related to its anchorage, which is due to the individual's resistance to occlusion strength. In turn, this condition is related to the mechanical properties of bone on the fixation of dental implants [6].

Bearing in mind that each individual responds in a different way, and that the biological formation of bone tissue depends on the health conditions of each person, the response of bone regeneration may not meet normal clinical expectations. To improve the response to treatment, the application of mechanical stimuli causes an increase in cell activity and bone density, for satisfactory recovery of mandibular functions [7].

In a brief overview of some of the major studies, Wolff was the first to analyze the behavior of the bone tissue structure subjected to loads. From his pioneering work, studies on the modeling and remodeling of bone tissue began. Cowin and Hegedus [2] describe bone tissue as an elastic material that adapts its structure to the load applied. Huiskes and Weinans [8] present a study on adaptive remodeling using energy density as a control variable to determine bone density. Frost [9] introduces structural adaptations of the skeleton to mechanical stress, whose biological, biomechanical and clinical-pathological knowledge was not available in previous studies. Yang et al. [10] propose a method for analyzing a set of elastic constants of the spongy bone, resulting in Hooke's orthotropic law, which depends on the fraction of solid volume for spongy bone. Crupi et al. [11] study on mechanical stimulus, corresponding to the maximum value of the overload stress, through the application of Taylor's theory of crack propagation.

Currently, there are methods capable of providing data to satisfy mathematical equations applicable to assess the variation in bone mineral density (BMD). However, this assessment is still a complex task, given the countless variables and parameters that constitute the boundary conditions. Computer simulations constitute an alternative, which allows for varying the initial conditions of the problem, generating results in real-time, comparative analyzes, making research less costly, faster and capable of evaluating multiple scenarios.

In this context, the present study aims to evaluate the variation in bone mineral density (BMD) of maxilla and mandible through bone remodeling under mechanical stimuli, considering static and variable loads. Moreover, variation in BMD was also compared to results reported in the literature, available for analysis with static loads.

Results reported in the literature on modeling bone density variation have been based on the Euler method [12], for the integration of the differential equation that describes the behavior of the tissue in response to static stimuli. As a contribution to the advancement in this area of knowledge, the present study introduces a model based on the fifth-order Rung-Kutta method, which provides a more accurate integration, with less computational effort.

II. MATERIALS AND METHODS

To analyze the evaluate the variation in bone mineral density, a novel mathematical model based on partial differential equations was developed, with an algorithm written in Python language, for simulating static and variable mechanical stimuli. At the beginning of the process, the model simulated the application of static loads, which remains constant for a period of time (equation 1):

$$\frac{d\rho}{dt} = B\left(\left(\frac{\sigma^2}{2C\rho^4}\right) - k\right) - D\left(\left(\frac{\sigma^2}{2C\rho^4}\right) - k\right)^2 \qquad (1)$$

where, the value of each constant is given according to Huiskes and Weinans (1992), k (J.g^{-1}) is the limit value for the stimulus, B (g.cm^{-3})^2 . (MPa . time unit)$^{-1}$), and D (g.cm^{-3})^3 . (MPa^{-2} . time unit)$^{-1}$) are constants. Bone density is given by $\boldsymbol{\rho}$ (g.cm^{-3}). C (MPa) is the compression module, as Carter and Hayes [13]. The variation in bone density is expressed as a function of mechanical stimuli [8], where the range of bone density variation is $\mathbf{0} < \boldsymbol{\rho} \leq \boldsymbol{\rho cb}$, and $\boldsymbol{\rho cb}$ (g.cm^{-3}) is the maximum bone density.

