AN OBJECT ORIENTED MODELING FRAMEWORK FOR THE ARTERIAL WALL

by

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DOCTORAL THESIS

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UN GENERADOR DE MODELOS ORIENTADO A OBJETOS PARA LA PARED ARTERIAL

Por

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To God: the Holy Trinity: Father, Son, Holy Spirit

To my Heavenly Mother Mary

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Abstract

A general object oriented framework for the modeling of the arterial wall is presented and illustrated by the use of a toy model, an ideal case study. The main utility and novelty of the presented framework is the possibility to design, develop and implement highly customizable artery models, taking advantage of the continuously improving field of imaging technology. Additional strategic uses of the presented framework are:

- The implementation of simulators to optimize the design and production of biomedical solutions such as vascular grafts and vascular angioplasty devices and procedures.
- The implementation of hemodynamics simulators.
- The development of artery models to be included in higher scope whole body models such as Physiome, injury and trauma simulators.
- The implementation of case studies for educational purposes.

In our present knowledge, this is the first initiative leading to model the arterial wall from the object oriented perspective. The existing models do not allow a close structural mapping with the real artery as in the present object oriented modeling framework. In the other hand, object oriented models are highly portable, upgradable and understandable. The arterial wall, differs substantially from a homogeneous or composite material. It is composed of a great variety of autonomous living and nonliving objects. The passive behavior of arterial wall was considered and in this way, the tunica adventitia was the objective system. In the case study, an object oriented model of arterial wall was designed, developed and implemented. The model implementation was made first in UML (Unified Modeling Language), in order to facilitate its study, communication and maintenance, and then implemented in JAVA. Together with the model, a simulation engine, based on matrix structural mechanics was implemented. In order to verify the model, two series of simulation experiments were conducted: one series for axial loading and the other one for pressure-volume. Each series began with a sensitivity analysis in order to determinate the best parameter combination that will produce both physically meaningful results as close to pre-determined analog controls: one calves' artery in the case of axial loading and one rat mesenteric artery. The truss structures that best reproduced the control analog plots were a truss with one layer and four rings for axial loading and a truss with one layer and three rings for pressure-volume loading.

In both cases the simulated results reproduced qualitatively and quantitatively the analog stress-strain plots: calves' artery and rat mesenteric artery. After some improvements and an additional testing, this model can be used for explore and evaluate the validity of a set of hypothesis on arteries microstructure, its long term dynamical behavior, and modified to include new components such as tunica adventitia ground substance, tunica media and tunica intima. In the case of tunica media, the model can be used to explore active arteries behavior under pulsatile regime.

Resumen

Se presenta una metodología general, orientada a objetos, para el modelado de la pared arterial y es ilustrada mediante el uso de un prototipo, un caso de estudio idealizado. La principal utilidad y novedad de la metodología presentada es la posibilidad de diseñar, desarrollar e implementar modelos arteriales altamente adaptables a casos particulares, sacando provecho de la tecnología de imágenes en permanente evolución.

Otros usos estratégicos de la presente metodología son:

- La implementación de simuladores para el diseño y producción óptima de soluciones biomédicas tales como los injertos vasculares y los dispositivos y procedimientos usados en angioplastia vascular
- La implementación de simuladores de hemodinámica
- El desarrollo de modelos de arterias para ser incluidos en modelos de cuerpo humano completo tales como el Fisioma y los simuladores de lesiones y trauma.
- La implementación de casos de estudio para propósitos educativos.

Según lo que conocemos actualmente, esta es la primera propuesta para el modelado orientado a objetos de la pared arterial. Los modelos existentes no permiten una representación estructural tan próxima a la real como lo hace la presente metodología orientada a objetos. De otra parte, los modelos orientados a objetos son altamente portables, actualizables y entendibles. La pared arterial difiere substancialmente de un material homogéneo o de uno compuesto. Dicha pared está conformada por una gran variedad de objetos autónomos tanto vivos como no vivos. En una primera aproximación al modelado orientado a objetos de la pared arterial, solo se consideró el comportamiento pasivo de la pared arterial y, de esta forma, la túnica adventicia fue el sistema objeto. En el presente trabajo se diseñó, desarrolló e implementó un modelo orientado a objetos de pared arterial. La implementación del modelo fue realizada, en primera instancia, en UML (Lenguaje Unificado de Modelado) para facilitar su estudio, comunicación y mantenimiento, y luego fue implementado en JAVA. Junto al modelo se implementó un motor de simulación con base en la teoría de la mecánica estructural matricial. Con el fin de verificar el modelo, se realizaron dos series de experimentos de simulación: una serie para carga axial y la otra para presión-volumen. Cada serie comenzó con un análisis de sensibilidad para determinar la mejor

combinación de parámetros que diese como producto resultados físicamente significativos y con la mayor aproximación a aquellos reportados por las muestras análogas de control predeterminadas: una arteria de ternero y una arteria mesentérica de rata. La armadura espacial que mejor reprodujo las gráficas correspondientes a las muestras análogas de control fue una estructura con una capa y cuatro anillos para la carga axial y una armadura de una capa y tres anillos para el caso de presión-volumen. En ambos casos los resultados de las simulaciones reprodujeron en una buena aproximación, tanto cualitativa como cuantitativamente las gráficas correspondientes a las muestras de control análogas. Tras algunas mejoras y pruebas adicionales, este modelo puede usarse para realizar ensayos sobre la validez de hipótesis referentes a la micro estructura de las arterias, su comportamiento dinámico de largo plazo, y modificado para incluir nuevos componentes como por ejemplo la substancia base de la túnica adventicia, la túnica media, y la túnica íntima. En el caso de la túnica media, el modelo puede usarse para explorar el comportamiento activo de las arterias bajo régimen pulsátil.

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Introduction

The cardiovascular system, composed by the heart, blood vessels and blood, has as main functions:

1. Transportation of oxygen and nutrients to all body tissues.
2. Transportation of carbon dioxide and metabolic waste products from the tissues to the lungs and excretory system organs.
3. Distribution of water, electrolytes and functional proteins throughout the body.
4. Contribute to the function of immune system
5. Thermoregulation.

In order to accomplish those functions, the heart acts as a pump giving to the blood the necessary kinetic energy in order to reach all the body tissues.

In each phase of the heart's mechanical cycle (pulsatile regime), the mechanical energy generated as a result of the work done by the heart on the blood is dynamically driven (transported, buffered, and dissipated) as blood's kinetic energy, vessels strain energy and dissipative work (heat) due to the blood´s viscosity.

Any change, in the shape of a vessel or in its mechanical properties, leads to an abnormal physiological state of the whole cardiovascular system and as a consequence to pathological temporary states such as ischemia, in some cases to irreversible damage to and organ (chronic diseases) and in another cases to death.

Changes in a vessel shape, mainly an abrupt radius change (narrowing: stenosis, widening: aneurism) produces turbulence in the motion of the blood.

When blood is in an appropriate physiological state, its motion is laminar: the velocity field lines of the fluid are all parallel with minimal loss of fluid's kinetic energy. In the case of turbulence, velocity field lines curls and there is a high loss of fluid's kinetic energy slowing down the transport processes in the blood together with local production of heat which activates bio-physical-chemical processes leading to local phase transitions, thrombus formation: ischemia and causing tissue poor irrigation and tissue death.

On the other hand, when there is arterial wall hardening or softening, the strain energy buffering function of the vessel is altered and as a consequence its compliance (impedance) changing the interference patterns of pressure waves in the blood and, again, a slowing down of transport processes.

The dynamical state of the blood and the shape and mechanical properties of the vessels are therefore interdependent features of the cardiovascular system which is quantitatively represented by the mathematical and computational models of hemodynamics.

As every science, hemodynamics knowledge is a set of models: an abstract representation of cardiovascular system's attributes and behaviors.

In the case of blood, there are well established mathematical models to represent its mechanical behavior (motion): Navier-Stokes equations for short range fluid motion, Moens-Korteweg equation for pulsatile regime transport processes (pressure waves) and Poiseuille equation, the master equation relating blood flux, Φ (blood volume per second across an unitary volume), with the axial pressure gradient ΔP, the local inner radius, r, and the local transport resistance, R, due to the vessel's wall.

Actually, Poiseuille equation considers vessel's resistance just as a function of blood's viscosity and do not take into account the mechanical properties of the wall. Also, the local inner radius is considered as uniform which is not true in the real life, specially in the case of diseased vessels.

Those limitations and the critical importance of the mechanical behavior of the arterial wall in hemodynamics have given rise to the field of arterial wall constitutive modeling.

Different models of the mechanical behavior of the arterial wall have been proposed and implemented.

Deterministic models such as Kelvin–Voight, Maxwell and the linear standard solid have been obtained from analogies with lumped parameters mechanical systems composed by springs and dashpots.

Those models give a relation between applied forces and resulting deformations in the form of a constitutive equation obtained by combining the elementary constitutive relations = for the springs and = — for the dashpots, where represents the stress supported by the element, the elastic modulus of the spring, the strain of the element, the damping constant of a dashpot and — its strain rate.

In order to produce analytically solvable differential equations for the variables under investigation, materials are considered as hyper-elastic, homogeneous and isotropic. Of course, arterial wall differs substantially of a material with those characteristics.

To overcome this difference, a great variety of modifications have been introduced, such as consider the wall as an orthotropic material and to express its elastic property in terms of parameters given as functions of position. Those modified models are studied under the general field of finite element models.

All those deterministic and probabilistic models have limitations when used in situations where the arterial wall composition and microstructure changes in time. For example, after angioplasty, the wall remodels changing geometry and composition. Therefore, a static model can not predict accurately the final diameter of the wall post angioplasty.

To produce dynamical models, different strain energy functions have been introduced by Fung, Takamizawa, Holzapfel and others allowing the implementation of probabilistic constitutive models for the wall expressing its mechanical properties as probability functions of position and time.

Strain energy function based models have improve the modeling capabilities but still generic in nature and do not allow to explode the growing benefits of imaging technology in order to produce specific case models.

In consequence, the objective of this work is to design, propose and illustrate an objet oriented modeling framework that allow the construction of specific case models by considering microstructure and micro-structural components properties.

The specific objectives of the present work are:

- To acquire the knowledge in Anatomy and Physiology, Cardiovascular Dynamics and Complex Systems Modeling required undertaking the project.
- To design an arterial wall model, a simulation system, simulation experiments, a data analysis system and verification experiments.
- To implement the previously obtained arterial wall model, a simulation system and to perform simulation experiments, data analysis and verification simulation experiments.
- To summarize and synthesize the obtained results.

1. Theoretical Framework

In this chapter, at a first stage the macroscopic anatomy and physiology of arterial wall are reviewed. At a second stage, there is an outline of the main facts about classical hemodynamics. Third, a short discussion on continuum mechanics, structural mechanics and constitutive models of arterial wall whose state of the art is reviewed. Following, there is an outline of the tunica adventitia and its micro structural components and organization. The complexity of arterial wall is discussed having as framework the up to the date definitions and criteria on complexity. The chapter finishes with a description of the epistemological and theoretical foundations of the methodology used to design and develop the object oriented model of arterial wall.

1.1. Anatomy and Physiology of the Arterial Wall

Arteries are vessels that transport blood from the heart to the tissues and organs and supply these tissues with nutrients and oxygen. The arterial vessels are prominent organs composed of soft tissues which transform the pulsatile heart output into a flow of moderate fluctuations serving as an elastic energy buffer.

As shown in figure 1.2, along the vascular network, beginning in the heart and ending in the capillaries, the arterial wall changes in geometry and composition, giving as a result a broad classification of arteries as elastic, muscular and capillaries.

"Elastic (proximal) arteries, proximal to the heart, have relatively large diameters and their composition includes a great amount of elastic fibers (collagen and elastin) and a lower measure of muscular tissue. The main function of elastic arteries is the transport of a high flux of blood and in this way, they must support high pressure [1]".

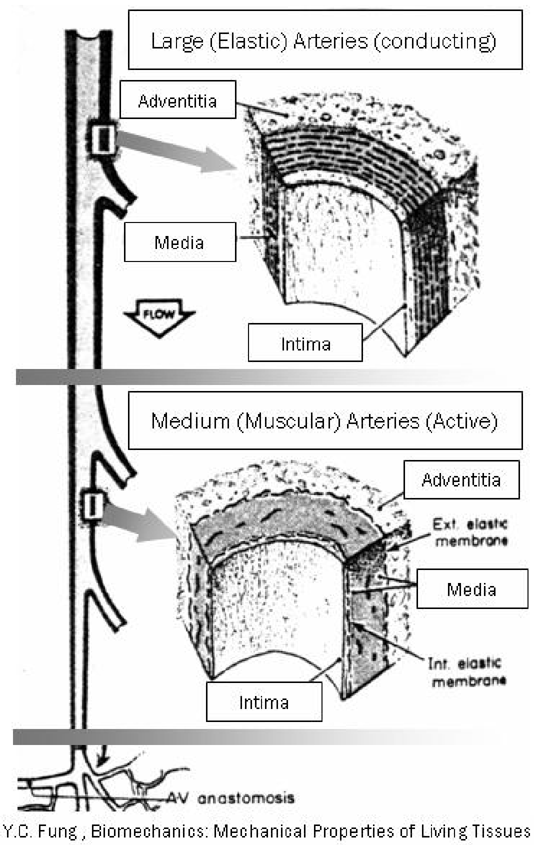

Figure 1.2 *Arterial Wall in elastic a muscular arteries* [1]

"Muscular (distal) arteries are located at the periphery and show pronounced viscoelastic behavior with hysteresis that are relatively insensitive to strain rates. Muscular arteries have a big amount of muscle tissue what allows them to actively control blood flow" (1).

In spite of relative differences between elastic and muscular arteries, avoiding relative size differences between the tunics and layers that compose them, it is possible to define a "generic arterial wall structure" for large arteries: figure 1.3.

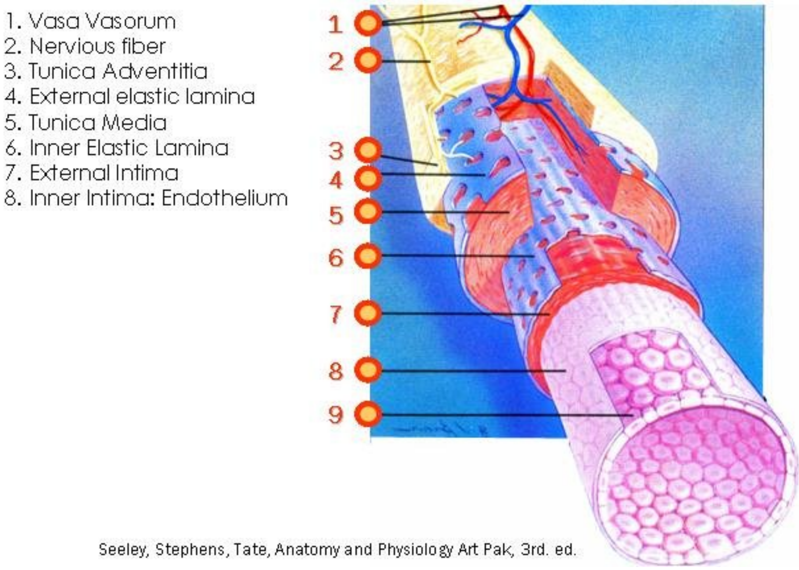

Figure 1.3 *Generic structure of large arteries.*
(From Seely, Stephens, Tate, "Anatomy and Physiology Art Pack")

The arterial wall of large arteries is composed by three primary layers: the *tunica intima* (innermost layer), the *tunica media* (middle layer) and the *tunica adventitia* (outermost layer).

The Tunica Intima, see figure 1.4, is a biologically functional membrane that serves as a direct interface between the thrombogenic media and the blood.

