A MATHEMATICAL MODEL OF THE GROWTH PLATE

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The growth plate is a structure formed of cells called chondrocytes; these are arranged in columns and provide the elongation of bone due to their proliferation and hypertrophy. In each column, we can see chondrocytes in their proliferating state, which are constantly dividing, and in hypertrophic state, which grow in a nearly spherical shape. These cells express different proteins and molecules throughout their half-life and exhibit a special behavior depending on their local mechanical and biochemical environments. This article develops a mathematical model that describes the relationship of geometry, growth by proliferation and hypertrophy, and vascular invasion with biochemical and mechanical factors present during endochondral ossification.

Keywords: Growth plate; mathematical model; endochondral ossification; mechanobiology.

1. Introduction

The prenatal initial development of long bones results from chondrocyte proliferation and hypertrophy. Chondrocytes are placed in a structure known as growth
plate, which promotes longitudinal bone elongation during growth.\(^1\) Chondrocytes can be located in reserve, proliferation, and hypertrophy states in this structure.\(^1,2\)

Cells in reserve state serve as stem cells that proliferate and undergo hypertrophy by biochemical and mechanical actions, thereby elongating cells and longitudinally extending bone. Each long bone has at least two growth plates, one at each end.\(^2\) Each plate promotes growth in the bone’s axial direction and remains until the end of adolescence when proliferation ceases; chondrocytes undergo hypertrophy and become invaded by osteoblasts, thereby closing the growth plate. This closure is influenced by local and systemic biochemical and mechanical factors.\(^1,3\)

Parathyroid hormone-related (PTHrP) and Indian hedgehog (Ihh) have been identified as major actors in proliferation and hypertrophy processes from a biochemical viewpoint.\(^4,7\) This pair of substances control the initial development of bone, forming a negative inhibitor–activator interaction loop.\(^1,2,7,8\) It has been demonstrated\(^9\) that PTHrP negatively regulates chondrocyte hypertrophy in the growth plate and Ihh positively regulates chondrocyte entry into the proliferation zone. Other molecules have also been found to influence hypertrophy, such as bone morphogenetic protein (BMP), Wnt, and fibroblast growth factors (FGFs).

It has been found\(^3\) that chondrocyte proliferation and hypertrophy processes also depend on the magnitude of compressive and tensile loads. The growth plate structure depends on mechanical stress; therefore, physical exercise\(^10,11\) becomes an important factor for the proper maintenance and growth of the bone structure. There are internal forces, such as those produced by the development of the secondary ossification center, and external forces, such as those produced by the muscles, the ring of Ranvier, and the periosteum.\(^12\) The proper function of the growth plate requires tensile or compressive loads, as described by Delpech,\(^13\) and it is called the Heuter-Volkmann law. This law states that within physiological limits, compression increases growth rate. However, beyond physiological limits, growth becomes delayed when compressive loads are excessive, and it is accelerated with tensile loads.\(^13,14\) Moreover, it is believed that compression stimulates bone growth when loads are cyclical or intermittent.\(^15\) Stokes \textit{et al.}\(^16\) described that the variation of compressive load increases the growth rate more effectively than bone plate distraction. In a later article, Stokes \textit{et al.}\(^17\) confirmed their previous findings where sustained compressive load decreased growth. The paper published the results of applying compression to vertebrae and tibia of Sprague-Dawley rats, loading the growth plate steadily for 24/24 h (sustained load), 12/24 (day loading), 12/24 (night loading), and 0/24. The vertebra became less influenced by the sustained load than the tibia in this experiment.

The longitudinal growth of long bones is still being studied because there may be deformations and abnormal or less growth than the expected in some individuals. For example, Modi \textit{et al.}\(^18\) showed that loads and non-physiological postures of the spine produce abnormal growth in the vertebral body of teenagers (a condition
called scoliosis). The Blount disease, which consists of a shear strain of the proximal tibia, related with overweight, short height, and premature walking in babies, also is associated with abnormal growth plate. Distraction of the epiphyseal plate has been proposed as a treatment for correcting such deformity; this treatment is designed for the correction of angular deviations and, following slow application, it can lead to an increased length due to the hyperplasia of the articular cartilage. Epiphyseal distraction is still being studied due to the debate regarding speed and application time.

Growth of the epiphyseal plate has been studied from a computational viewpoint by using the finite element method. Stevens et al. developed an ossification model in long bones from the eighth week of pregnancy up to two years after birth for simulating endochondral development. They used the maturity index reflecting the progression of a cartilage region through the sequence of proliferation, hypertrophy, and mineralization. In this article, growth depended on the biological control (time-dependent) and the mechanical contribution of octahedral shear stresses and hydrostatic pressure for a full-load cycle. They took into account that high octahedral stresses and low hydrostatic stresses could increase cartilage maturity. Beaupré et al. used the osteogenic rate to simulate ossification during growth. Brouwers et al. developed a biochemical model that only took into account the molecular interaction of PTHrP and Ihh and its effect on proliferating and hypertrophic chondrocyte maturity. Garzón-Alvarado et al. also described a reaction-diffusion model of high growth plate stability regarding the two main hormones controlling growth (PTHrP and Ihh).

The main objective of this work is to develop a mathematical model of growth plate mechanical-biological behavior. We model the geometry of the chondrocytes columns and the effect of mechanical loads and biochemistry over them. A set of equations was thus produced describing local mechanical and biochemical effects on growth plate structure, especially on chondrocyte proliferation and hypertrophy.

2. Materials and Methods

Long bones are formed from endochondral ossification. This process starts with the condensation of mesenchymal cells into chondrocytes to form a first mold of cartilage that will become the future bone. Chondrocyte hypertrophy takes place in the central part of the mold, preceding the mineralization and ossification of bone. This first area of chondrocyte differentiation is called the primary ossification center. The chondrocytes then undergo hypertrophy to form secondary ossification centers (postnatal stage) in bone extremes (epiphyses) (see Fig. 1).

The growth plate is formed at the end of the primary ossification center. This structure has three distinct areas: the chondrocyte resting area, the chondrocyte proliferating zone, and the hypertrophic zone. Chondrocytes in resting state are the pantry serving as stem cells for entering the proliferation stage. Chondrocytes divide, mature, and undergo hypertrophy during the proliferation stage.
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Fig. 1. Endochondral ossification. The primary ossification center is shown in the center. Chondrocyte differentiation, vascular invasion, bone formation, epiphysis, epiphysis growth plate, metaphysis, trabecular bone, hypertrophic chondrocytes, diaphysis, trabecular bone, metaphyseal growth plate.