An algorithm was built to solve equation (1), which corresponds to the variation of bone density over time. As an innovation in this study, equation (2) was modified to analyze the rate of change in bone tissue density, through exposure to various mechanical stimuli using two waveforms: sine wave and wave generated by the linear combination of sine-cosine. Stress variable $\boldsymbol{\sigma}$ was replaced by the simple harmonic motion equation, where A is the stress amplitude applied, ω is the frequency of the oscillatory motion, t the time, and α is the initial phase, so that:

$$\sigma = A \,.\, sen\,(\omega t + \alpha) \qquad (2)$$

Replacing the eq. 2 in eq. 1 we have equation 3, which represents the simulation of the variation of bone density as a function of variable mechanical stimuli by periodic waves with sinusoidal shape:

$$\frac{d\rho}{dt} = B\left(\left(\frac{(A\,.\,sen(\omega t + \alpha))^2}{2C\rho^4}\right) - k\right) - D\left(\left(\frac{(A\,.\,sen(\omega t + \alpha))^2}{2C\rho^4}\right) - k\right)^2 \qquad (3)$$

In the analysis of the variation in bone density, applying mechanical stimuli with periodic waves, mechanical stimuli were also evaluated when applied through waves with a format generated by the linear combination of sine-cosine. Likewise, the stress σ has been replaced by the simple harmonic motion equation, where A is the stress amplitude, ω is the pulsation, t is the time, Φ and α are the initial phase for cosine and sine respectively, so that:

$$\sigma = A\,.\,(cos(\omega t + \phi) + sen(\omega t + \alpha)) \qquad (4)$$

Replacing the eq. 4 in eq. 1 we have equation 5, which represents the simulation of bone density variation as a function of variable mechanical stimuli by periodic waves, due to the linear combination of sine and cosine.

$$\frac{d\rho}{dt} = B\left(\left(\frac{(A\,.(cos(\omega t + \phi) + sen(\omega t + \alpha)))^2}{2C\rho^4}\right) - k\right) - D\left(\left(\frac{(A\,.((cos(\omega t + \phi) + sen(\omega t + \alpha)))^2}{2C\rho^4}\right) - k\right)^2 \qquad (5)$$

The application of varied mechanical stimuli in this study aimed to analyze the behavior of bone tissue, when subjected to this type of loading, and to verify whether the change in the form of application of loads offers any benefit for increasing bone mineral density.

Considering the mathematical model of equation (1), an algorithm for the analysis of bone remodeling and adaptation was built, based on the Range Kutta method of order 5, considering the same parameters proposed by Jianying (Li et al., 2007): k = 0.004 Jg^{-1}; B = 1.0 $(gcm^{-3})^2$ (MPa time unit)$^{-1}$; C = 3790 MPa $(gcm^{-3})^{-2}$; D = 60.0 $(gcm^{-3})^3$ MPa-2 (time unit)$^{-1}$. The constant time interval Δt adopted was 10^{-4}. This very small value of the integration step has the function of avoiding specific errors or truncation in the process of numerical integration of the partial differential equation. The initial bone density was adopted as ρ_0 = 1.0 $g.cm^{-3}$.

In the case of variable mechanical stimuli, the following were also considered: ω = π / 100; α = zero; and Φ = zero. For a period of π / 100, the frequency will be 0.01 Hz. The definition for a very low frequency was made due to the behavior of the bone remodeling process in relation to different frequency levels. After performing a simulation using frequencies from 1 to 20 Hz, it was found that the density variation does not show growth in the bone mass rate, that is, the higher the frequency, the greater the resorption. This corroborates that, even when the rate of cell activation increases as a function of frequency, the rate of change in bone density is inversely proportional [14].

III. RESULTS

In the simulation of static mechanical stimuli on a bone sample submitted to a uniaxial load, the model provided the results shown in Figure 1, in which the evolution of bone density variation from different stress levels can be observed.

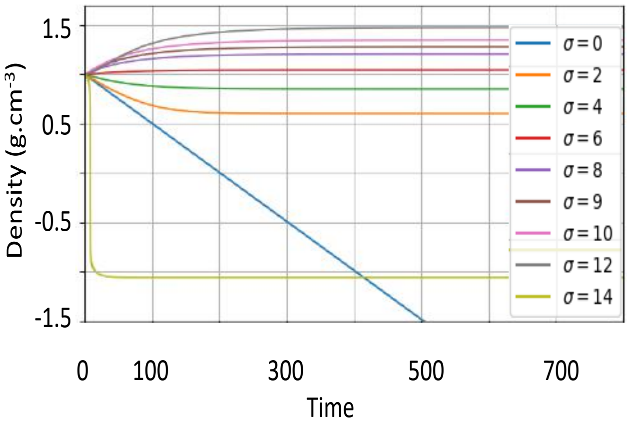

Fig.1. Density variation as response of static mechanical stimuli over time.