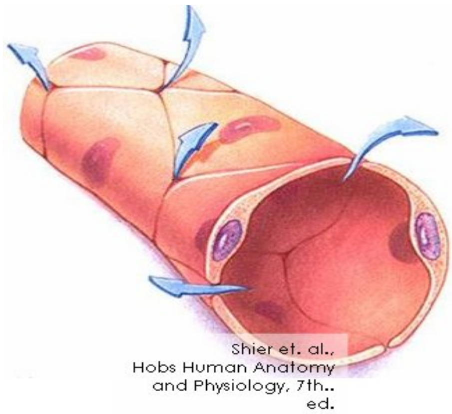

Figure 1.4 *Tunica intima.*
(From Shier et.al., "Hobs Human Anatomy and Physiology")

In healthy young arteries the intima is a very thin layer and does not contribute to the mechanical behavior of the arterial wall. The intima thickens and stiffens with age (atherosclerosis) and in this way, its mechanical behavior and properties become relevant. The main components of tunica intima are epithelial cells, and a ground substance mostly composed of proteoglycans and scarce amounts of elastic fibers.

The Tunica media, see figure 1.5, is composed of a complex three dimensional network of smooth muscle cells, mostly arranged as a helical spring, and coupled with another network of elastic fibers inside a ground substance matrix. This helical shape, gives the media high strength, resilience and the ability to resist loads both in axial and circumferential directions. Because of its high elasticity, the media transfers most of the mechanical load to the next external layer, the tunica adventitia. The role of tunica media is mostly the active control of blood flow by changing its diameter due to signals coming from the coupling between nervous and muscle fibers.

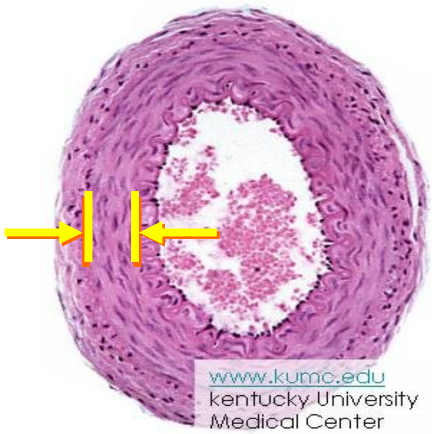

Figure 1.5 *Tunica media.*
(From www.kumc.edu)

The Tunica Adventitia, figure 1.6, is the most important layer in the case of an unhealthy artery because its structure and components set the arterial mechanical resistance to pressures over the physiological range.

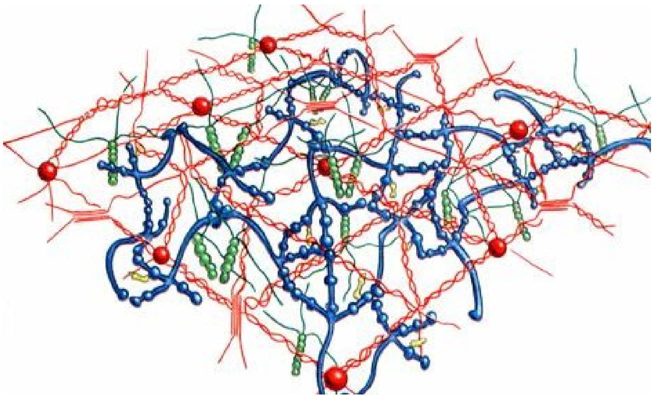

Figure 1.6 *Tunica adventitia, microscopic structure (polymeric fibers network).*
(From Alberts et.al. "Molecular Biology of the Cell, 3rd. ed.")

The adventitia is an "entropy repository" because it keeps all the plastic memory due to cyclic stress [(2)]. The tunica adventitia is composed of a three dimensional network of collagen and elastin fibers connecting the fibroblasts immersed in the fibers network and the proteoglycans ground substance. Adventitia has a high tensile strength (higher than 1.0 MPa).

1.2. Hemodynamics and the Arterial Wall

Along the arterial side of the vascular bed, there is a wide range of diameters and blood pressures, the latter changing from over 100 mm Hg in the aorta to very low values in the capillaries.

The vascular system has as main function to transport blood and oxygen to all cells and tissues of the body, in amounts related to the needs of the various organs and tissues. This differential distribution of blood is actively controlled by muscular arteries by changing the vessel diameter (vasodilatation, vasoconstriction) and in this way, the relative resistance to blood flow.

The most elementary model relating the axial pressure gradient with blood flux and considering arterial wall as a rigid body, is the law of Poiseuille [(2)]

$$\Phi = \Delta P \times \left(\frac{\pi}{8}\right) \times \left(\frac{1}{\eta}\right) \times \left(\frac{r^4}{l}\right) \qquad (1.1)$$

Where Φ represents blood flow, ΔP the axial pressure gradient, $\left(\frac{1}{\eta}\right)$ is the "viscosity factor" and $\left(\frac{r^4}{l}\right)$ is the "geometrical factor" involving r, the mean arterial radius and l, the length of the considered vessel segment. By definition, the "resistance to flow", R is the ratio of the driving force (the pressure gradient) to the flow, Φ which results in

$$R = \frac{\Delta P}{\Phi} = \left(\frac{8}{\pi}\right) \times \eta \times \left(\frac{l}{r^4}\right) \qquad (1.2)$$

The resistance depends on the two factors, the viscosity factor η, and the geometrical factor $\left(\frac{l}{r^4}\right)$. This "fourth power law" expresses a highly sensitive control of the distribution of blood flow by the geometry of the vessels (mainly diameter). One important limitation of the Poiseuille model is that the viscosity is constant (Newtonian fluid) and therefore, does not consider the rate of flow and diameter dependence of η and so, of the resistance. However, it has been found that in the physiological range of blood flow for a healthy vessel, blood behaves as if it were Newtonian.

In opposition to Poiseuille model, blood vessels are distensible and their geometry depend upon the transmural pressure, P_{TM}, within them. In this way, the Poiseuille model becomes inadequate to define a flow – pressure relation and does not contain all the information to determine the flow. It is necessary to add an equation which recognizes the dependence of the vessels geometry with the transmural pressure (a "constitutive" equation) with the shape:

$$\frac{1}{r^4} = f\left(P_{TM}\right) \qquad (1.3)$$

Where $f\left(P_{TM}\right)$ represents some function, which may be called "distensibility function". It becomes very important to build this function (again, which later will be called "constitutive equation" or, as in the present project, the "Arterial Wall

Model").

Laplace's law relates transmural pressure with vessel's surface tension, which is instrumentally measurable, and wall thickness.

$$P_{TM} = T\left(\frac{1}{r_1} + \frac{1}{r_2}\right) \qquad (1.4)$$

Where T represents vessel's surface tension, r_1 and r_2 represent the inner and outer vessel radius. Additional geometry – transmural pressure are available, but mostly made to express active (muscle driven) wall behavior.

1.3. Constitutive Models of Arterial Wall

Due to the unlimited diversity of material objects, physics classifies them in a small set of abstract material bodies categories: particles, rigid solids, deformable solids, fluids, viscoelastic bodies and some additional specialized categories.

Actually, this is an artificial classification because depending upon the spatial and temporary scales of observation and on the range of applied forces, any body may be classified in any category.

In agreement with the spatial scales, temporary scales and forces ranges present in physiological conditions, arteries are considered as deformable solids and the most common used models are those coming from continuum mechanics.

In addition to continuum mechanics, the experimental methods used to characterize deformable bodies will be briefly exposed. However, in order to comply with the proposed epistemological approach of the present work, object orientation, structural mechanics will be used in the design of the arterial wall modeling framework and in the implementation of the simulation engine used for the model framework verification.

Continuum mechanics

"A material continuum is a material for which the densities of mass, momentum and energy exist in the mathematical sense. The mechanics of such a material continuum is continuum mechanics" (3)

When a given set of forces or a force field is applied to an elastic body, there is a "volumetric distribution of force" in the body which is characterized by a stress field and a strain field. Those fields together represent the complete mechanical state of the body.

From a general perspective, stress and strain are mathematically represented by one tensor respectively. A tensor is a 3x3 matrix, where each row is a vector that quantify the tensor in a specific address, generally normal to a symmetry plane of the body.

In order to illustrate what tensors are and how to represent them, let us consider what occurs with a hollow cylinder with a thick wall (an ideal model of an arterial segment).

The cylinder has three symmetry directions: radial, circular and axial. Each direction corresponds to one point cylindrical coordinate: r, θ and z, respectively and to a deformation mode: volumetric (inflation): change in "r", torsion: change in "θ" and tension (traction, axial): change in "z", see figure 1.7.

As illustrated by figure 1.8, the stress tensor is the matrix composition of three stress vectors, each one corresponding to a plane of symmetry:

$$\vec{\sigma}_r = \sigma_{rr}\hat{r} + \sigma_{r\theta}\hat{\theta} + \sigma_{rz}\hat{z} \text{ where } \sigma_{rr} = \frac{1}{A_r}\vec{F}_r.\hat{r},\ \sigma_{r\theta} = \frac{1}{A_r}\vec{F}_r.\hat{\theta},\ \sigma_{rz} = \frac{1}{A_r}\vec{F}_r.\hat{z} \quad (1.5.a)$$

$$\vec{\sigma}_\theta = \sigma_{\theta r}\hat{r} + \sigma_{\theta\theta}\hat{\theta} + \sigma_{\theta z}\hat{z} \text{ where } \sigma_{\theta r} = \frac{1}{A_\theta}\vec{F}_\theta.\hat{r},\ \sigma_{\theta\theta} = \frac{1}{A_\theta}\vec{F}_\theta.\hat{\theta},\ \sigma_{\theta z} = \frac{1}{A_\theta}\vec{F}_\theta.\hat{z} \quad (1.5.b)$$

$$\vec{\sigma}_z = \sigma_{zr}\hat{r} + \sigma_{z\theta}\hat{\theta} + \sigma_{zz}\hat{z} \text{ where } \sigma_{zr} = \frac{1}{A_z}\vec{F}_z.\hat{r},\ \sigma_{z\theta} = \frac{1}{A_z}\vec{F}_z.\hat{\theta},\ \sigma_{zz} = \frac{1}{A_z}\vec{F}_z.\hat{z} \quad (1.5.c)$$

And the complete stress tensor is:

$$\sigma = \begin{pmatrix} \vec{\sigma}_r \\ \vec{\sigma}_\theta \\ \vec{\sigma}_z \end{pmatrix} = \begin{pmatrix} \sigma_{rr} & \sigma_{r\theta} & \sigma_{rz} \\ \sigma_{\theta r} & \sigma_{\theta\theta} & \sigma_{\theta z} \\ \sigma_{zr} & \sigma_{z\theta} & \sigma_{zz} \end{pmatrix} \qquad (1.6)$$

$\vec{F}_r$ represents the net force on the "r" plane with normal $\hat{r}$ and area A_r, in an analog way $\vec{F}_\theta$ represents the net force on the "θ" plane with normal $\hat{\theta}$ and area A_θ and, finally, $\vec{F}_z$ represents the net force on the "z" plane with normal $\hat{z}$ and area A_z.

In the same way, a strain tensor represents the state of deformation at the point whose neighborhood is the volume element ΔV:

$$\varepsilon = \begin{pmatrix} \varepsilon_{rr} & \varepsilon_{r\theta} & \varepsilon_{rz} \\ \varepsilon_{\theta r} & \varepsilon_{\theta\theta} & \varepsilon_{\theta z} \\ \varepsilon_{zr} & \varepsilon_{z\theta} & \varepsilon_{zz} \end{pmatrix} \qquad (1.7)$$

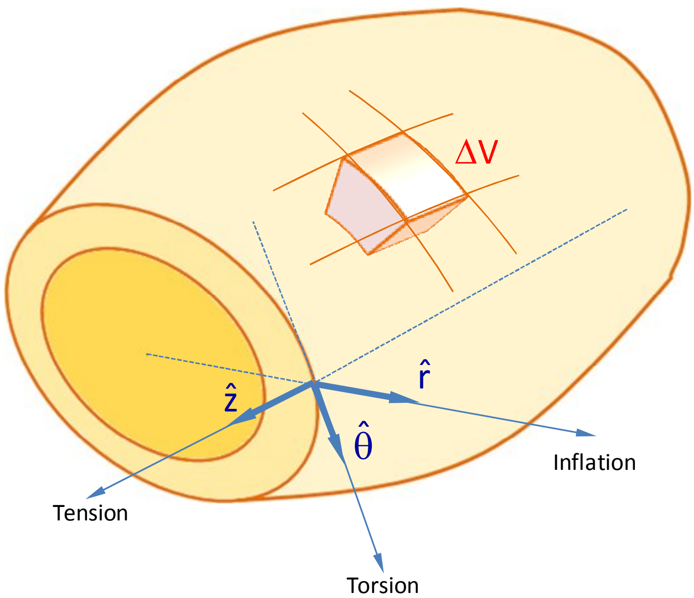

Figure 1.7. *Axis of symmetry of artery and cylindrical coordinates*

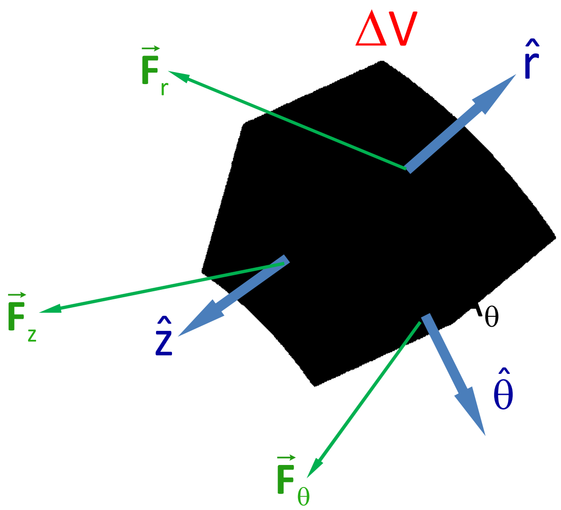

Figure 1.8. *Planes of symmetry of an element of volume, normal vectors and plane forces*

As torsion is not a physiological mode of arterial deformation, the experimental mechanical characterization of arteries proceeds with pure tensional testing obtaining σ_{zz} vs. ε_{zz} (tension (axial stress) vs. axial strain) plots and with pressure-volume testing obtaining σ_{rr} vs. ε_{rr} (circular stress vs. circular strain), see figure 1.9.

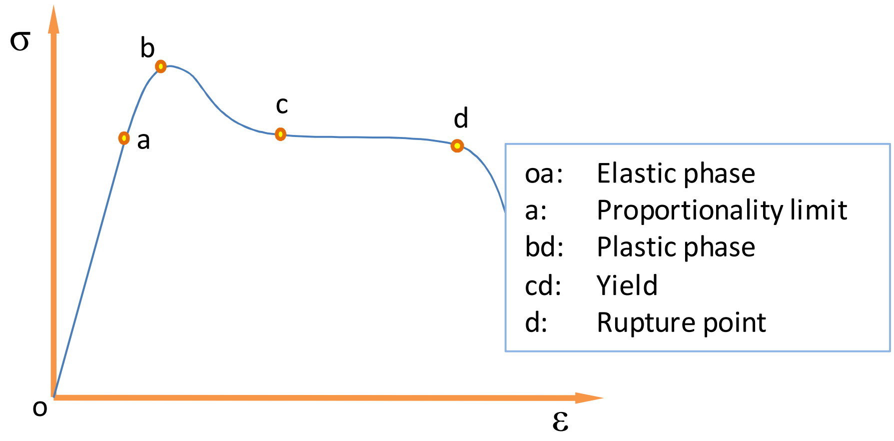

Figure 1.9. *A typical stress-strain plot*

The equation relating stress and strain, which also involves the mechanical identity of the body is called its "constitutive equation":

$$\sigma = E\varepsilon \qquad (1.8)$$

where σ, E and ε are respectively the stress, elastic modulus and strain tensors.

Structural mechanics

In structural mechanics it is assumed that the body is not a continuum but a structure composed of members joined together in points called nodes.