Fig. 2. (a) Growth plate location, and (b) growth plate micrograph.

Chondrocytes become elongated during hypertrophy to allow longitudinal bone growth. Matrix proliferation, hypertrophy, synthesis, and degradation thus determine bone growth rate. Figure 2 illustrates the growth plate histology.

Figure 2 shows how chondrocytes are arranged in columns parallel to the growth axis. Each column is made up of daughter cells from a single cell located at the top of the column. Therefore, several growth plate models studied a single column of condrocytes. Olney et al. showed that the number of cells in each column is unique in steady state; i.e., the number of cells proliferating is equal to the number of cells undergoing hypertrophy. Growth is thus a linear (piecewise) function over time intervals in which growth is considered stable.

Bone growth depends on biological, genetic, biochemical, and mechanical factors. We develop a mathematical model representing endochondral growth, describing chondrocyte proliferation and hypertrophy processes. We develop tools for a geometric description of column formation and growth plate pattern and we describe their interaction with the main growth variables; i.e., biochemical
and mechanical factors. Column formation and biochemical processes are thus influenced by chondrocytes that release the main molecular factors regulating the growth plate. Moreover, proliferation and hypertrophy alter growth plate mechanical behavior. Vascular invasion and mineralization of hypertrophic chondrocytes then takes place, leading to the progress of metaphysis and thus bone growth. Figure 3 gives a conceptual scheme for the model.

2.1. Growth plate molecular regulation

Following the scenario described by different experimental authors\textsuperscript{7–9,12} and based on the work done by Garzón-Alvarado \textit{et al.}\textsuperscript{27} we propose in this paper a mathematical model of the biochemical effects on endochondral ossification (Fig. 4). We explore the hypothesis that endochondral ossification is controlled by a hormonal reaction–diffusion process between Ihh and PTHrP. Two continuously interacting processes are thus involved in growth: molecular (hormonal) and cellular. The molecular process occurs in each chondrocyte and takes into account the PTHrP-Ihh loop. The chondrocyte consumes (inhibits) Ihh in the presence of PTHrP and produces (active) PTHrP in the presence of Ihh. These molecular factors regulate cell population evolution as a biological signal, so that chondrocyte proliferation is promoted where there is PTHrP, and Ihh and hypertrophy are delayed where there is PTHrP.

The hypothesis proposed by Garzón-Alvarado \textit{et al.}\textsuperscript{27} was extended by Fasano \textit{et al.}\textsuperscript{9} who made a complete study of the molecular factors existing in the growth plate and developed a mathematical model showing the high stability of the
PTHrP-Ihh loop control: PC: proliferating chondrocytes, HC: hypertrophic chondrocytes, PTHrP: parathyroid hormone related peptide, and Ihh: Indian hedgehog.

Fig. 4. PTHrP — Ihh loop control: PC: proliferating chondrocytes, HC: hypertrophic chondrocytes, PTHrP: parathyroid hormone related peptide, and Ihh: Indian hedgehog.

This paper has assumed that hormonal factor Ihh and PTHrP balance is described by the following equation:

\[
\frac{\partial S_j(x,t)}{\partial t} + \text{div}(S_j v) = b_j + \text{div}(D_j \nabla S_j),
\]  

where \( S_j(x,t) \) is the concentration of the \( j \)th species present in the growth plate, \( v \) is the local growth speed of bone, \( b_j(x,t) \) is the net external production of the \( j \)th substance by reaction or inhibition, and \( D_j \) is the diffusion coefficient. As an initial working hypothesis, it is assumed that diffusion followed Fick's law.\(^9,14,15,36\)

It also suggested that PTHrP and Ihh were synthesized by chondrocytes (which are expressed through the variable \( C \)),\(^5\) so the source term (or reactive) is given by:

\[
b_{\text{PTHrP}}(x,t) = C(\alpha_1 - \beta_1 S_{\text{PTHrP}} + \gamma_0 S_{\text{PTHrP}}^2 S_{\text{Ihh}}),
\]  

\[
b_{\text{Ihh}}(x,t) = C(\alpha_2 - \gamma_0 S_{\text{PTHrP}}^2 S_{\text{Ihh}}),
\]  

where \( \alpha_1 \) and \( \alpha_2 \) are constant source terms, \( \beta_1 \) is a constant quantifying PTHrP degradation rate, and \( \gamma_0 \) is the reaction constant indicating existing nonlinear control inside cells by the presence of the two factors. It should be noted that all previous constants could also be regarded as functions of the molecular concentrations of additional factors, such as BMP, FGF, and RUNX21.\(^5,7\) However, this has not been considered in this first work. The above equations are similar to those described by Schnakenberg,\(^16-18\) which have been widely used in biological systems.
Fig. 5. Growth plate. Note the high PTHrP concentration in the upper area (reserve and proliferating area) and high Ihh concentration in the hypertrophic area. Vascular invasion occurs from the primary ossification center (taken from Fasano et al.9).

2.2. Growth plate structure description geometric tensor

This work assumes that bone form changes were due to differences in proliferation and hypertrophy and column formation and direction.33 A description of the concentration of each cell group is given by \( C_{PC} \) and \( C_{HB} \), for proliferating and hypertrophic chondrocytes, respectively. However, cellular organization micrographs (see Fig. 2) show that chondrocyte spatial distribution cannot be described by a scalar variable because these cells have a preferential direction of proliferation and hypertrophy; therefore, a second-order transversely isotropic tensor, initially introduced by Garzón-Alvarado et al.27 is used for describing the cell pattern and is given by (4):

\[
R_{PC} = \sqrt[3]{\frac{C_{PC}}{r_{PC}}} (1 + (r_{PC} - 1)n \otimes n),
\]

where \( r_{PC} \) is the ratio of the number of cells in preferential proliferation direction, \( n \) to the number of cells in orthogonal direction, and 1 is a second-order unit tensor (with unit diagonal), as illustrated in Fig. 6. Thus, the determinant for tensor \( R_{PC} \)
is the proliferating chondrocyte concentration value (5):

\[ C_{PC} = \det(R_{PC}) = \varepsilon_{ijk}(R_{PC})_{i1}(R_{PC})_{j2}(R_{PC})_{k3}. \] (5)

Likewise, during hypertrophy (see Fig. 5), chondrocytes change their geometry from being quasioval to becoming spherical, allowing longitudinal bone elongation. This growth is transversely isotropic and can be described by a second-order tensor as that presented previously (6):

\[ R_{HC} = \frac{C_{HC}}{r_{HC}} \sqrt{1 + (r_{HC} - 1)n \otimes n}, \] (6)

where \( r_{HC} \) is the ratio of the number of cells in preferential hypertrophic elongation direction, \( n \), to the number of cells in orthogonal direction. Similarly, chondrocyte concentration could be found from the tensor determinant given by \( C_{HC} = \det(R_{HC}) \).

