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A first order system model of fracture healing*

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Abstract: A first order system model is proposed for simulating the influence of stress stimulation on fracture strength during fracture healing. To validate the model, the diaphyses of bilateral tibiae in 70 New Zealand rabbits were osteotomized and fixed with rigid plates and stress-relaxation plates, respectively. Stress shielding rate and ultimate bending strength of the healing bone were measured at 2 to 48 weeks postoperatively. Ratios of stress stimulation and fracture strength of the healing bone to those of intact bone were taken as the system input and output. The assumed first order system model can approximate the experimental data on fracture strength from the input of stress stimulation over time, both for the rigid plate group and the stress-relaxation plate group, with different system parameters of time constant and gain. The fitting curve indicates that the effect of mechanical stimulus occurs mainly in late stages of healing. First order system can model the stress adaptation process of fracture healing. This approach presents a simple bio-mathematical model of the relationship between stress stimulation and fracture strength, and has the potential to optimize planning of functional exercises and conduct parametric studies.

Key words: First order system, Fracture healing, Stress adaptation, Simulation
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INTRODUCTION

Fracture healing is an important research subject in biomechanics. During the last years, many theories and simulation models have been proposed for developing a comprehensive view of the mechanisms controlling bone morphogenesis. Pauwels (1960) was one of the first authors to propose a theory of tissue differentiation in response to local mechanical stress and strain. He assumed that deviatoric stresses comprise the specific stimulus for the formation of fibrous connective tissue or bone, whereas hydrostatic stresses control the formation of cartilaginous tissue. Later, many authors used computational models, mainly based on finite elements, to estimate local strains and stresses during the different stages of fracture healing (Carter *et al*., 1988; Blenman *et al*., 1989; Claes and Heigele, 1999; Gardner *et al*., 2000), since there is experimental evidence (Goodship and Kenwright, 1985; Claes *et al*., 1995) that tissue differentiation is mechanically dependent on.

Apart from stress and strain, other parameters were also used for modelling of fracture healing. Ament and Hofer (2000) proposed a tissue regulation model based on a set of fuzzy logic rules derived from medical experiments, using the strain energy density as the mechanical stimulus that controls cell differentiation. Bailón-Plaza and van der Meulen (2001) studied the fracture healing process regulated by growth factors. They used finite differences method to simulate the sequential tissue regulation and the different cellular events and studied the evolution of the several cells existing in the callus. García *et al*.(2002) developed a continuum mathematical model that simulates the process of tissue regulation and callus growth, taking into account different cellular events, matrix synthesis, degradation, damage, calcification and remodelling over time.

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Previous research on modelling of fracture healing focused mainly on the relationship between mechanical stimulus and tissue differentiation. In this new approach, however, our target is fracture strength. Since healing is the return of function and the chief function of bone is the resistance to stress, it is logical to study the fracture strength. This study is aimed at developing a bio-mathematical model of the relationship between stress stimulation and fracture strength during fracture healing.

FIRST ORDER SYSTEM MODEL

First order system is a mathematical model in the field of automatic control. It is the simplest type of linear control system. Many higher order systems can often be simplified into first order. The differential equation of first order system is

$$T\frac{\mathrm{d}[c(t)]}{\mathrm{d}t}+c(t)=Kr(t) \quad (1)$$

where t stands for the time, $r(t)$ for the input over time and $c(t)$ for the output. T and K are the system parameters of time constant and gain. The transfer function of the first order system is

$$G(s)=\frac{C(s)}{R(s)}=\frac{K}{Ts+1} \quad (2)$$

where s stands for the complex independent variable, $R(s)$ and $C(s)$ are Laplace transform of the system input and output.

The structure of first order system is shown in Fig.1, indicating that first order system is a closed loop feedback control system with a forward pathway and a feedback pathway. The system output is fed back and compared with the input to generate a pilot signal, which makes the output adapted to the input.

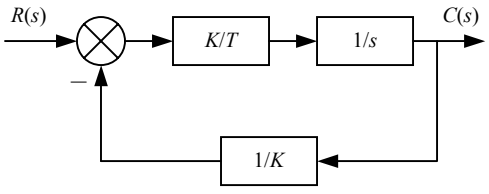

Fig.1 Structure of first order system

This seems to be appropriate for describing the stress adaptation process of bone remodelling. So we suppose the relationship between mechanical stimulus and the fracture healing outcome to be of first order, and then try to validate the supposition by animal experiment.