In general, each structure member have three deformation modes: torsion, flexion and axial deformation (tension or compression). If the members are allowed just to have axial deformations, the structure is called a "truss".

From the approach used in the present work, an arterial segment is a 3D cylindrical truss.

The most used mathematical framework to study structural mechanics is matrix structural mechanics which may be divided in two sub-methods: flexion matrix method and stiffness matrix method. Stiffness method, the method used in the present work, is given here in a succinct way because it is essentially a computational technique whose details will be discussed in the methodology section (4).

In essence, the matrix stiffness method is a matrix method that makes use of the members' stiffness relations for computing member forces and displacements in structures.

In the stiffness method the whole structure is represented by an (n x n) matrix (n: numbers of degrees of freedom of the whole structure) called the **stiffness matrix of the truss**, $\mathbf{K}$, which is connected to the applied node load vector, $\mathbf{F}$ and to the displacements vector $d\mathbf{X}$ by the matrix form of the Hooke's law:

$$\mathbf{F} = \mathbf{k} * d\mathbf{X} \qquad (1.9)$$

The most important and difficult part of applying the stiffness method is the stiffness matrix construction which is built from individual members stiffness matrix, a six by six (space members) matrix.

Once the stiffness matrix has been built, the unknown displacements matrix $d\mathbf{X}$ may be obtained from the known nodal forces vector, $\mathbf{F}$, and the inverse of the stiffness matrix, $\mathbf{k}^{-1}$ from the matrix solution equation:

$$\mathrm{d}\mathbf{X} = \mathbf{k}^{-1}\mathbf{F} \qquad (1.10)$$

Since the cylindrical truss is a statically determined system and because of symmetry (translational invariance of local groups) it may be shown (4) that the stiffness matrix is upper triangular and easily solved by the Gauss Jordan method.

Constitutive equation and constitutive model

The passive mechanical behavior of the arterial wall is governed mainly by its microstructure: the configuration of its fibrous network and the mechanical state and properties of its micro-components such as collagen and elastin fibrous bundles (fibrils).

However, up to the date, all the proposed constitutive models describe the wall in an artery as a macroscopic system avoiding small regional variations which being small in size influence greatly the whole cardiovascular system.

From a general standpoint, a constitutive equation is an equation relating external actions or agents (i.e. force, magnetic field) with the objects response (acceleration, deformation, magnetization) and with the material properties of the object (mass, elastic modulus, magnetic susceptibility).

In recent days the concept of "constitutive model" has been isolated from the "constitutive equation" in order to represent the object without dependence of the external agents condition.

In this way, the term "arterial wall constitutive model" refers to the representation of the mechanical identity of the wall of a particular artery by a mathematical structure (a number, a matrix) or a computational data structure, not the cause-consequence equation or computational function.

The closer the constitutive model to the real artery, better (more useful and accurate) the predictions or prognostics made by the use of a constitutive equation or a simulation computer program.

Present constitutive models of arterial wall may be classified in:

C1. Models with deterministic, global, time independent parameters: Maxwell, Voigt, Standard Linear solid [4].
C2. Models with deterministic, position dependent, time independent parameters: Fung, Takamizawa [1].
C3. Models with probabilistic, position dependent, time independent parameters: Holzapfel, Baajiens, Barocas and Tranquillo [2] [6] [7].
C4. Empirical models

Deterministic parameters models are derived from analogy between an arterial segment and a mechanical analog model made of springs and dashpots. The main used analog models are Maxwell solid model, Voigt model and Standard Linear Solid, which are shown in figure 1.7:

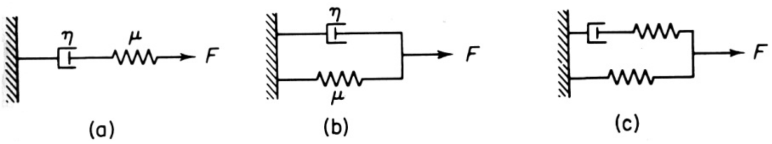

Figure 1.7 *Models of linear viscoelastic solids: (a) Maxwell, (b) Voigt, (c) Standard Linear Solid (From Y. C. Fung: "Continuum Mechanics" [3])*

Those models have as parameters: the stiffness constant, μ, of each used spring and the coefficient of viscosity, η, of each used dashpot.

Deterministic, global, time independent parameters are used under homogeneity and isotropy hypothesis and allow to explore, from a general standpoint, hysteresis, relaxation and creep behaviors of the modeled arterial segment. As an example, see figures 1.8 and 1.9:

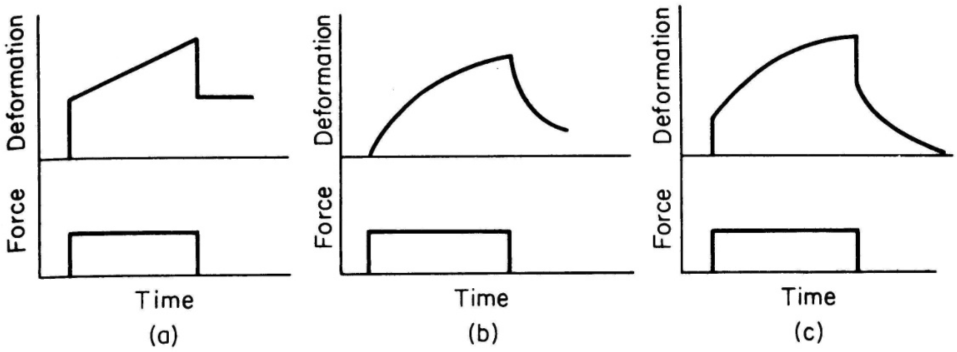

Figure 1.8. *Creep behavior of (a) Maxwell, (b) Voigt, (c) Standard Linear Solid (From Y. C. Fung: "Continuum Mechanics" [(3)])*

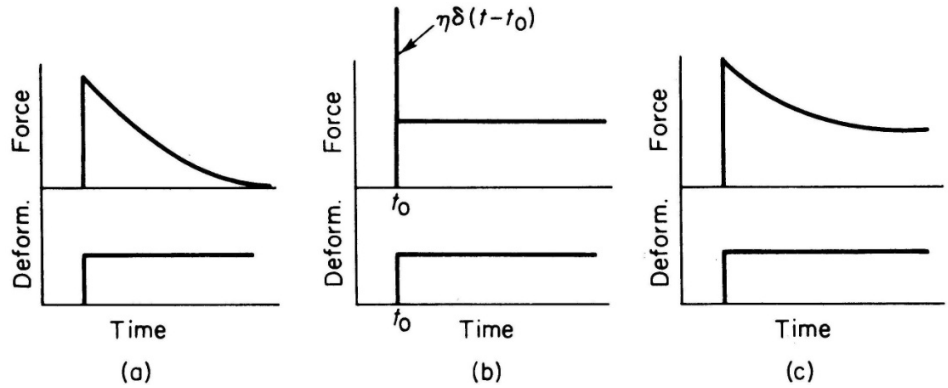

Figure 1.9. relaxation behavior of (a) Maxwell, (b) Voigt, (c) Standard Linear Solid (From Y. C. Fung: "Continuum Mechanics" [(3)])

Deterministic, position dependent, time independent parameters, have essentially the same properties as global models differing in the fact that the material parameters are given as a function of the position, = (, ,) and = (, ,) where (, ,) are cylindrical coordinates associated with the arterial segment shape.

Probabilistic, position dependent, time independent parameters models express those material parameters as probability density functions. In order to take advantage of optimization techniques and the Monte Carlo method, those probability functions correspond to expressions for strain energy density functions.

In the Monte Carlo method, a process is simulated by the generation of random values, based upon probability function, feed a decision engine who tests if those input values or derived values fulfill a set of selection rules (in general, optimization rules). Depending on those rules incorporate outputs into the simulated history.

In the case of mechanical simulations, the used probability functions are strain energy density functions and the selection rules are derived from different approaches: Lagrange or Hamilton principles, D'Alembert principle, Virtual Work Principle or some other energy-derived methods.

The most common strain-energy functions are of exponential type, although polynomial, logarithmic forms, and mixed forms are also used [1] [5] [6] (7).

Finally, empiric models are obtained from experimental data interpolation, mostly given as polynomial structures attempting to give physically meaning to the coefficients.

1.4. Arterial Wall Microstructure: Collagen Fibrils

The extra-cellular matrix (ECM) in connective tissues can be considered as a fiber reinforced composite containing collagen fibrils reinforcing a hydrated proteoglycans rich gel.

Collagen fibrils are ancient evolutionary macromolecular assemblies of collagen molecules, brought together by covalent bonds. They are extremely slender with lengths ranging from nanometer to micrometer while diameters stay within the nanometer scale.

The ability of collagen fibrils to provide reinforcement for connective tissues depends on several factors. Several contributory factors has been identified which influence the function of collagen and hence the mechanical properties of the tissue. These are: the shape of the fibrils, relative modulus of the collagen and interfacial bonding [8].

By shape, it is intended the tapered ends of fibrils and the aspect ratio, i.e. the ratio of length to the diameter.

The relative modulus refers to the ratio of stiffness of collagen fibrils to that of the hydrated gel.

Interfacial adhesion is pointed out because when a tissue is subjected to an external load, interfacial adhesion plays an important role in regulating effective stress transfer from the hydrated gel to the fibrils.

Common general properties of collagen molecules and fibrils are:

- Composition: groups of tropocollagen units formed by 3 procollagen polypeptide chains (α chains) coiled about each other into left-handed triple helixes.
- Collagen molecule length: ~280 nm, diameter: ~1.5 nm.
- Collagen fibril length: from 1 to 10 times collagen molecule length, diameter : 110-120 nm in young adults.
- Types of collagen fiber:
  - Type I : found in bone, tendon, ligament, and skin
  - Type II : found in articular cartilage, nasal septum, and sternal cartilage
  - Type III : found in loose connective tissues, the dermis of the skin, and blood vessel walls
- Tensile strength of collagen fiber:
- closely associated with the number and quality of the cross-links within and between the collagen molecules
- Stress-strain curve for an ideal collagen fiber (figure 1.7)
  - When the magnitude of the tensile strength is relatively small, a toe region with an elastic modulus of about 1 MPa is present because the relaxed, wavy collagen fiber is straightened
  - When the magnitude of the tensile strength is small, the elastic behavior of the collagen fiber follows Hooke's law and there the value of its elastic modulus is between 0.5 and 5 GPa.
  - Slope change at an approximate strain of 0.2 and rupture at 0.8 strain.

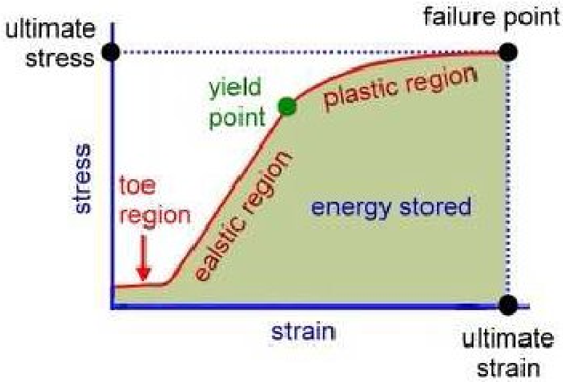

Figure 1.10 *Stress-strain curve of single collagen fibril.*
(*From http://www.pt.ntu.edu.tw/hmchai/Biomechanics/BMmaterial/Collagen.htm*)

1.5. Arterial Wall Microstructure: Elastin Fibrils

Unlike collagen, which is organized into dense fibrous bundles, elastin is somewhat amorphous and arranged in relaxed cross-linked coils.

As it is shown in figure 1.8, when tissue is stretched, the elastin molecule is elongated into a more linear conformation. When the stretching force is released, the elastin returns to the more stable random-coil structure. In this respect, elastin fibers function much like rubber bands.

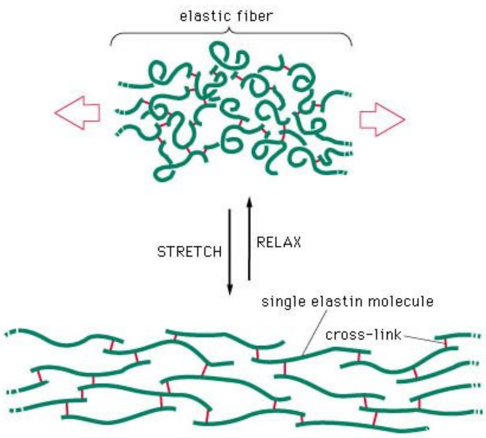

Figure 1.11 *Elastin bundles structure.*

(From http://medinfo.ufl.edu/pa/chuck/summer/handouts/connect.htm)

Elastin fibers allow strains beyond 2 without changing substantially its mechanical properties, mainly maintaining its elastic modulus which is between 0.5 and 5 MPa.

1.6. Arterial Wall Microstructure: Ground substance

Ground substance, see figure 1.9, where cells and fibers are immersed, is composed of soluble, gel-like polymers known as proteoglycans: large hydrophilic polysaccharide chains (glycosaminoglycans) covalently linked to a core of protein. Specific glycosaminoglycans found in proteoglycans include hyaluronic acid, chondroitin sulfate, dermatin sulfate, keratan sulfate, and heparan sulfate. Proteoglycans osmotically attract water to the extracellular matrix resulting in swelling (turgor). Pressure from turgor helps the extracellular matrix resist compressive forces applied to tissues. Tissues rich in these molecules have a spongy, cushion-like quality and function like shock absorbers.

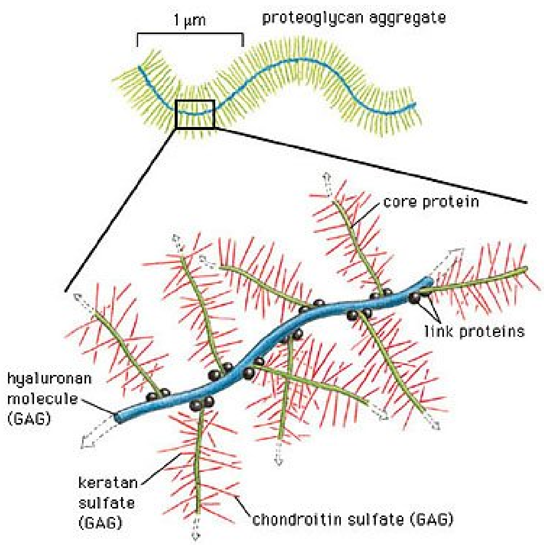

Figure 1.12 *Ground substance molecular components.*
(From http://medinfo.ufl.edu/pa/chuck/summer/handouts/c)

In artery's tunica adventitia, ground substance plays a major role in dynamic wall short time response but it is of minor importance in long term force application (passive behavior).

1.7. Arterial Wall as a complex system

In spite of the lack of consensus about what are the main concepts defining the emerging science of complexity, what they mean and how to quantify them, it is possible to establish a minimum set of features which a system needs in order to be called a "complex system" [9] [10] [11]:

- *Instability*: Complex systems tend to have many possible modes of behavior, often shifting between these modes as the result of small changes in some factors governing the system.
- Arterial wall is a perfect instance of instability: it behaves as a perfect elastic body when supports loads in the physiological range but gets stiffer as the load increases beyond a threshold. Also, as it will be shown in the present work, the rupture process has a special dynamics revealing its structural levels.
- *Irreducibility*: Complex systems come as a unified whole; they cannot be studied just by breaking them into their component parts, looking at them in isolation and superposing the resulting variables. The behavior of the system is determined by the interaction among the parts, and the problem of integration of the individual part models into a global one is of major importance.
- *Adaptability*: Complex systems tend to be composed of many intelligent agents, who take decisions and actions on the basis of partial information about the entire system. Moreover, these agents are capable of changing their decision rules on the basis of such information. In the case of arterial wall, it is possible to find to different levels of autonomy: first in the relay between elastin and collagen fibers when supporting loading and second in a much higher complexity level, the biological response mainly leaded by fibroblasts consisting in the expression of fibrogens and other extracellular matrix remodeling factors.
- *Emergence*: Complex systems produce surprising behavior; in fact, they produce behavioral patterns and properties that just cannot be predicted from knowledge of their parts taken in isolation. These so-called "emergent properties" are probably the single most distinguishing feature of complex systems. In arterial wall, one highly remarkable instance of emergence is atherosclerosis: changes in the

mechanical behavior of one small region produce critical events in hemodynamics and in the systemic physiology of a human being.

