Research Article

# Numerical investigations of bone remodelling around the mouse mandibular molar primordia

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## ARTICLE INFO

## ABSTRACT

The formation of the alveolar bone, which houses the dental primordia, and later the roots of tooth, may serve as a model to approach general questions of alveolar bone formation. In this respect, this study aimed to investigate the potential interactions between the alveolar bone formation and tooth eruption by using finite element (FE) methods, and to figure out whether the expanding tooth systems induce shear stresses that lead to alveolar bone formation. 3D geometric surface models were generated from the 3D histological data of the heads of mice (C57 Bl/6J) ranging from stages embryonic (E) to postnatal (P) stages E15 to P20 using the reconstruction software 3-Matic. Bone, dentin, enamel and dental follicle around the primordia were generated and converted into 3D FE models. Models were imported into the FE software package MSC.Marc/Mentat. As material parameters of embryonic dentine, pulp, enamel, dental follicle, and bony structures basically are unknown, these were varied from 1% to 100% of the corresponding known material parameters for humans and a sensitivity analysis was performed. Surface loads were applied to the outside surface of dental follicle ranging from 0.1 to 5.0 N/mm². The validity of the model was analysed by comparing the activity pattern of the alveolar bone as determined in the histological study with the loading pattern from the numerical analysis. The results show that when varying the surface loads, the distribution of shear stresses remained same, and while varying the material properties of the hard tissues, the location of highest shear stresses remained stable. Comparison of the histologically determined growth regions with the distribution of shear stresses computed in the numerical model showed a very close agreement. The results provide a strong proof to support Blechschmidt's hypothesis that the bone in general is created under the influence of shear forces.

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## 1. Introduction

The degradation of the alveolar bone over time is a common clinical finding in most human adults (Abuohashish et al., 2018; Lee et al., 2013), and subclinical chronic inflammation is one of the most common conditions resulting in the loosening and/or loss of teeth due to the loss of alveolar bone (Iqbal et al., 2017; Minamizato et al., 2018; Ozaki et al., 2017). Therefore, periodontal regenerative ther-

apy aiming to maintain the height and shape of the alveolar bone is critical for dental health. However, the restoration of the alveolar bone has been a challenge in periodontal regenerative therapy for years (Ou et al., 2015). The challenge is not only the regeneration of the alveolar bone, but also its formation. The alveolar bone is prone to damage by occlusal pressure, inflammation, and disease, and detailed understanding of alveolar bone development is necessary to improve the treatment involving periodontal tissue regeneration.

Alveolar bone development is closely related to tooth eruption. During tooth eruption, the dental follicle around the tooth germ is considered as one of the main sources of periodontal structures, including alveolar bone (Wise and King, 2008). The dental follicle not only serves as a source of periodontal tissue, but also trans-

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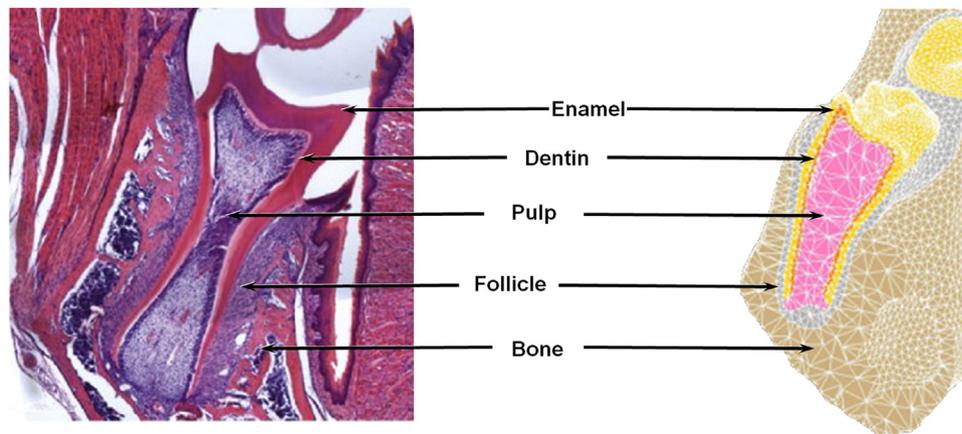
**Fig. 1.** Histological section through dental primordium m1, stage P10, vertical plane, stained H.&E., taken from a continuous series of sections (left) and 3D FE model (right). Histological serial sections were segmented and reconstructed in 3D (Radlanski et al. 2015) and the datasets converted into 3D finite element models by using the software Mimics and MSC.Marc/Mentat. As an example, the transition from a single histological section to the FE finite element model is shown here, using the primordium of m₁ in developmental stage P10.

mits the forces from tooth to the alveolar bone which may induce the bone development (Kjaer, 2014). The formation of the tooth-bone-interface (Alfaqeeh et al., 2013; Fleischmannova et al., 2010; Lungová et al., 2011) has become the focus of current research. From the biochemical and mechanical point of view, the active interaction between the related tissues may be well expected from their close proximity: Bony encapsulation of dental primordia, as a spatial impediment, may be seen as one of the morphogenetic factors (Oralová et al., 2014; Radlanski, 2018).

