# FSI simulations to study eye biomechanics during a Non Contact Tonometry

Elena Redaelli<sup>1</sup>, Begoña Calvo<sup>1,2</sup>, José Felix Rodríguez Matas<sup>3</sup>, Giulia Luraghi<sup>3</sup>, Jorge Grasa<sup>1,2</sup>

<sup>1</sup> Aragón Institute of Engineering Research (I3A), Universidad de Zaragoza, Spain
<sup>2</sup> C de Invest Biomecánica en Red en Bioingenieria, Biomateriales y Nanomedicina (CIBER-BBN)
<sup>3</sup> Dept. of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Italy.

#### Abstract

Understanding the corneal mechanical properties has great importance in the study of corneal pathologies and the prediction of refractive surgery outcomes. Non-Contact Tonometry (NCT) is a non-invasive diagnostic tool intended to characterize the corneal tissue response in vivo by applying a defined air-pulse. The development of a strong FSI tool amenable to model the NCT, applied to different structural and anatomical configurations, provides the basis to find the biomechanical properties of the corneal tissue in vivo. This paper presents a high-fidelity finite-element model of a patient-specific 3D eye for in-silico NCT. A fluid-structure interaction (FSI) simulation is developed to virtually apply a defined air-pulse to a patient-specific eye model comprising cornea, limbus, sclera, and humors. Three different methodologies are tested to model the humors and the best approach is chosen. Then, a Montecarlo simulation is performed varying both the parameters describing the mechanical behaviour of the corneal tissue and the IOP. The analysis reveals that the mechanical properties of the corneal tissue and the IOP are perfectly coupled. A stiffer material with a low IOP can give the same deformation result on the cornea as a softer material with an higher IOP.

#### 1 Introduction

The cornea is the outermost layer of the eye, responsible of 75% of the total refractive power [1]. The corneal optical capabilities are closely related to its mechanical properties [2], making an understanding of corneal mechanical behaviour crucial for studying ocular pathologies such as keratoconus and for predicting the outcomes of refractive surgeries [3]. The cornea is strictly connected to the aqueous humor, which is the filling fluid of the eye, pressurized at an intraocular pressure (IOP) between 8-30 mmHg. Non-Contact Tonometry (NCT) is a non-invasive diagnostic tool intended to measure the IOP and estimate the corneal mechanical properties in-vivo. It employs an high-velocity air-puff which induces a deformation of the cornea. Corvis ST® is a commercially available Non Contact Tonometer (Corvis, Oculus Optikgeräte GmbH, Wetzlar, Germany) that records the dynamic deformation of the cornea's equatorial plane using a Scheimpflug camera, capturing 140 horizontal 8 mm frames over 33 ms [1][4]. In this context, numerical simulations could be a powerful tool to study the NCT, and estimate in a more reliable way the IOP and the mechanical properties of the corneal tissue. Various approaches have been used to model the NCT, in particular to model the interaction between the air puff and the eye's structure. Initial studies used the structural finite element analysis (FEA) technique. In studies by Eliasy et al.[5] and Rahmati et al.[6], the eye was treated as the structural component with appropriate mechanical properties, while the air puff test was simulated using a time-dependent pressure. However, FEA modelling lacks correlation between external air pressure, corneal geometry, and mechanical properties of corneal tissue since the air pressure is considered equal in each patient. To address this limitation, other works [7][8][9] conducted computational fluid dynamic (CFD) analysis to determine the correct pressure profile to be applied to the corneal tissue. In those cases, the air was modelled as a fluid and the eye as a rigid body. Once the air pressure was detected from the CFD simulation, the deformable eye was loaded with the pressure profile derived from the CFD. However, in those simulations, the pressure profile was not modulated by the corneal mechanical properties as occurs in reality. Thus, fluid-structure interaction (FSI) analysis, combining the structural domain of the eye and the fluid domain of the air, gained significant interest. Ariza-Gracia et al. [10] demonstrated that FSI was the most suitable numerical approach for reproducing NCT. However, most of the current FSI studies still have limitations, such as considering a 2D model [10] or a limited fluid domain [11] [12]. Moreover, none of them considered the cornea's anisotropy. Recently, our group [13] proposed a methodology to model the NCT for an idealized 3D eye considering the anisotropic behaviour of the corneal tissue. In this paper, we present a high fidelity Fluid Structure Interaction simulation of the Corvis ST for a patient specific geometry of an eye and a Montecarlo simulation varying both the parameters describing the mechanical properties

of the corneal tissue and the IOP in order to study their influence on the deformation of the cornea during the air-puff.