When considering the problem of complex systems modeling it is possible to find two main currents of thinking and working: One, the "physical science approach", still reductionist and by using ideas as chaos, continues in search of a minimum set of principles to explain every natural process. The second one, which will be followed in the present work, the "cybernetic (systemic) approach" sees complexity as the feature of a system consisting in the fact that it is impossible to reduce a high diversity of causal relations (input –output) along the hierarchy of system components to just one causal relation, or at least a minimum set of macro causal relations.

Cybernetic approach works upon the idea that a complex system can be modeled as the integration of a set of autonomous subsystems which will be modeled in an independent way and integrated by considering those parts as part of a control system.

It is possible to think that this cybernetic approach may be unreal because puts aside synergistic (mostly chemical and biological) phenomena. However, it is more realistic than the approach of considering that it is possible to reduce a high diversity of autonomous objects and subsystems to just one.

To follow the cybernetic line of thinking and working, Arterial Wall as a complex system means that it is considered as a ***system*** composed of ***subsystems*** (collagen fibers, elastin fibers, ground substance and with a higher level of autonomy, fibroblasts) In order to predict the global system impact of individual subsystem properties and behaviors, it is necessary to first abstract and model individual subsystems, then integrate the subsystem models into just one system model and finally, to simulate its behavior exploring one diversity of possible scenarios: loading conditions.

1.8. Epistemological Framework: Object Oriented Modeling

Up to the present, after a deep bibliographical search, an object oriented model of arterial wall or of artery has not been developed. Because of that, another reason to justify the present work it is the exploration consisting in the construction of a pure object oriented model, where the behavior of the modeled system is reproduced by the intercommunication of individual autonomous objects instead of using an analytical approach where the simulated system's states come from the solution of a set of equations written on the hypothesis of continuity in space and time of the variables used to abstract the identity of the modeled system (12) (13) (14) (15) (16).

Object oriented modeling deals with two central concepts in science: **object** and **model**.

In the present work one **object** is one entity that is matter of knowledge and that have identity: attributes, behaviors and states.

A **model** is one object used as representation of another object called "the real object".

A **system** is a composed object: one object that has as main attribute its **structure**.

The action ok knowing always involves two main steps: one, to discretize reality into separate units and specify what of those units will be the matter of knowledge: to interpose (*objicere* verb in Latin) between reality and the observer just one entity: the **object** of knowledge.

The second major step is to extract the main features of the object: those attributes and behaviors that will allow to the observer to assign one identity to the object. This step, abstraction of the object's identity, gives as a result one idealized representation of the object: an object's **model**.

Galileo's idea, considered as the start of modern science, was to catch the knowledge, just on the **behavior** of things, by using structures (mainly equations) involving variables which represent features of its behavior more than its very identity.

In this way of thinking, object oriented modeling is not just a programming methodology but a new form (or one coming from the beginning of humankind but made explicit) of representing knowledge, not about the behavior of the things, but about the things in themselves by constructing a computer encapsulation of data and behavior: an object oriented object's model.

In object oriented modeling the object's identity is abstracted into a new object, the model (a "virtual object") which, in computer science, is an encapsulation of data structures (the object's attributes) and programs (the object's behavior).

The act of knowing in object oriented modeling begins by specifying the system's components to be considered, the result of this step depends strongly on the phenomenological context (the **universe of discourse**) where the model is built and on the available measurement resources.

It is important, however, to remark that this second restriction, the measurement possibility, may be replaced at a first gross stage, by the introduction of "imaginative elements" such as what was done in the modeling of the atom with the introduction of the concepts of "electron", "proton", "neutron", etc.

2. Methodology and Tools

In order to accomplish the planned objectives, the used methodology is composed of three main steps, which are described in this chapter:

- Model design and implementation
- Simulation system implementation
- Verification experiments and results

The model design and implementation section begins by the requirements specification and establishing the boundaries of the context. Then a description of the model is given and also a discussion on the used tools. Following to the general description of the model, individual UML object component models are described. A description of the implemented simulation engine is given, a matrix structural mechanics program implemented from the Weaver-Gere book referenced in the bibliography. Finally, an account of the model verification protocol is specified.

2.1 Model design and implementation

In addition to the reasons exposed at the previous section, about modeling the arterial wall as a complex system, the objectives established in the present work impose the necessity to design, develop and test an object oriented computer model of arterial wall under the following premises:

- The contribution of this work is a first implementation and should serve just as a backbone to be extended, improved and used. In this way of thinking, completeness is not, at this stage, the main objective but maintainability.
- The simulation engine uses matrix structural mechanics as the background theory and the implemented structure deformation engine is a previously developed program for the field of structural analysis (5). This simulation engine will be used just for the controlled manipulation of the project's kernel: the model. The simulation engine will be only described but not discussed.

- The model should be simple enough as to allow maintainability and understandability but complex enough as to show the main complexity features of arterial wall
- The model should allow straightforward inclusion of biological objects such as fibroblasts represented by automata. In the same way of thinking, it should allow easy modification, inclusion, deletion and replacement of component models
- The model should allow easy discussion and analysis in interdisciplinary contexts
- The model should be independent of the simulation engines and produce equivalent results
- The model should be highly portable between different computer platforms.

Regarding those premises, the model will be designed by using UML as the modeling language, JAVA as the implementation language and, just because of easy implementation of visual interfaces and because of UML embedding, Microsoft Visual J# ("jay sharp") 2005 has been used as the development system.

As a result of extensive (one year) literature review, acquisition, reading and discussion, the arterial wall, in the universe of discourse of its passive behavior (under the presence of time independent force fields) may be represented by a three dimensional hollow cylindrical spring network (in structural mechanics language, a space truss), figure 2.1, which nodes may serve as cell placeholders (not implemented at this instance) and the springs (truss members) are periodically distributed across the hole cylinder in such way that each node will be connected to its six nearest neighbors by: one angular left member, one angular right member, one axial forward member, one axial back member, one radial upper member and one radial lower member, figure 2.2.

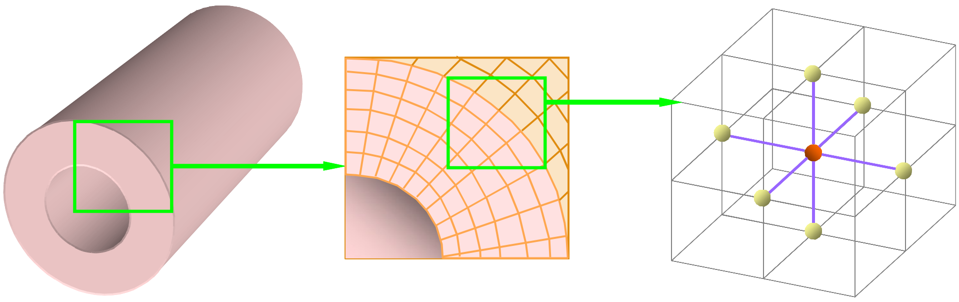

Figure 2.1. *Truss model of artery.*

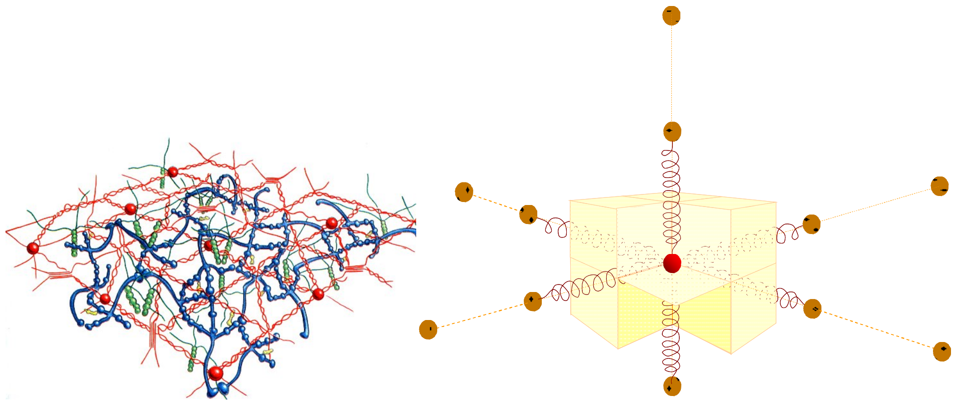

Figure 2.2. *Truss node and its six nearest neighbors.*

2.2. Ontology of the artery in the universe of discourse of arterial wall simulator

In the universe of discourse of arterial wall simulator, the artery is a truss composed by members which correspond to a single elastic fiber equivalent to an elastin fiber connected in parallel to a collagen fiber. Before rupture of collagen fiber, this parallel connection may be in one of two states:

- State one, figure 2.3: the collagen fiber is coiled and the load on the parallel fibers system is supported mostly by the elastin fiber.
- State two, figure 2.4: The collagen fiber is uncoiled and the mechanical resistance of the parallel fiber system is supported mainly by the collagen fiber.

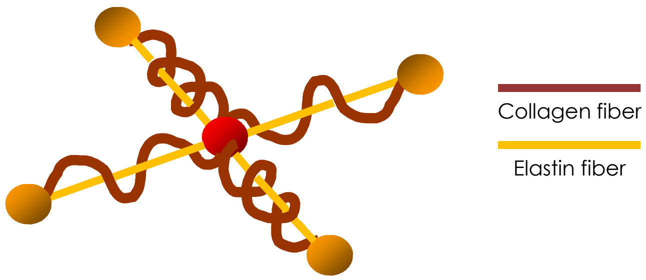

Figure 2.3 Truss local group before collagen uncoil.

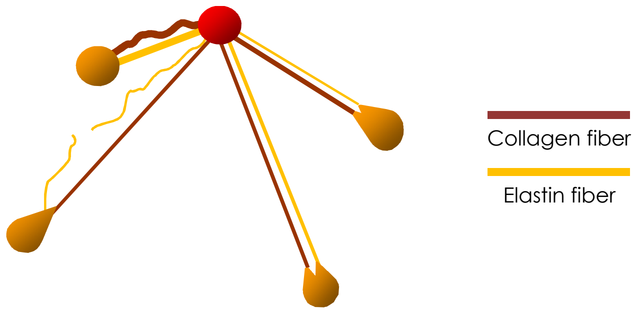

Figure 2.4 Truss local group after collagen uncoil.

2.3. Simulation system implementation

The artery is represented in the object oriented model as a space truss: a three dimensional network of nodes (cells) joined together by members (fibers).

From this perspective, the deformation of the artery corresponds to collective displacements of the nodes and the resulting stretching (torsion and flexion are not allowed as degrees of freedom of fibers) of the fibers connected to the displaced nodes.

In this way, the main task of the simulation engine is to produce a stream of strain-stress pairs: (σ, ε), corresponding to the successive application of increasing values of loads applied in a specific deformation mode (in this case, axial and pressure-volume deformations).

2.4. Verification simulation experiments protocol

It is important to remark the use of the word "verification" instead of "validation".

Model verification refers to a process intended to compare simulations results with typical behaviors of an object class, here an arterial segment.

Model Validation explores the coincidence between simulations and the behavior of a specific instance of an object class.

As the purpose of the present work is to propose a modeling framework, to realize a validation is out of its scope because parallel analog experimentation should be executed.

Verification will be executed in two stages for each deformation mode.

First, a parameter set will be obtained by a sensitivity analysis, having as choice criterion the stress-strain simulated plots coincidence with typical analog plots obtained from literature, where differences between samples are mostly in numerical values than in plot shapes.

Second, with the chosen parameters, for each deformation mode a set of simulations is executed and the average plot compared with an appropriate analog plot obtained from literature: a calves' artery segment for axial deformation (7) and a rat mesenteric artery (20) for pressure – volume experiments.

3. Results

In this chapter, the model design and implementation results are presented. The simulator engine is also presented as a result. The verification simulation experiments results are reported. Two kinds of verification experiments have been done: axial loading (axial stress-strain) and pressure-volume (circular stress-strain). First, the axial sensitivity analysis results are presented ending with the simulation to analog plot comparison. Second, the pressure-volume simulation results are reported, both sensitivity analysis and simulation to analog comparison.

3.1. Model design and implementation

To outline the object oriented structure of artery model figure 3.1 represents its hierarchical organization by an UML class diagram

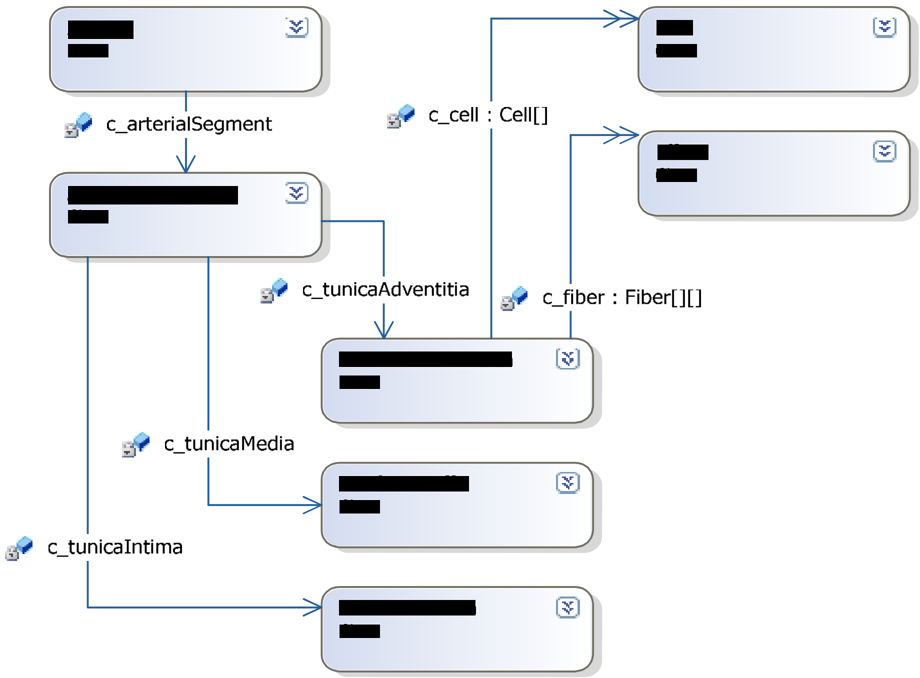

Figure 3.1 *UML class diagram of object oriented artery model.*

Each box in the UML object oriented model of artery represents a class: a template to create objects as instances of the class.

Each class include a set of data fields abstracted to represent the attributes of the class objects in the given universe of discourse.

In addition, the class includes a set of methods (code blocks to modify attributes values and in this way upgrade object's states) to represent class objects behaviors.

In the following paragraphs, going across the hierarchical structure of the model a short description of each class will be done.

As some object oriented programmers use, a prefix convention to identify the field type that it represents: 1. the prefix "a_" means that the field represents an attribute, 2. the prefix "c_" means that the field represents a component and 3. the prefix "s_" means that the field represents a state variable.

3.1.1. Class Artery

In the context of the model, an artery is a composition of arterial segments. The fields (attributes) included in the class are: 1. the number of segments in which the artery is divided for the model construction and 2. the set of implemented segments, the segment[] field (a "segment" objects array). Because of the nature and objectives of the present work, in the verification section of the model just one segment arteries will be considered.

As every class, there is a constructor method to create instances of the class, the Artery() method.

To represent the main deformation behaviors of an artery, there are two methods called axialDeform() and PressureVolume() which produce data points to construct a stress-strain plot. Figure 3.2 gives a close up of Artery class definition.

