BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Pinsky, Peter Michael

eRA COMMONS USER NAME (credential, e.g., agency login): PINSKYPM

POSITION TITLE: Professor of Mechanical Engineering

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Wales, Swansea, UK	B.S.	06/1969	Civil Engineering
University of Toronto, Canada	M.S.	06/1971	Structural Mechanics
University of California, Berkeley	Ph.D.	06/1981	Computational Mechanics
University of California, Berkeley	Postdoctoral training	09/1982	Computational Mechanics

A. Personal Statement

My research interests lie at the intersection of biology, mechanics, biophysics and chemistry. I have a broad background in mathematical modeling, computational simulation and experimental characterization of biological tissues and systems including the middle ear and cochlea of the vertebrate ear, the human epidermis and transdermal drug transport, and the human cornea. A common thread in my work is the development of theories that bridge atomistic, molecular, and macroscopic scales with the goals of elucidating fundamental mechanisms of action and of creating predictive tools. I have lead several projects as PI or co-PI on university-, NSF- and NIH-funded grants and through which I have developed a number of modeling concepts that will be valuable for the proposed research and I have trained twenty four doctoral and post-doctoral students in my role as professor of mechanical engineering at Stanford University. My published research work on the human cornea has had a special focus on the mechanics of corneal tissue, including collagen-proteoglycan interaction and the mechanisms by which the anisotropic collagen organization underlies the shape and transparency of the cornea. This background is particularly relevant for the aims of the proposal since any constructed corneal analog must duplicate these features of the tissue. The theories of collagen and proteoglycan electro-mechanics that I developed and validated for the *in vivo* cornea can now be usefully transferred and adapted to understanding, predicting and optimizing collagenous stromal analogs *de novo*.

A brief summary of my primary research areas is as follows:

a. *Ocular mechanics:* Structural modeling of the collagen architecture based on x-ray diffraction and second harmonic-generated images; electrolyte properties of the corneal stroma; active ionic transport and stromal hydration; collagen-swelling interaction; molecular-level mechanics of glycosaminoglycans (GAGs) and the mechanics of corneal transparency; nutrient transport and metabolic processes; applications to corneal implants and laser surgery for vision correction; experimental studies in the mechanical behavior of corneal tissue; vitreous kinetics and retinal drug delivery.

b. *Mechanics of hearing:* Finite element modeling of acousto-mechanical coupling in the middle ear; mechanics of the tympanic membrane; multiscale modeling of hair-cell mechanics in the

inner ear including physical mechanisms for the activation of mechanically-gated ion channels; mechanics of lipid bilayer cell membranes and their interaction with the cytoskeleton.

c. *Multiscale modeling of transdermal drug delivery:* Molecular-to-macroscopic computational framework for the study of passive trandermal drug diffusion; theory of homogenization for effective diffusivity of the stratum corneum; finite element modeling of transdermal drug transport; drug delivery platform design.

1. X Cheng, PM Pinsky, (2013), "Mechanisms of self-organization for the collagen fibril lattice in the human cornea," Journal of The Royal Society Interface, 10 (87), DOI 20130512.
2. SJ Petsche, PM Pinsky, (2013), "The role of 3-D collagen organization in stromal elasticity: a model based on X-ray diffraction data and second harmonic-generated images," Biomechanics and Modeling in Mechanobiology, 12 (6), 1101-1113.
3. SJ Petsche, X Cheng, PM Pinsky, (2015), "A structural model for the in vivo human cornea including collagen-swelling interaction," Journal of The Royal Society Interface, 12 (109), 20150241.
4. S.J. Petsche, D. Chernyak, J. Martiz, M.E. Levenston and P.M. Pinsky, (2012), "Depth-Dependent Transverse Shear Properties of the Human Corneal Stroma," Investigative Ophthalmology and Visual Science, Vol. 53, No. 2, pp. 873-880.

B. Positions and Honors

Positions and Appointments

1982-1983	Assistant Professor of Engineering, Brown University
1984-1990	Assistant Professor, Department of Civil Engineering and Department of Mechanical Engineering (by courtesy), Stanford University
1990-1995	Associate Professor, Department of Civil Engineering and Department of Mechanical Engineering (by courtesy), Stanford University
1993-1996	Associate Professor, Department of Ophthalmology (by courtesy), School of Medicine, Stanford University
1995-present	Professor, Department of Mechanical Engineering and Department of Civil and Environmental Engineering (by courtesy), Stanford University Professor, Institute for Computational and Mathematical Engineering, Stanford University Member of Stanford Bio-X
1995-2014	Chair, Division of Mechanics and Computation, Department of Mechanical Engineering, Stanford University

Other Experience and Professional Memberships

Member	U.S. Association for Computational Mechanics.
Member	International Association for Computational Mechanics.
Member	American Academy of Mechanics.
Member	The Association for Research in Vision and Ophthalmology
Member	American Society of Cataract and Refractive Surgery
Member	European Mechanics Society
Member	European Society of Cataract & Refractive Surgeons
Member	Society for Industrial and Applied Mathematics.
Member	Society of Engineering Science