The functional adaptation of alveolar bone to applied loading and forces is important for bone formation (Field et al., 2008). The forces originating from the tooth development and eruption are transmitted by mesenchyme to the dental follicle, and induce the expanding forces. The mode in which expanding forces of teeth are transferred into the alveolar bone justifies the need to clarify the distributions of stress and relate them to biological responses such as the bone remodelling. Bone deformation is studied by investigating its ability to sustain strain, which is a biological reaction to changes in the environment. Although the mechanism that drives bone remodelling through mechanical strain is still not very clear, a phenomenological relationship between force and bone reaction is obvious (Rungsiyakull et al., 2011; Sarrafpour et al., 2012; Torcasio et al., 2014).

Nowadays, the finite element method (FEM) plays an important role in solving engineering problems in many fields of science. The FEM can successfully be applied in simulations of biomechanical systems (Martinez Choy et al., 2017; Pahr and Zysset, 2016; Prochor and Sajewicz, 2018). The very dynamic temporal change in bone structure by healing and bone remodelling cannot directly be detected, neither by experimental methods nor using standard finite element methods. There is a paucity of studies on the morphological and biomechanical level dealing with the structural formation of alveolar bone and the tooth eruption. The formation of the alveolar bone, which houses the dental primordia, and later the roots of tooth, may serve as a model to approach general questions of alveolar bone formation. In this respect, this study aims to investigate the potential interactions between the alveolar bone formation and tooth eruption by using finite element methods, and to figure out whether the expanding tooth systems induce shear stresses that lead to alveolar bone formation.

## 2. Material and methods

In a previous study (Radlanski et al., 2015), 38 heads of mice (C57 Bl/6J) at different stages (embryonic (E) days 13, 14, 15, 16, 17, and 18 and postnatal (P) days 0, 4, 6, 8, 10, 14, 10 and 20) were used to prepare histological serial sections. The mouse of embryonic day 13 was recorded as E13 stage or stage E13, and so on in the other stages. For each stage, 3D reconstructions were made to study the morphogenesis of the mandibular molar primordia concomitantly with their surrounding bone. The thickness of each section was 8 μm in the prenatal stages, and 10 μm in the postnatal stages. The sections were photographed and digitized using a VS 100 (Olympus, Berlin) microscope, equipped with a motorized stage (x, y, and z axes) at magnifications between 1.25× to 40×. The 3D-module of the software Analysis (SIS-Olympus, Münster, Germany) was used to generate 3D-images from the serial sections. The single sections were brought into alignment according to the general rules of 3D reconstructions (Gaunt and Gaunt, 1978). Regions of apposition and resorption were mostly verified by analyzing the predominant cell type (osteoblasts and osteoclasts) morphologically (Garant, 2003), and also the presence of resorptive lacunae. Details can be found in previous papers (Radlanski et al., 2015, 2016).

3D data of specimens were imported into 3-Matic research 9.0 (Materialise NV, Leuven, Belgium). Thereafter, bone, dentin, enamel and dental follicle around the primordia were generated respectively and converted into 3D FE models using 4-noded tetrahedral elements, i.e. linear Lagrangian elements were used. Models were imported into the FE software package MSC.Marc/Mentat 2010 (MSC.Software, Santa Ana, CA, USA, Fig. 1). Material properties of the relevant anatomical structures were derived from values stated in the literature (Sarrafpour et al., 2013): As material parameters of embryonic bone, dentin, enamel and dental follicle structures basically are unknown, these were varied from 1% to 100% of the corresponding known material parameters for humans (Table 1) and a sensitivity analysis was performed. Surface loads were applied to the surface of dental follicle (Fig. 2) ranging from 0.1 N/mm² to 5.0 N/mm² (Burn-Murdoch, 1981) and the results were compared with the histological results. To ensure definiteness of the problem, we applied fixed boundary conditions in all three planes of space on a series of outer nodes of the mesh, at the basal aspect of the alveolar bone.

**Table 1**
Material properties used in the numerical models.

| Material | Young's modulus | Poisson's ratio |
|---|---|---|
| Bone[a] | 150–1500 | 0.30 |
| Enamel | 841–84,100 | 0.20 |
| Dentin | 186–18,600 | 0.31 |
| Pulp & papilla | 2 | 0.45 |
| Follicle & epithelium | 12 | 0.45 |

[a] The bone is taken as spongious bone because the cortical bone is not yet formed according to the histologic sections.
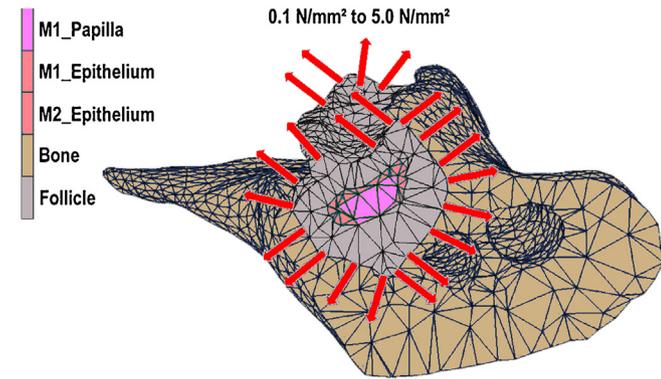


**Fig. 2.** Expanding of dental primordia loading conditions where the surface of dental follicle is subjected to surface loads of 0.1 to 5.0 N/mm² (red arrwos), using model of the dental follicle in development stage E16 as an example.