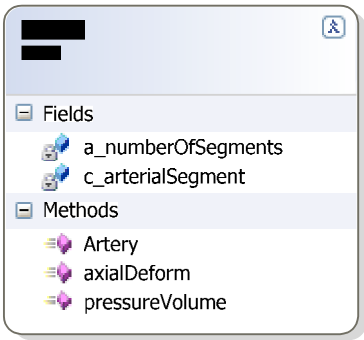

Figure 3.2 *Artery class definition.*

3.1.2. Class ArterialSegment

As figure 3.3 indicates, each arterial segment includes: 1. a tunica adventitia component object, 2. a tunica media component object and a tunica intima component object. Because the scope of the present work is passive behavior of arterial wall, just the c_tunicaAdventitia field is implemented.

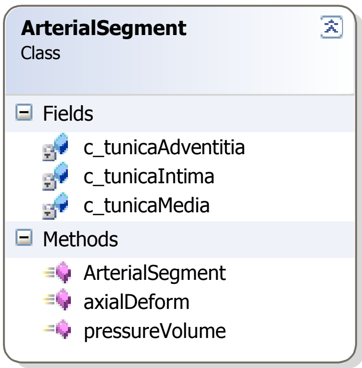

Figure 3.3 *ArterialSegment class definition.*

The implemented arterial segment behaviors are: ArterialSegment(), the constructor method and two deformation methods: axialDeform() and PressureVolume() method.

3.1.3. Class tunicaAdventitia

The class tunicaAdventitia is the main class of the model. A one dimensional cells object array (structure nodes) and a two dimensional fibers field object array are implemented As the main attributes of the tunica adventitia.

The tunicaAdventitia class contains the simulation engine: the deformStructure() method and the methods that check and upgrade the individual fibers state and the global artery state.

The tunica adventitia state is defined by macrostate variables and by microstate variables. Macrostate variables are: artery stress, artery strain, axial elastic modulus and circular elastic modulus.

Figure 3.4 shows the complete TunicaAdventitia class definition.

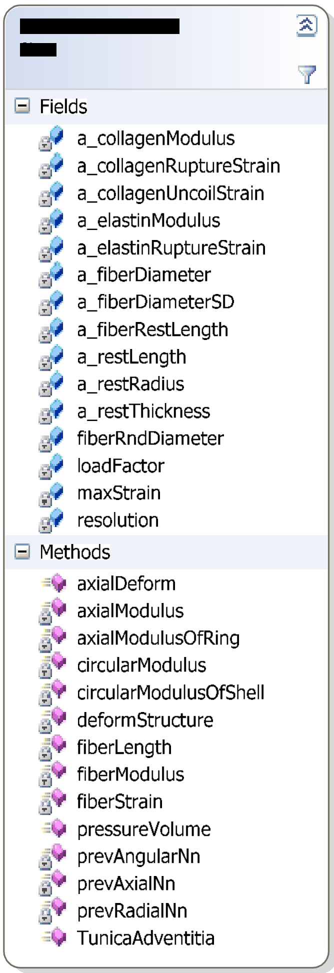

Figure 3.4. *Class TunicaAdventitia.*

Microstate adventitia state is defined by a set of methods that read individual fibers attributes values, upgrade them and combines them to produce macrostate values.

The set of unloaded attributes values (artery rest length, rest inner radius, rest thickness, rest fibers length, fibers diameter) are also part of the fields necessary to compute micro and macro state variables values.

3.1.4. Class Cell

Figure 3.5 shows UML Cell class box. At the present stage of development, the cell objects are just truss nodes but it is possible to implement in this place more complex objects whose methods represent real cells biological activities such as produce (or induce the production of) new fibers.

As the class box indicates, the only attribute of a cell object is position and its behaviors are: 1. cell instance constructor Cell(), 2. position getters get_x(), get_y() and get_z() to retrieve each Cartesian component of cell's position, 3. move() to change one or all components of cell's position and 4. set_coordinates() to *ad hoc* define cell position.

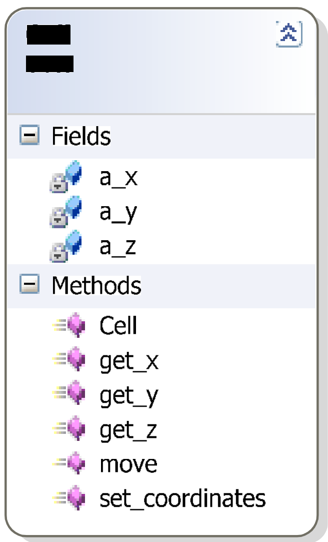

Figure 3.5 *Class Cell.*

3.1.4. Class Fiber

The last implemented class is class fiber. As in the case of cell class, its implementation may be dramatically improved by using more complex fiber models as these coming from molecular dynamics and quantum physics.

Here, the fiber model corresponds to a system composed of two springs (an elastin fiber and a collagen fiber) connected in parallel which elastic modulus depends upon the length state of the fiber. Figure 3.6 shows the class fiber structure.

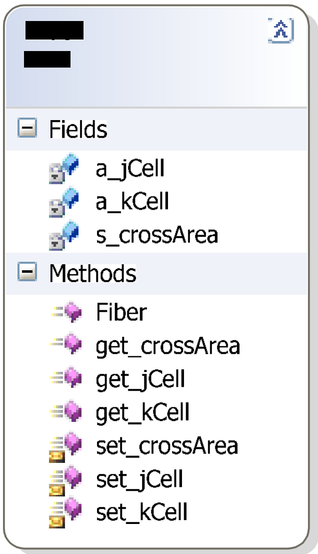

Figure 3.6 *Class Fiber.*

The fields a_jCell and a_kCell represent the indexes of the extreme nodes connected by the fiber.

The fields s_elasticModulus and s_isBroken are the heart of the model.

Because of the state of the fiber determined by the values of its elastic modulus and if the fiber is broken or not, the global elastic modulus of the artery changes with the state of each fiber leading to a high nonlinearity of the global elastic behavior of artery.

The remaining components of the Fiber Class are the constructor method, the getter and setter methods (methods to retrieve and set the field values of the class).

The code implementation of the model is given as an appendix, together with the simulation engine code and the simulations data files.

3.1.5. Parameters input interface

The first step in order to attain meaningful results is the calibration of the model by exploring the appropriate set of input values that will produce appropriate simulations output. Figure 3.7 shows the model's input interface

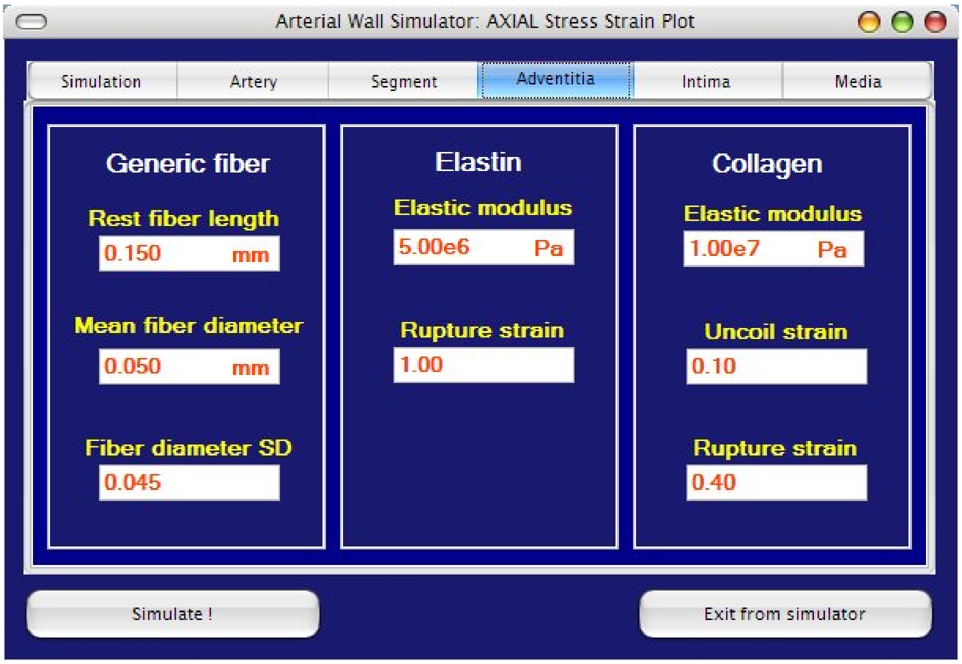

Figure 3.7 *Arterial Wall Mechanics Simulator input interface.*

The input parameters to calibrate, starting from values reported in literature [20], were:

- Macroscopic geometrical arterial segment parameters:
  - Segment length, default value: 10 mm
  - Segment inner radius: default value: 1 mm
  - Segment thickness: default value: 0.5 mm
- Microscopic arterial components properties:
  - Generic fiber rest (unloaded) length: default value: 0.01 mm
  - Generic fiber diameter default value: 0.001 mm
  - Elastin fibers modulus of elasticity: default value: $0.6x10^6$ Pa
  - Standard deviation of elastin modulus: default value: $0.1x10^6$
  - Collagen fibers modulus of elasticity 1: default value: $1.0x10^5$ Pa
  - Standard deviation of collagen modulus 1: default value: $0.5x10^5$ Pa
  - Collagen fibers modulus of elasticity 2: default value: $1.0x10^9$ Pa
  - Standard deviation of collagen modulus 2: default value: $0.5x10^9$ Pa
  - Collagen fibers uncoil strain: default value: 0.20
  - Collagen fibers rupture strain: default value: 0.40
- Experimental conditions depending upon the type of deformation load (axial or pressure): Load factor, which is a combined account of strain rate and ground substance mechanical properties not included individually as experimental parameters, maximum strain and strain resolution.

3.2. Simulation system

The main simulation algorithm implemented in JAVA code used to generate the stream of successive strain-stress pairs is shown in figure 3.8.

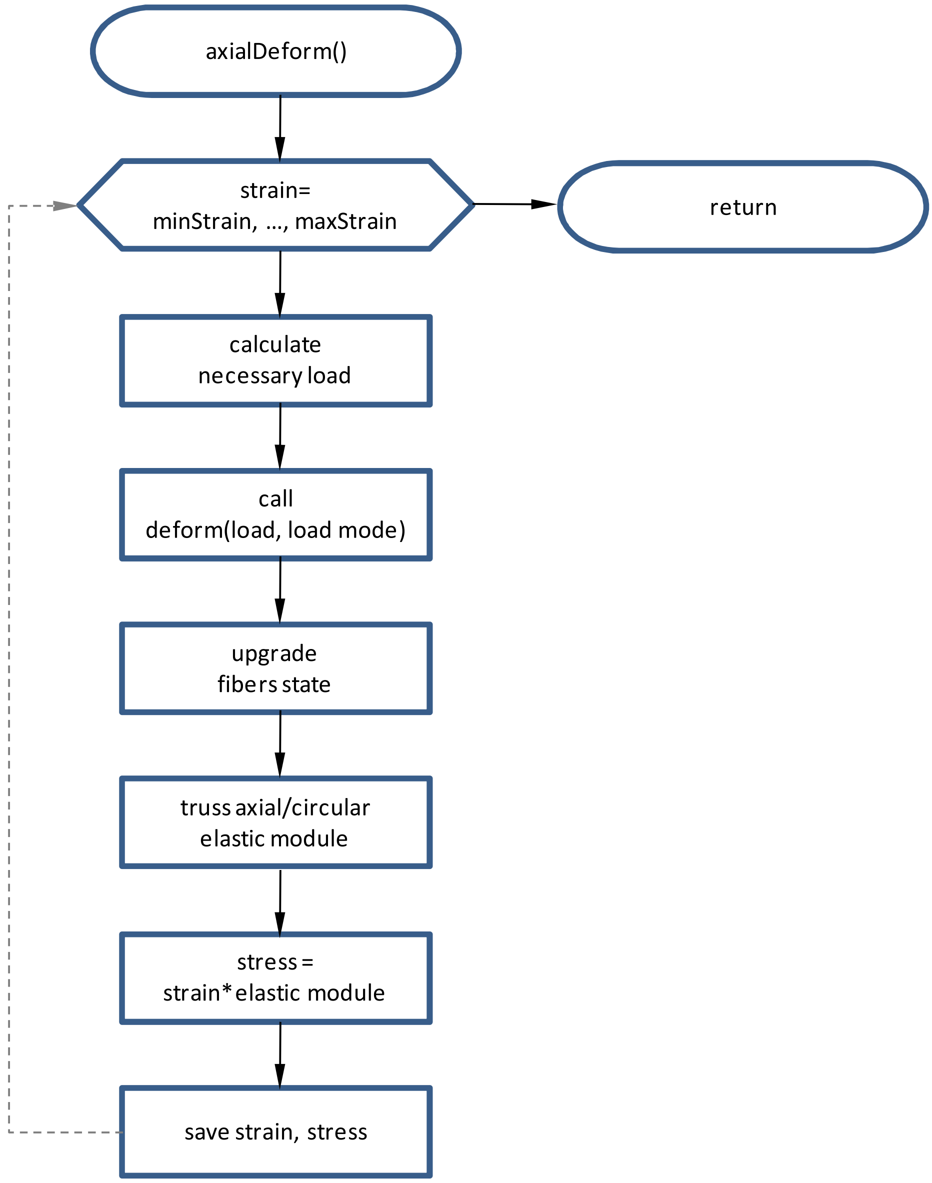

Figure 3.8 *Simulation engine code algorithm.*

And the algorithm used to deform the structure is illustrated in the figure 3.9.

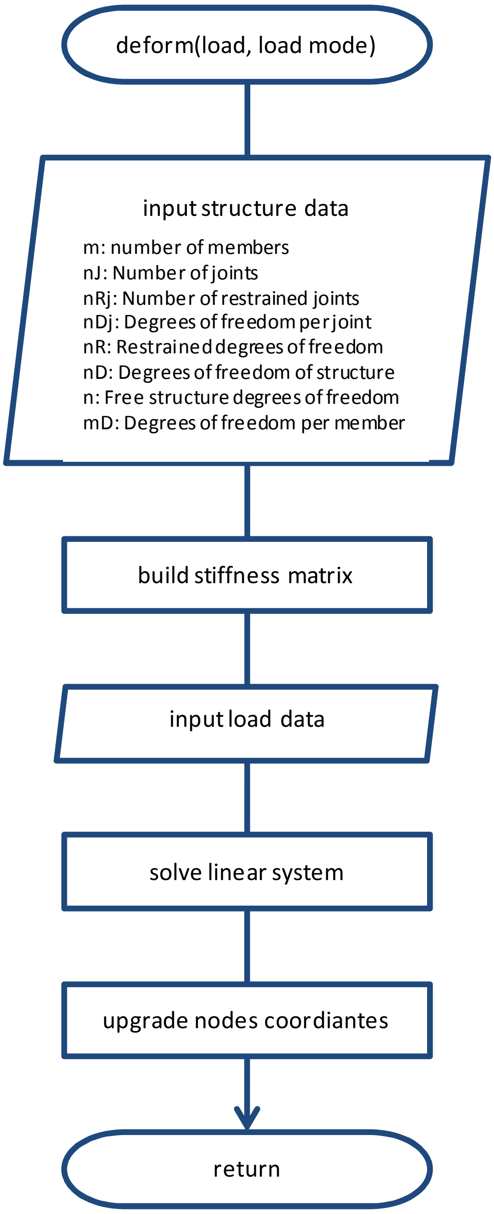

Figure 3.9 *Truss deformation algorithm.*

3.3. Simulation experiments results

Eleven simulation sets of experiments were conducted in order to verify the implemented arterial wall model.

Six sets of experiments for axial deformation: five stress strain sensitivity simulations sets for number of structural components (rings, layers), load factor which includes non-specified factors such as strain rate, elastin modulus of elasticity, collagen modulus of elasticity, and fiber diameter standard deviation. For axial deformation, a set of simulations with the chosen parameters from sensitivity analysis were conducted and an average plot obtained.