Applying a stress from 0 to 4 MPa, we verify that the density decreases indicating loss of mass, when submitted to low or zero stresses. In this stress range, bone loss occurs because the stimuli are not sufficient to cause deformations capable of triggering biochemical processes necessary for bone remodeling. Under 6 MPa it is possible to note a variation in BMD, indicating that from this level of stress occurs stimuli of the tissue to the point of provoking the beginning of biochemical reactions, which activate the cells and the remodeling process. For stresses from 8 to 12 MPa, we observed that the BMD undergoes a considerable increase over the time of exposure to the mechanical stimulus, due to a greater cellular activity. On the other hand, with higher stresses, from 14 MPa, the BMD decreases abruptly due to the resorption overload. When there is a very high-stress level the behavior of bone tissue responds with loss of density due to tooth resorption [12]. Excessive mechanical stimuli applied to bone tissue present an inversion of the cellular biochemical process, not only canceling the effect of increasing bone density, but also causing rapid and total loss of bone mass. This effect would be close to that of rupture of bone tissue.

Figure 2 presents the results of the variable mechanical stimuli with frequency of sine waves. The effect of stress variations on bone density using this type of waves is due to sinusoidal fidelity. The sine waves enter and leave a linear system in the same way, being able to undergo changes in amplitude and phase, but always maintaining the original frequency.

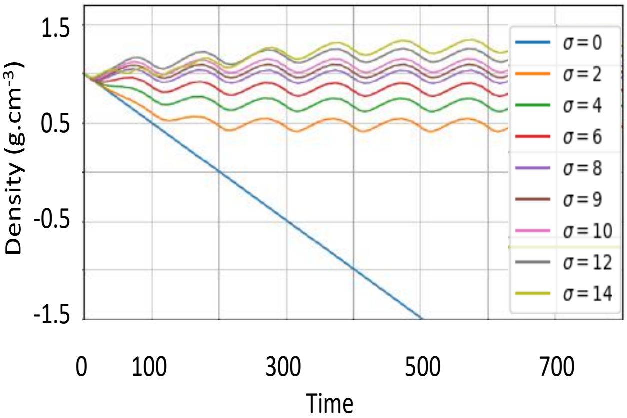

Fig.2. Density variation as response of variable mechanical stimuli, with frequency of sine waves over time.

For a stress of up to 6 MPa, it is noted that BMD decreases, showing bone loss when subjected to a variable tension oscillating in a sine wave frequency. The bone density values for this stress range vary from zero to 0.76 g.cm^{-3}. Applying a sinusoidal oscillatory stimulus with a frequency of 0.01 Hz, it appears that the stress range keeps the bone tissue at rest, incapable of deformations that trigger biochemical reactions, necessary to increase bone density. Under the action of a stress of 8 MPa, the bone density undergoes little variation, showing a very small density gain, maximum of 1.05 g.cm^{-3}. From that level of stress, the deformations are sufficient to provoke biochemical reactions. However, still inefficiently to cause an increase in bone density. For higher stresses, between 9 and 12 MPa, we observed that the BMD undergoes a considerable increase over the time of exposure to the mechanical stimulus, whose maximum values reach 1.25 g.cm^{-3}. From 14 MPa on, BMD increases, reaching a maximum value of 1.35 g.cm^{-3}, changing the behavior of bone tissue in relation to a static loading that presents bone resorption. In the simulation of the variable mechanical stimulus for this stress level, there was a change in the behavior of the bone tissue, leaving a resorption condition for a bone density increase regime.

The results obtained with the processing of the algorithm, considering mechanical stimuli with frequency of waves by the linear combination of sine-cosine, are presented in Figure 3.