METHODS

Plates and gaskets

Four-hole plates, 40 mm in length, 7 mm in width and 2 mm in thickness, were made of stainless steel (316L). The diameter of the hole was 2.2 mm, while the screw had an external diameter of 2 mm and length of 12 mm. The gaskets put in the holes were made of macromolecular polyethylene and had external and internal diameters of 2.2 mm and 2 mm, respectively.

Experimental design

Seventy adult New Zealand rabbits, weighing 2.5~3.0 kg, were used in this study. Vein anesthesia was carried out with 2.5% sodium pentobarbital. The middle parts of the bilateral tibial diaphyses were exposed and osteotomized transversely. The left tibia was fixed with rigid plate (RP) as the controls, whereas the right tibia was fixed with stress-relaxation plate (SRP) with a viscoelastic gasket in every hole. The bone plates were fixed to the anterior aspect in both groups. All screws were tightened with a uniform torque of 0.4 N·cm. The animals were then fed separately in cages, randomly divided into 7 groups (n=10), and sacrificed at 2, 4, 8, 12, 24, 36 and 48 weeks post-operation, respectively.

Radiographic evaluations

Six rabbits in every group were sacrificed to harvest their whole tibiae with fixing plates. Medial-lateral X-ray film of the tibia was taken to assess callus formation and the rate of fracture healing.

Biomechanical measurements

After the radiographic evaluations, a strain gauge was attached to the anterolateral tibial cortex adjacent to the plate. A non-destructive axial compressing test was performed using a materials testing machine (Model AG-20KNA, Japan). The tibia was

quasi-statically loaded at a displacement rate of 0.5 mm/min up to a maximum force of 200 N. The strain value was recorded by a static electric resistance strain gauge (Model YDT-5, China). In addition, the strain values on the corresponding parts of 6 normal tibiae were measured. The stress-shielding rate was calculated by following formulas.

$$\sigma=E\varepsilon \tag{3}$$

$$p=(1-\frac{\sigma_{\text{experimental}}}{\sigma_{\text{normal}}})\times 100\% \tag{4}$$

where σ stands for stress, E for elastic modulus, ε for strain and p for the stress shielding rate. As stress of the fractured site is what we are concerned about, we define stress stimulation q as the percentage of stress of the healing bone to that of intact bone.

$$q=1-p=\frac{\sigma_{\text{experimental}}}{\sigma_{\text{normal}}}\times 100\% \tag{5}$$

After the stress shielding rate testing, the plates were removed. A three-point bending test was performed in the materials testing machine. The loading point was situated on the tibial cortex opposite to the plate and at the midpoint of the two middle pin holes. The distance between the 2 supporting points on the plate side was 50 mm. The tibiae were quasi-statically loaded at a displacement rate of 3 mm/min. The ultimate bending moment of the united fracture was recorded. The same test was performed on 6 intact tibiae as controls. The fracture strength b was defined as the percentage of the ultimate bending strength of the healing bone to that of intact bone.

$$b=\frac{M_{\text{experimental}}}{M_{\text{normal}}}\times 100\% \tag{6}$$

where M stands for the ultimate bending moment.

RESULTS

X-ray findings were previously reported by Zhang *et al*.(2000). The aim of this study was to model the influence of mechanical stimulus on fracture healing, so we listed only the experimental data of the biomechanical measurements, shown in Table 1.

MODEL VALIDATION

As the experimental animals were lying down most of the time during the first week post-operation, their activities increased gradually. After two weeks, their activities were almost normal. Therefore, we took stress stimulation as a series of lines starting from the first week and connected each of the experimental data points into the dashed line shown in Fig.2. The data fitting was carried out using a non-linear least square curve fitting program (MATLAB). The initial values of time constant T and gain K were randomly selected, and the fitting error was calculated. Then the system parameters were modified iteratively to decrease the fitting error. The final fitting curve and estimates T and K are shown in Fig.2.

As shown in Fig.2, the fitting curve can approximate the experimental data on fracture strength very well, both for the SRP group and the RP group. Therefore, we accepted the hypothesis that first order system model is appropriate for describing the relationship between stress stimulation and fracture strength during the fracture healing process.