#### 2 Materials and Methods

We present a strongly coupled, 2-way and boundary fitted FSI simulation which consists in a structural part modelling the eyeball and a fluid part modelling the air-jet. The structural part is solved through a dynamic implicit structural solver, whereas the air is modelled as an incompressible fluid and solved using the implicit ICFD solver. The simulations are performed on an Intel i9-10940X (3.30 GHz) using the release R14 of LS-DYNA (LSTC, Livermore CA, United States).

#### 2.1 Structural model

#### 2.1.1 Geometry

The 3D structural model is composed of cornea, limbus, sclera and humors. A patient specific corneal geometry is constructed based on data retrieved by Oculus *Pentacam*®. *Pentacam* is a topographer which creates an elevation map of the anterior and posterior surfaces of the cornea in the form of a point cloud. The available topographic data from *Pentacam* are usually limited to a corneal area between 8 and 9 mm in diameter, as shown in Figure 1.a. In order to achieve a 12 mm diameter cornea, the point cloud both of the anterior and the posterior surfaces are adjusted by means of Zernike polynomials (Fig. 1.b, 1.c) [14]. The patient specific model of the cornea is then linked to a model of limbus and sclera with averaged dimensions and the whole eye is meshed with hexahedral solid elements (Fig. 1.d) with full integration. The mesh is realized through the commercially available software *ANSA Pre Processor v22.01 (BETA CAE Systems, Switzerland)*.



Figure 1: a) Elevation data from Pentacam for the anterior and posterior surfaces of the cornea. b) Zernike coefficients found to adjust the Pentacam data. c) Reconstructed patient-specific corneal surfaces. d) Structural model of the eye.

#### 2.1.2 Constitutive Material models

The cornea and the limbus are modelled as anisotropic nearly incompressible hyperelastic materials to account for the influence of the collagen fibres composing the tissues. The cornea is composed of two families of collagen fibres perpendicular to each other [19], whereas the limbus is composed of one circumferential family of fibres. The Holzapfel Gasser Ogden strain energy function [15] is adopted for the whole thickness of the cornea and the limbus.

$$\Psi = C_{10} \cdot (\overline{l_1} - 3) + \frac{k_1}{2k_2} \sum_{i=4,6} e^{(k_2 \cdot (\overline{l_i} - 1)^2)} + \frac{1}{k} (J - 1)^2$$

where  $C_{10}$  is the material constant associated with the extracellular matrix behaviour,  $k_1$  is the material constant associated with the fibres stiffness and  $k_2$  with the fibres non linearity. k is the bulk modulus, in case of nearly incompressibility the parameter can be thought of as a penalty factor enforcing the incompressibility constraint. The material used to model the behaviour of cornea and limbo is set by means of the keyword **\*MAT\_ANISOTROPIC\_HYPERELASTIC** consisting of an isotropic nearly

incompressible Neo Hookean model (ITYPE = -1,  $\mu_1 = 2 \cdot C_{10}$ ,  $\alpha_1 = 2$ ) and an anisotropic nearly incompressible Holzapfel Gasser Ogden model (ITYPE = -1) without fibers dispersion (A=0, B=1). The same mechanical properties have been assumed for all families of fibres. The sclera is modelled as an isotropic hyperelastic material with a Neo Hookean strain energy density function by means of the keyword **\*MAT HYPERELASTIC RUBBER**.

$$\Psi = C_{10} \cdot (\overline{l_1} - 3) + \frac{1}{k}(J - 1)^2$$

#### 2.1.3 Humors modelling

The humors are incompressible fluids pressurized at a spatially homogenous intraocular pressure (IOP). We demonstrated in our previous publication [13] that the internal structures of the eye like the cristalline lens and the vitreous membrane, does not play a significant role in the deformation of the eye during the NCT. For this reason, the humors are modelled as a single chamber with the same IOP. Three methodologies to model the humors are tested.