In the case of pressure-volume deformation, sensitivity analysis were executed for pressure - volume load factor, elastin rupture strain, collagen uncoil strain, collagen rupture strain.

Finally, as in the axial deformation case, a set of simulations with the sensitivity chosen parameters were executed and averaged in a pressure – volume stress-strain plot.

3.3.1. Parameters Sensitivity analysis for axial deformation

Structural parameters sensitivity

The cylindrical 3D truss that represents an arterial segment is composed of three structural patterns: arcs, rings and layers (shells). Needed computational resources are very sensible to the number of structural components, mainly to the number of arcs.

In order to be able to explore simulations sensitivity to the relations: segment length to fiber length (number of rings), and segment thickness to fiber length (number of layers), the segment inner radius and in this way, the number of arcs were maintained as a constant while modifying the number of rings and the number of layers of the model.

Figures 3.10 to 10.13 show simulations results obtained in the sensitivity analysis for structural parameters in the axial deformation mode.

Considering shape and critical values similarity with the reference plot (7), figure 3.11, the chosen structure is the cylindrical truss with one layer and four rings, which produced the closest simulated plot to the reference plot.

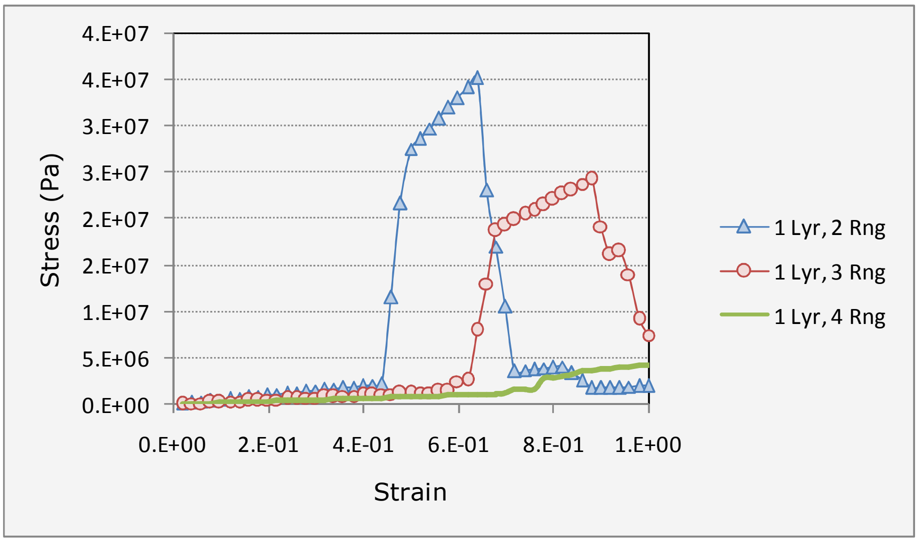

Figure 3.10 *Stress-strain plot sensibility for truss structures with one layer (Lyr) and variation of rings number (Rng).*

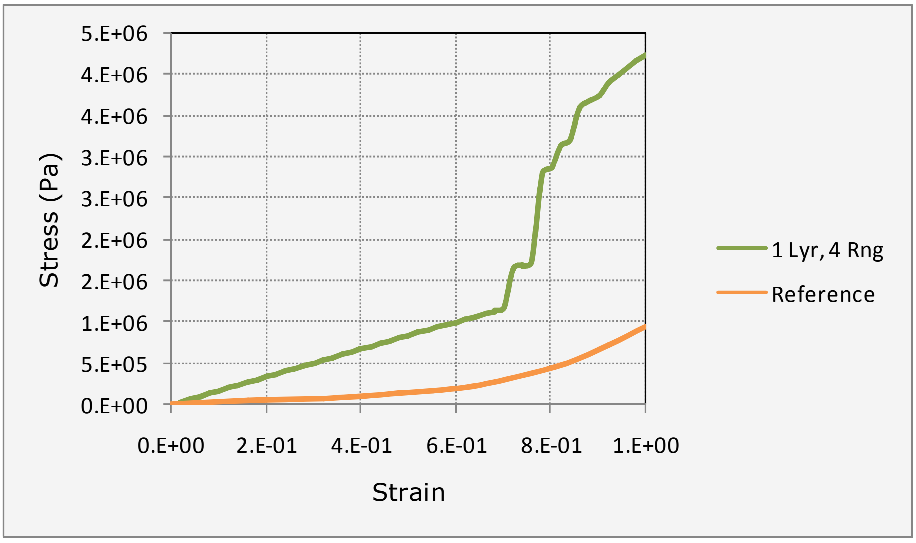

Figure 3.11 *Simulated stress-strain plot for a model truss with one layer and four rings (zoomed from figure 3.10), compared with the reference plot.*

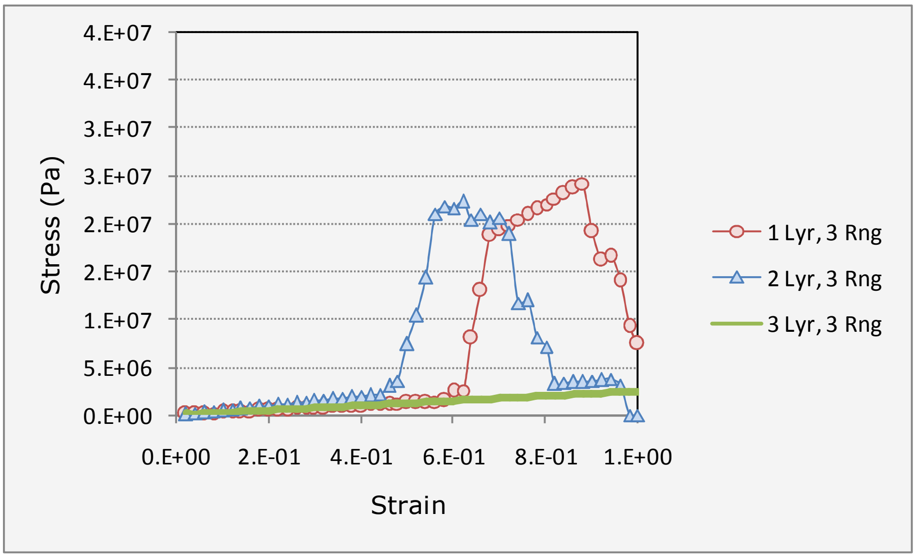

Figure 3.12 *Stress-strain plot sensibility for truss structures with variation of layers number and three rings.*

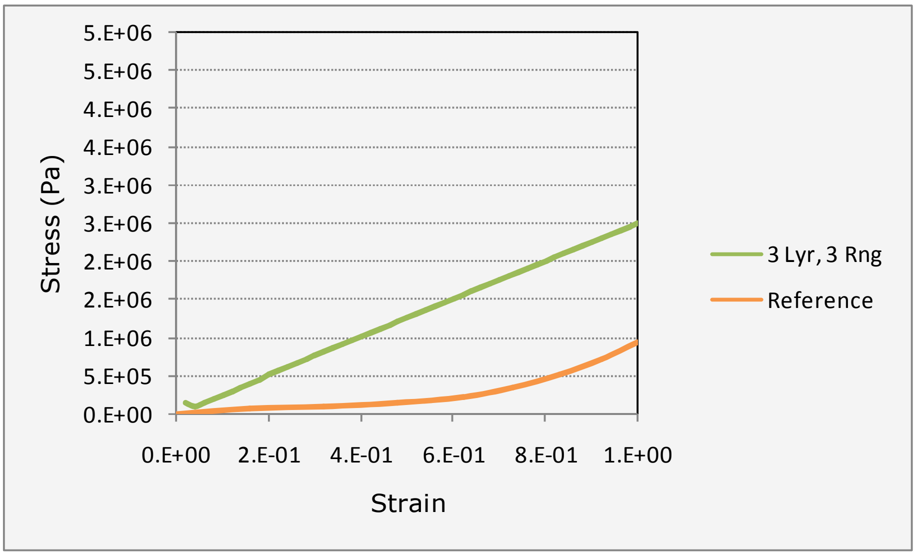

Figure 3.13 *Simulated stress-strain plot for a model truss with three layers and three rings (zoomed from figure 3.11), compared with the reference plot.*

Load factor sensitivity and calibration

Load factor is a calibration factor that affects the applied external load. Load factor replaces in the simulations the effect of unspecified variables such as strain rate.

As seen in figure 3.14, load factor introduces a mere homogeneous scaling effect in stress-strain plot. In this case, the 0.0015 value was chosen because of the slope change (collagen uncoil strain) at a 0.6 strain and rupture at 0.8 strain (values chosen for coincidence with literature reports for those critical points).

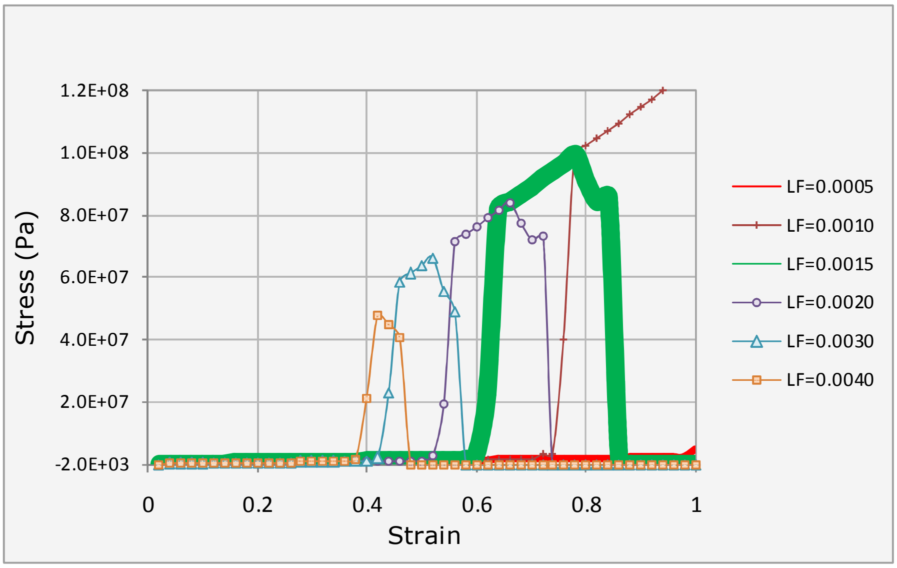

Figure 3.14 *Load Factor variation (LF) for axial loading with a model truss of one layer and four rings.*

Elastin elastic modulus sensitivity

Figures 3.15 and 3.16 show axial stress-strain plots for the standard and yet calibrated parameters, with variation of elastin elastic modulus.

As the zoom plot, figure 3.16 indicates, the E_e=2.0x10^5 Pa plot is the best choice, given its coincidences in size and critical values with the reference plot.

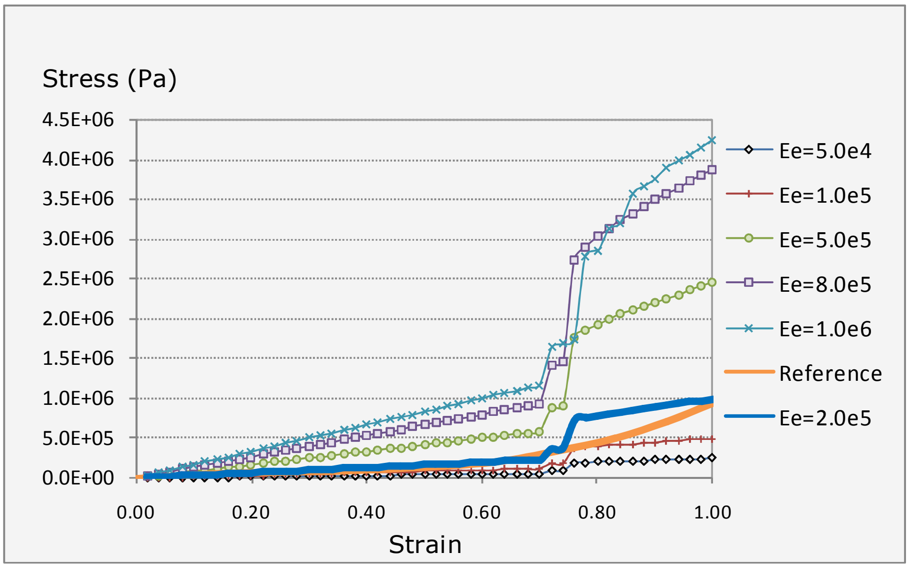

Figure 3.15 *Plots for previously optimized parameters and elastin elastic modulus variation. Ee refers to elastin elastic modulus.*

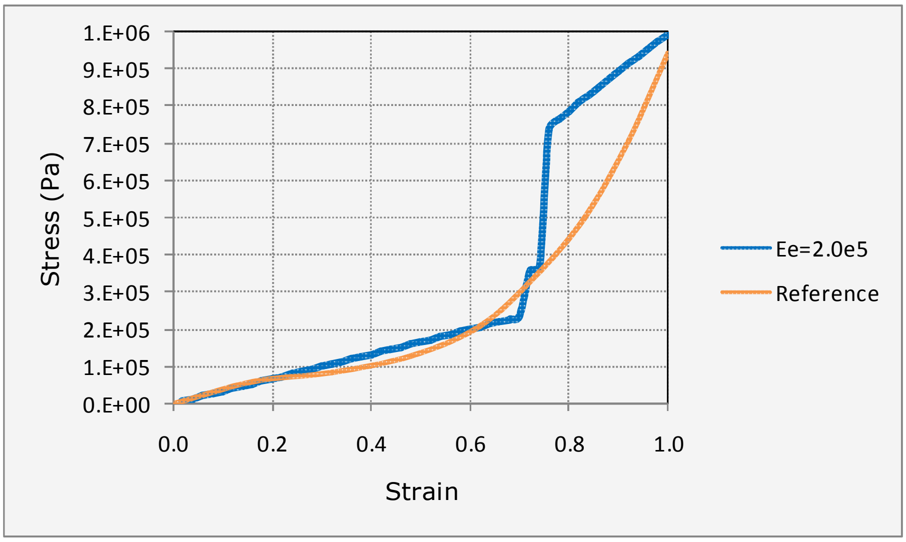

Figure 3.16 *Zoom plot for the chosen elastin modulus parameter, Ee=2.0x10^{5}Pa, contrasted with the reference plot.*

Collagen elastic modulus sensitivity

In figure 3.17, stress-strain plots for variation of collagen elastic modulus, it is observed a progressive increase in segment rigidity (second linear slope) followed by a third lower slope, indicating a softening due to the collagen fibers breaking until a critical value where segment failure begins. This progressive behavior allows to choose any of those values giving an appropriate response together with the proper elastin modulus value.

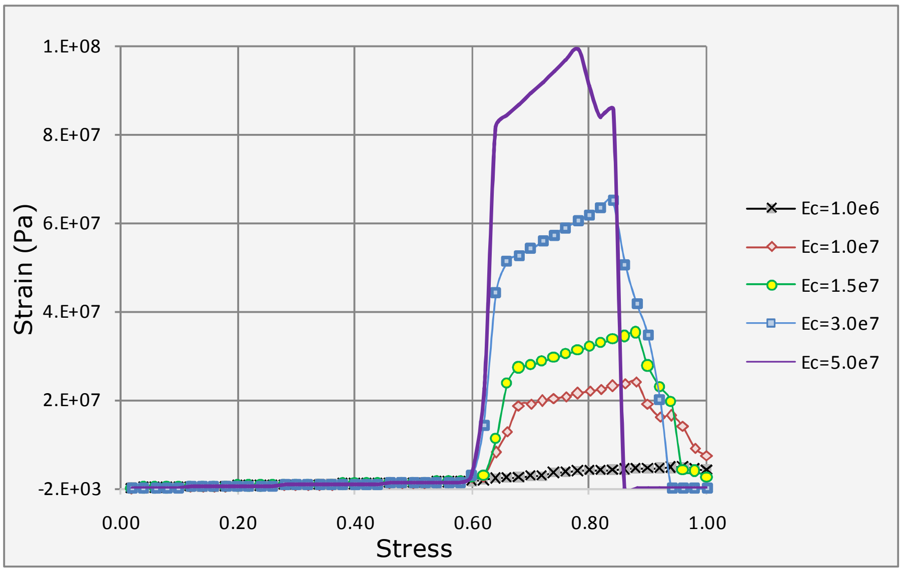

*Figure **3.17** Stress-strain Plots for variation of collagen elastic modulus. Ec refers to collagen elastic modulus.*

Fiber diameter standard deviation sensitivity

Simulation results shown in figure 3.18, indicate a high sensitivity of stress-strain plots to structural disorder.

