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Technical note

Is the callus shape an optimal response to a mechanobiological stimulus?

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ABSTRACT

After bone trauma, the natural response to restore bone function is the formation of a callus around the fracture. Although several bone healing models have been developed, none have effectively perceived early callus formation and shape as the result of an optimal response to a mechanobiological stimulus.

In this paper, we investigate which stimulus regulates early callus formation. An optimal design problem is formulated, and several objective functions are defined, each using a different mechanobiological stimulus. The following stimuli were analysed: the interfragmentary strain, the second invariant of the deviatoric strain tensor and a generic inflammatory factor. Different regions for callus formation were also evaluated, such as the gap region, the periosteum and the periosteum border. Each stimulus was computed using the finite element method, and the callus shape was optimised using the steepest descent method.

The results demonstrated that the inflammatory factor approach, the interfragmentary strain and the second invariant of the deviatoric strain tensor over the inner gap provided the best results when compared with histological callus shapes. Therefore, this work suggests that callus growth can be an optimal mechanobiological response to either local mechanical instability and/or local inflammatory reaction.

1. Introduction

When a fracture occurs, bone tissue is disrupted and mechanical stability is impaired [1]. To restore bone tissue continuity and bone mechanical function, secondary bone healing takes place. Secondary bone healing is a four-stage process [2]. Initially, inflammation occurs [2–4], and a soft callus gradually appears. The callus serves as a splint, reducing interfragmentary strain and increasing stability. As stability increases, bone tissue advances next to cortical bone by intramembranous ossification and into the soft callus through endochondral ossification, utterly creating a hard, bony callus. After this stage, the bone mechanisms of modelling and remodelling take over to improve weight bearing [5].

Several models have been proposed to simulate the healing phenomenon [6], most of which have been based on Pauwel's hypothesis of mechanically driven tissue differentiation [7]. Claes et al. [8] proposed a set of differentiation rules based on hydrostatic pressure and the second invariant of deviatoric strain; Carter et al. [9] suggested tissue differentiation based on the history of hydrostatic stress and tensile strain. Prendergast et al. [10–12] predicted tissue differentiation patterns during bone healing. Using the second invariant of the deviatoric strain, Garcia-Aznar et al. [13] focused on cell differentiation and callus growth dynamics. Ament and Hofer [14] proposed a fuzzy logic model, and Bailón-Plaza and van der Meulen [15] considered osteogenic and chondrogenic factors as differentiation stimuli. Geris et al. [16] further completed the latter work and incorporated the influence of callus vascularisation. More recently, Comiskey et al. [17] analysed the callus shape with evolutionary structural optimisation, and Wehner et al. [18] stressed the importance of fracture stability in a numerical study.

In this work, we assume that the callus shape is a biological structure and, consequently, an optimal response to a physical stimulus [19,20]. Given this assumption, we pose the following question: optimal to what stimulus? With the aim of identifying the stimulus that most likely drives callus growth during the first stage

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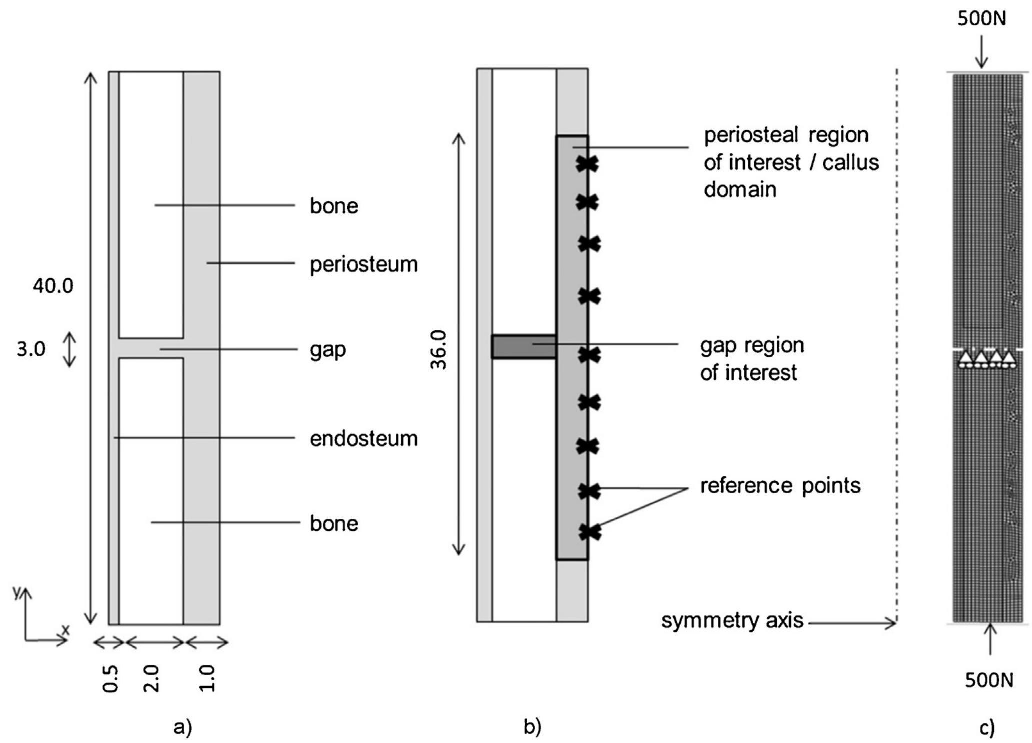