The physical meaning of each tensor component can be seen in Fig. 6. Each \( R_{PC} \) and \( R_{HC} \) tensor component expresses the number of chondrocytes per unit of length in each direction using Cartesian coordinates (assuming the horizontal axis to be \( x \) and the vertical, also called \( y \)) and physiological conditions. For
example, the following expressions are obtained in direction $n$ (y-axis):

$$ (R_{PC})_{22} = \sqrt[3]{\frac{C_{PC}}{r_{PC}}}, \quad (7) $$

$$ (R_{HC})_{22} = \sqrt[3]{\frac{C_{HC}}{r_{HC}}}, \quad (8) $$

where Eq. (7) determines the number of chondrocytes in a proliferating state per unit of length in the direction of growth and Eq. (8) expresses the number of chondrocytes per unit of length in a hypertrophic state in the direction of cell elongation. Figures 2 and 7 show how the chondrocytes were arranged in columns parallel to the axis of growth.$^{31}$ Following Olney et al.$^{31}$ it can be assumed that the number of proliferating cells are equal to the number of hypertrophied cells in a physiological steady state. Moreover, proliferating cell size and linear density in the direction of growth are unique in normal growth conditions.$^{32}$ When chondrocytes begin to hypertrophy, they increase in size.$^{27,32}$ Garzón-Alvarado et al.$^{27}$ assumed that elongation in a perpendicular direction to growth vector can be neglected because column width and location remain constant. Hunziker et al.$^{32}$ considered that maximum growth in chondrocyte hypertrophy is about four times proliferating cell width, as illustrated in Fig. 7. It should be noted that chondrocyte density in proliferating and hypertrophic states can be modified by the effect of mechanical$^{37-39}$ and biochemical$^{2,9,26,27,36}$ environments.

It can be assumed that the number of columns in the growth plate is unique during steady state$^{38}$; therefore, the other two geometric tensor components are
constant and given by:

\[(R_{PC})_{11} = (R_{PC})_{33} = \sqrt{\frac{C_{PC}}{r_{PC}}} = N_c, \quad (9)\]

\[(R_{HC})_{11} = (R_{HC})_{33} = \sqrt{\frac{C_{HC}}{r_{HC}}} = N_c, \quad (10)\]

where \(N_c\) is the number of columns per unit of length, being constant over a time interval of growth in physiological state. Therefore, \((R_{PC})_{11} = (R_{PC})_{33} = (R_{HC})_{11} = (R_{HC})_{33}\). Thus, growth plate geometry and cell distribution are given by only three variables depending on mechanical load and biochemical factors at local level: \(r_{PC}\), \(r_{HC}\), and \(n\). The evolution of each is described in the following sections.

### 2.3. Relative linear density variable evolution regarding chondrocyte proliferation and hypertrophy

The number of chondrocytes in bone preferential growth direction is affected by mechanical load and biochemical factors systemically produced at local level. This section shows the theoretical foundation of the existing effects on the growth plate and the mathematical model representing proliferating and hypertrophic chondrocyte relative density.

From a mechanical viewpoint, the growth plate is regulated by local stresses and deformation.\(^4\) Compressive mechanical loads have been widely studied; however, there are also reports regarding the effect of tensile, torsional, and bending loads on the growth plate.\(^3\) It has been reported that mechanical loads, sustained over time, affect bone growth.\(^3\) Mechanical loads also affect cell behavior. Alberty et al.\(^3\) found that sustained compressive load reduces the number of proliferating cells. Stokes et al.\(^4\) showed that the change of the growth rate is proportional to the change in the number of proliferating and hypertrophic chondrocytes. Several researchers\(^5\) reported that compressive load reduces the degree of hypertrophy and the number of chondrocytes; however, the proliferative activity remains. Contrary to compressive load, tensile load (or distraction) increases growth plate size.\(^6\) Chondrocyte proliferation does not change even if there is a proliferative elongation zone\(^6\) and a disruption in the growth plate is generated.

Other studies\(^7\) have suggested that octahedral and hydrostatic mechanical loads play an important role in bone development. Carter et al.\(^8\) indicated that the mechanical stresses occurring during prenatal development stages guide endochondral bone ossification patterns. The results of numerous computer simulations, from a mechanobiological perspective support the view that, in terms of physiological loading conditions, cartilage maturation and ossification are inhibited by intermittent hydrostatic compressive stress and are accelerated by non-destructive intermittent octahedral shear. Hydrostatic pressure maintains a chondroprotective
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effect by contrast with octahedral shear stress that activates hypertrophy expression
in chondrocytes.42

This article considers that the proliferative term depends on PTHrP and Ihh
concentrations, mechanical load, and other molecular factors (11):  
\[ \frac{dP}{dt} = \left( g_{\text{proliferation}}(S_{\text{Ihh}}, S_{\text{PTHrP}}) - g_{\text{hypertrophy}}(S_{\text{Ihh}}, S_{\text{PTHrP}}) \right) \]

\[ - (k_1 \sigma_E(x,t) + h_1 \sigma_H(x,t)) + \frac{P_B}{\text{other effects}}, \]  

(11)

where \( g_{\text{proliferation}} \) quantifies the rate of proliferating chondrocytes, \( g_{\text{hypertrophy}} \) represents the level of cell transformation from proliferative to hypertrophic stage, \( k_1 \) is a constant quantifying the impact of mechanical deviatoric loads (deviatoric stress \( \sigma_E \)), \( h_1 \) is a constant that takes the effect of hydrostatic load (hydrostatic stress \( \sigma_H \) into account; \( \sigma_H \) has a positive sign when it is compressive), and \( P_B \) is a factor that takes into account other systemic or external biochemical characteristics, e.g.
estrogen, radiation, and fractures.

