

A model for loading-dependent growth, development, and adaptation of tendons and ligaments

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Abstract

The geometric and material properties of tendons and ligaments change during growth and development. While some of the changes occur in the absence of mechanical loading, normal development requires the mechanical stimulus provided by normal physical activity. We have developed an analytical framework for quantitatively describing changes in uniaxial tendon and ligament properties throughout ontogeny. In our approach, cross-sectional area, modulus, and strength undergo baseline levels of development due to inherent time-dependent biological influences. The properties also change in response to mechanobiological influences by adapting to maintain a constant daily strain stimulus under changing load conditions. We have implemented a computer algorithm based on these concepts and obtained results consistent with experimental observations of normal tendon and ligament growth and development reported by other investigators. Additional results suggest that these concepts can also explain tendon and ligament adaptation to increased or decreased loading experienced during development. Published by Elsevier Science Ltd.

Keywords: Tendon; Ligament; Development; Adaptation

1. Introduction and background

Skeletal connective tissues are load-bearing tissues that adapt to meet the functional demands placed on them. Carter (1987) has suggested that the principles governing bone growth and development also regulate the functional adaptation of bone. We hypothesize that a comparable principle may apply to tendons and ligaments. To explore this hypothesis, we present a computational model that describes the growth and development of tendons and ligaments under both normal and altered loading conditions.

Several investigators have proposed mathematical models for soft tissue growth and adaptation (Cowin, 1985, 1996; Olsen et al., 1995; Oster and Murray, 1989; Rodriguez et al., 1994; Tözeren and Skalak, 1988). To date, these formulations have been largely theoretical and typically have not incorporated clinical or experimental data in specific applications. In the present study,

we introduce an analytical approach for the growth and adaptation of tendons and ligaments based on experimental findings reported in the literature.

Experimental studies have shown clear changes in tendon and ligament properties during development. Cross-sectional area, modulus, and strength increase rapidly in early life until relatively stable properties are achieved at maturity (Haut, 1983; Ingelmark, 1945; Morein et al., 1978; Nakagawa et al., 1996; Torp et al., 1975). Mechanical loading affects this development. In mature animals, exercise generally leads to increased cross-sectional area, modulus, and strength (Ingelmark, 1945, 1948; Tipton et al., 1986; Woo et al., 1980), while immobilization leads to reductions in these properties (Amiel et al., 1982; Loitz et al., 1989; Noyes, 1977; Woo et al., 1987). Similar effects have been reported for immature animals (Ingelmark, 1945; Walsh et al., 1993). Mechanical stresses may also influence the structure of ligaments in their insertional regions (Matyas et al., 1995).

Tendon and ligament failure stresses change during development and adaptation, but failure strains do not change (Loitz et al., 1989; Nakagawa et al., 1996; Noyes, 1977). Failure and physiologic strains also remain

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constant across species and between different tendons and ligaments (Beynon et al., 1992; Butler et al., 1986; Haut, 1983; Morein et al., 1978; Torp et al., 1975; Woo et al., 1990, 1992; Yamamoto et al., 1992). Because strains are conserved with respect to age, species, and anatomical location, we will consider mechanical loading in terms of the strains created during physical activity.

In this paper, we present a theoretical framework for understanding the growth and development of tendons and ligaments using principles that can also explain the functional adaptation of these tissues. We propose relationships linking changes in tendon and ligament properties to biological influences and mechanical loading. We incorporate these relationships in a computer algorithm used to simulate normal growth and development. We also use the algorithm to predict the effects of increased and decreased loading on growth and development as a preliminary example of tendon and ligament adaptation.

2. Methods

Consider an idealized tendon or ligament for which we track changes in the cross-sectional area, modulus, and strength over time. For modeling purposes, we decompose the changes in these properties into *biological* and *mechanobiological* components. The biological component represents a basal level of growth and development that depends on age without any influence from

mechanical loading. The mechanobiological component represents the changes associated with mechanical loading. The biological and mechanobiological contributions determine the overall changes in cross-sectional area and modulus. We assume a constant ultimate strain failure criterion, which makes the changes in strength proportional to the changes in modulus.

We have developed a time-dependent algorithm to predict and track changes in the tendon and ligament properties (Fig. 1). We begin by specifying an initial cross-sectional area $A(t_i)$ and modulus $E(t_i)$ at time $t = t_i$. Based on the animal age t , we determine the biological components of the specific rate of area change $(\dot{A}/A)_{\text{bio}}(t)$ and of the rate of modulus change $\dot{E}_{\text{bio}}(t)$. For a time step Δt , we specify the forces $F(t)$ applied to the tendon or ligament. These forces are then used in combination with the area and modulus to determine a daily strain stimulus ξ . This stimulus determines the mechanobiological components of the specific rate of area change $(\dot{A}/A)_{\text{mech}}(\xi)$ and of the rate of modulus change $\dot{E}_{\text{mech}}(\xi)$. The biological and mechanobiological components sum to give the total specific rate of area change