Fig. 1. (a) Geometrical model dimensions (in mm) and different bone parts considered, (b) regions of interest for the optimisations, (c) mesh considered and load application.

of secondary healing, we develop an optimisation approach and evaluate different stimuli from both a mechanical and a chemical perspective.

2. Methods

Generally, an optimisation problem can be stated as

$$\begin{aligned} &\min f(x_1, x_2, \ldots, x_n) \\ &\quad g(x) \le 0 \\ &\quad L_L \le x_i \le U_L \end{aligned} \tag{1}$$

where x_i is the vector of design variables and U_L and L_L are its upper and lower limits, respectively, f is a suitable cost function and g is a constraint function.

We represent a sheep metatarsus by an axisymmetric 2D geometry (Fig. 1a), considering two geometrical parts: the bone and its surrounding soft tissues [1,12,21]. Soft tissues are the periosteum, endosteum and gap, which are essential to trigger callus growth [22]. As the callus grows from the periosteum, we define 9 reference points uniformly spaced along the periosteum border (Fig. 1b). Each of these points is free to move horizontally, and thus the X-coordinate of each point is one x_i design variable for the optimisation process (Fig. 2).

As the objective function we consider both mechanical and chemical stimuli. Thus, the bone geometry is converted into a 0.2 mm^2 square element mesh to compute any necessary stimuli *via* the finite element method (Fig. 1c). From a mechanical perspective, a 500 N axial load is applied on both bone segments [23], and a finite element poroelastic analysis is conducted to compute the mechanical stimulus. From a chemical perspective, a diffusion analysis is performed to compute the concentration of molecular factors. The material and diffusion properties of the tissues considered are presented in Table 1.

As the callus grows, we continue to assume that the callus is composed of granulation tissue because we are considering the early callus formed during the initial healing stage [23,24].

2.1. Optimisation problem – constrained and unconstrained

For each stimulus, we assign a different objective function, and for each objective function, we define an optimisation problem.

In the constrained optimisation approach, we define a constraint function g that limits callus growth based on the assumption that

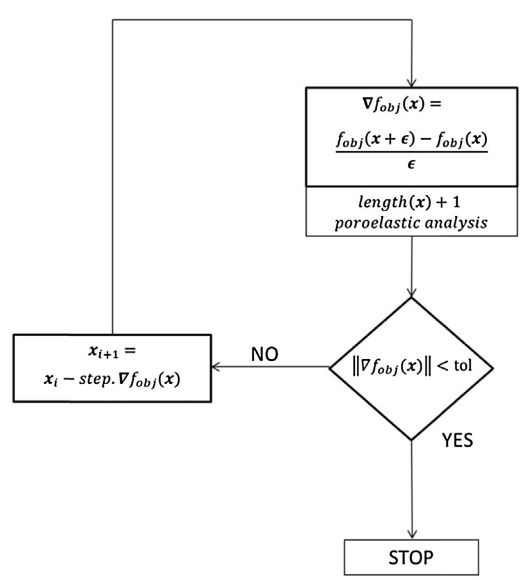

Fig. 2. Flowchart of the optimisation process used to predict the callus shape, where x_i are the design variables at iteration i; f_{obj} is the objective function used and ∇f_{obj} is the gradient of the objective function; ϵ is a small increment; and *tol* is the user-defined stop condition.