Industry consultant to: Abbott, AMO, VISX, KeraVision, AcuFocus, ReVision Optics

Honors

1983	NSF Research Initiation Award
1998	Elected Fellow, American Society of Mechanical Engineers
2002	Elected Fellow, International Association of Computational Mechanics
2000-	Editorial Board, Engineering Computations
2001	Editorial Board, Computer Methods in Applied Mechanics and Engineering
2003-	Editorial Board, Journal for Modeling in Ophthalmology, International Biomechanics
2003-	Editorial Board, International Biomechanics

C. Contribution to Science

1. *Model for Refractive Surgery* Refractive surgery aims to correct refractive defects of the eye by modifying the refractive surface of the cornea. Surgeons attempt to achieve the desired correction through a number of techniques that have included combinations of cutting, removing or adding to the corneal stroma. However, achieved refractive outcome may differ from the planned outcome because of mechanically-induced deformations in the tissue resulting from the surgery. This can be an acute issue in refractive surgery because of the exceptionally high precision required of the correction. The organization of the stromal collagen was beginning to be revealed by X-ray scattering studies and it was generally appreciated that stromal collagen was a crucial feature underlying both the cornea's shape and it's response to surgery. I was the first to propose and develop a continuum mechanics-based theory for the mechanics of the cornea which incorporated a quantitative description of collagen orientation over the cornea. The approach was based on employing the X-ray scattering data to define the probability of collagen orientation at each point in the cornea. The orientation probability was combined with a model for the collagen elasticity giving a prediction for the elastic anisotropy of the tissue. The theory was embedded in a computational model (finite element method) and provided the first truly predictive tool for refractive surgery. This early work laid the foundations for subsequent studies in which the three-dimensional organization of the stromal collagen was obtained by synthesizing data from X-ray scattering and second harmonic-generating imaging. Funding and selected findings are noted below.

    a. R01EY009284-03 (NEI) "Mechanical Modeling of Keratoplasty." Peter Pinsky (PI), 7/91-3/96.
    b. P.M. Pinsky and D.V. Datye, (1991), "A Microstructurally-Based Finite Element Model of the Incised Human Cornea," Journal of Biomechanics, Vol. 24, No. 10, pp. 907-922.
    c. P.M. Pinsky, D. van der Heide and D. Chernyak, (2005), "Computational modeling of mechanical anisotropy in the cornea and sclera," Journal of Cataract and Refractive Surgery, v.31, no.1, pp.136-145.
    d. SJ Petsche, PM Pinsky, (2013) "The role of 3-D collagen organization in stromal elasticity: a model based on X-ray diffraction data and second harmonic-generated images," Biomechanics and Modeling in Mechanobiology, 12 (6), 1101-1113.

2. *Corneal transparency.* The transparency of the human cornea depends on the regular lattice arrangement of the collagen fibrils and on the maintenance of an optimal hydration -- the achievement of both depends on the presence of stromal proteoglycans (PGs) and their linear sidechains of negatively charged glycosaminoglycans (GAGs). While the GAGs produce osmotic pressure by Donnan effect, the means by which they exert positional control of the lattice had not been clarified. In this study, a theoretical model based on equilibrium thermodynamics was used to describe restoring force mechanisms that control and maintain the fibril lattice and underlie corneal transparency. An electrostatic-based restoring force that results from local charge density changes induced by fibril motion, and an entropic elastic restoring force that arises from duplexed GAG structures that bridge neighboring fibrils, was postulated. The model allows for the possibility that fibrils have a GAG-dense coating which adds an additional fibril force mechanism preventing fibril aggregation. The model suggests that the electrostatic restoring force is dominant, with the entropic forces from GAG duplexes an order or more smaller. The effect of a random GAG organization was considered in a dynamic model of the lattice which incorporates randomness in both the spatial distribution of GAG charge and the topology of the GAG bridges. A striking result was that the electrostatic restoring forces alone are able to reproduce the image-based lattice distribution function for the human cornea, and thus dynamically maintain the short-range order of the lattice.

    a. Stanford University, "Connective tissue mechanics," 1124578-1-WXALFX (2010-2012)
    b. Cheng, PM Pinsky, (2013) "Mechanisms of self-organization for the collagen fibril lattice in the human cornea," Journal of The Royal Society Interface, 10 (87), DOI 20130512.