$$(\dot{A}/A) = (\dot{A}/A)_{\text{bio}}(t) + (\dot{A}/A)_{\text{mech}}(\xi) \tag{1}$$

and the total rate of modulus change

$$\dot{E} = \dot{E}_{\text{bio}}(t) + \dot{E}_{\text{mech}}(\xi). \tag{2}$$

We use these rates to update the area and modulus,

$$A_{t+\Delta t} = A_t + (\dot{A}_t/A_t)A_t \Delta t \tag{3}$$

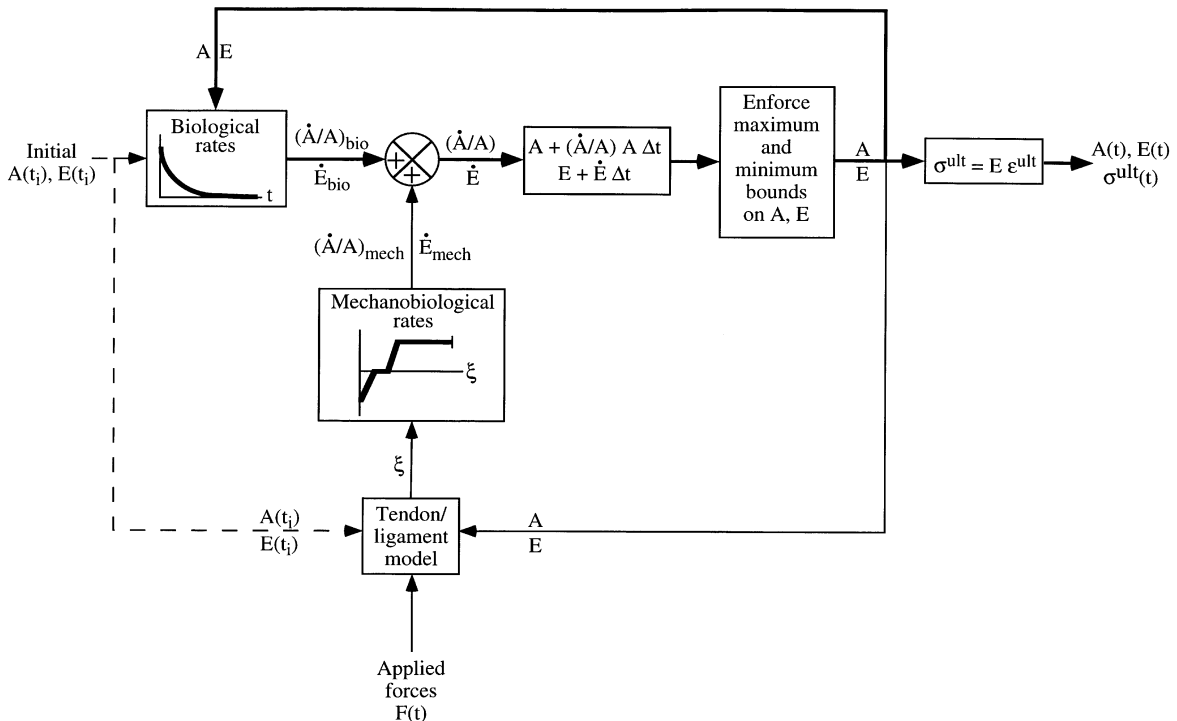


Fig. 1. Flow chart for the algorithm used in the simulations.

and

$$E_{t+\Delta t} = E_t + \dot{E}_t \Delta t, \quad (4)$$

with the restriction that the new values remain between specified upper and lower bounds. The upper bounds denote the maximum attainable cross-sectional area for a particular tendon or ligament and the maximum attainable modulus for the tissue comprising all tendons and ligaments. The lower bounds represent the growth that would occur in the complete absence of mechanical loading, that is, the growth contributed by the biological component alone.

To estimate the strength of the tendon or ligament, we assume a linear constitutive relationship and a constant failure strain ε^{ult} to compute the failure stress

$$\sigma_{t+\Delta t}^{\text{ult}} = E_{t+\Delta t} \varepsilon^{\text{ult}}. \quad (5)$$

Given the updated properties, we proceed to the next time step. To complete our description of the algorithm, we need only characterize the applied loading and determine the relationships used to define the biological and mechanobiological contributions.

3. Force input and daily strain stimulus

Tendons and ligaments experience primarily uniaxial tensile forces (Ault and Hoffman, 1992). For a tendon, these forces are generated by a muscle. During normal development, the maximum muscle force F increases approximately in proportion to body mass (Carrier, 1983). Since ligament loading during development has not been studied to the same extent as tendon loading, we assume that ligament loads also increase in proportion to body mass.