High values in fiber diameter standard deviation ("isotropy") produce plots with tendency to be linear with some dynamic fluctuations. In opposition, low standard deviation values ("anisotropy") in fiber diameter produce the expected bilinear plots. Some small degree in disorder becomes necessary in order to achieve more realistic plots.

The plot corresponding to a standard deviation of 0.2 for fiber diameter reflects a behavior closer to the reference plot.

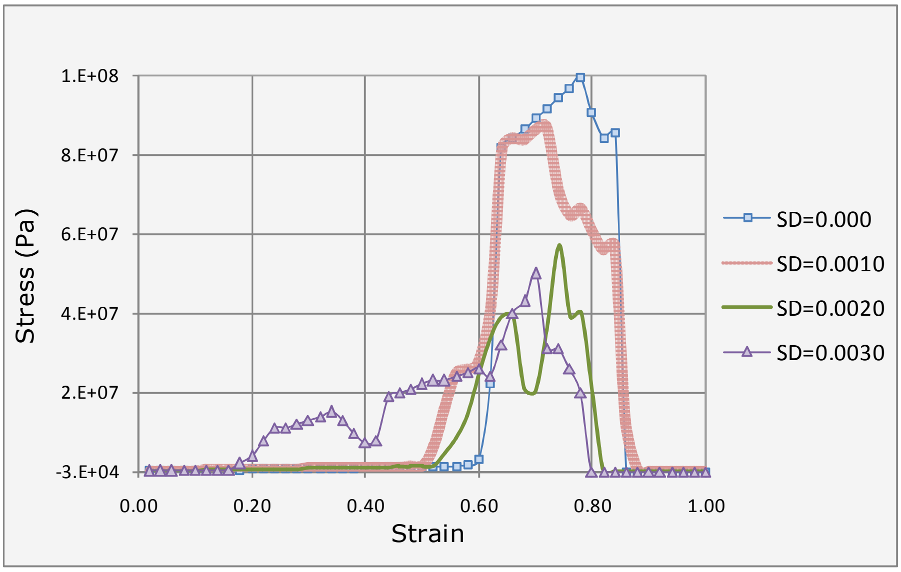

Figure 3.18 *Stress-strain plots for variation of fiber diameter standard deviation (SD).*

Verification simulation plot

Figure 3.19 displays stress-strain plot for the sensitivity analysis chosen parameters, contrasted with the reference plot.

The simulation plot corresponds to the average plot obtained from five simulation experiments executed with identical values for the structural and simulation parameters:

Structure:	One layer, four rings
Load factor:	0.0015
Rest fiber length:	0.150 mm
Fiber diameter:	0.050 mm
Fiber diameter SD:	0.010 mm
Elastin modulus:	2.0e5 Pa
Elastin rupture strain:	1.00 Pa
Collagen modulus:	5.00x107 Pa
collagen uncoil strain:	0.10
collagen rupture strain:	0.50

Zoom plots, figure 3.20 for the elastin driven region and figure 3.21 for collagen driven region, indicate high similarity in macroscopic mechanical behavior between object oriented model and reference arterial segment.

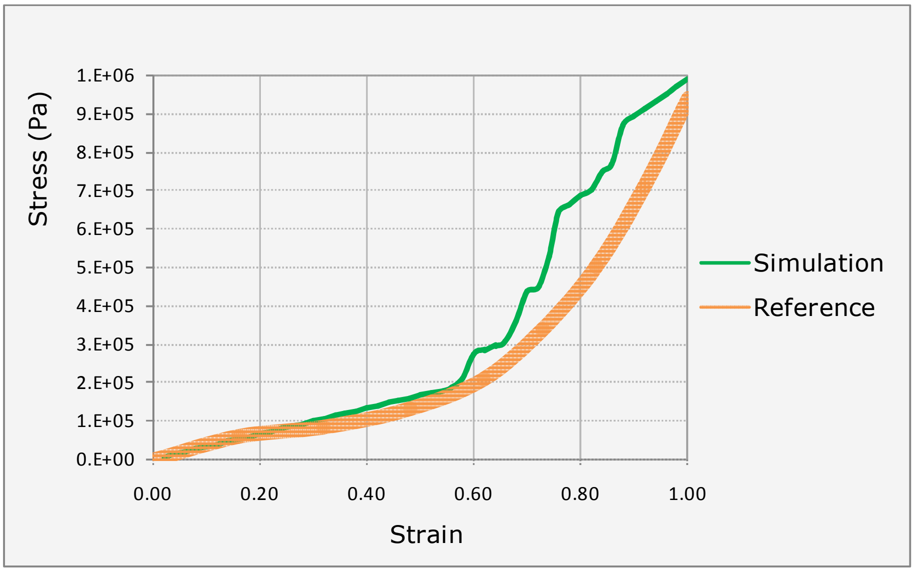

Figure 3.19 *Verification plot, showing stress-strain Plots from simulations contrasted with the reference plot.*

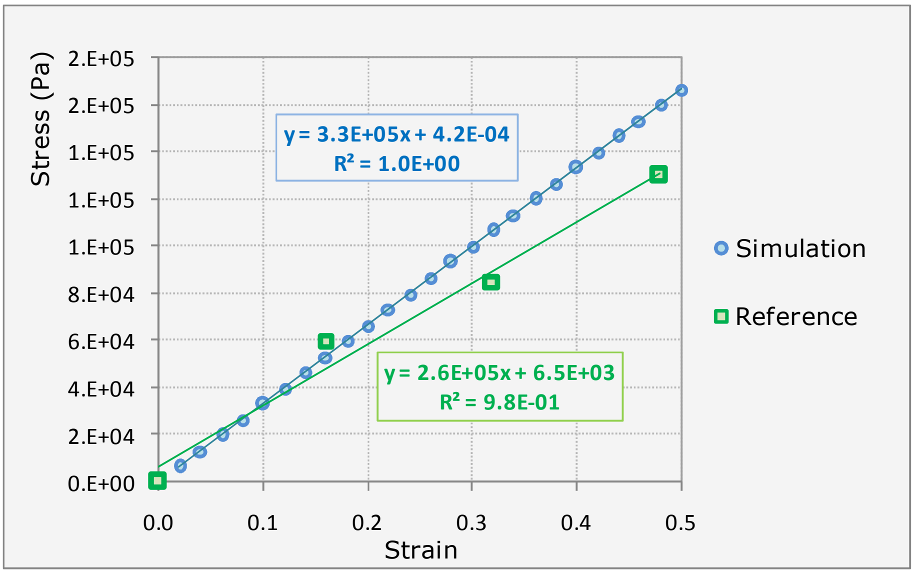

Figure 3.20 *Verification plot zoom for toe (elastin driven) region with linear fit equations and squared correlation coefficient,* R^2.

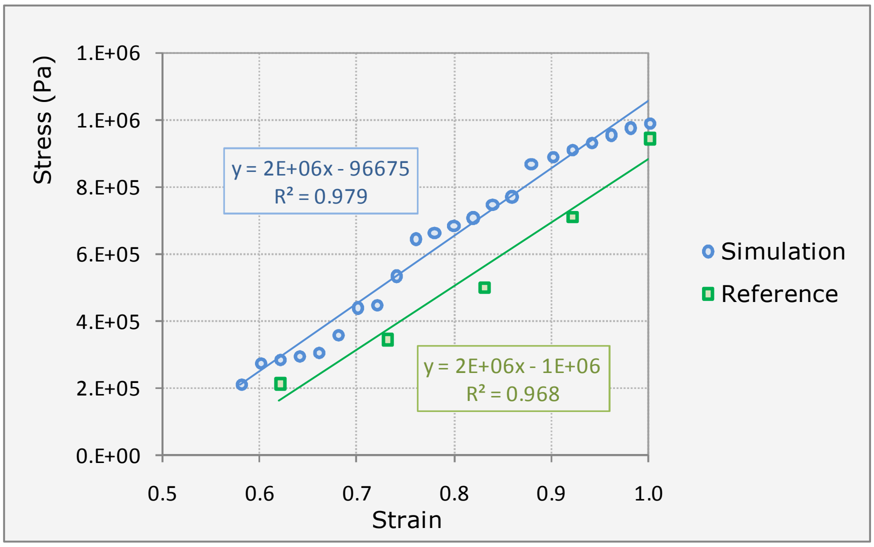

Figure 3.21 *Verification plot zoom for collagen driven region.*

3.3.2. Parameters Sensitivity analysis for pressure-volume experiments

Load factor

Load factor variation effect on circular stress-strain, pressure-volume plots is shown in figure 3.22:

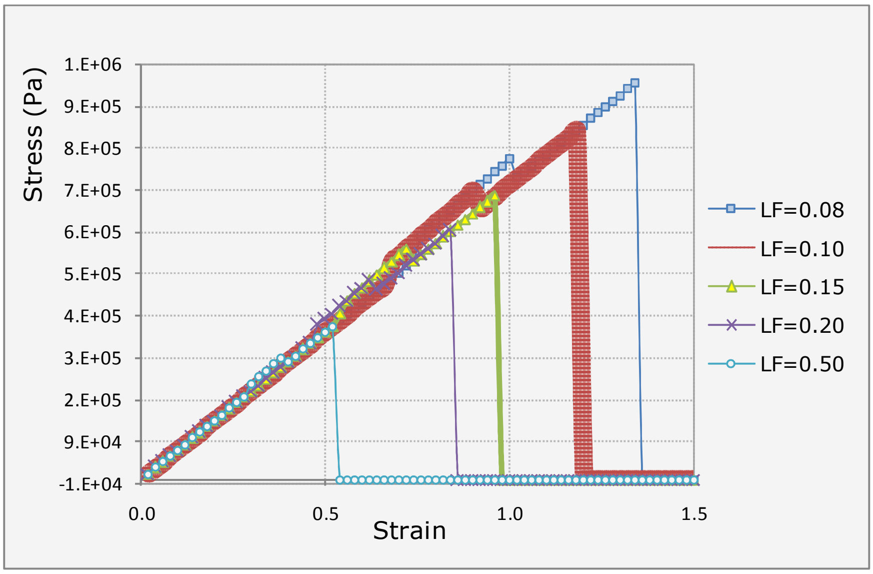

Figure 3.22 *Pressure-volume, variation of load factor.*

Before calibration of critical parameters such as elastin rupture strain, collagen uncoil strain and collagen rupture strain, pressure-volume stress-strain plots include light deviations from completely elastic behaviors. Considering failure strain values, the chosen load factor in order to continue other parameters exploration is LF=0.10.

Elastin rupture strain, collagen uncoil strain and collagen rupture strain

As expected, simulations corresponding to figures 3.23 to 3.25, show a great dependency of critical values (first change in slope, second change in slope, rupture point and rupture pattern).

It is very important, in order to reproduce the mechanical properties of collagen and elastin, that the lower critical strain correspond to collagen uncoil, the intermediate critical strain correspond to collagen rupture strain and the largest critical strain to elastin rupture. these facts were verified by simulations results.

In the three sensitivity analysis, the selection criterion was the proximity of critical values in the selected plot, to those reported in literature and specifically to those in the reference plot.

The selected values were:

- Collagen uncoil strain: 0.15
- Collagen rupture strain: 0.65
- Elastin rupture strain: 1.00

Figure 3.23 shows the obtained plots for variation of elastin fibers rupture strain, figure 3.24 for collagen fibers uncoil strain and figure 3.25 for collagen fibers rupture strain.

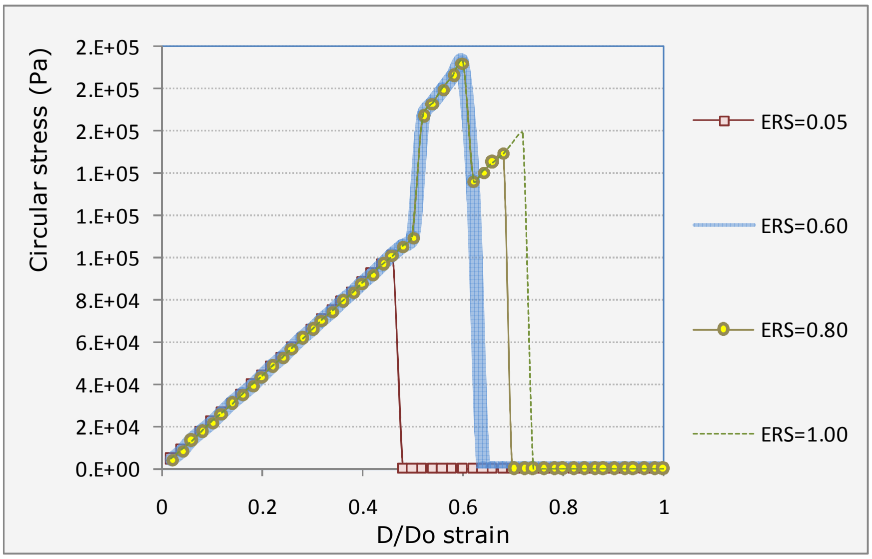

Figure 3.23 *Elastin fibers rupture strain (ERS) sensitivity plots*

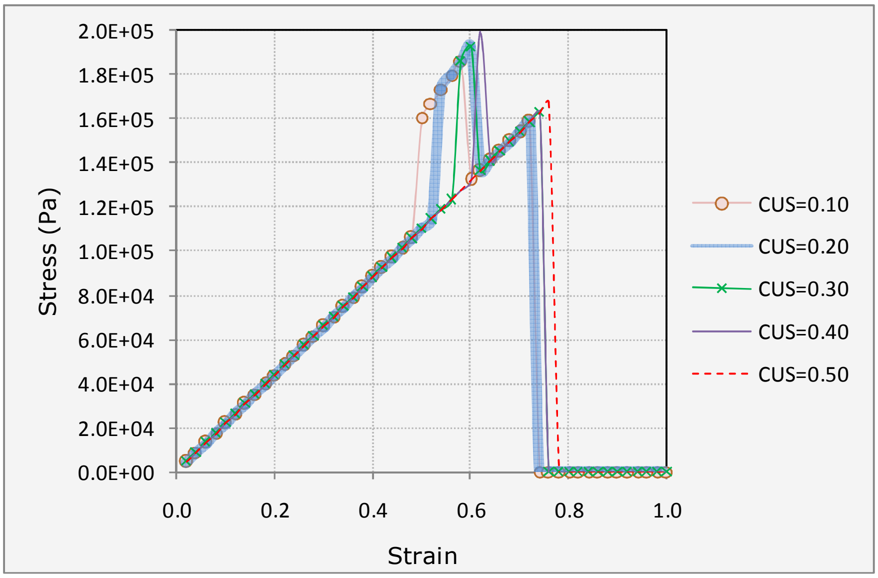

Figure 3.24 *Collagen fibers uncoil strain (CUS) sensitivity plots*

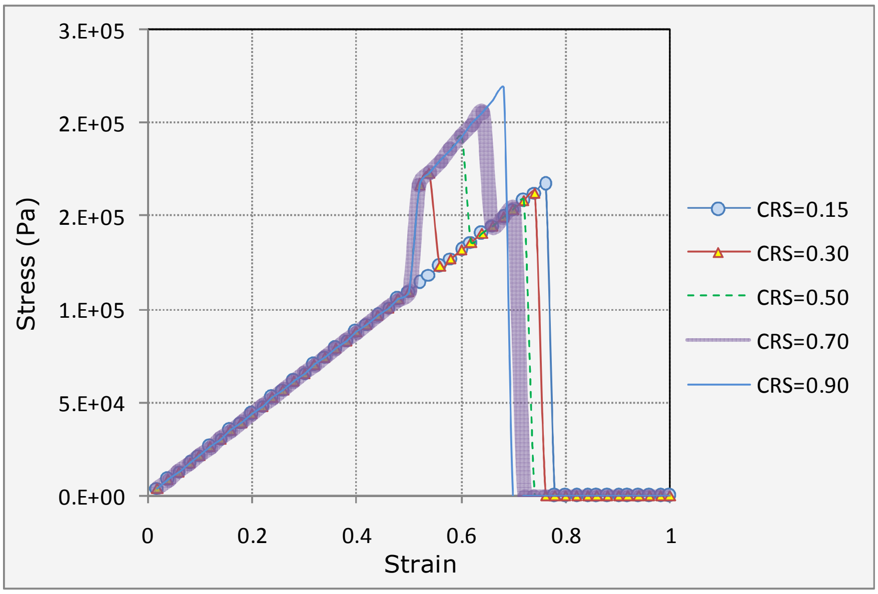

Figure 3.25 *Collagen fibers rupture strain (CRS) sensitivity plots*

Finally, the comparison plot (verification) between simulation and analog measurement in the case of pressure-volume loading is given in figure 3.26.