- Constant pressure approach (Fig 2.a). The **\*SEGMENT\_SET** comprising the internal elements of the structure is loaded with a constant pressure (**\*LOAD\_SEGMENT\_SET**) during the whole duration of the simulation.
- Control volume approach (Fig 2.b). The humors are modelled as a fluid cavity, in particular shell control define the elements the boundary of volume and the keywords \*DEFINE CONTROL VOLUME and \*DEFINE CONTROL VOLUME INTERACTION are set in order to define the cavity and its interaction with the outside. Since the initial pressure of the cavity is zero, a positive input flow rate is imposed until the target IOP of 15 mmHg is reached. Then, the volume is closed, no flow is allowed to go in or out, and the humors behave as incompressible fluids.
- Lagrangian approach (Fig 2.c). The humors are modelled as a lagrangian part with mass, through a proper 3D mesh and material with the same properties of the water. In particular, the **\*MAT\_NULL** material is used associated with the equation of state **\*EOS\_GRUNEISEN**. The constants used in both the material and the equation of state are taken from *Ariza-Gracia et al.*[10].



Figure 2: Different approaches tested to model the humors.

#### 2.1.4 Zero pressure configuration

Since when the patient undergoes to Pentacam examination the humors are pressurized, the geometry of the eye presented in Fig. 1.d corresponds to the pressurized configuration. Therefore, in a first step of the simulation, the zero-pressure configuration of the eye need to be found. In our work we implemented in Python 3.6 the iterative algorithm described in *Ariza-Gracia et al.* [25].

#### 2.2 Fluid model

The air domain of the NCT is the same presented in our previous work [13] and depicted in Figure 3.a. It presents a nozzle with an inlet Gaussian air-puff velocity (with a maximum of 120 m/s during a period of 30 ms) at 11 mm from the corneal apex, that is the distance between the device and the eye as reported by the manufacturers. Zero pressure is imposed as an outlet boundary condition. The automatic volume mesher of the ICFD solver fills with tetrahedral elements the input meshed surfaces. 5 boundary layers are set at the FSI interface. The fluid is modelled with density and dynamic viscosity of the air. A turbulence model based on a variational multiscale approach is assumed. At the interface between the structure and the fluid a no-slip condition is adopted.

#### 2.3 Montecarlo simulation

Since the corneal mechanical properties and the IOP of the patient are not know a priori, a Montecarlo simulation is conducted in order to find the best combination of parameters which allows the simulation to have the same results as the clinical output. The range of mechanical properties and IOP are taken from *Ariza-Gracia et al.* [16]. A uniform distribution of parameters is assumed as shown in Figure 3.b since there is no a priori data on the dispersion of the mechanical parameters in the human cornea, and therefore a total ignorance about the population is assumed. A total of 100 simulations was carried out.



Figure 3: a. Fluid domain of the FSI simulation. b. Corneal material parameter and IOP used in the Montecarlo simulation. Count indicates the number of simulations in which each parameters assumed a value in a certain range.

# 3 Results and Discussion

# 3.1 NCT simulation

The simulation set up consists in a first phase in which the cornea undergoes pressurization from the zero pressure configuration and then, at 50 ms, the air puff is shot on the corneal surface. The cornea, during the NCT, undergoes a concave deformation and then returns to its original shape. The Corvis ST tonometer, from the analysis of corneal deformation, calculates some parameters to characterize the corneal response. The most important is the deflection amplitude [17], that is the displacement of the apex during the air-puff. The instant of highest concavity (HC) of the cornea is the instant when the highest deflection amplitude is achieved. The maximum air pressure over the apex corresponds with the instant of maximum concavity of the cornea as shown in Figure 4.a. The maximum air-pressure is located at the apex of the cornea to then decrease. The pressure is zero for a distance from the apex higher than 5.5 mm, meaning that from this position, the eye does not perceive directly the air jet, the pressure component is negligible, and the flow follows the eye shape as shown in Figure 4.b. In the instant of HC, there is a region where the air pressure is negative lending support to previous findings in the literature [7], [10], [18]. Negative pressure occurs if the fluid reflects from the corneal surface in the opposite direction to the flow, causing the change of concavity of the cornea in the deformed state. For this reason, a FSI simulation is necessary to model the NCT test. From a structural point of view, the cornea physiologically works in tension because it is subjected to the IOP. However, during the airpuff, the cornea undergoes bending, therefore its anterior surface changes its state of tension to a compression state, whereas the posterior surface carries on working under tension (Figure 4.c). This means that the collagen fibres in the anterior surface do not contribute to load bearing during most of the duration of the air-puff, relying in this case on the mechanical properties of the matrix under compression. On the other hand, the posterior surface works in tension and the fibres play a contribution in the deformation. The stress strain behaviour of the cornea during the air puff is shown in Figure 4.d. The difference behaviour in tension and compression reveals the contribution of the collagen fibers in tension. Corvis ST could be in fact a powerful tool to characterize the mechanical behaviour of the cornea in-vivo.