## 3. Results

The contours of the shear stresses developed in every relative stiffness scenario are shown in Fig. 3. For each development stage the location of highest shear stresses and distribution of shear stress remained stable under variation of the material properties of the hard tissues. Taking the model of bone in developmental stage E16 as an example, Fig. 3 shows that the highest shear stress increased from 4.5e-3 to 5.5e-2 with the relative stiffness of hard tissue increasing from 1% to 100%. However, the location of highest shear stresses and distribution of shear stress remained stable. The shear stress analysis showed that in all the cases the shear stresses were mainly distributed on the outer side of the alveolar bone and the highest shear stress was located nearby at the top of the alveolar bone.

For each development stage, the distribution of shear stresses remained the same while the value of the surface loads varied (Fig. 4). Taking the model of bone in development stage E16 as an example, the surface of dental follicle was applied 50 different surface loads from 0.1 N/mm² to 5.0 N/mm². Models with surface loads of 0.1 N/mm², 0.5 N/mm², 1.0 N/mm², 5.0 N/mm² are displayed in Fig. 4, and the values of highest shear stress were 4.5e-3, 2.5e-2, 5.0e-2 and 3.0e-1, respectively. Moreover, the distribution of shear stresses in all models remained the same. The shear stresses were mainly distributed on the outer side of the alveolar bone.

Comparison of the histologically determined growth regions with the distribution of shear stresses computed in the numerical models showed a very close agreement between experimental and numerical results (Figs. 5 and 6). The marginal ridges of the dental crypts and the outer side of the alveolar bone showed bone apposition in the 3D reconstruction from histological serial sections and the bottom of the dental crypts were characterised by resorption in the previous study (Radlanski et al., 2016). The numerical results indicated that both, the apposition regions and the shear stress areas, were distributed almost at the same regions, the marginal ridges of the dental crypts and the outer side of the alveolar bone.

## 4. Discussion

Blechschmidt (1948, 2004) has put forward a hypothesis that bone formation in the embryo is found in regions, where the connective tissue undergoes detraction. He arrived at this assumption after meticulous studies of histological serial sections of different
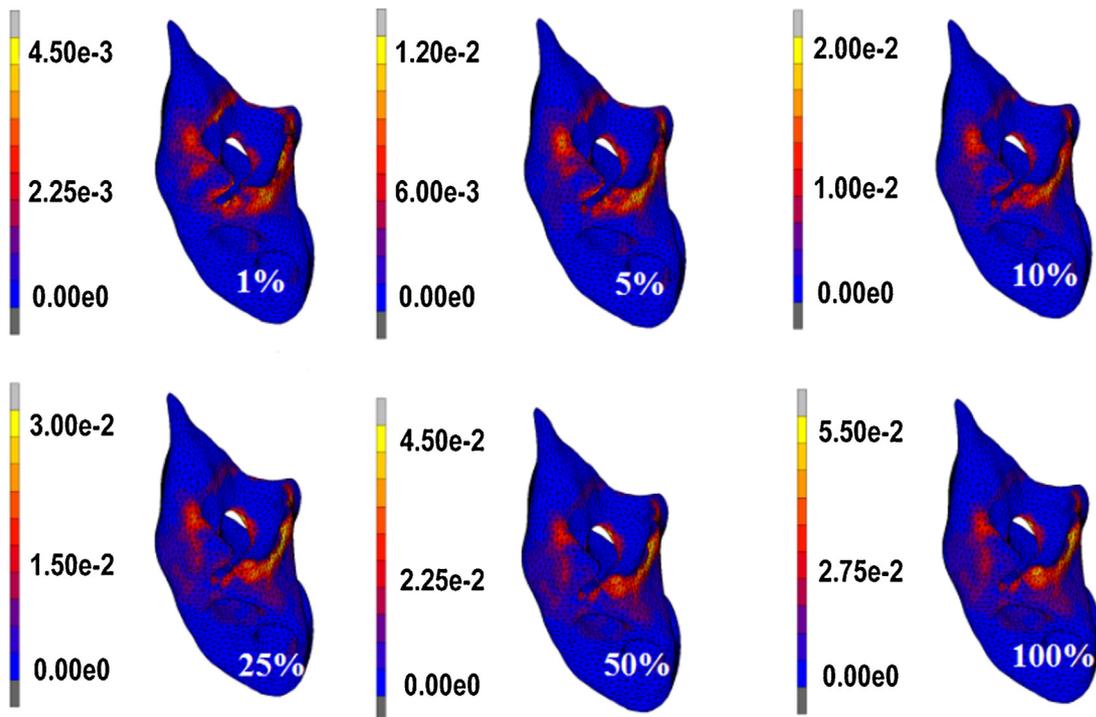