Proliferation depends on the amount of PTHrP and Ihh in the cell environment. Thus, according to Garzón-Alvarado et al.,27 it is assumed that proliferation is given by:

\[ g_{\text{proliferation}} = b_0 p_2(S_{\text{Ihh}}, S_{\text{PTHrP}}) \left( 1 - \frac{p_2(S_{\text{Ihh}}, S_{\text{PTHrP}})}{p_0^2} \right), \]

(12)

where \( b_0 \) is a constant of proliferation, \( p_0 \) is a dimensionless term representing load capacity,27 and \( p_2 \) is an activation factor related to the gradient of the molecular factors in tissue, given by:

\[ p_2(S_{\text{Ihh}}, S_{\text{PTHrP}}) = b_1 \nabla S_{\text{PTHrP}} + b_2 \nabla S_{\text{Ihh}}, \]

(13)

where \( b_1 \) and \( b_2 \) are constants quantifying the influence of each molecular factor on chondrocyte proliferation.27 On the other hand, \( g_{\text{hypertrophy}} \) is given by:

\[ g_{\text{hypertrophy}} = \left( f \frac{d^n}{S_{\text{PTHrP}} + d^n} \right), \]

(14)

where \( f \) is the frequency of differentiation of proliferating to hypertrophic cells and \( d^n/(S_{\text{PTHrP}} + d^n) \) is a function defining the concentration at which hypertrophy occurs (defined by the threshold value \( d \)) in terms of PTHrP concentration and constant \( n \).27

Similarly, hypertrophic chondrocytes’ linear density ratio, given by \( r_{HC} \), is determined by:

\[ \frac{dr_{HC}}{dt} = \frac{(g_{\text{hypertrophy}})}{\text{local biochemical effects}} + \frac{(k_2 \sigma_E(x,t) - h_2 \sigma_H(x,t))}{\text{local mechanical effects}} + \frac{H_B}{\text{other effects}}. \]

(15)
It should be noted that Eqs. (11) and (15) express the number of chondrocytes (per unit of length) in the preferential growth direction and that each equation is completely determined by the proper use of the initial conditions, corresponding to growth plate stabilization. Two important experimental facts should be noted at this point:

1. The central hypertrophy and proliferation loop (PTHrP-Ihh) remains without its expression mechanism being affected due to mechanical load. Garzón-Alvarado et al.27 and Garzón-Alvarado et al.36 have shown that this regulatory loop can be described by a highly stable reaction-diffusion (RD) and does not depend on the initial conditions of the molecules. In fact, this system is determined as a Turing instability providing an unstable spatial pattern which is, however, stable over time. This may be explained, to some extent, because proliferating to hypertrophic chondrocyte transition is insensitive to mechanical loading.

2. Stokes et al.41 have shown that there is an average stress ($\sigma_m$ (MPa), with $\sigma_{Hm}$ as average hydrostatic stress and $\sigma_{Em}$ average deviatoric stress) that is considered to be physiological stress. Compressive loads of higher hydrostatic stress at physiological levels reduce growth whilst lower loads increase it. This experimental fact is extended to deviatoric stress in this article. There is an average physiological deviatoric stress above which hypertrophy occurs and below which chondroprotection is induced.

Using these two experimental facts and assuming that, deviatoric stress and other biochemical and biological effects are in physiological equilibrium, we can argue that Eqs. (11) and (15) become:

\[
\frac{dP_C}{dt} = 0 = (g_{\text{proliferation}}(S_{Ihh}, S_{\text{PTHrP}}) - g_{\text{hypertrophy}}(S_{Ihh}, S_{\text{PTHrP}})) - (k_1\sigma_{Em}(x,t) + h_1\sigma_{Hm}(x,t)) + P_{Bm}, \tag{16}
\]

\[
\frac{dH_C}{dt} = 0 = (g_{\text{hypertrophy}}) + (k_2\sigma_{Em}(x,t) - h_2\sigma_{Hm}(x,t)) + H_{Bm}. \tag{17}
\]

Therefore, the ratio of the number of chondrocytes in preferential elongation direction (in proliferative and hypertrophic state) to the number of cells in orthogonal direction is unique, under physiological or normal conditions. Replacing Eqs. (16) and (17) in Eqs. (11) and (15), respectively, we obtain:

\[
\frac{dP_C}{dt} = [(g_{\text{proliferation}}(S_{Ihh}, S_{\text{PTHrP}}) - g_{\text{hypertrophy}}(S_{Ihh}, S_{\text{PTHrP}})) - (k_1\sigma_{Em}(x,t) + h_1\sigma_{Hm}(x,t)) + P_{Bm}] + [- (k_1\Delta\sigma_{E}(x,t) + h_1\Delta\sigma_{H}(x,t)) + \Delta P_{B}], \tag{18}
\]

\[
\frac{dH_C}{dt} = [(g_{\text{hypertrophy}}) + (k_2\sigma_{Em}(x,t) - h_2\sigma_{Hm}(x,t)) + H_{Bm}] + [(k_2\Delta\sigma_{E}(x,t) - h_2\Delta\sigma_{H}(x,t)) + \Delta H_{B}], \tag{19}
\]
where we have assumed that \( \sigma_E(x, t) = \sigma_{Em}(x, t) + \Delta \sigma_E(x, t) \), \( \sigma_H(x, t) = \sigma_{Hm}(x, t) + \Delta \sigma_H(x, t) \), \( P_B = P_{Bm} + \Delta P_B \), and \( H_B = H_{Bm} + \Delta H_B \). Therefore, Eqs. (11) and (15) only depend on the deviatoric and hydrostatic stresses at each point of the growth plate; i.e.,

\[
\frac{dr_{PC}}{dt} = -(k_1 \Delta \sigma_E(x, t) + h_1 \Delta \sigma_H(x, t)) + \Delta P_B, \tag{20}
\]

\[
\frac{dr_{HC}}{dt} = (k_2 \Delta \sigma_E(x, t) - h_2 \Delta \sigma_H(x, t)) + \Delta H_B. \tag{21}
\]

An additional condition is given by the existing interface between proliferative and hypertrophic areas; i.e., the change in chondrocyte linear density in growth direction was determined by cell elongation. The point where elongation starts determining the hypertrophic zone; therefore, the condition at the point where the interface is presented is:

\[
\left.r_{PC}\right|_{x_{\text{hypertrophy}}} = \left.r_{HC}\right|_{x_{\text{hypertrophy}}}. \tag{22}
\]

2.4. Evolution of the preferential direction of growth

Many authors\(^{37-39}\) have reported that increased compressive mechanical load decreases growth plate thickness and can alter column alignment. The loss of column alignment may be due to small variations in compressive load throughout the growth plate. By contrast, Apte et al.\(^{42}\) shown that distraction does not stimulate proliferation. By contrast, distraction accumulates hypertrophic chondrocytes and disorganized columns and a decreased proliferation can be observed.