To determine adaptation rates from the applied loads, we must relate the loads to the daily strain stimulus. For the applied force F , we use the cross-sectional area A and modulus E to compute the stress

$$\sigma = F/A. \quad (6)$$

As a first approximation, we assume a linear constitutive relationship to determine the associated strain

$$\varepsilon = \sigma/E. \quad (7)$$

Mikić and Carter (1995) have defined the daily strain stimulus as

$$\zeta = \left[\sum_{\text{day}} n_i \Delta \bar{\varepsilon}_i^m \right]^{1/m} \Big|_{\text{per day}}, \quad (8)$$

where n_i is the number of cycles of load type i , $\Delta \bar{\varepsilon}_i$ is the cyclic strain range of the energy equivalent strain for load type i , and m is an empirical constant. For convenience, we simplify this expression by assuming that the stimulus is dominated by the single load case described above. We

also assume that the strain magnitude affects the stimulus much more than the number of loading cycles, i.e. m is large. The daily strain stimulus then reduces to

$$\zeta \approx \Delta \bar{\varepsilon} \Big|_{\text{per day}} = (\varepsilon - 0) \Big|_{\text{per day}} = \varepsilon \Big|_{\text{per day}}. \quad (9)$$

This stimulus determines the mechanobiologic components of the area and modulus adaptation.

4. Biological component

During development, the tendon and ligament properties change in part due to biological influences such as growth factors (Storm and Kingsley, 1996; Wolfman et al., 1995) not affected by mechanical loading. These influences have their strongest effect early in life and minimal effect once the animal has reached maturity. The biological components of the specific rate of cross-sectional area change $(\dot{A}/A)_{\text{bio}}$ and of the rate of modulus change \dot{E}_{bio} reflect their dependence on cell density, which decays exponentially with animal age (Ingelmark, 1945). Mathematically, the biological contributions are defined as

$$(\dot{A}/A)_{\text{bio}}(t) = (\dot{A}/A)_{\text{bio}}^{\text{max}} \exp(-t/\tau) \quad (10)$$

and

$$\dot{E}_{\text{bio}}(t) = \dot{E}_{\text{bio}}^{\text{max}} \exp(-t/\tau), \quad (11)$$

where t is the animal age, τ is a time constant, and $(\dot{A}/A)_{\text{bio}}^{\text{max}}$ and $\dot{E}_{\text{bio}}^{\text{max}}$ are scaling constants. The exponential $\exp(-t/\tau)$ decays to a negligible value of 0.005 when $t = 5\tau$. We select the time constant τ so that the animal matures at age $t = 5\tau$.

5. Mechanobiological component

While the development attributed to the biological component occurs with or without mechanical loading, additional mechanically stimulated development is required to attain normal tendon and ligament properties. We represent this mechanobiological influence using the curves in Figs. 2a and b. The two curves in Fig. 2 have the same shape because, for mature animals in which the biological contributions have become negligible, changes in loading produce parallel effects in cross-sectional area and modulus (Woo et al., 1980, 1981, 1987).

The shape of the mechanobiological curves has several notable features. Strain stimulus values of 1.5 to 3%/day associated with strains between 1.5 and 3% promote tissue homeostasis. Physiologic tendon and ligament strains are in this approximate range (Beynon et al., 1992; Woo et al., 1990). Higher values of the strain stimulus lead to increases in the area and modulus, and lower stimulus values lead to decreases in these parameters. The more extreme the strains, the faster the

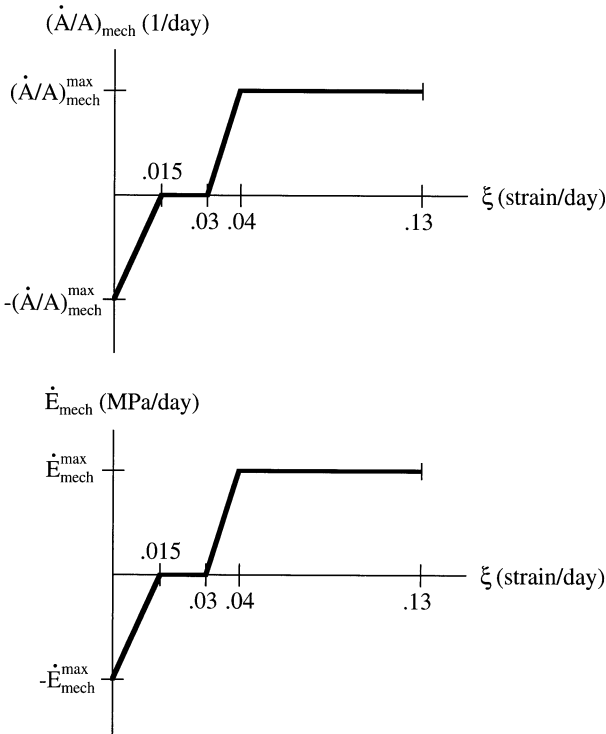


Fig. 2. Mechanobiological components of (a) the specific rate of cross-sectional area change and (b) the rate of modulus change.

properties change up to the maximum rates $\pm (\dot{A}/A)_{\text{mech}}^{\text{max}}$ and $\pm \dot{E}_{\text{mech}}^{\text{max}}$. Consequently, the tendons and ligaments always progress towards homeostasis as increases in the area and modulus reduce excessive strains while decreases in the area and modulus elevate excessively low strains.