**Fig. 3.** Distribution of shear stresses and location of the highest shear stresses remained stable in all models with hard tissue assigned relative stiffness ranging from 1% to 100% of relevant human mechanical properties, using the model of bone in development stage E16 as an example.
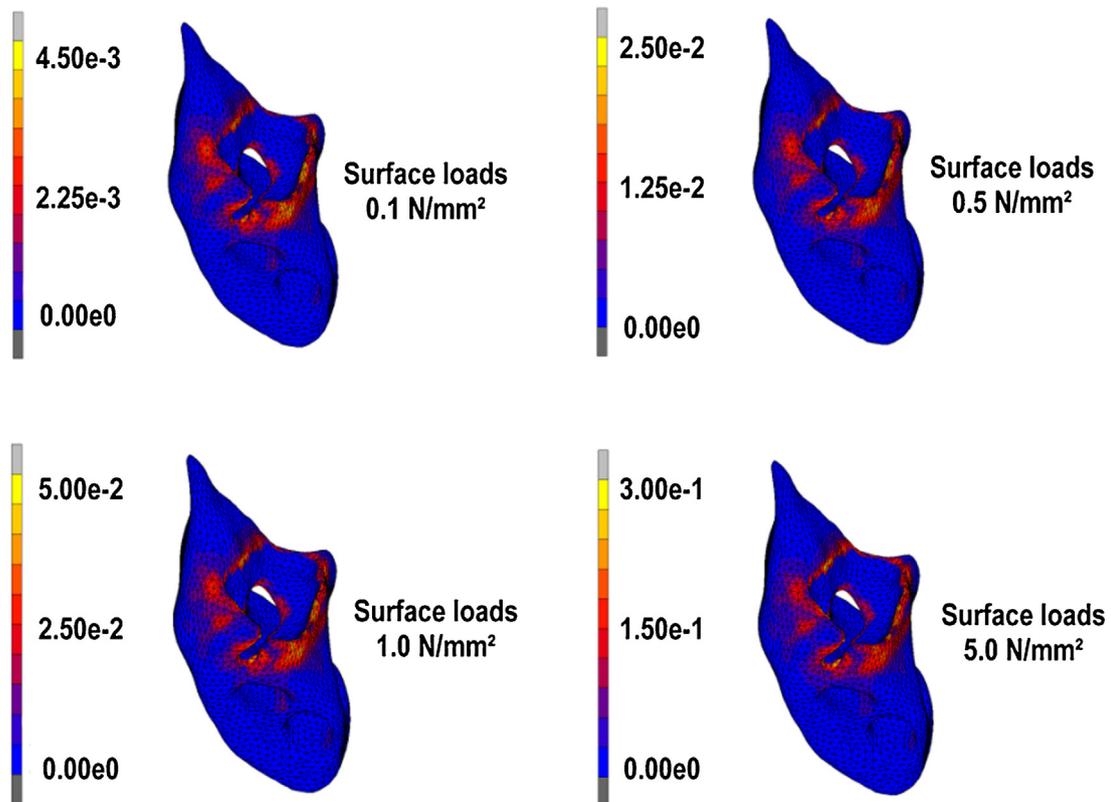
**Fig. 4.** Distribution of shear stress maintains equal (or similar) in all models with the surface of the dental follicle with altered surface loads from 0.1 N/mm$^2$ to 5.0 N/mm$^2$, using the model of bone in development stage E16 as an example.
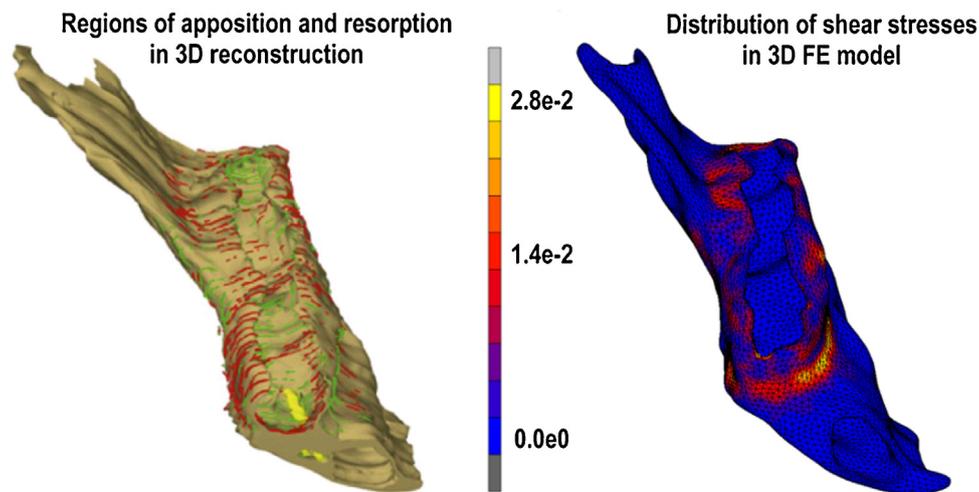


**Fig. 5.** 3D reconstruction of the molar region of the right half of the mandible in an anterior and 45° cranial view created from histologic serial sections. Dental primordia removed, ocre: bone; mandibular bone with superimposed remodelling marks (red for apposition, green for resorption). Marked apposition and resorption areas in the 3D reconstruction relate to histological findings in the serial sections. Here, the model of bone in development stage P10 was used as an example. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

developmental stages of human embryos (Blechschmidt, 1960). Due to technical obstacles, this hypothesis cannot easily be tested in living specimens, but there are hints and obvious findings that detraction can be derived from celluar shape next to newly formed bone. Although, "signalling" did predominate explanations (Mina, 2001), of how form is being created, mechanical quantities such as strain and stress play a role (Ingber, 2005), or at least, a combination of both (de la Fuente and Helms, 2005; Radlanski and Renz, 2006; Papachristou et al., 2009). The tooth-bone-interface is an interesting location to study bone formation and bone shape.

