

# Computational modelling of biomaterial surface interactions with blood platelets and osteoblastic cells for the prediction of contact osteogenesis

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## ABSTRACT

Surface microroughness can induce contact osteogenesis (bone formation initiated at the implant surface) around oral implants, which may result from different mechanisms, such as blood platelet–biomaterial interactions and/or interaction with (pre-)osteoblast cells. We have developed a computational model of implant endosseous healing that takes into account these interactions. We hypothesized that the initial attachment and growth factor release from activated platelets is crucial in achieving contact osteogenesis. In order to investigate this, a computational model was applied to an animal experiment [7] that looked at the effect of surface microroughness on endosseous healing. Surface-specific model parameters were implemented based on *in vitro* data (Lincks et al. *Biomaterials* 1998;19:2219–32). The predicted spatio-temporal patterns of bone formation correlated with the histological data. It was found that contact osteogenesis could not be predicted if only the osteogenic response of cells was up-regulated by surface microroughness. This could only be achieved if platelet–biomaterial interactions were sufficiently up-regulated as well. These results confirmed our hypothesis and demonstrate the added value of the computational model to study the importance of surface-mediated events for peri-implant endosseous healing.

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## 1. Introduction

Contemporary research in the field of implant dentistry is focusing on the improvement of implant osseointegration by the enhancement of bone apposition on the implant surface itself [1–4]. A biological matrix (hematoma) must be established as early as possible, through which mesenchymal stem cells (MSCs) can migrate and attach to the implant surface, proliferate and differentiate into osteoblasts that can ultimately lay down a new bone matrix on the implant surface [4,5]. Animal studies have clearly demonstrated that implant surface characteristics, such as microtopography (defined by Davies and co-workers as surface features smaller than or equal to 3  $\mu\text{m}$ ) influence the rate and amount of bone apposition on the implant surface. For commercially pure (c.p.) titanium implants a greater amount of bone to implant contact has been noticed on (micro)rough implant surfaces compared with smooth implant surfaces [6–8]. Abrahamsson et al. [7] reported new bone formation that originated from the implant surface (so called contact osteogenesis [3]) for sandblasted and

acid-etched (SLA) (microrough) implant surfaces, while in the case of turned (smooth) surfaces new bone formation was only seen to start from the pre-existing host bone (so called distance osteogenesis [3]). *In vitro* studies have looked at the underlying biological mechanisms that may explain the effect of surface (micro)roughness on *in vivo* bone formation. Park and Davies [2] suggested that initial blood–biomaterial interactions are important determinants of peri-implant healing. Blood platelets play a central role in hemostasis and inflammation and their attachment to implant surfaces, activation and subsequent release of growth factors (such as PDGF, TGF- $\beta$ 1 and VEGF [3,9]) is enhanced by surface microtopography [2,10,11]. This may modulate other events further downstream, such as cell migration, proliferation and differentiation, thus regulating the peri-implant healing response. In addition, many *in vitro* studies have investigated the effect of surface characteristics on the behavior of osteoblast-like cells [12–24]. Limiting ourselves to the effect of surface microroughness in the case of titanium substrates, it has been demonstrated that surface microroughness enhanced osteoblast differentiation and local factor production, compared with smooth titanium substrates, while down-regulating their proliferation [12,13,15,17,19,20,24].

Apart from *in vitro* and *in vivo* experiments, computational modeling can also be used to increase our understanding of complex biological processes, such as endosseous healing around oral

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implants, and to perform in silico experiments. In the field of bone regeneration, mechanistic models that explicitly incorporate some of the biological variables and their interaction (so called bioregulatory models) have been developed for fracture healing (see Geris et al. [25] for a review of the literature) and peri-implant healing [26–28]. Ambard and Swider [26] focused on the importance of (osteoblast) cell migration, which in their model for implant osseointegration was mediated both by growth factors and matrix density. A more extensive implant osseointegration model, derived from the fracture healing model of Bailòn Plaza and van der Meulen [29], was developed by our group, but did not include the effect of cell–biomaterial interactions [27]. A first step towards incorporating the influence of implant surface microtopography on bone healing was made by Moreo et al. [28], who considered, among other things, the presence of adsorbed proteins, platelet attachment and activation, the last two processes depending on the concentration of adsorbed proteins and growth factors. In their model the amount of protein adsorption was also dependent on the implant surface characteristics.

The goal of this study is to develop a computational model of endosseous healing around oral implants which takes into account the effect of biomaterial surface characteristics. More specifically, the effect of surface microroughness on activated platelets, on the one hand, and on MSC and osteoblast behavior, on the other, will be studied. Furthermore, we hypothesize that the influence of microroughness on attachment and growth factor release from activated platelets is crucial in achieving contact osteogenesis around microrough implant surfaces. In order to investigate this hypothesis, the model will be applied to the above mentioned experimental study of Abrahamsson et al. [7] that looked at endosseous healing around smooth (turned) versus microrough (SLA) c.p. titanium (oral) implants.