6. Parameter values and application

As an example application, we have used our algorithm to simulate the growth and development of a rabbit Achilles tendon. Table 1 lists the parameter values used in the simulations. We selected these values based on experimental data from the literature. The available data come from various tendons and ligaments from several different animals.

For the biological components, we selected a time constant of $\tau = 2$ months. This would make the biological contribution negligible at $5\tau = 10$ months, the approximate maturation age for rabbits (Gibb and Williams, 1994). We selected scaling constants of $(\dot{A}/A)_{\text{bio}}^{\text{max}} = 0.03 \text{ d}^{-1}$ and $\dot{E}_{\text{bio}}^{\text{max}} = 1 \text{ MPa d}^{-1}$ to produce lower bounds that reflect the reductions in area and modulus observed after the immobilization of mature animals (Woo et al., 1987).

For the mechanobiological components, we first selected the maximum rates of modulus increase and

Table 1
Parameter values used in the simulations

Parameter	Value	Relevant Figure/Equation	Specific to application?
τ	2 months	Eqs. (10) and (11)	Yes
$(\dot{A}/A)_{\text{bio}}^{\text{max}}$	0.03 d^{-1}	Eqs. (10)	No
$\dot{E}_{\text{bio}}^{\text{max}}$	1 MPa d^{-1}	Eqs. (11)	No
$(\dot{A}/A)_{\text{mech}}^{\text{max}}$	0.01 d^{-1}	Fig. 2a	No
$\dot{E}_{\text{mech}}^{\text{max}}$	5 MPa d^{-1}	Fig. 2b	No
A^{max}	18 mm^2	Fig. 3a	Yes
E^{max}	1500 MPa	Fig. 3b	No
ϵ^{ult}	13%	Eq. (5)	No

decrease. Between the ages of 2 and 3 months, rat tail tendon increases in modulus at an average of 5.05 MPa d^{-1} (Morein et al., 1978). The medial collateral ligaments of immobilized rabbits decrease in modulus at a maximum rate of -5.4 MPa d^{-1} (Woo et al., 1987). We therefore set the maximum rates of modulus increase and decrease at $\pm \dot{E}_{\text{mech}}^{\text{max}} = \pm 5 \text{ MPa d}^{-1}$. For a typical tendon or ligament with modulus 500 MPa , these rates correspond with specific rates of change of $(\pm 5 \text{ MPa d}^{-1})/(500 \text{ MPa}) = \pm 0.01 \text{ d}^{-1}$. As noted previously, loading changes have similar effects on cross-sectional area and modulus in adult animals. We therefore set the maximum specific rate of cross-sectional area change at $\pm (\dot{A}/A)_{\text{mech}}^{\text{max}} = \pm 0.01 \text{ d}^{-1}$.

For the upper bounds, we selected values of 18 mm^2 for the cross-sectional area of rabbit Achilles tendons and 1500 MPa for the modulus of all tendons and ligaments. Exercise studies have reported cross-sectional area increases of approximately 20% for adult animals (Woo et al., 1980). The maximum area of 18 mm^2 represents a 20% increase over the normal mature cross-sectional area of 15 mm^2 reported by Nakagawa et al. (1996). For the modulus of tendons and ligaments, investigators have reported values as high as 1488 MPa (Derwin et al., 1994). We set the maximum modulus at 1500 MPa to accommodate this modulus.

To compute the failure stress, we assigned a failure strain of $\epsilon^{\text{ult}} = 13\%$. This value falls in the range of 7–17% reported for most tendons and ligaments (Butler et al., 1986; Haut, 1983; Morein et al., 1978; Torp et al., 1975; Woo et al., 1992; Yamamoto et al., 1992).

As input for our simulations, we began with an initial cross-sectional area of $A(t_i) = 2.8 \text{ mm}^2$ and an initial modulus of $E(t_i) = 281 \text{ MPa}$ for three week old rabbits (Nakagawa et al., 1996). To determine the force input, we used the body weight data of Gibb and Williams (1994). An exponential curve fit to this data gives

$$M(t) = -2 \exp(-t/3.7) + 1.83, \tag{12}$$

where M is the mass of the rabbit in kilograms and t is the rabbit age in months. We used this mass to estimate

the force applied to the tendon

$$F(t) = 133M(t), \tag{13}$$

where the force is measured in Newtons and the mass in kilograms. We selected the coefficient 133 to give a force of 243 N for a mature rabbit with mass 1.83 kg (Gibb and Williams, 1994). We computed the force at maturity as $F = AE\varepsilon = 243$ N, where the cross-sectional area $A = 15.3$ mm² and modulus $E = 530.5$ MPa came from Nakagawa et al. (1996) and the strain $\varepsilon = 0.03$ came from Fig. 2.