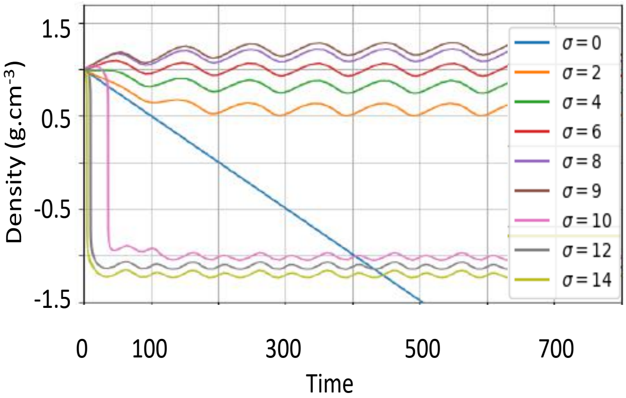

Fig.3. Density variation as response of variable mechanical stimuli, with frequency of sine-cosine waves over time.

Subjecting the bone tissue to a stress from 0 to 4 MPa, we observed that the density decreases, showing resorption when applied low or zero stresses, varying over time according to a wave generated by the linear combination of sine and cosine. The values obtained for this tension range reached 0.74 g.cm^{-3}. The findings for this stress range shows that even changing the form of application of the mechanical stimulus, whether static, varying like a sine wave or a wave resulting from the linear combination of sine and cosine, the resting region remains the same. Under 6 MPa, the BMD undergoes little variation, showing the beginning of density gain, with a maximum value of 1.10 g.cm^{-3}. This analysis showed the best result among the simulations performed. Deformations were greater, indicating an increase in biochemical reactions that activate bone density gain. When applied stresses between 8 and 9 MPa, we observed that the BMD increases over time of exposure to the mechanical stimulus, whose maximum values presented were 1.22 and 1.29 g.cm^{-3}, respectively. In this stress range, the values were slightly higher than those generated by static mechanical stimuli. This result indicates that, in this range, varying the shape of the mechanical stimulus can provide density gain. However, under higher stresses, from 10 MPa onwards, BMD decreases rapidly and abruptly, due to the resorption overload. From this stress level, the load applied by this type of vibration present deformations that exceed the resistance of the bone tissue, leading to rupture.

IV. DISCUSSION

In view of the clinical demand for better treatment conditions, scholars have sought to advance in understanding the variation in BMD [7]. The present study sought to contribute with a mathematical model for computer simulation, based on parameters related to the boundary conditions reported in the literature [8, 11, 12, 15]. The novel model was able to emulate the behavior of bone tissue subjected to static and varied stimuli over time.

BONE TISSUE BEHAVIOR

In dynamic load simulations, the frequency of vibration also influenced the behavior of bone tissue, affecting the BMD. The results show that the lower the frequency of vibration, the greater the increase in bone density until reaching the resorption limit. The results show that the behavior of bone tissue can be defined in three states, according to the stress range and type of stimuli (Table 1).

Table 1. Bone tissue behavior as loading ranges (MPa).

Type	Stimuli	First	Second	Third
Static	Constant	0 ≤ σ < 6	6 ≤ σ ≤ 12	σ > 12
Variable	Sine wave	0 ≤ σ < 8	8 ≤ σ ≤14	σ > 14
Variable	Sine-cosine wave	0 ≤ σ < 6	6 ≤ σ ≤ 9	σ > 9

The first range consists of the idle zone, in which the stresses are insufficient to cause bone remodeling. In this range, bone resorption occurs, causing a reduction in BMD. The loading values vary according to the type of load application, as well as due to the variation of the application parameters. Therefore, the idle zone does not provide a linear response to the behavior of bone tissue in relation to mechanical stimuli. The simulation with static and varied stimuli, according to a sine-cosine wave, presents the same stress range for the idle zone, between 0 and 4 MPa. In turn, the simulation with loading varied according to a sine wave presents a more comprehensive idle zone, reaching 6 MPa. For this wave pattern, and parameters adopted in the study, the simulation shows that the idle zone can vary in the level of stress capable of causing sufficient deformations, with the capability of changing the flow of canalicular fluid, and trigger the biochemical and cellular response.