Figure 4: NCT results: a. air pressure and b. air velocity contours at the instant of highest concavity. c. First principal stress distribution in the anterior and posterior surfaces at the instant of highest concavity. d. Corneal material behaviour during the NCT simulation, the red line indicates tension state and the blue line compression state.

# 3.2 Humors modelling

When the air jet deforms the corneal surface, the intraocular pressure (IOP) increases due to the incompressibility of the internal fluids. The second and third approach tested, considering the humors as fluid cavity or as fluid with mass (lagrangian approach), exhibit an IOP increment close to 2-3 times the physiological IOP, consistent with [10]. The results in terms of corneal deformation reveal distinct patterns. Modeling the humors as a load leads to a higher deflection amplitude of the eye, as the internal pressure remains constant. Conversely, using a control volume or a Lagrangian approach shows a reduction of the deflection amplitude during the air puff. This implies that neglecting the incompressibility of the humors affects the maximum displacement of the cornea. Consequently, overlooking the incompressibility of the humors would result in an overestimation of corneal stiffness. For this reason, assuming a uniform pressure during the simulation of the NCT test is inaccurate. On the other hand, the lagrangian approach has a significantly higher computational cost if compared to the control volume. Since the results in terms of corneal deformation are similar, the control volume approach is used for the Montecarlo simulation presented in the following section.

#### 3.3 Montecarlo simulation results and comparison with clinical results

The Montecarlo simulation performed varying the mechanical properties of the corneal tissue and the IOP give as output the corneal deformation during the air puff. For each simulation, some of the biomarkers given as clinical output of the device are computed. In particular, the deflection amplitude, the peak distance and the apex velocity are analysed. Figure 5.a depicts the deflection amplitude calculated for the whole dataset of simulations and, in red, the clinical result for the patient considered. The clinical result is in the range of the numerical results, meaning that the parameters tested are able to describe the real behaviour of a human cornea. Looking at the deflection amplitude at highest concavity we find values between 0.6 and 2 mm (Figure 5.b), that is in the physiological range of Corvis. The deflection amplitude at HC for the patient analysed was 0.964 mm. There were 6

numerical cases with a difference lower than 5% with respect to the deflection amplitude at HC measured in clinics. For these six cases, the mechanical properties of the corneal tissue were analysed. In Figure 5.d the stress-strain behaviour of some elements of the cornea during the air puff is plotted. It is evident that in order to have the same deflection amplitude at HC, the stiffer mechanical behaviour of the tissue was associated with a lower IOP and viceversa. Looking at the other computed biomarkers for these six cases we did not find significant differences. Moreover, if we compare the deformed shape of the cornea in each simulation, the result is the same in the six cases. This analysis reveals that in a NCT simulation the mechanical properties of the corneal tissue and the IOP are perfectly coupled.



Figure 5: Results of the Montecarlo simulation. a. Deflection amplitude computed for each simulation, b. Value of the deflection amplitude at highest concavity (HC). c. Percentage difference between the numerical deflection amplitude at HC and the clinical deflection amplitude at HC. d. Analysis of the mechanical properties of the corneal tissue and of the IOP for the cases where the difference in the deflection amplitude is lower than 5%.

# 4 Conclusions

The FSI proposed is 2-way and strongly coupled, thus iteratively the solid mechanics solver transfers the displacements of the eyeball to the fluid solver while the fluid solver transfers the air pressure to the solid mechanics solver. Thanks to this interaction, it is possible to appreciate the negative pressure in correspondence to the corneal peaks at the instant of maximum concavity, thus the dependence of the pressure on the biomechanical behaviour of the eyeball tissues as shown in Figure 4.a.