In addition to the simulation of normal growth and development, we performed simulations in which we increased or decreased the loading during development. To simulate exercise, we increased the applied forces by 30% starting at 4.5 months of age. To simulate immobilization and remobilization, we decreased the loading to 10% of normal between the ages of 3 and 6 months.

7. Results

For normal growth and development, the simulations predict rapid increases in the cross-sectional area, modulus, and strength prior to maturity (Fig. 3a–c). The increases slow as the animal matures, and stable values

are maintained in the adult. These results are consistent with the rabbit Achilles tendon data of Nakagawa et al. (1996).

Increased loading produces results consistent with the findings of Ingelmark (1945). Ingelmark found that trained mice have larger tendon cross-sectional areas than untrained mice. Our simulation results exhibit such an increase in cross-sectional area for tendons subject to elevated loads (Fig. 3a). Our results also predict corresponding increases in the tendon modulus (Fig. 3b) and strength (Fig. 3c).

Decreased loading produces results consistent with the findings of Walsh et al. (1993). Walsh and colleagues found that immobilization leads to a significant decrease in the stiffness of immature rabbit medial collateral ligaments while the cross-sectional area increases despite immobilization. Our simulation results capture these differences. Because the biological component accounts for much of the development of cross-sectional area, the area increases despite immobilization (Fig. 3a). The development of modulus requires a larger mechanobiological contribution, allowing for large losses of modulus (Fig. 3b) and strength (Fig. 3c) during immobilization.

When we restore normal loading, the area, modulus, and strength increase rapidly to stable values (Fig. 3a–c). These values differ from those attained during normal

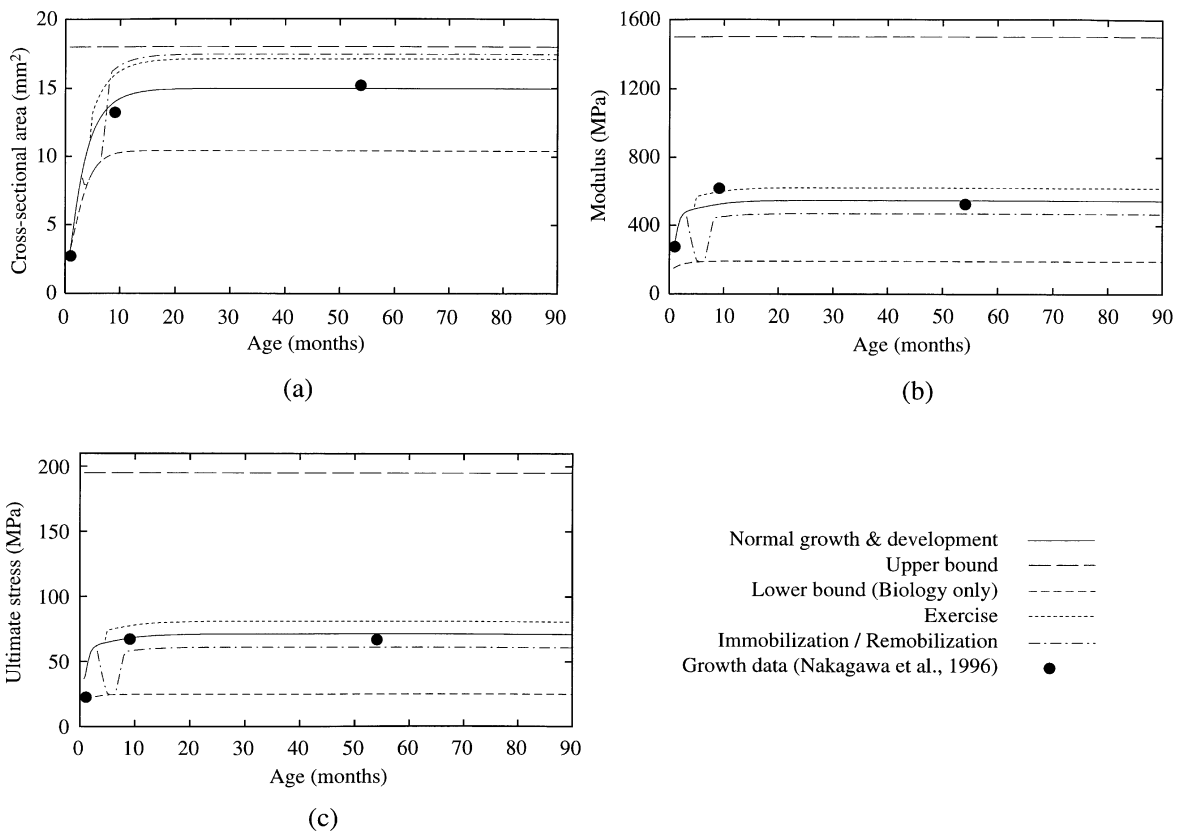


Fig. 3. Simulation results and experimental data illustrating changes in (a) the cross-sectional area, (b) the modulus, and (c) the strength of growing rabbit Achilles tendons.

development. Because the area reaches its minimum before the modulus, remobilization begins with a larger area relative to the modulus than seen during normal development. The area and modulus increase at the same rates as during normal development, resulting in a higher final area and lower modulus following remobilization.