This paper assumes that growth plate disorganization is due to chondrocyte columns alignment to withstand mechanical loads; therefore, any small misalignment of stress can induce inadequate reorientation of chondrocyte columns. Following a similar approach to that proposed by Garzón-Alvarado et al.\(^{27}\) we propose that change in preferential direction of growth is given by:

\[
\frac{\partial n}{\partial t} = n \times (w \times n) + k_n (n_\lambda^\alpha - n), \tag{23}
\]

where \( n \) is the preferential direction of growth, \( k_n \) is a constant quantifying the effect of mechanical load on the direction of the columns, \( n_\lambda^\alpha \) is the main direction of stress tensor corresponding to maximum principal value, and \( w \) takes into account biochemical process and it is established in terms of the gradient of the molecular factors as:

\[
w = b_{11} \nabla S_{\text{PTHrP}} - b_{12} \nabla S_{\text{Ihh}}. \tag{24}
\]

In physiological conditions, the mechanical stress do not alter the regulatory loop or the PTHrP and Ihh distribution pattern,\(^{43-45}\) thus \( w = n \). Besides, \( n_\lambda^\alpha = n \) occurs whenever the load is aligned with the growth axis. Therefore, Eq. (23) is reduced
to the principal vector of excess of stress given by the non-physiological mechanical loads; i.e.,

$$\frac{dn}{dt} = k_n(n^\sigma - n).$$

(25)

Figure 8 shows a pattern on the differential vector that affects the direction of chondrocyte column formation. Additionally, it illustrates the secondary ossification center (SOC), mechanical loads (ML), growth plate (GP), and vascular invasion zone (IZ).

2.5. Determining growth due to proliferation and hypertrophy

Stokes et al.\textsuperscript{14} have shown that a change in growth rate is proportional to the change in the number of proliferative and hypertrophic chondrocytes, which can be written as:

$$\dot{\epsilon}(x, S_{PTH}, S_{Ihh}, \sigma_E, \sigma_H, t) = d_{\text{proliferation}}(x, S_{PTH}, S_{Ihh}, \sigma_E, \sigma_H, t) + d_{\text{hypertrophy}}(x, S_{PTH}, S_{Ihh}, \sigma_E, \sigma_H, t),$$

(26)

where $d_{\text{proliferation}}$ and $d_{\text{hypertrophy}}$ are velocity strain tensors due to proliferation and hypertrophy, respectively.

It is considered that growth in the proliferative zone is due to cell mitosis occurring in the preferential direction of growth. Each cell at the top of the column is the mother of the cells at the bottom.\textsuperscript{31} Alberthy et al.\textsuperscript{37} found that sustained compression load reduces the number of proliferating cells; therefore, the growth tensor...
in the chondrocyte proliferation zone is given by:

\[
d_{\text{proliferation}}(x, S_{\text{PTHrP}}, S_{\text{Ihh}}, \sigma_E, \sigma_H, t) = (P_{\text{biochemical}}(S_{\text{PTHrP}}, S_{\text{Ihh}}) \\
+ P_{\text{mechanical}}(\sigma_E, \sigma_H)) \mathbf{n} \otimes \mathbf{n}. \tag{27}
\]

It can be argued that the regulatory loop is highly stable\textsuperscript{27,36,43–45} and there is a physiological mechanical load allowing stable\textsuperscript{41} physiological proliferation; the Eq. (27) thus takes the form:

\[
d_{\text{proliferation}}(x, \sigma_E, \sigma_H, t) = (K_{\text{proliferation}} + P_{\text{mechanical}}(\sigma_E, \sigma_H)) \mathbf{n} \otimes \mathbf{n}, \tag{28}
\]

where \(K_{\text{proliferation}}\) is a constant establishing vertical elongation depending on the animal species being studied and the type of growth plate and is given by

\[
K_{\text{proliferation}} = n_p \frac{d_n}{l_p}, \tag{29}
\]

where \(n_p\) is the number of proliferating chondrocytes per unit of time (cell/day or month), \(d_n\) is chondrocyte width in preferential growth direction, and \(l_p\) is growth plate width, as shown in Fig. 9. Note that \(d_n\) is the distance between minor axis vertices of the ellipse representing the cell.

The mechanical contribution to proliferation is given by:

\[
P_{\text{mechanical}}(\sigma_E, \sigma_H) = -(n_s \Delta \sigma_E(x, t) + n_{HP} \Delta \sigma_H(x, t)) \frac{d_n}{l_p}, \tag{30}
\]

Fig. 9. Graphic description of the geometric evolution of proliferating and hypertrophic chondrocytes. \(s\): distance between the center of proliferating chondrocyte ellipse to the apex of the minor axis, \(d_n = 2s\), \(R\): radius of the sphere representing a hypertrophic chondrocyte, \(r\): radius of the major axis of the proliferative chondrocyte ellipse, and \(l_p\): growth plate length.
where \( n_\sigma \) is the number of chondrocytes that become lost in the proliferation stage per day (or month) and per deviatoric stress unit (Pa), and \( n_{\text{HP}} \) is the number of chondrocytes lost proliferating in a day (or month) and per hydrostatic stress unit (Pa).

Moreover, following a similar procedure to that used for proliferation, growth hypertrophy is due to the pre-hypertrophic or proliferative cells stacked in the columns of chondrocytes present at this stage. An ovoid form rise to a mainly spherical form, as growth primarily occurs in the preferential direction of growth \( n_\text{hypertrophy} \):

\[
d_{\text{hypertrophy}}(x, \sigma_E, \sigma_H, t) = \left( \frac{2}{l_d} \sum_{i \in C_H} \left( \frac{R_i(t) - s}{\Delta t_i} \right) \right) n \otimes n,
\]

where \( R_i \) is the instantaneous radius of the \( i \)th chondrocyte in direction of growth once hypertrophy begins, \( s \) is the minor radius of the chondrocyte (in proliferating state, \( d_n = 2s \)), and \( \Delta t_i \) is the time that had elapsed since the \( i \)th chondrocyte enters the hypertrophy phase and reaches radius \( R_i \). It should be noted that maximum hypertrophy time is given by \( t_E \) (time extension) that represents the time required for a proliferating chondrocyte to progress to being fully hypertrophied; therefore, \( \Delta t_{\text{max}} \leq t_E \).

The influence of mechanical loading on growth (elongation) of hypertrophic chondrocytes can be modeled from two perspectives: (1) assuming that value \( t_E \) can decrease or increase with mechanical load and hence chondrocyte maturation does not reach its maximum possible length or (2) assuming that the growth function of the radius changes as a function of stress, i.e.:

\[
R_i(t) = s + \frac{R_{\text{max}}(\Delta \sigma_E, \Delta \sigma_H) - s}{t_E} \Delta t_i
= s + \frac{(R_{\text{max}} + \alpha_1 \Delta \sigma_E - \alpha_2 \Delta \sigma_H) - s}{t_E} \Delta t_i,
\]

where \( R_{\text{max}} \) is the radius of the sphere that represents a hypertrophic chondrocyte in physiological conditions, \( \alpha_1 \) is the elongation (in units of length) achieved for each unit of deviatoric stress, and \( \alpha_2 \) is the loss of growth (in length units) per unit of hydrostatic compression (see Fig. 8).