Blechschmidt postulated that bone formation is triggered by shearing forces (Blechschmidt, 1948, 2004). Thus we analysed the distribution of shear stresses in the bone around the mouse mandibular molar primordia under expanding forces generated by the emerging teeth. For each development stages, comparison of the histologically determined growth regions with the distribution of shear stresses computed in the numerical model showed a very close agreement between experimental and numerical results (Fig. 5). This fully demonstrates the close correlation between shear stresses and the alveolar bone remodelling. It indicates that dur-
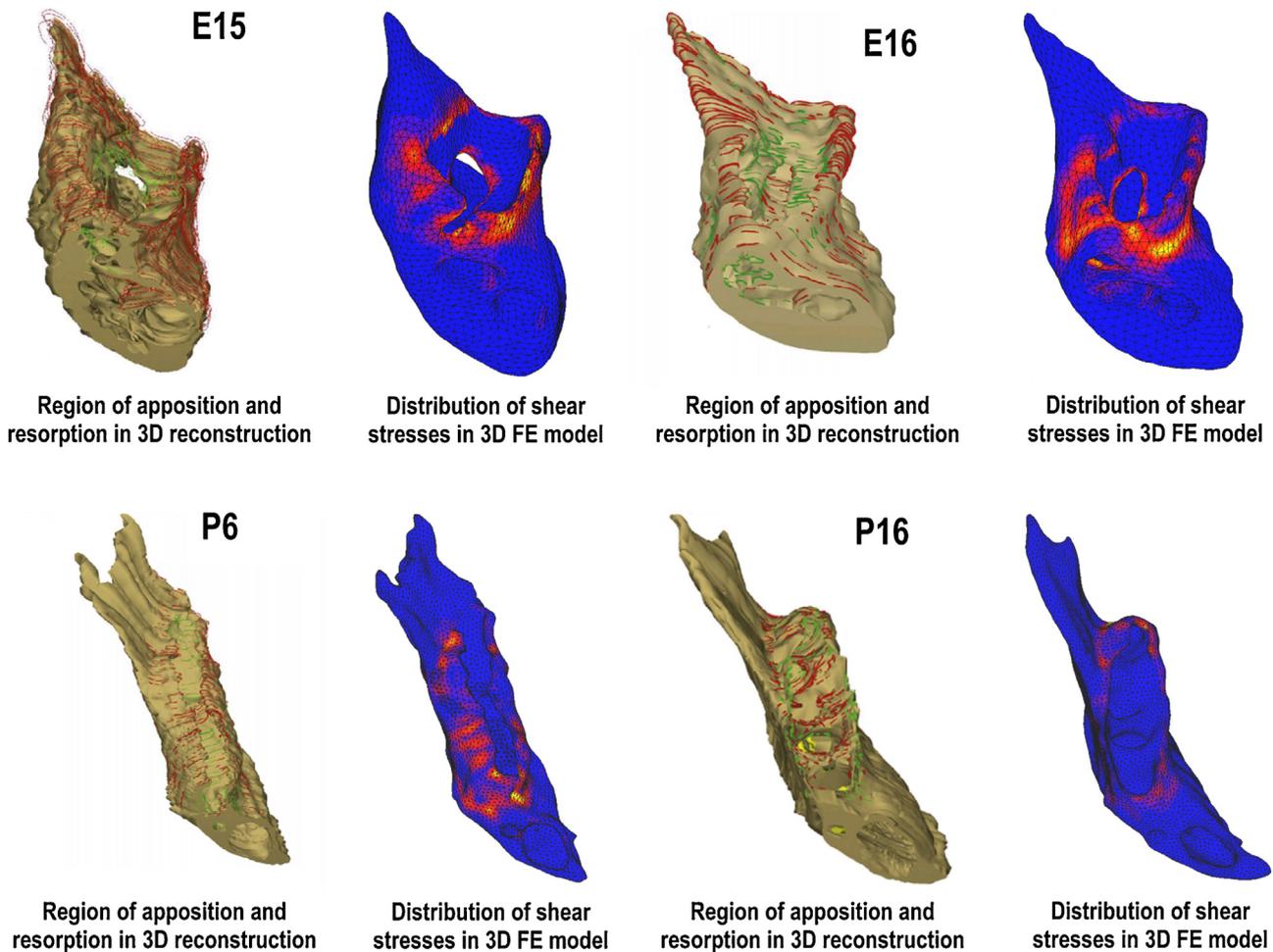
**Fig. 6.** Comparison of histologically determined remodelling regions in 3D reconstruction and distribution of shear stresses in FE models at each development stages. For color codes, refer to Fig. 5.

ing the process of volume increase and tooth eruption, the shear stress produced from expanding dental primordia may lead to the formation of alveolar bone.