Fig. 4 compares the simulation results for normal growth and development with additional data from the literature. We normalized the results to allow comparison between different tendons and ligaments from different animals. We normalized animal age by an approximate maturation age for each animal, using 3 months

for rats (Morein et al., 1978), 9 months for rabbits (Nakagawa et al., 1996), and 18 yr for humans (Sinclair, 1985). We normalized the simulation results using the final values predicted for the cross-sectional area, modulus, and strength. We normalized the experimental data using a ‘mature value’ for each data set determined by averaging all data points at or beyond the maturation age. The normalized simulation results are consistent with data for various rabbit, rat, and human tendons (Ingelmark, 1945; Morein et al., 1978; Torp et al., 1975).

8. Discussion

We have presented an analytical approach for studying the growth, development, and adaptation of tendons and ligaments. Our approach captures the general trends observed in experimental studies. To our knowledge, this is the first attempt at applying analytical methods to study tendon and ligament growth, development, and adaptation in the context of experimental findings.

As the first model of its type, this model is admittedly very basic. It assumes linear elastic constitutive behavior and does not account for viscoelastic effects. It is also a phenomenological model. Microstructural parameters such as fiber volume fraction, fiber alignment, fiber diameter, and cross-link density determine the modulus and strength of tendons and ligaments (Parry et al., 1978; Viidik, 1990; Woo et al., 1992; Wren and Carter, in press). Future models may explore this microstructural basis for loading-induced material properties changes.

The current model provides insight into tendon and ligament adaptation beyond that provided by experimental studies. Ingelmark (1945) showed that training increases the cross-sectional area of mouse Achilles tendons. Our simulations predict not only this increase, but also increases in the modulus and strength. In addition to reproducing the differences observed by Walsh et al. (1993) in how immobilization affects ligament cross-sectional area and modulus, our approach suggests a possible explanation for these differences. Our results also illustrate how tendons and ligaments can achieve a desired stiffness by adjusting both their size and their material properties.

The lower bounds contribute to the behaviors observed by Walsh et al. (1993). The upper bounds provide a possible explanation for the apparent lack of adaptation of certain tendons. Ker et al. (1988) have reported that while most tendons experience physiologic stresses below 50 MPa, certain tendons experience significantly higher stresses without corresponding increases in their material properties. According to our theory, a tendon or ligament loses its ability to adapt to increased loads when its cross-sectional area and modulus both reach their maximums. A tendon or ligament in this state would fail

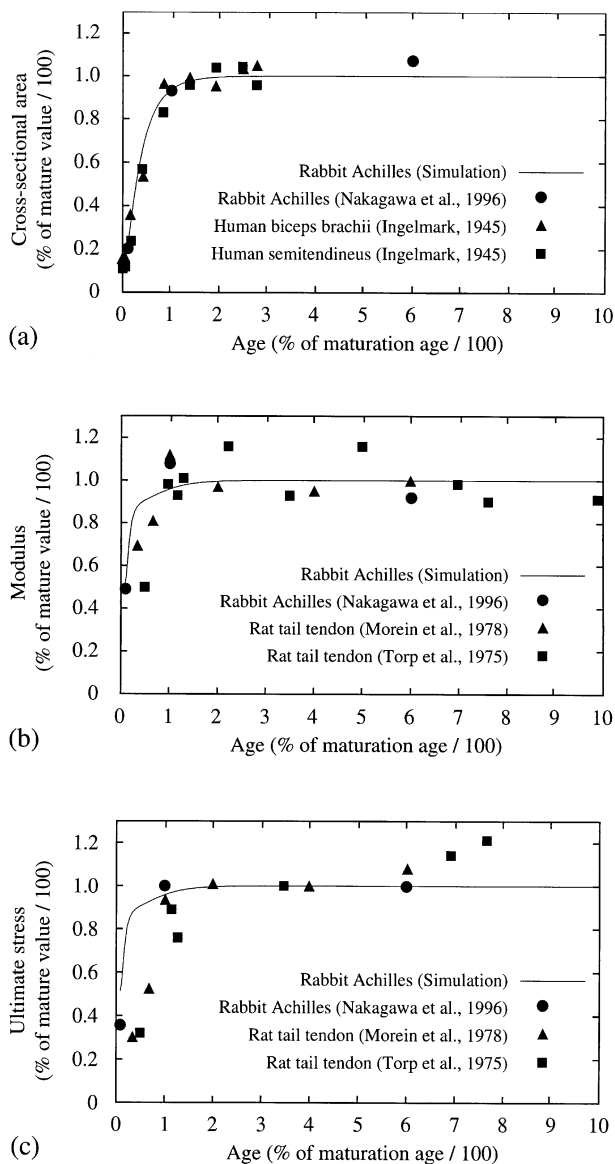


Fig. 4. Normalized simulation results and experimental data illustrating changes in (a) the cross-sectional area, (b) the modulus, and (c) the strength of tendons undergoing normal growth and development. Horizontal axis indicates multiples of maturation age.

to respond to increased loads and become 'ill-adapted' and more susceptible to injury. Changes in tissue phenotype such as calcification might also occur (Rooney, 1994).