Replacing Eq. (32) in Eq. (31), the following can be obtained:

\[
d_{\text{hypertrophy}} = \left( \frac{2}{l_d} \sum_{i \in C_H} \left( \frac{R_{\text{max}} + \alpha_1 \Delta \sigma_E - \alpha_2 \Delta \sigma_H - s}{t_E} \right) \right) n \otimes n
= \left( \frac{2N_{\text{HP}}}{l_d} \left( \frac{(R_{\text{max}} - s)}{t_E} + \frac{(\alpha_1 \Delta \sigma_E - \alpha_2 \Delta \sigma_H)}{t_E} \right) \right) n \otimes n.
\]

Therefore, the sum can be replaced by \( N_{\text{HP}} \), which is the number of hypertrophic chondrocytes in hypertrophic state in direction \( n \). Then, replacing Eqs. (29), (30),
and (33) in Eq. (26) we have:

$$
\dot{\epsilon}(x, S_{\text{PTHrP}}, S_{\text{Ihh}}, \sigma_E, \sigma_H, t) = \left\{ \left[ n_p \cdot \frac{d_n}{l_p} - (n_\sigma \Delta \sigma_E(x, t) + n_{\text{HP}} \Delta \sigma_H(x, t)) \frac{d_n}{l_p} \right] + \frac{2N_H}{l_d} \left( \frac{(R^l_{\text{max}} - s)}{l_E} + \frac{(\alpha_1 \Delta \sigma_E - \alpha_2 \Delta \sigma_H)}{l_E} \right) \right\} n \otimes n. \tag{34}
$$

Equation (34) can be ordered in such a way as to take the fully identified physiological and mechanical terms, which leads to:

$$
\dot{\epsilon} = \begin{cases} 
\frac{1}{l_p} \left( n_p d_n + \frac{2N_H(R^l_{\text{max}} - s)}{l_E} \right) & \text{physiological term} \\
\frac{1}{l_p} \left[ \Delta \sigma_E \left( \frac{2\alpha_1 N_H}{l_E} - n_\sigma d_n \right) - \Delta \sigma_H \left( n_{\text{HP}} d_n + \frac{2\alpha_1 N_H}{l_E} \right) \right] & \text{mechanical term}
\end{cases} n \otimes n. \tag{35}
$$

### 2.6. Vascular invasion and ossification front

The speed of bone growth depends on the velocity at which advances the metaphysis in time; i.e., the growth rate is given by the number of hypertrophic chondrocytes in elongation. Hypertrophied chondrocytes secrete vascular endothelial growth factor (VEGF), which induces cells in the perichondrium (in this moment periosteum) to form new blood vessels. These blood vessels can invade the hypertrophied chondrocyte zone in which ossification will begin. When the blood vessels arrive, other types of cells and growth factors also appear, the pressure of oxygen and carbon dioxide changes, and hence chondrocytes enter apoptosis.

Stem cells arrive with the blood vessels (undifferentiated mesenchymal cells) that will form part of the bone marrow. Therefore, vessels in the primary ossification center extend to the ends of long bones.

The process begins with the release of Matrix Metallo-Proteases (MMPs) by chondrocytes in hypertrophic state. These MMPs degrade the cartilage matrix and prepare the tissue for vascular invasion, an event run by the VEGF that attracted the blood vessels. Figure 10 shows the front of vascular invasion. An excellent model of vascular invasion was introduced by Herrera and Lóopez where they considered the advance of ossification as traveling waves; in fact, the wave front moved without changing its form. Such work considered that a model could include the angiogenic agent (VEGF), the MMP, and an angiogenic inhibitor agent, so that the wave front could be modeled with three equations similar to...
Fig. 10. Micrograph of the lower hypertrophic zone and of the front of vascular invasion and ossification. Taken from Refs. 46.

a Fisher-KPP system. This article assumed that the lower hypertrophic chondrocytes released MMPs and VEGF during apoptosis for bone invasion. We propose a first simple model, where the MMP release is as an indicator of degradation and vascularization, is given by:

$$\frac{\partial S_{\text{MMP}}}{\partial t} = D_{\text{MMP}} \nabla^2 S_{\text{MMP}} + \xi(t) C_H \frac{\ln(2)}{\tau_{\text{med}}} S_{\text{MMP}},$$  \hspace{1cm} (36)

where $S_{\text{MMP}}$ is the MMP concentration that depends on time and space, $D_{\text{MMP}}$ is the MMP diffusion coefficient, $\xi(t)$ is the amount of MMP released per chondrocyte and per unit of time, $C_H$ is the hypertrophic chondrocyte concentration and the term $\frac{\ln(2)}{\tau_{\text{med}}} S_{\text{MMP}}$ refers to MMP degradation due to its half-life $\tau_{\text{med}}$.\textsuperscript{26} The function $\xi(t)$ depends on each hypertrophic chondrocyte’s apoptosis time; therefore, a linear function is assumed, such that:

$$\xi(t) = \begin{cases} \xi \cdot (t - t_0) & \text{if } t_0 \leq t \leq t_{\text{max}}, \\ 0 & \text{otherwise}, \end{cases} \hspace{1cm} (37)$$

where $t_0$ is the time of initiation of apoptosis and $t_{\text{max}}$ is the maximum time it takes the chondrocyte to release the MMP and the VEGF. Therefore, the advance of the ossification front is given by the following expression:

$$\frac{dy_{\text{ossification}}}{dt} = \begin{cases} \gamma n & \text{if } S_{\text{MMP}} \geq S_{\text{Thr}}^{\text{MMP}}, \\ 0 & \text{otherwise}, \end{cases} \hspace{1cm} (38)$$
where $\gamma_{\text{ossification}}$ is the ossification length measured from the center of the bone (primary ossification center), $\gamma$ is a constant quantifying the ossification speed, and $S_{\text{Thr}}^{\text{MMP}}$ is the threshold value of MMP, for which occurs the vascular invasion and ossification.