The second range contains the stress limits at which bone remodeling can occur, causing an increase in BMD [16]. This range causes the expected effect on the behavior of bone tissue, resulting in increased density and promoting osseointegration. The simulations indicate that the behavior of the bone tissue becomes even more non-linear as the stress level increases. In this range, stressess cause deformations that alter the flow pattern of canalicular fluid to the point of triggering bone remodeling with increasing density. In the varied loading with sine-cosine wave pattern, the bone remodeling range is the one with the lowest amplitude (6 and 9 MPa) among the simulated ones, and in the varied loading with sine pattern this range starts from a higher stress level (8 MPa).

The third loading range has an overload level that does not promote bone remodeling, but causes resorption with loss of bone density. In this range, the deformations can be increased to the point of causing fractures in the bone tissue. The stresses also has no linear behavior for each type of loading. The response of the behavior of bone tissue in relation to the level of overload may vary depending on the type of loading and the form of variation, and increase or decrease the limit of overload of the tissue. The results show that for a static load the overload limit is 12MPa, while for varied loading with a sine wave pattern the overload limit rises to 14 MPa. However, when the sine-cosine wave pattern is varied, the overload limit drops to 9 MPa (Figure 4).

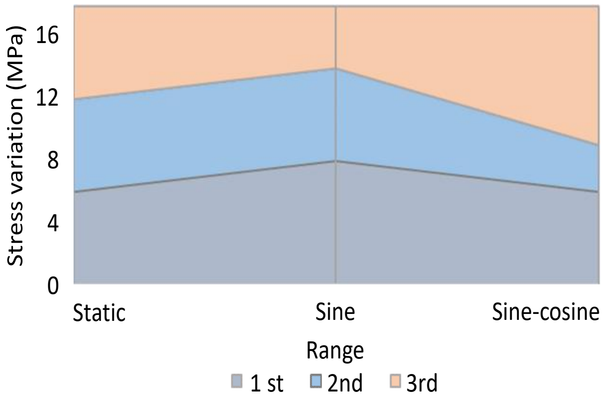

Fig.4. Loading ranges - Stress variation x Stimulus type.

From the above, the simulations point out that the way of applying mechanical stimuli influences the bone density response, being able to alternate between resorption and remodeling for the same loading level. Thus, the model developed can contribute to meeting clinical demands, since it provides the responses of bone behavior as a function of mechanical stimuli.

VARIATION ACCORDING TO STIMULUS AND STRESS

Findings show that there is no single condition of mechanical stimulus capable of providing an increase in bone density, but that changing the type of loading allows variable responses to be reached for the same stress levels (Table 2). The reference value used in the simulation for the standard density was 1.0 g.cm^{-3}.

Table 4. Variation in BMD according to stimulus and stress.

Stress (MPa)	Static loading		Variable loading: Sine wave		Variable loading: Sine-cosine wave	
	Density (g.cm^{-3})	Variation (%)	Density (g.cm^{-3})	Variation (%)	Density (g.cm^{-3})	Variation (%)
0	0.00	-----	0.00	-----	0.00	-----
2	0.60	-40	0.41	-59	0.50	-50
4	0.85	-15	0.61	-39	0.74	-26
6	1.04	4	0.76	-24	1.10	10
8	1.20	20	1.05	5	1.22	22
9	1.28	28	1.10	10	1.29	29
10	1.35	35	1.15	15	0.00	-100
12	1.48	48	1.25	25	0.00	-100
14	0.00	-100	1.35	35	0.00	-100

The application of static mechanical stimuli provided a bone density variation with an increase in density between stress levels 6 and 12 MPa, allowing bone tissue development from 4 to 48% by mass. On the other hand, stress levels outside this range (6 to 12 MPa) cause bone loss.

In the varied loading with sine wave pattern, the results show a different behavior. The increase in bone density starts from 8 MPa and goes up to 14 MPa, varying between 5% and 35%. It is worth mentioning that for the stress level of 14 MPa, the simulation pointed out that the type of loading alters the behavior of bone tissue, influencing from resorption to increased density. The simulation with sine-cosine wave pattern resulted in an increase in density between 10% and 29% in the stress range of 6 to 9 MPa. The outcomes show that the density gain is greater than those obtained in other types of loading for the same stress levels.

These findings indicate that the use of different forms of load influences the increase in BMD, but also can cause the increase in bone loss (Figure 5).