We have proposed basic principles that help to explain the growth and development of tendons and ligaments. These principles appear to apply not only to normal growth and development, but also to growth and development under conditions of increased or decreased loading. This preliminary model demonstrates the utility of analytical approaches in contributing to our understanding of soft tissue growth, development, and adaptation and may serve as a starting point for future investigations.

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References

- Amiel, D., Woo, S.L.-Y., Harwood, F.L., Akeson, W.H., 1982. The effect of immobilization on collagen turnover in connective tissue: a biochemical-biomechanical correlation. *Acta Orthopaedica Scandinavica* 53, 325–332.
- Ault, H.K., Hoffman, A.H., 1992. A composite micromechanical model for connective tissues: Part II – Application to rat tail tendon and joint capsule. *Journal of Biomechanical Engineering* 114, 142–146.
- Beynon, B., Howe, J.G., Pope, M.H., Johnson, R.J., Fleming, B.C., 1992. The measurement of anterior cruciate ligament strain in vivo. *International Orthopaedics* 16, 1–12.
- Butler, D.L., Kay, M.D., Stouffer, D.C., 1986. Comparison of material properties in fascicle-bone units from human patellar tendon and knee ligaments. *Journal of Biomechanics* 19, 425–432.
- Carrier, D.R., 1983. Postnatal ontogeny of the musculo-skeletal system in the black-tailed jack rabbit (*Lepus californicus*). *Journal of Zoology* 201, 27–55.
- Carter, D.R., 1987. Mechanical loading history and skeletal biology. *Journal of Biomechanics* 20, 1095–1109.
- Cowin, S.C., 1985. A model of stress adaptive anisotropy for soft tissue. In: Langrana, N.A., (Ed.), *Advances in Bioengineering American Society of Mechanical Engineers*, New York, pp. 26–27.
- Cowin, S.C., 1996. Strain or deformation rate dependent finite growth in soft tissues. *Journal of Biomechanics* 29, 647–649.
- Derwin, K.A., Soslowky, L., Green, W.D.K., Elder, S.H., 1994. A new optical system for the determination of deformations and strains: calibration characteristics and experimental results. *Journal of Biomechanics* 27, 1277–1285.
- Gibb, J.A., Williams, J.M., 1994. The rabbit in New Zealand. In: Thompson, H.V., King, C.M., (Eds.), *The European Rabbit. The History and Biology of a Successful Colonizer*. Oxford University Press, Oxford, p. 188.
- Haut, R.C., 1983. Age-dependent influence of strain rate on the tensile failure of rat-tail tendon. *Journal of Biomechanical Engineering* 105, 296–299.
- Ingelmark, B.E., 1945. Über den Bau der Sehnen während verschiedener Altersperioden und unter verschiedenen funktionellen Bedingungen. Eine Untersuchung der distalen Sehnen des *Musculus biceps brachii* und *Musculus semitendineus* des Menschen sowie der Achillessehnen von Kaninchen und weissen Mäusen. *Uppsala Läk-För. Förh.* 50, 357–395.
- Ingelmark, B.E., 1948. Der Bau der Sehnen während verschiedener Altersperioden und unter wechselnden funktionellen Bedingungen. I. Eine quantitative morphologische Untersuchung an den Achillessehnen weisser Ratten. *Acta Anatomica* 6, 113–140.
- Ker, R.F., Alexander, R.M., Bennett, M.B., 1988. Why are mammalian tendons so thick? *Journal of Zoology* 216, 309–324.
- Loitz, B.J., Zernicke, R.F., Vailas, A.C., Kody, M.H., Burstein, A.H., 1989. Effects of short-term immobilization versus continuous passive motion in a non-weight-bearing model. *Clinical Orthopaedics Related Research* 244, 265–271.
- Matyas, J.R., Anton, M.G., Shrive, N.G., Frank, C.B., 1995. Stress governs tissue phenotype at the femoral insertion of the rabbit MCL. *Journal of Biomechanics* 28, 147–157.
- Mikić, B., Carter, D.R., 1995. Bone strain gage data and theoretical models of functional adaptation. *Journal of Biomechanics* 28, 465–469.
- Morein, G., Goldfefer, L., Kobylansky, E., Goldschmidt-Nathan, M., Nathan, H., 1978. Changes in the mechanical properties of rat tail tendon during postnatal ontogenesis. *Anatomica Embryology* 154, 121–124.
- Nakagawa, Y., Hayashi, K., Yamamoto, N., Nagashima, K., 1996. Age-related changes in biomechanical properties of the achilles tendon in rabbits. *European Journal of Applied Physiology* 73, 7–10.
- Noyes, F.R., 1977. Functional properties of knee ligaments and alterations induced by immobilization. A correlative biomechanical and histological study in primates. *Clinical Orthopaedics Related Research* 123, 210–242.
- Olsen, L., Sherratt, J.A., Maini, P.K., 1995. A mechanochemical model for adult dermal wound contraction and the permanence of the contracted tissue displacement profile. *Journal of Theoretical Biology* 177, 113–128.
- Oster, G.F., Murray, J.D., 1989. Pattern formation models and developmental constraints. *Journal of Experimental Zoology* 251, 186–202.
- Parry, D.A.D., Barnes, G.R.G., Craig, A.S., 1978. A comparison of the size distribution of collagen fibrils in connective tissues as a function of age and a possible relation between fibril size distribution and mechanical properties. *Proceedings Royal Society London B* 203, 305–321.
- Rodriguez, E.K., Hoger, A., McCulloch, A.D., 1994. Stress-dependent finite growth in soft elastic tissues. *Journal of Biomechanics* 27, 455–467.
- Rooney, P., 1994. Intratendinous ossification. In: Hall, B.K. (Ed.), *Bone*, Vol. 8: *Mechanisms of Bone Development and Growth*. CRC Press, Boca Raton, pp. 47–83.
- Sinclair, D., 1985. *Human Growth After Birth*. Oxford University Press, New York.
- Storm, E., Kingsley, D.M., 1996. Joint patterning defects caused by single and double mutations in members of the bone morphogenetic protein (BMP) family. *Development* 122, 3969–3979.
- Tipton, C.M., Vailas, A.C., Matthes, R.D., 1986. Experimental studies on the influences of physical activity on ligaments, tendons and joints: a brief review. *Acta Medica Scandinavica* 711 (Suppl), 157–168.
- Torp, S., Arridge, R.G.C., Armeniades, C.D., Baer, E., 1975. Structure-property relationships in tendon as a function of age. In: Atkins, E.D.T., Keller, A. (Eds.), *Structure of Fibrous Biopolymers*. Butterworths, London, pp. 197–221.
- Tözeren, A., Skalak, R., 1988. Interaction of stress and growth in a fibrous tissue. *Journal of Theoretical Biology* 130, 337–350.