Table 1 Experimental data on stress stimulation and fracture strength (mean±mean square deviation)%

t (week)	SRP group (%)		RP group (%)	
	q	b	q	b
2	31.3±5.2	16.70±1.23	29.2±4.3	16.38±1.73
4	35.4±4.8	45.24±4.42	31.9±4.6	41.24±5.71
8	45.1±3.7	58.90±7.50	32.7±3.8	47.39±4.80
12	54.1±4.8	78.69±6.77	31.6±5.0	64.46±7.19
24	68.2±3.2	88.38±9.36	33.5±4.8	60.00±8.25
36	71.7±2.9	89.48±6.71	34.3±3.3	58.23±5.91
48	72.8±1.7	93.63±5.24	34.7±3.0	57.95±4.63

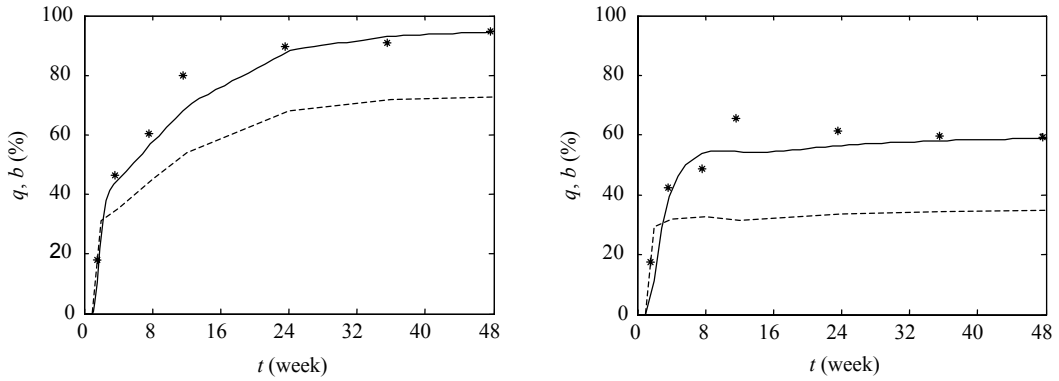

Fig.2 Data fitting and parameters estimation (a) SRP group T=0.4, K=1.3; (b) RP group T=1.4, K=1.7
The dashed and real lines are the system input (q) and output (b) respectively, and "*" stands for the experimental data

DISCUSSION

To develop this simulation of the fracture healing process, several simplifications were necessary. First, we assumed the difference in fracture healing outcome of the two groups was caused mainly by the mechanical factor, i.e., stress stimulation of the fracture site. For this purpose, the SRP and RP used in the experiment were made with the same dimensions, but different mechanical nature. The experiment was performed with uniform surgical procedure and the animals were treated equally to eliminate the influence of other factors. We assumed anthropometric differences had little effect on the model. To justify this simplification, we took the ratios of stress stimulation and fracture strength of the healing bone to that of intact bone as the system input and output. Despite these two assumptions, the model successfully reproduced the biomechanical feature of the healing bone, i.e. it correctly simulated fracture strength with the input of stress stimulation over time.

According to Wolff's law, when bone is subjected to stress higher than physiological level, it responds with osteogenesis, whereas abnormally low stress led to bone absorption. Wolff's law may be extended to the fracture healing process. As shown in Fig.2, fracture strength of both groups increased rapidly in the first 8 weeks. Then because of the consistent low stress stimulation, the fracture strength remained almost unchanged in the RP group. While in the SRP group, the healing process continued as the stress stimulation increased, with the final value being considerably higher than or 93.63% to 57.95% that of the RP group. The model indicated that fracture strength is the result of biofeedback of stress adaptability.

Fracture strength provides a measure of the rate of healing and an objective definition of union. The relationship between stress stimulation and fracture strength must be known to guide patients' functional exercise. The fitting curve suggests that the effect of mechanical stimulus occurs mainly after 8 weeks. More stress stimulation is needed in late stages of fracture healing to promote bone remodelling. With this in mind, functional exercises may be arranged to optimize the mechanical environment of the fracture site and to enhance fracture healing.

The first order model provides a simple bio-mathematical expression of the influence of mechanical stimulus on fracture healing. The model is characterized by two system parameters, i.e., the time constant and the gain. Time constant stands for the time delay of the increase of fracture strength in response to mechanical stimulus, and the gain stands for the multiplication factor of fracture strength to stress stimulation. The first order model presents a comprehensive view of the biomechanical feature of fracture healing and potential use for parametric study.

A limitation of the model is that it considers only the influence of mechanical stimulus, and does not include biological factors such as growth factors and vascularisation. As a consequence, prediction cannot be made solely from the mechanical factor. The target of simulation, i.e., the fracture strength, is only the phenomenon of the healing bone's mechanical prop-

erty. Tissue differentiation inside the healing fractures cannot be determined. Moreover, it is very difficult to obtain quantitative conclusions from computer simulations because of anthropometric and metabolical differences between patients and animal species. Further improvement of the model concentrates on incorporating biological factors, on the basis of which more complex and realistic computer simulations could be developed.

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