3. *Collagen-proteoglycan interaction and corneal swelling.* A structural model of the *in vivo* cornea which accounts for tissue swelling behavior, for the three-dimensional organization of stromal fibers, and for collagen-swelling interaction was proposed. This study was based on the recognition that the swelling behavior of the tissue cannot be modeled by any of the existing elastic theories. For the first time, this

study modeled the cornea as a binary electrolyte gel in thermodynamic equilibrium. To account for active endothelial ionic transport in the *in vivo* cornea, which modulates osmotic pressure and hydration, stromal mobile ions were shown to satisfy a modified Boltzmann distribution. The model was implemented in a finite element framework and employed to predict free and confined swelling of stroma in an ionic bath. For the *in vivo* cornea, the model is used to predict corneal swelling due to increasing IOP, and was adapted to model swelling in Fuch's corneal dystrophy. The biomechanical response of the *in vivo* cornea to a typical LASIK surgery for myopia was also analyzed, including tissue fluid pressure and swelling responses. The model provides a new interpretation of the corneal active hydration control mechanism and results illustrate the importance of fiber inclination in corneal stability.

a. SJ Petsche, X Cheng, PM Pinsky, (2015) "A structural model for the in vivo human cornea including collagen-swelling interaction," Journal of The Royal Society Interface, 12 (109), 20150241.
b. Winkler, Moritz; Shoa, Golroxan; Xie, Yilu; et al., (2013), "Three-Dimensional Distribution of Transverse Collagen Fibers in the Anterior Human Corneal Stroma," Investigative Ophthalmology & Visual Science 54 (12) 7293-7301.
c. S.J. Petsche, D. Chernyak, J. Martiz, M.E. Levenston and P.M. Pinsky, (2012), "Depth-Dependent Transverse Shear Properties of the Human Corneal Stroma," Investigative Ophthalmology and Visual Science, Vol. 53, No. 2, pp. 873-880.

4. *Cornea metabolic model*. The connection between the metabolic and biomechanical states of a tissue is a complex and open problem that is relevant for many tissues. In this study I proposed a multiphasic theory applicable to the human cornea with the goal of creating a fully three-dimensional theory. The model has three principal elements. The first is a diffusion-reaction model for cellular metabolism with reactions modeling aerobic respiration and anaerobic fermentation. The second element describes how metabolism-based ion production and active ion transport in the corneal endothelium modify the tissue osmotic pressure. Finally, the coupling between osmotic pressure and mechanical expansion of the tissue is addressed. The model has been shown to able to accurately predict corneal edema and oxygen depletion due to contact lens wear. To illustrate the interactions between metabolism and biomechanics under more extreme metabolic conditions, the model was used to predict the hypoxia and consequent swelling response of the cornea resulting from the introduction of an impermeable lamellar inlay (implant). The coupling of metabolism modeling with structural modeling represents a significant step with numerous clinical applications.

   a. P.M. Pinsky, (2014), "3-D modeling of metabolic species transport in the cornea with a hydrogel intrastromal inlay," Investigative Ophthalmology & Visual Science, 55(5), 3093-3106.
   b. Cheng, X and Pinsky, P.M. "A numerical model for metabolism, metabolite transport and edema in the human cornea," accepted, Computer Methods in Applied Mechanics and Engineering

5. *A theory for active ion transport in the human corneal endothelium.* The movement of fluid and solutes across biological membranes facilitates the transport of nutrients and maintains the fluid and osmotic pressures in biological systems. Understanding the pressure balances across membranes is crucial for studying fluid and electrolyte homeostasis in living systems, and is an area of active research. In this study, a set of enhanced Kedem-Katchalsky (KK) equations is proposed to describe fluxes of water and solutes across biological membranes, and is applied to analyze the relationship between fluid and osmotic pressures, accounting for active transport mechanisms that propel substances against their concentration gradients and for fixed charges that alter ionic distributions in separated environments. The equilibrium analysis demonstrated that the theory recovers the Donnan osmotic pressure and can predict the correct fluid pressure difference across membranes, a result which cannot be achieved by previously existing theories. The model suggested a new pressure mechanism in active membranes which had not been previously identified. I applied the model to study transendothelial fluid pressure in the *in vivo* cornea, which is crucial for maintaining the hydration and transparency of the tissue. The results showed the importance of the proposed pressure mechanism in mediating stromal fluid pressure and provided a new interpretation of the pressure modulation mechanism in the *in vivo* cornea.

   a. X. Cheng and P.M. Pinsky, (2015), "The Balance of Fluid and Osmotic Pressures across Active Biological Membranes with Application to the Corneal Endothelium," PLOS ONE 10(12), e0145422.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01DC007910 Steele (PI) 10/01/2005-06/30/2017
Three-Dimensional and Multiscale Organ of Corti Biomechanics
Multiscale modeling of hair-cell mechanics in the inner ear including physical mechanisms for the activation of mechanically-gated ion channels; mechanics of lipid bilayer cell membranes and their interaction with the cytoskeleton

Completed Research Support

Multiscale modeling the elasticity of the extracellular matrix
School of Engineering, Stanford University, October 2009 – September 2011
Goal: Investigations into the fundamental biomechanical properties of the extracellular matrix of connective tissue using a multi-scale modeling approach
Role: PI

Connective Tissue Elasticity: Bridging the Scales Between Chemical Morphology and Engineering Models
Stanford University, Bio-X Program, January 2009 – December 2011
Goal: To study and measure the molecular origins of connective tissue elasticity
Role: PI