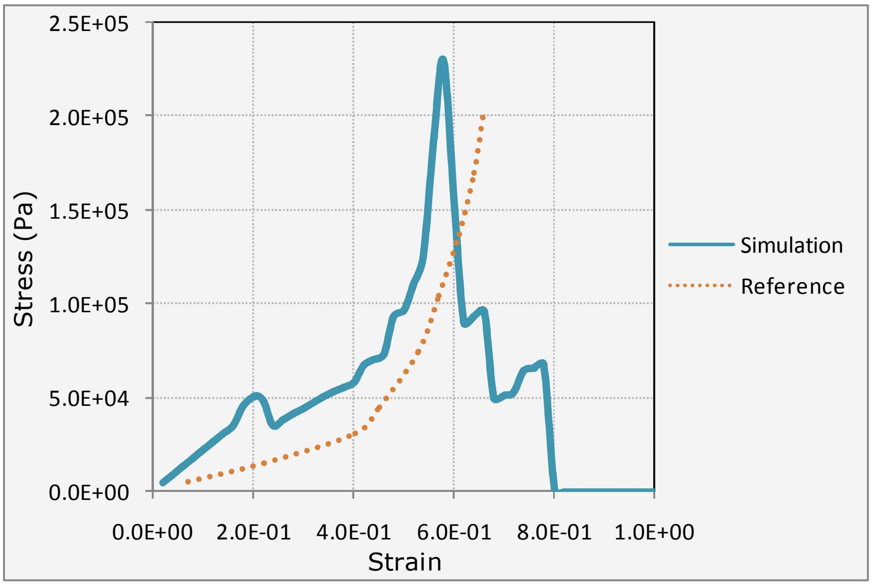

Figure 3.26 *Pressure-volume verification plot: comparison between simulations average plot and reference plot.*

4. Discussion

The implemented arterial wall model is reviewed and discussed considering its importance and difference with other models. The model utility is explored. The simulation system is discussed. The obtained simulation plots are analyzed. Each step in the sensitivity analysis is described.

4.1. Model design and implementation

An object oriented model of arterial wall has been designed, developed, implemented and verified. Despite of the verification results, which into the scope of the proposed objectives are satisfactory, the main result of the thesis work is the object oriented nature of the model which allows a modular and progressive extension, improvement and refinement. Another important benefit of the object oriented nature of the model is the possibility to individually focus the study attention into each wall component, both microscopic and macroscopic. By parameter sensitivity analyses it is possible to set and refine hypothesis on micro component attributes and organization. To our best knowledge, this the first object oriented model of the arterial wall, including micro structural components, with results and verification. Even in the field of structural mechanics, there are few references giving account of the use of object oriented methodologies as an alternative to the continuum approach.

The presented arterial wall model might be used as starting point to model another collagenous tissue organic structures such as lung, eye, pericardium, and skin. In these structures the long term behavior is strategically important.

4.2. Simulation system

The implemented simulation system belongs to the field of matrix structural mechanics. This is a well established field and in permanent growth. Because of the periodic nature of the truss model and the orthogonality of the members, the stiffness matrix was well behaved, allowing a good solution approach by simple methods such as Gauss-Jordan method. If structural disorder is included into the model, (which in the present work has been successfully replaced by the dynamical disorder introduced by the randomness in fibers diameter) the mathematical tools should be highly improved. It would be of a great importance to explore the use of stochastic mechanics methodologies and optimization theory.

4.3. Axial loading experiments

Sensitivity analysis

Two were the conditions of choice:

- The J-shaped pattern of the plot, with the critical points located close to a strain of 0.3 for the first change in slope (the end of the "toe" region) and to 0.8 for the beginning of the rupture pattern
- The similarity of the plot with the plot coming from analog experimental characterization of the calves' artery, reported by Leondes[38].

The first step in the sensitivity analysis was to find an appropriate truss structure: number of rings and number of arcs. The plot closer to the previously established criteria, was the one corresponding to one layer and four rings. The plots indicated that for a lower number of rings the global rigidity of artery was substantially higher than 1 MPa, the most common value found in literature for maximum stress of small arteries. For a number of layers greater than one, no changes in the slope of the plots were obtained, which differs from the common behavior of small arteries and in general, collagenous tissues. The best simulation parameters, for axial loading found by the sensitivity analysis were:

- Load factor: 0.0015
- Fiber diameter mean: 0.050 mm
- Fiber diameter SD: 0.010 mm
- Elastin modulus: 2.0e5 Pa
- Elastin rupture strain: 1.00
- Collagen modulus: 5.0e7 Pa
- Collagen uncoil strain: 0.10
- Collagen rupture strain: 0.50

The global elastic modulus of artery from simulations is 30 kPa for the toe region, while from analog measurement is 26 KPa, there is a 13% of discrepancy between those values, see figure 4.1.

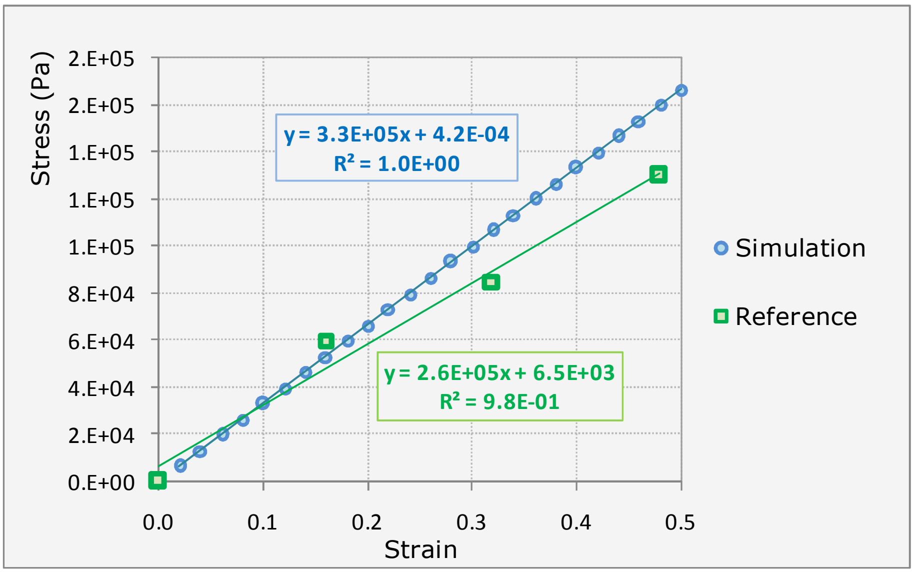

Figure 4.1 *linear fit for elastin driven mechanical resistance.*

Both, the simulation plot and the analog claves' artery, give as global artery elastic modulus 2 MPa for the collagen fibers driven phase, figure 4.2.

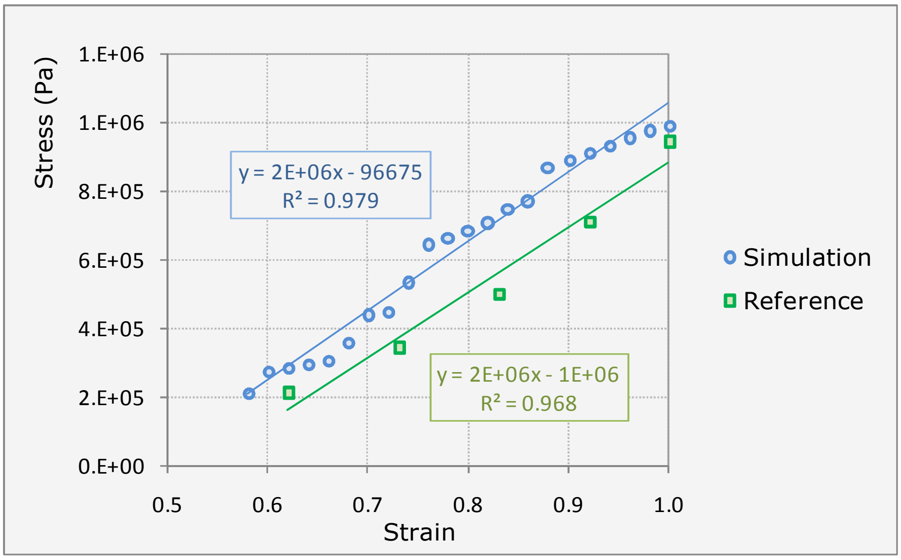

Figure 4.2 *linear fit for elastin driven mechanical resistance.*

4.4. Pressure-volume experiments

The same criteria were used in order to verify pressure-volume simulation results. The analog measurement control in this case was a stress-strain plot corresponding to a rat's small mesenteric artery reported in the paper by Adrian et. al. [21]

Sensitivity analysis

The best simulation parameters, for pressure-volume experiments found by the sensitivity analysis were:

- Load factor: 0.100
- Fiber diameter mean: 0.050 mm
- Fiber diameter SD: 0.050 mm
- Elastin modulus: 0.6 MPa
- Elastin rupture strain: 1.00
- Collagen modulus: 1.0 GPa
- Collagen uncoil strain: 0.15
- Collagen rupture strain: 0.65

Verification plot for pressure-volume

From the simulation data, at the toe (elastin driven) region, the global circular elastic modulus of artery is 0.14 MPa, while from rat artery characterization is 0.11 MPa, which means that there is a 25% of discrepancy between those values.

At the collagen driven region there is a good similarity between the plots, however, because of the curvature of the plots, a linear fit comparison is not representative.

Considering the obtained results in both deformation models, some facts are worth of remark:

- The best structure approach was for one layer
- There is a notorious difference in the standard deviation between axial and circular deformation modes, which may mean that the fiber bunches are

preferentially axially aligned.

- The range of extensibility in the circular deformation is greater than in axial deformation.

5. Conclusions

Arterial wall object oriented model

An object oriented model of arterial wall has been designed, implemented and verified. This model brings up into the world of tissue mechanics modeling the object oriented paradigm and, with that, the possibility to start evolutionary modeling of collagenous structures.

Despite that the purpose of the present work was not a pursue for accuracy on prediction, the obtained results were not just physically meaningful but insightful on exploring the best possible structure of adventitia fibrous network.

The truss arterial segment models that gave better results, in agreement with the established verification criteria, were: one layer, four rings for axial loading mode and one layer, three rings for pressure-volume mode.

Tacitly, it becomes remarkable the necessity to work on the inclusion of ground substance into the arterial wall model, surely relevant in order to use the model in the active behavior of artery, as the inclusion of a tunica media model too.

The verification results proved the importance of having stochasticity as an essential element when modeling real complex systems, as in the case of arterial wall. One fruitful strategy in order to include stochasticity into the models is the "permutation" between structural and dynamical disorder. This idea, becomes from the world of spin glass materials and was extensively worked in the author's masters' thesis [22].

The implementation of the model using UML gives the opportunity to explore these modeling paradigm advantages to implement and communicate interdisciplinary knowledge.

Simulation system

The implemented simulation engine, together with the object oriented arterial wall model, produced physically meaningful results. These results were in a general approach, close to the results obtained by experimental characterization of the considered specimens.

The idea of representing the mechanical identity of a complex system (a structure in the context of civil, mechanical and aerospace engineering) by a stiffness matrix is useful and intellectually beautiful. That idea, allows the researcher to take advantage of the linear algebra, and in general, modern algebra legacy.

The simulation engine program was composed by two nested procedures: one first level estimating the necessary applied load to produce a given whole segment strain, then calling the second level: a truss analysis procedure whose function was to propagate the calculated macro load across all the micro members of the truss and calculate the entire strain field. This two nest process was repeated at successive equal strain increments, producing after each iteration a stress-strain point.

A secondary contribution, but strategically important, of the present work is to bring up structural mechanics into the world of tissue and organs mechanics.

Simulation experiments

Despite that in the scope of the present work, predictability was not a main target, the obtained results were similar to the chosen verification controls.

The best simulation parameters, for axial loading found by the sensitivity analysis were:

- Load factor: 0.0015
- Fiber diameter mean: 0.050 mm
- Fiber diameter SD: 0.010 mm

- Elastin modulus: 0.2 MPa
- Elastin rupture strain: 1.00
- Collagen modulus: 50 MPa
- Collagen uncoil strain: 0.10
- Collagen rupture strain: 0.50

Also, in the axial case of loading, the global elastic modulus of artery from simulations was 30 kPa for the toe region, while from analog measurement was 26 kPa giving a 13% of discrepancy between those values.

In the case of pressure-volume deformation mode, the best simulation parameters found by the sensitivity analysis were:

- Load factor: 0.100
- Fiber diameter mean: 0.050 mm
- Fiber diameter SD: 0.050 mm
- Elastin modulus: 0.6 MPa
- Elastin rupture strain: 1.00
- Collagen modulus: 1.0 GPa
- Collagen uncoil strain: 0.15
- Collagen rupture strain: 0.65

In pressure–volume mode, from the simulation data at the toe (elastin driven) region, the global circular elastic modulus of artery was 0.15 MPa, while from rat artery characterization is 0.11 MPa, a 25% of discrepancy between these values.

The simulations results support the idea that computer simulation should become a strategically important tool to be used in activities where instrumentation is expensive or sometimes inexistent, as in the case of cell, and tissue engineering.

It is possible to realize, by the obtained results, the importance of sensitivity analyses in order to calibrate computer models of complex systems.

Of course, there is a lot of work in front of us in order to take full advantage of the ideas presented at the present work:

- Improve mathematical method to solve the deformation problem, possibly by implementing energy optimization algorithms
- Improve individual fiber models

- Implement 2D and 3D graphical outputs, mainly 3D representation of stress and strain fields
- In addition to already available dynamical disorder representation, it would be useful to introduce controlled structural disorder into the model.
- Execute further analog verification experiments
- And, what is most important, to introduce all this ideas into the clinical world. These ideas and methods will allow to explore a deeper level of control of arterial wall state, with this, to design more effective solutions and, less traumatic clinical interventions.

Epilogue

The present work just pretended to be a seed, but a fresh and fruitful seed.

After the lived experience by the author during the time that doing this thesis took, the best advice is that projects on complex system modeling should be teamwork, and mainly interdisciplinary teamwork.

Because of that necessary interdisciplinariety, culture: teamwork values, a common epistemological platform and a common knowledge representation language (as UML is) is a matter of transcendental and strategic importance.

There is no reversal for the humankind in the XXI century in order to deal with its emergent challenges: isolation is important (the analytical method) but is useless if not finished up by good integration. In the other hand, good integration will always preserve identity.

Philosophy, culture and humbleness are and always will be the root of humankind work in science and engineering

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