Ecole Doctorale 352
Physique & Sciences de la Matière

Proposition de thèse en imagerie optique biomédicale & biomécanique

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Laboratory :

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Title:

Optical diagnosis of biomechanical properties of the human cornea: application to the early detection of keratoconus and to the identification of old keratoplasty.

Description :

The cornea, an essential organ of vision, mainly made up of collagen, possesses properties of transparency uncommon in biological matter (transmission coefficient of more than 90% in the visible). This transparency is mainly linked to a very regular structural organization of the corneal tissue (stroma), which also gives it very specific biomechanical properties. The DiMABio team of the Fresnel Institute has been interested in the optical properties of this tissue for several years in order to develop new tools for the diagnosis of corneal pathologies, in collaboration with the ophthalmology department of the APHM (Assistance Publique des Hôpitaux de Marseille) and the tissue bank of the EFS-Paca Corse (Établissement Français du Sang).

One of the major challenges in ophthalmology and ophthalmic surgery today is the non-invasive detection of certain corneal tissue anomalies. Some of these abnormalities result in a modification of the biomechanical properties of the stroma. In particular, a non-inflammatory pathology of the cornea, called keratoconus, is characterized by a progressive thinning and bulging of the cornea, accompanied in the advanced and severe stages by a significant deterioration of the visual capacity (myopia, pronounced astigmatism, complex uncorrectable aberrations, blur and loss of transparency, photophobia...). The search for suspected or sub-clinical keratoconus ("fruste" keratoconus) is an essential step in the pre-operative assessment of refractive surgery [1] in order to avoid the

occurrence of ectasia (irreversible deformation of the cornea) after the operation. With Lasik technology, for example [2], the incidence of postoperative ectasia is estimated to be between 0.013% and 0.935% for a worldwide annual number of operations >1M [3]. It is suspected that it results from the decompensation of subclinical keratoconus, accentuated by the stromal cutting and alteration of corneal biomechanics induced by laser surgery [4]. However, these early stage keratoconus remain particularly difficult to detect with the usual means of investigation (pachymetry measurements, Pentacam® analysis, standard optical coherence tomography...).
In addition, the detection and visualization in depth in the corneal stroma of remnants of scars from refractive surgery, for example, is another current challenge that the imaging techniques available in the office or in the ophthalmology department are not able to meet at the moment. This problem represents a challenge for the long-term follow-up of patients after surgery, but also for the selection, before transplantation, of corneal grafts which must be rejected in certain types of transplantation if the donor has undergone refractive surgery during his life.

In this clinical and scientific context, the proposed thesis aims at continuing the development of instruments for characterization and imaging of the cornea carried out within the Fresnel Institute for several years. The challenge of the thesis is to provide these instruments with a polarimetric sensitivity (i.e. to make them sensitive to the polarization of light, which is the direction of vibration of the electromagnetic wave). Indeed, the interactions between polarized light and matter are very dependent on the structural organization of the material when the latter presents an anisotropy in space, and can therefore inform on the arrangement of the tissue constituents in a non-invasive way. Furthermore, it is well known that optical anisotropy properties (typically linear birefringence) can be modulated under the effect of mechanical constraints. Thus, by providing a polarization-sensitive measurement capability, it should be possible to gain indirect, but non-invasive, access to certain biomechanical properties of the imaged/characterized tissues, which may shed light on the presence of keratoconus or scarring in the corneal stroma. Indeed, it has been established that keratoconus leads to a disorganization of the corneal stroma, with loss of the orthogonal arrangement of collagen fibrils [5].

The thesis project is thus divided into several work areas, covering optical instrumentation, experimental measurement campaigns, and multiphysical modeling (optical and biomechanical):

- First, the OCT (Optical Coherence Tomography) microscopy frame developed in the team [6] will be upgraded to provide polarimetric sensitivity. This laboratory instrument has a higher optical resolution than commercial systems (µm) and allows 3D imaging of the corneal structure. The objective is to complement the existing full-field OCT microscopy setup to allow polarimetric contrast measurements on biological samples provided by physician partners or the EFS. At the end of this step, we will have an instrument that could provide a fast and reliable way to detect remnants of refractive surgery scars on corneal grafts [7], or even the presence of keratoconus. This instrument will also allow for the continuation of the thesis work to feed the physical models developed and used by the DiMABio team to compare the local measurements with the "macroscopic" characterizations by scatterometry (resolved in angle and polarization) (see axes 2 & 3).