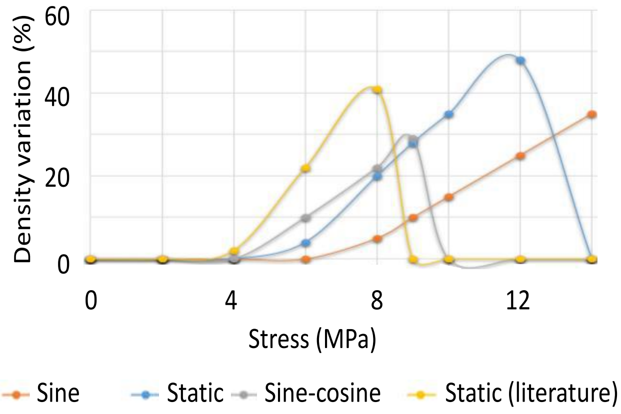

Fig.1 Density Variation x Strees level by type of loading.

Previous results have been based on the Euler method, to emulate the behavior of the tissue in response to mechanical stimuli [12]. As an alternative, this study introduced a model based on the 5th order Rung Kutta (RK) integration method, which provides more accurate results, with less computational effort. The outcomes obtained by Li et al. [12] are presented in Table 5.

Table 5. Variation in bone density in response to loading.

Stress (MPa)	Density (g.cm^{-3})	Variation(%)
0	0.00	-100
2	0.72	-28
4	1.02	2
6	1.22	22
8	1.41	41
9	0.00	-100

Source: elaborated from Li et al. [12].

Analyzing Table 5, it is noted that the authors applied the maximum limit of 9 MPa, with a reference density value for analysis of variation equal to 1.0 g.cm-3, the same one adopted in our study. The results of the literature indicate that the first stress range, which represents insufficient levels to activate cellular processes, is between 0 and 2 MPa. The increase in BMD starts from 4 MPa and extends to 8 MPa (second range), with the overload level reached 9 MPa (third range). Table and Figure 6 present a comparison between the results in the literature and those obtained in this study.

Table 6. Comparison of results for static loading.

	Range 1 (MPa)	Range 2 (MPa)	Range 3 (MPa)
fifth-order Rung-Kutta	$0 \leq \sigma < 6$	$6 \leq \sigma \leq 12$	$\sigma > 12$
Li et al. (2007)	$0 \leq \sigma < 4$	$4 \leq \sigma \leq 8$	$\sigma > 8$

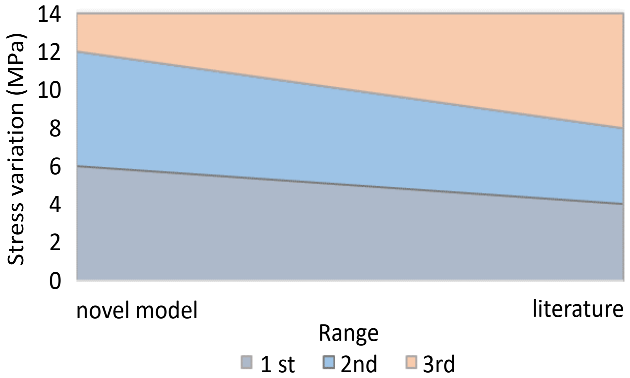

Fig.6. Comparison of results for static loading.

V. CONCLUSION

Assessing the variation in bone mineral density (BMD) remains a complex task, given the countless variables and parameters that constitute the boundary conditions. This study introduced a novel model developed to analyze the variation in BMD, as a response to the application of mechanical stimuli. From our results, it is highlighted that the behavior of bone tissue doesn't have a linear response to different types of mechanical stimuli, both static and variable. The loading ranges, both for stresses that cause bone resorption, for those capable of promoting an increase in density, or causing fractures in the tissue, may vary according to the type of mechanical stimulus. In conclusion, the results corroborate the promising viability of using mechanical stimuli to increase bone density. The simulations pointed that the loadings can be applied with different types of stimulus. The modeling was able to measure stress loads, indicated to obtain a better response to dental treatments.

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An acknowledgement section may be presented after the conclusion, if desired.

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