## 2. Materials and methods

### 2.1. Experimental animal model

The histological data used to corroborate the computational model was taken from Abrahamsson et al. [7]. The solid screw-shaped implants were designed with a U-shaped circumferential trough (depth 0.4 mm) within the thread region. This represented the wound chamber and served to investigate the early phases of peri-implant endosseous healing (Fig. 1A). Implants were inserted into the alveolar bone of the mandible of Labrador dogs, such that the peripheral portions of the pitches engaged the host bone, providing good primary mechanical stability of the implants. No oral prosthesis was installed on the implants, avoiding any direct mechanical loading of the implants. The three-dimensional surface roughness  $S_a$  of the turned and SLA surfaces amounted to

$0.35 \pm 0.17$  and  $2.29 \pm 0.59$   $\mu\text{m}$ , respectively [30]. The animals were killed at different time points ranging from day 0 (2 h) to 12 weeks, to perform histological analyses of the tissues in the wound chamber [7,31].

### 2.2. Computational model

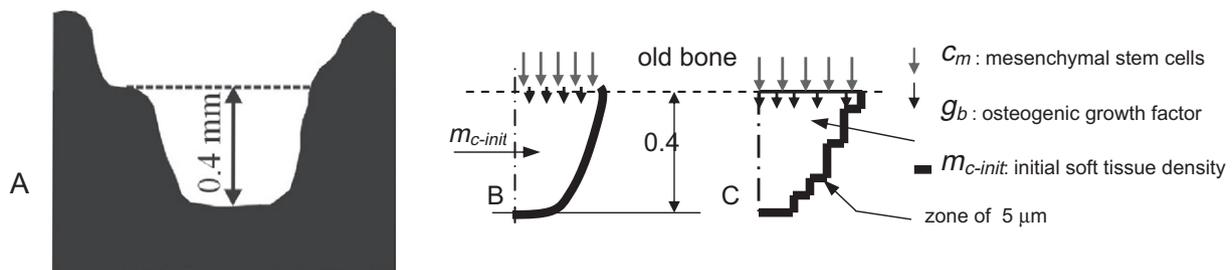
#### 2.2.1. Biological framework

The mathematical model further builds on the model previously developed by Amor et al. [27], which in turn was derived from a fracture healing model [29,57]. More details on these bioregulatory models (that include biological but not mechanical effects) can be found in these papers [27,29,57]. Briefly, the previous model describes the spatio-temporal evolution of five variables representing the densities of MSCs ( $c_m$ ), osteoblasts ( $c_b$ ), soft (fibrous) tissue extracellular matrix ( $m_s$ ) and bone extracellular matrix ( $m_b$ ) and the concentration of a generic osteogenic growth factor ( $g_b$ ). The following (cellular) processes were considered, which govern the change in the dependent variables: cell migration (involving diffusion and haptotaxis), proliferation, differentiation, removal (or apoptosis), extracellular matrix synthesis and degradation and growth factor production and decay. Compared with Amor et al. [27] the model was extended with the following variables and processes.

**2.2.1.1. Blood platelets, degradation and the release of growth factors.** Activated platelets (or activated cell fragments, with a density  $c_{ap}$ ) were added as an additional dependent variable. Platelet degradation and the subsequent release of a generic growth factor ( $g_b$ ) were considered as well, the latter being crucial for the regulation of other downstream events, such as cell migration and differentiation (see below). A constant degradation rate ( $\lambda_{cap}$ ) and growth factor release rate ( $E_{gcap}$ ) were assumed.

**2.2.1.2. Chemotaxis.** The previous model [27] already took into account MSC migration by means of diffusion (random cell motility) and haptotaxis (directed cell motility in the direction of a positive gradient of extracellular matrix density). Experimental in vitro studies have demonstrated the importance of chemotaxis for MSC migration [32–36]. As activated platelets release their growth factors in the peri-implant wound domain chemotaxis also plays an important role in the attraction of MSCs in the case of peri-implant healing [3,32–34]. Chemotaxis was modelled using a receptor-kinetic form [58], with a maximum response at a particular growth factor concentration, as has been observed in experiments [32,34,35]:

$$\chi_{cm\_gb} = \frac{C_{mch}}{(K_{ch}^2 + g_b^2)} g_b \quad (1)$$



**Fig. 1.** Part of a screw-shaped titanium implant, designed with a U-shaped circumferential trough within the thread region (adapted from Abrahamsson et al. [7]). The area within the thread region represents the wound compartment (A). For symmetry reasons only half of the derived wound compartment was considered (B) and further simplified (C). The corresponding applied boundary conditions are shown by arrows (B and C, grey for the mesenchymal stem cell source and black for the osteogenic growth factor source). Initially, soft (fibrous) tissue fills the entire wound domain and the activated cell platelets are concentrated in a 5  $\mu\text{m}$  thick zone in the vicinity of the implant surface (C), in which the surface-specific parameter values were applied as well.

ID	Title	Pages
987	Computational modelling of biomaterial surface interactions with blood platelets and osteoblastic cells for the prediction of contact osteogenesis	12

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