- In the same way, it will be relevant to develop the corneal diffusometry framework developed by the DiMABio team at CERIMED (European Center for Research in Medical Imaging) to make it sensitive to the polarization of the scattered field. This time, the aim is to characterize the organ as a

whole, without spatial resolution, by probing the field scattered by the cornea (in transmission, but also in reflection) when it is illuminated by a collimated beam tunable in wavelength. The scattered flux in all directions is measured with a fine angular resolution thanks to a goniometric architecture, and with a very high sensitivity (by using a synchronous demodulation) to access the weak backscatter fluxes. In order to operate a polarization resolved measurement with high sensitivity, a dual synchronous detection and rotating polarizer/analyzer approach could be considered.

- In a third step, we will accumulate OCT and scatterometry measurements on samples of keratoconus corneas, or corneas that have undergone refractive surgery (and of course on healthy corneas for validation). From the experimental database, it will be interesting to compare the OCT and diffusometry measurements resolved in polarization in order to see if the "global" diffusometry approach would be able to detect scars or keratoconus. This work will rely on the EFS and the AP-HM for the supply of samples of healthy and pathological corneas, and on the medical expertise of the doctors of the ophthalmology department of the AP-HM for the interpretation of the results. This part of the thesis will also include work on modeling the propagation of light in the tissues. Indeed, the three-dimensional structuring of the imaged corneas will be accessible thanks to the OCT measurements, allowing to propose a geometrical model of the organization of the corneal tissue [8] related to the considered pathology. Once this model is established, it will be possible to use electromagnetic or light scattering modeling tools (Monte-Carlo type), adapted to polarized light [9], to try to understand how this structuring affects the propagation in the presence of anomalies, and to identify the origin of the signatures measured in scatterometry.

- The last step of this thesis will consist in enriching the previous work with the modeling of the biomechanical behavior of the corneal tissue. Here again, the scientific objective will be to be able to link the mechanical constraints, potentially observed thanks to polarimetric imaging, with models of the deformation of the corneal tissue induced by keratoconus or a scar deep in the corneal stroma. For this, the expertise of the IRPHE laboratory in biomechanical modeling will be used to assist the PhD student in this study.

This thesis project constitutes an ambitious scientific objective for the understanding of the biomechanical properties of the cornea. It also has a strong applicative interest, as the early detection of keratoconus remains a major problem for ophthalmologists and for refractive surgery in particular. The results of this project could also be extended to other pathologies (corneal dystrophies, cornea guttata...), or for the evaluation of the effectiveness of drug treatments (anti-oedematous, cross-linking...)

References :

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[2] Moshirfar, Majid, Phillip Bennett, and Yasmyne Ronquillo. "Laser In Situ Keratomileusis." StatPearls [Internet]. StatPearls Publishing, 2021.

[3] Moshirfar, M., Tukan, A. N., Bundogji, N., Liu, H. Y., McCabe, S. E., Ronquillo, Y. C., Hoopes, P. C. Ectasia after corneal refractive surgery: a systematic review. Ophthalmology and Therapy, 10(4), 753-776, 2021.

[4] Vanathi, M., Azimeera, S., Gupta, N., & Tandon, R. (2020). Study on change in corneal biomechanics and effect of percent tissue altered in myopic laser-assisted in situ keratomileusis. Indian Journal of Ophthalmology, 68(12), 2964.

[5] Daxer, Albert, and Peter Fratzl. "Collagen fibril orientation in the human corneal stroma and its implication in keratoconus." Investigative Ophthalmology and Visual Science 38.1 (1997): 121-129.

[6] G. Latour, et al., “Full-Field Optical Coherence Microscopy in Ophthalmology”, Handbook for Full-Field Optical Coherence Microscopy: Technology and Applications, 2016.

[7] G. Latour, et al., “Human graft cornea and laser incisions imaging with micrometer scale resolution full-field optical coherence tomography”, J. Biomed. Opt., vol. 15, 056006, 2010.

[8] O. Casadessus, G. Georges, L. Siozade, C. Deumié, L. Hoffart. Light scattering from edematous human corneal grafts' microstructure: experimental study and electromagnetic modelization. Biomed. optics express, 3 (8), p. 1793-1810, 2012.

[9] Hind Oulhaj, Julien Wojak, Ugo Tricoli, Callum M. Macdonald, Vadim A. Markel, A. Da Silva. Diffuse Optical Tomography with polarized light: a GPU-accelerated polarization-sensitive Monte Carlo simulations for efficient Sensitivity Kernel computation. ECBO Conference, Jun 2019, Munich, Germany.

Estimated starting date of the thesis

Sept.-oct. 2023.

Required training

Engineering school and/or Master 2 graduate with a major in physics/optics and/or biomedical engineering.

Experience & skills

Good optical and modeling/programming skills are required.
Knowledge or interest in mechanics/biomechanics would be appreciated.
Programming: Matlab, Python, Labview.

How to apply

Send CV, transcripts, copies of diplomas, contact information for the Master's director and references for internship supervisors (especially M2)