### 2.7. Model of growth plate mechanical behavior

The growth plate is between hard bone and has a low exchange fluid (exudation and imbibition) because the adjacent bone has a very low permeability.\textsuperscript{35} This behavior is similar to the articular cartilage. The growth plate has viscoelastic behavior and has been modeled as being approximate biphasic nonlinear\textsuperscript{47} and, in some cases, has been considered transversely isotropic biphasic.\textsuperscript{48}

Sergerie \textit{et al.}\textsuperscript{49} found that the proliferative and hypertrophic zone had half the stiffness of the reserve zone along the growth axis in a newborn pig ulna model and was three times less rigid than in the transverse plane. The proliferative and hypertrophic zone was three times more permeable than the reserve zone in a radial direction. These data suggest that the reserve zone provided mechanical support for the growth plate in high weight animals having growth for long periods of time.\textsuperscript{50}

Variations have also been found in the elastic modulus in a perpendicular direction to growth. For example, it has been found to be 40% stiffer in the inner zone in samples of cattle and 75% less permeable than samples located at the periphery\textsuperscript{47} that was attributed to high cell concentration and water content at the periphery (Figs. 11 and 12).

![Fig. 11. Scheme of growth plate's mechanical behavior.](image-url)
The mechanical properties of the growth plate also vary with age and growth stage. It was found that stiffness decreased by 12% in 35-day-old rats in a model of a rat tibia\textsuperscript{51} and increased by 20 and 94% at 56 and 80 days compared to 21-day-old rats. A pig model of ulna revealed a 40% increase and 12 and 39% decrease in 4, 8, and 18-week-old pigs compared to newborn ones.

Thus, according to data reported by Villemure and Stokes\textsuperscript{35} and Lin \textit{et al.}\textsuperscript{52} a transversely isotropic biphasic material is considered, such descriptive model is given by the equations:

\begin{equation}
- \nabla \cdot \sigma + \nabla p = 0, \tag{39}
\end{equation}

\begin{equation}
\frac{\partial}{\partial t} (\nabla \cdot \mathbf{u}) - \nabla \cdot (\mathbf{k} \nabla p) = 0. \tag{40}
\end{equation}

Equation (39) is derived from the law of conservation of momentum; this equation couples linear elasticity ($\sigma$ corresponds to tissue stress tensors) with a term representing fluid pressure ($p$). Equation (40) refers to the change in solid matrix expansion (where $\mathbf{u}$ represents displacement) regarding the mechanical stress created by the divergence of the fluid pressure gradient. $\mathbf{k}$ is a constant matrix in Eq. (40), representing the solid permeability module in each direction.

Stress is related to strain through the constitutive equation for orthotropic materials; the following set of constitutive equations represent a system having $x', y', z'$ main orthotropic directions:

\begin{equation}
\varepsilon_1' = \frac{1}{E_1} \sigma_1' - \frac{\nu_{12}}{E_2} \sigma_2' - \frac{\nu_{13}}{E_3} \sigma_3',
\end{equation}

\begin{equation}
\varepsilon_2' = \frac{1}{E_2} \sigma_2' - \frac{\nu_{21}}{E_1} \sigma_1' - \frac{\nu_{23}}{E_3} \sigma_3'.
\end{equation}
where $E_i$ are elastic coefficients, $\nu_{ij}$ are Poisson coefficients, $\tau_{ij}$ are shear stresses, and $G_{ij}$ are stiffness modules. It should be noted that orthotropic preferential directions are orientated according to growth axis $\mathbf{n}$. They also have to meet the condition of symmetry:

$$E_1 \nu_{21} = E_2 \nu_{12},$$
$$E_1 \nu_{31} = E_3 \nu_{31},$$
$$E_2 \nu_{32} = E_3 \nu_{23}.$$  \hspace{1cm} (42)

The velocity of the fluid surrounding the tissue and mechanical stress can be obtained from the solution of these equations. Fluid velocity determines the convective transport of substances found in the tissue; i.e., substances PTHrP, Ihh, and MMP. This velocity is given by:

$$\mathbf{v} = k \nabla \mathbf{p}.$$  \hspace{1cm} (43)

The octahedral strain supporting the tissue determines the stress state that affects cell proliferation and hypertrophy. The following is used for quantifying octahedral stress:

$$\sigma_E = \sqrt{\frac{2}{3} J_2},$$ \hspace{1cm} (44)

where $J_2$ is the second invariant of Cauchy’s deviatoric strain tensor. Constant matrix permeability is also expressed in orthotropic main coordinates; therefore, we have:

$$k = \begin{pmatrix} k_{11} & 0 & 0 \\ 0 & k_{22} & 0 \\ 0 & 0 & k_{33} \end{pmatrix},$$ \hspace{1cm} (45)

and the system is then completed with the appropriate boundary conditions, as described by Oñate.
2.8. Comparing the proposed model with those of Stokes et al. and Carter and Wong

Lin et al.\textsuperscript{52} compared the models of Stokes et al.\textsuperscript{41} and Carter and Wong.\textsuperscript{42} That article showed that the growth pattern is different in the two models due to their hypotheses and mathematical representation. The Carter and Wong\textsuperscript{42} model takes 3D mechanical stimulus into account. Octahedral and hydrostatic strains are used as stimuli contributing toward the endochondral growth pattern; however, the model cannot represent growth orientation. Mechanical stimulus in the Stokes et al.\textsuperscript{41} model only takes axial loads into account for determining the growth pattern but cannot represent the effect of nonaxial loads, such as shear loads.

The model of Stokes et al.\textsuperscript{41} represents the Hueter-Volkmann law and is obtained from experimental data relating longitudinal bone growth to existing compressive loads on the growth plate. This can be mathematically expressed as\textsuperscript{52}:

\[
\Delta \varepsilon_l = \Delta G_l (1 + \beta l \sigma_{zz}),
\]

where \(\Delta \varepsilon_l\) (months\(^{-1}\)) is the longitudinal deformation of bone, \(\Delta G_l\) (months\(^{-1}\)) is the physiological (normal) deformation due to an unchanging stress level, \(\beta_l\) is a constant sensitive to mechanical stress (\(\beta_l = 1.71\) MPa\(^{-1}\)), and \(\sigma_{zz}\) is the mechanical stress existing in the growth plate in the direction of bone elongation (direction \(z\)). It can be seen that the model takes into account the effects of mechanical stress exerted on the growth plate because it involves the physiological growth \(\Delta G_l\) and the growth due to the effect of mechanical stress \(\Delta G_l \beta_l \sigma_{zz}\). Villemure and Stokes\textsuperscript{35} showed that Eq. (46) does not change for species or the age of the animal being studied, but differs due to the anatomical site where the experiment is conducted. For example, tibia and vertebra has 18.6\% and 15\% variations in growth for each 0.1 MPa, respectively.