With this study we could not experimentally test the hypothesis, if bone is being formed from connective tissue under the influence of detraction forces, as formulated by Blechschmidt (2004). However, we could show the formation of new bone around the developmental dental primordial. In a way, this is similar: Bone is being formed in regions, where it has not been before in previous stages, and it forms in regions where we could calculate shearing forces originating from the expanding dental primordial.

We know from bone remodelling that alveolar bone is linked with the condition of teeth. Especially, at the stage of dental development, the alveolar bone is continuously stimulated due to the constant change of teeth. Most scientists suggest that the mechanical stimulation of tooth eruption causes the remodelling of alveolar bone (Wise and King, 2008; Sarrafpour et al., 2013; Kjaer, 2014). However, until now it remains elusive, how and why the alveolar bone remodelling moves teeth along their eruptive path (Rakian et al., 2013; Lamani et al., 2015; Wang and Feng, 2017). To the best of our knowledge, this is the first time that biomechanical methods were used to study bone remodelling around the primordia and achieved gratifying results.

In this study, the material properties of the relevant anatomical structures in the FE models were taken from the literature whenever available. However, there is no material data available for bone, enamel and dentin at the development stages. It may be assumed

that they show higher elasticity in this state than the corresponding adult tissue. Therefore the stiffness of these materials was varied to a relative stiffness of 1%, 5%, 10%, 25%, 50% and 100% of respective adult values and the influence of relative stiffness on distribution of stress was analysed. It is found that although the highest value of shear stresses changed from $4.5 \times 10^{-3}$ to $5.5 \times 10^{-2}$, the location of the maximum values remained stable and the distribution of shear stresses also remained stable in the stage E16 under $0.1 \text{ N/mm}^2$ surface loads (Fig. 2). The results were also the same in other developmental stages.

As the exact size of the expanding force from dental primordial is unknown, we refer to an eruptive force of $0.1–1.1 \text{ N/mm}^2$, which has been measured for the continuously growing rodent incisor by Burn-Murdoch (1981). In our simulations, the value of the surface loads applied on the surface of dental follicle was varied from $0.1 \text{ N/mm}^2$ to $5.0 \text{ N/mm}^2$ and the results were compared with the histological results. Obviously, the distribution of shear stresses remained the same under different surface loads, just the values of the stresses varied. Thus it may be concluded that if the material properties of the relevant anatomical structures are determined, the exact size of the expanding force could be derived by applying the mechanostat theory. This suggests that an effective strain below 0.0008 or above 0.02 will enable the bone to resorb or turnover, respectively (Lerebours and Buenzli, 2016; Mahnama et al., 2013). This could lead to more accurate 3D FE models and respective simulation results.

The shear stress profiles within the bone around mouse mandibular molar upon expanding force of dental primordia were evaluated in varying stiffness values of hard tissue and varying surface load models, respectively. A detailed analysis into the biomechanics of the bone around the dental primordia as a result of tooth eruption force can be useful to gain insight to fully understand the biomechanical responses that are indicative of alveolar bone remodelling. Establishing relationships between tooth eruptive forces and resulting change in bone morphology around the primordia can considerably supplement clinical procedures in restorative alveolar bone therapy.

The morphology and microstructure of bone are largely influenced by mechanical load. The ability of bone to adapt to function load change is very important, and the biological response to mechanical stress is mainly based on tissue and cell deformation. It is maintained that alveolar bone is tooth-germ-related (Radlanski et al., 2016). During tooth eruption, the dental follicle has been described as the active tissue in regulating bone resorption and creating a path through the bone (Fontanetti et al., 2013; Tuncer et al., 2017; Wise et al., 2005; Wise et al., 2006). However, the exact biomechanical mechanism of tooth eruption, which eventually leads to bone remodelling, remains unclear.

It was assumed that shearing forces may be a trigger for bone formation during embryonic development (Blechschmidt, 1948, 2004) and during bone remodelling (Frost, 2003; Klein-Nulend et al., 2005; Proffit et al., 2006). The comparison between the regions of newly formed bone and the calculated presence of shearing forces, as we have done in this study, may be seen as a strong hint. The putative forces, however, which may be exercised by the expanding primordia, have not yet been elucidated, and to what degree this shearing force might induce cellular differentiation processes needs further clarification.

## 5. Conclusion

The results of this research provide a strong hint to support Blechschmidt's hypothesis that bone is being created under the influence of shear forces, which is exercised from neigboring tissue. In this study, we compared the regions of newly formed bone around expanding dental primordia with possible forces calculated from FE-models obtained from the data sets of the histological 3D-reconstruction. We found newly formed bone in the same regions, where calculated shearing forces were highest.

It is one of the keys to understand the mechanisms of the alveolar bone formation and remodelling and might contribute to the regenerative treatment of alveolar bone atrophy in clinical practice.

In future research, we will clarify the size of the expanding force from the dental primordia and determine the material properties of the relevant anatomical structures, enabling the generation of more accurate numerical models with more reliable results, even more consistent with the available histological data.