- Viidik, A., 1990. Structure and function of normal and healing tendons and ligaments. In: Mow, V.C., Ratcliffe, A., Woo, S.L-Y. (Eds.), *Biomechanics of Diarthroidal Joints*, Vol. I. Springer, New York, pp. 3–38.
- Walsh, S., Frank, C., Shrive, N., Hart, D., 1993. Knee immobilization inhibits biomechanical maturation of the rabbit medial collateral ligament. *Clinical Orthopaedics Related Research* 297, 253–261.
- Wolfman, N.M., Celeste, A.J., Cox, K., Hattersley, G., Nelson, R., Yamaji, N., DiBlasio-Smith, E., Nova, J., Song, J.J., Wozney, J.M., Rosen, V., 1995. Preliminary characterization of the biological activities of rhBMP-12. *Journal of Bone and Mineral Research* 10, S148.
- Woo, S.L-Y., Ritter, M.A., Amiel, D., Sanders, T.M., Gomez, M.A., Kuei, S.C., Garfin, S.R., Akeson, W.H., 1980. The biomechanical and biochemical properties of swine tendons — Long term effects of exercise on the digital extensors. *Conn. Tissue Research* 7, 177–183.
- Woo, S.L-Y., Gomez, M.A., Amiel, D., Ritter, M.A., Gelberman, R.H., Akeson, W.H., 1981. The effects of exercise on the biomechanical and biochemical properties of swine digital flexor tendons. *Journal of Biomechanical Engineering* 103, 51–56.
- Woo, S.L-Y., Gomez, M.A., Sites, T.J., Newton, P.O., Orlando, C.A., Akeson, W.H., 1987. The biomechanical and morphological changes in the medial collateral ligament of the rabbit after immobilization and remobilization. *Journal of Bone and Joint Surgery* 69A, 1200–1211.
- Woo, S.L-Y., Weiss, J.A., Gomez, M.A., Hawkins, D.A., 1990. Measurement of changes in ligament tension with knee motion and skeletal maturation. *Journal of Biomechanical Engineering* 112, 46–51.
- Woo, S.L-Y., Newton, P.O., MacKenna, D.A., Lyon, R.M., 1992. A comparative evaluation of the mechanical properties of the rabbit medial collateral and anterior cruciate ligaments. *Journal of Biomechanics* 25, 377–386.
- Wren, T.A.L., Carter, D.R., in press. A microstructural model for the tensile constitutive and failure behavior of soft skeletal connective tissues. *Journal of Biomechanical Engineering*.
- Yamamoto, N., Hayashi, K., Kuriyama, H., Ohno, K., Yasuda, K., Kaneda, K., 1992. Mechanical properties of the rabbit patellar tendon. *Journal of Biomechanical Engineering* 114, 332–337.