It should be noted that Stokes et al.\textsuperscript{41} represent linear growth as being subject to the action of axial strains on bone; therefore, they do not take into account the change in direction of columns formation (column misalignment). Comparing Eq. (46) with Eq. (35), we have:

\[
\Delta G_m = \frac{1}{l_p} \left( n_p d_n + \frac{2 N_H (R_{\text{max}}^l - s)}{l_E} \right),
\]

Equation (47) shows that the physiological effect of growth depends on chondrocyte geometry, represented by \(d_n\), \(R_{\text{max}}^l\) and \(s\) and the number of chondrocytes present at the growth site, which may be different from one long bone to another and for the upper and lower extremities. The number of chondrocytes in each anatomical site is represented by the number of proliferating chondrocytes that appears per unit of time \(n_p\) and the number of chondrocytes in a state of elongation during the same period of time \(N_H\).

The term \(\beta_l\) of Eq. (46) cannot be directly correlated with the model proposed here because the model of Stokes et al.\textsuperscript{41} does not differentiate unidirectional
traction strains while we take into account the hydrostatic and deviatoric stress components.

The model of Carter and Wong\(^2\) represents a law of endochondral ossification that takes into account hydrostatic and deviatoric stresses, but does not heed the direction of growth (i.e., the thermal expansion simulating growth was isotropic). This model has a biological and a mechanical component given by the following equation:

\[
\dot{\varepsilon} = \dot{\varepsilon}_B + (a\sigma_E + b\sigma_H), \tag{48}
\]

where \(\dot{\varepsilon}_B\) (months\(^{-1}\)) is the longitudinal deformation of bone due to biological characteristics \(a\) and \(b\), which are constants of dynamic growth taking into account the action of deviatoric and hydrostatic stresses, respectively.

Comparing the model of Carter and Wong with the one proposed, we have:

\[
\dot{\varepsilon}_B = \frac{1}{t_p} \left( n_p d_n + \frac{2N_H(R_{f\text{max}} - s)}{t_E} \right). \tag{49}
\]

The relationship between constants \(a\) and \(b\) with the proposed model can be found from Eq. (48), obtaining:

\[
a = \frac{1}{t_p} \left( \frac{2\alpha_1 N_H}{t_E} - n_\sigma d_n \right), \tag{50}
\]

\[
b = \frac{1}{t_p} \left( n_{\text{HP}} d_n \frac{2\alpha_2 N_H}{t_E} \right), \tag{51}
\]

where it is observed that the constants depend on chondrocyte geometry and the effect that mechanical load exerted on such geometry, represented by \(\alpha_1, n_\sigma, n_{\text{HP}}, \) and \(\alpha_2\).

3. Discussion and Conclusions

We proposed a new mathematical model describing epiphyseal plate growth. The model takes into account the geometry of the chondrocytes in the physis and its distribution by defining a new second-order tensor that represents adequately the cell concentration, the cell anisotropy, and the formation of columns. The description of the cell distribution constitutes a breakthrough in understanding the functioning of the physis, because it allows to describe several geometric properties simultaneously and simplifies the analysis to a single variable in each area of the epiphyseal plate; i.e., \(r_{PC}\) and \(r_{HC}\) in the proliferative and hypertrophic areas, respectively. Each variable represents the ratio of the number of cells in the growth direction to the number of cells in transverse direction. The problem of cell proliferation and hypertrophy is thus determined by a single 1D variable, the direction of growth \(n\).
Under the assumption that the central biochemical loop (PTHrP-Ihh) inducing proliferation and hypertrophy is insensitive to mechanical stress and is highly stable, the biochemical process can be simplified and let to arguing that mechanical loads play an important role in the changes occurring during endochondral development. The major effect on variables $r_{PC}$ and $r_{HC}$ are the mechanical stresses that can decrease the number of proliferative and hypertrophic chondrocytes subjected to high mechanical compressive loads. Anisotropic cell distribution and cell concentration have not been described in previous models such as those reported by Carter and Wong and Stokes et al.

The mathematical model takes into account the effect of mechanical stress on cell organization and the direction of growth, which has been described in Eqs. (23) and (25), with change of direction $n$ in terms of main stress tensor directions. Unlike the models of Carter and Wong and Stokes et al. this model can predict the column organization and direction by mechanical stress. Carter and Wong only considered isotropic growth; this being similar to what occurs by thermal expansion. On the other hand, Stokes et al. only considered growth in an axial direction.

The final result of the description of growth (growth tensor) was similar to that in the model of Carter and Wong; however, the deduction proceeds from biological and not phenomenological aspects. We take into account stresses supported by the growth plate; i.e., deviatoric and hydrostatic stresses. The growth tensor is thus described from chondrocyte geometry and relates it with the cells’ behavior due to the supported stress level; therefore, the model can describe each biological constant used in the model of Carter and Wong, as described in Eqs. (49)–(51).

Like all biological mathematical models, there are limitations that should be discussed. We only take into account chondrocyte geometry; however, we do not consider the construction of the adjacent matrix where the cells are found. Olney et al. showed that growth mainly depends on the number of hypertrophic chondrocytes that are becoming lengthened. However, Villemure and Stokes highlighted the fact that growth depends on proliferation, hypertrophy, and matrix synthesis and degradation in the growth plate. Therefore, we only introduce proliferative and hypertrophic chondrocyte growths to ease their geometric representation and relationship with bone elongation. Future studies may include an additional term in Eqs. (34) and (35) heeding matrix synthesis. Measurements should thus be taken for ascertaining the amount of synthesized matrix and its share of growth rate.

Growth Eqs. (34) and (35) do not take into account the effects of other molecules that may have helped the metaphyseal closure. None of the models proposed until now can simulate the effect of estrogen and aging; therefore, the model is limited to intervals of active growth where proliferation and hypertrophy rates are constant and decrease by aging caused by systemic hormones, as in the case of estrogen.

Although the model heeds vascular invasion and ossification, these processes involve more than biological variables that are not taken into account in this article. Herrero and López reported an excellent model taking ossification into account.
in a wave front that did not become changed and involved three types of chemical species (VEGF, MMP, and an angiogenesis inhibitor agent).

Despite these limitations, this mathematical model represents the mechanical and cellular activity of the growth plate. The model was biologically-derived and represents a contribution toward knowledge regarding physis structure. The model represents the geometry of the cellular distribution of chondrocytes, quantifies the number of cells in each direction of the growth plate and models growth and progress of the ossification front. Based on this model, it will be carried out computer simulations that will be presented in a second article. We will list the constants used, numerical tests of the model will be carried out, and discuss the clinical implications of the results.

References