## Acknowledgements

## References

Abuohashish, H.M., Khairy, D.A., Abdelsalam, M.M., Alsayyah, A., Ahmed, M.M., Al-Rejaie, S.S., 2018. In-vivo assessment of the osteo-protective effects of eugenol in alveolar bone tissues. Biomed. Pharmacother. 97, 1303–1310.

Alfaqeeh, S.A., Gaete, M., Tucker, A.S., 2013. Interactions of the tooth and bone during development. J. Dent. Res. 92, 1129–1135.

Blechschmidt, E., 1948. Mechanische Genwirkungen. Musterschmidt, Göttingen.

Blechschmidt, E., 1960. The Stages of Human Development before Birth. Karger Basel.

Blechschmidt, E., 2004. In: Freeman, B. (Ed.), The Ontogenetic Basis of Human Anatomy: The Biodynamic Approach to Development from Conception to Adulthood. North Atlantic Books, Berkely.

Burn-Murdoch, R.A., 1981. The effect of applied forces on the eruption of rat maxillary incisors. Arch. Oral Biol. 26, 939–943.

Field, C., Li, Q., Li, W., Swain, M., 2008. Influence of tooth removal on mandibular bone response to mastication. Arch. Oral Biol. 53, 1129–1137.

Fleischmannova, J., Matalova, E., Sharpe, P.T., Misek, I., Radlanski, R.J., 2010. Formation of the tooth-bone interface. J Dent. Res. 89, 108–115.

Fontanetti, P.A., De Lucca, R.C., Mandalunis, P.M., Vermouth, N.T., 2013. Impairment of rat tooth eruption in pups born to mothers exposed to chronic stress during pregnancy. Arch. Oral Biol. 58, 1643–1651.

Frost, H.M., 2003. Bone's mechanostat: a 2003 update. Anat. Rec. A Discov. Mol. Cell. Evol. Biol. 275, 1081–1101.

de la Fuente, L., Helms, J.A., 2005. Head, shoulders, knees, and toes. Dev. Biol. 15, 294–306.

Garant, P.R., 2003. Oral Cells and Tissues. Quintessence Publishing Co., Chicago.

Gaunt, P.N., Gaunt, W.A., 1978. Three Dimensional Reconstruction in Biology. Pittman Medical Publications, London.

Ingber, D.E., 2005. Mechanical control of tissue growth: function follows form. PNAS 102, 11571–11572.

Iqbal, H., Ali, M., Zeeshan, R., Mutahir, Z., Iqbal, F., Nawaz, M.A.H., Shahzadi, L., Chaudhry, A.A., Yar, M., Luan, S., Khan, A.F., Rehman, I.U., 2017. Chitosan/hydroxyapatite(HA)/hydroxypropylmethyl cellulose (HPMC) spongy scaffolds-synthesis and evaluation as potential alveolar bone substitutes. Colloids Surf B Biointerfaces 160, 553–563.

Kjaer, I., 2014. Mechanism of human tooth eruption: review article including a new theory for future studies on the eruption process. Scientifica (Cairo) 2014, 341905.

Klein-Nulend, J., Bacabac, R.G., Mullender, M.G., 2005. Mechanobiology of bone tissue. Pathol. Biol. (Paris) 53, 576–580.

Lamani, E., Gluhak-Heinrich, J., MacDougall, M., 2015. NFI-C2 temporal-spatial expression and cellular localization pattern during tooth formation. Dev. Growth Differ. 57, 625–638.

Lee, J.Y., Kim, Y.K., Yi, Y.J., Choi, J.H., 2013. Clinical evaluation of ridge augmentation using autogenous tooth bone graft material: case series study. J. Korean Assoc. Oral Maxillofac. Surg. 39, 156–160.

Lerebours, C., Buenzli, P.R., 2016. Towards a cell-based mechanostat theory of bone: the need to account for osteocyte desensitisation and osteocyte replacement. J. Biomech. 49, 2600–2606.

Lungová, V., Radlanski, R.J., Tucker, A.S., Renz, H., Míšek, I., Matalová, E., 2011. Tooth-bone morphogenesis during postnatal stages of mouse first molar development. J. Anat. 218, 699–716.

Mahnama, A., Tafazzoli-Shadpour, M., Geramipanah, F., Mehdi Dehghan, M., 2013. Verification of the mechanostat theory in mandible remodeling after tooth extraction: animal study and numerical modeling. J. Mech. Behav. Biomed. Mater. 20, 354–362.

Martinez Choy, S.E., Lenz, J., Schweizerhof, K., Schmitter, M., Schindler, H.J., 2017. Realistic kinetic loading of the jaw system during single chewing cycles: a finite element study. J. Oral Rehabil. 44, 375–384.

Mina, M., 2001. Regulation of mandibular growth and morphogenesis. Crit. Rev. Oral Biol. Med. 12, 276–300.

Minamizato, T., Koga, T., I, T., Nakatani, Y., Umebayashi, M., Sumita, Y., Ikeda, T., Asahina, I., 2018. Clinical application of autogenous partially demineralized dentin matrix prepared immediately after extraction for alveolar bone regeneration in implant dentistry: a pilot study. Int. J. Oral Maxillofac. Surg. 47, 125–132.

Oralová, V., Chlastáková, I., Radlanski, R.J., Matalová, E., 2014. Distribution of BMP6 in the alveolar bone during mouse mandibular molar eruption. Connect. Tissue Res. 55, 357–366.

Ou, M., Zhao, Y., Zhang, F., Huang, X., 2015. Bmp2 and Bmp4 accelerate alveolar bone development. Connect. Tissue Res. 56, 204–211.

Ozaki, Y., Koide, M., Furuya, Y., Ninomiya, T., Yasuda, H., Nakamura, M., Kobayashi, Y., Takahashi, N., Yoshinari, N., Udagawa, N., 2017. Treatment of OPG-deficient mice with WP9QY, a RANKL-binding peptide, recovers alveolar boneloss by suppressing osteoclastogenesis and enhancing osteoblastogenesis. PLoS One 12, e0184904.

Pahr, D.H., Zysset, P.K., 2016. Finite element-based mechanical assessment of bone quality on the basis of in vivo images. Curr. Osteoporos. Rep. 14, 374–385.

Papachristou, D.J., Papachroni, K.K., Papavassiiou, G.A., Pirttiniemi, P., Gorgoulis, V.G., Basdra, E.K., 2009. Functional alterations in mechanical loading of condylar cartilage induces changes in bony subconylar region. Arch. Oral Biol. 54, 1035–1045.

Prochor, P., Sajewicz, E., 2018. A comparative analysis of internal bone remodeling concepts in a novel implant for direct skeletal attachment of limb prosthesis evaluation: a finite element analysis. Proc. Inst. Mech. Eng. H 232, 289–298.

Proffit, W.R., van der Linden, F.P., McNamara, J., Radlanski, J., Pancherz, R.J.H., 2006. Facial Growth, Dentition and Function. Quintessence Publishing Group, Berlin.

Radlanski, R.J., Renz, H., 2006. Genes, forces, and forms. mechanical aspects during prenatal craniofacial development. Dev. Dyn. 235, 1219–1229.

Radlanski, R.J., Renz, H., Zimmermann, C.A., Mey, R., Matalova, E., 2015. Morphogenesis of the compartmentalizing bone around the molar primordia in the mouse mandible during dental developmental stages between lamina, bell-stage, and root formation (E13-P20). Ann. Anat. 200, 1–14.

Radlanski, R.J., Renz, H., Zimmermann, C.A., Schuster, F.P., Voigt, A., Heikinheimo, K., 2016. Chondral ossification centers next to dental primordia in the human mandible: a study of the prenatal development ranging between 68 to 270 mm CRL. Ann. Anat. 208, 49–57.

Radlanski, R.J., 2018. Oral Structure and Biology. Quintessence Publishing, Chicago.

Rakian, A., Yang, W.C., Gluhak-Heinrich, J., Cui, Y., Harris, M.A., Villarreal, D., Feng, J.Q., Macdougall, M., Harris, S.E., 2013. Bone morphogenetic protein-2 gene controls tooth root development in coordination with formation of the periodontium. Int. J. Oral Sci. 5, 75–84.

Rungsiyakull, C., Rungsiyakull, P., Li, Q., Li, W., Swain, M., 2011. Effects of occlusal inclination and loading on mandibular bone remodeling: a finite element study. Int. J. Oral Maxillofac. Implants 26, 527–537.

Sarrafpour, B., Rungsiyakull, C., Swain, M., Li, Q., Zoellner, H., 2012. Finite element analysis suggests functional bone strain accounts for continuous post-eruptive emergence of teeth. Arch. Oral Biol. 57, 1070–1078.

Sarrafpour, B., Swain, M., Li, Q., Zoellner, H., 2013. Tooth eruption results from bone remodelling driven by bite forces sensed by soft tissue dental follicles: a finite element analysis. PLoS One 8, e58803.

Torcasio, A., Jähn, K., van Guyse, M., Spaepen, P., Tami, A.E., vander Sloten, J., Stoddart, M.J., van Lenthe, G.H., 2014. Trabecular bone adaptation to low-magnitude high-frequency loading in microgravity. PLoS One 9, e93527.

Tuncer, I., Delilbasi, C., Deniz, E., Soluk Tekkesin, M., Olgac, V., Sencift, K., 2017. Effects of pamidronate administration on tooth eruption and mandibular growth in new born rats. J. Istanbul Univ. Facult. Dent. 51, 8–14.

Wang, J., Feng, J.Q., 2017. Signaling pathways critical for tooth root formation. J. Dent. Res. 96, 1221–1228.

Wise, G.E., Yao, S., Odgren, P.R., Pan, F., 2005. CSF-1 regulation of osteoclastogenesis for tooth eruption. J. Dent. Res. 84, 837–841.

Wise, G.E., Yao, S., Liu, D., 2006. Injections of osteoprotegerin and PMA delay tooth eruption. Clin. Anat. 19, 19–24.

Wise, G.E., King, G.J., 2008. Mechanisms of tooth eruption and orthodontic tooth movement. J. Dent. Res. 87, 414–434.