The simulation corroborates the findings from *Ariza-Gracia et al.* [10] that the humors need to be modelled as a fluid-like material with a specific density when simulating a NCT test. Since the eye-ball is a closed system and the humors behave as an incompressible fluid, the deformation of the cornea during the air-puff causes an increase in the IOP up to a 50% of the nominal value. Corvis ST estimates the IOP at the first applanation time of the cornea. From the results of the Montecarlo simulation we found out an increase between 4% and 12% of the IOP at the time of first applanation. Actually, this increase is not taken into account and could be an improvement to be introduced in the device. The deformation of the cornea during the NCT is the result of the combination of different biomechanical factors, in particular the Montecarlo simulation performed reveals that the mechanical properties of the corneal tissue and the IOP are coupled in the corneal response to the air puff. These results demonstrate the interplay between the mechanical properties of the eye and the IOP and the importance of taking into account this interaction when interpreting the results from a NTC test.

The simulation make use of a patient specific geometry, for this reason it is reliable the comparison between the clinical data and the numerical data.

#### 5 Summary

The cornea plays a crucial role in the eye's optical capability since it accounts for 75% of its refractive power. Understanding the cornea's mechanical behavior is essential for studying eye pathologies and predicting outcomes of refractive surgeries. The cornea is closely connected to the humors, the eye's filling fluid pressurized at intraocular pressure (IOP) between 8-30 mmHg. Non-Contact Tonometry (NCT) is a non-invasive diagnostic tool that measures IOP and estimates corneal mechanical properties by using a high-velocity air-puff to deform the cornea. To study NCT more accurately, numerical simulations have been carried out; indeed, various approaches have been used to model NCT, including structural finite element analysis (FEA) and computational fluid dynamic (CFD) analysis. However, both methods have limitations, leading researchers to use fluid-structure interaction (FSI) analysis, which combines the eye's structural domain with the fluid domain of the air. Although this approach has shown promising results, current studies need to be improved. We propose a high-fidelity FSI simulation to model NCT for a patient-specific eye geometry, considering the anisotropic behavior of the corneal tissue. The simulations reveal the impact of modelling the humors with different methodologies on corneal deformation. Neglecting the incompressibility of the humors can lead to an overestimation of corneal stiffness; for this reason, assuming a uniform pressure during NCT simulation is inaccurate. The study also uses a Montecarlo simulation to find the best combination of corneal tissue mechanical properties and IOP that matches clinical results. The results demonstrates the coupling between corneal mechanical properties and IOP in the eye's response to the air-puff during NCT. In conclusion, the FSI simulation provides valuable insights into the biomechanics of the eye during NCT and emphasizes the importance of accurately modeling the humors and considering the interaction between corneal properties and IOP. A patient- specific approach together with a reliable comparison with clinical data make it a valuable tool for understanding corneal behavior and improving NCT interpretations.

#### 6 Acknowledgement

This project has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 956720.

#### 7 Literature

- J. Chong and W. J. Dupps, "Corneal biomechanics: Measurement and structural correlations," *Exp. Eye Res.*, vol. 205, no. November 2020, p. 108508, 2021, doi: 10.1016/j.exer.2021.108508.
- [2] F. J. Ávila, M. C. Marcellán, and L. Remón, "On the Relationship between Corneal Biomechanics, Macrostructure, and Optical Properties," *J. Imaging*, vol. 7, no. 12, 2021, doi: 10.3390/jimaging7120280.
- [3] S. Kling and F. Hafezi, "Corneal biomechanics a review," *Ophthalmic Physiol. Opt.*, vol. 37, no. 3, pp. 240–252, 2017, doi: 10.1111/opo.12345.
- [4] J. Hong *et al.*, "A new tonometer-the corvis ST tonometer: Clinical comparison with noncontact and goldmann applanation tonometers," *Investig. Ophthalmol. Vis. Sci.*, vol. 54, no. 1, pp. 659–665, 2013, doi: 10.1167/iovs.12-10984.
- [5] A. Eliasy *et al.*, "Determination of Corneal Biomechanical Behavior in-vivo for Healthy Eyes Using CorVis ST Tonometry: Stress-Strain Index," *Front. Bioeng. Biotechnol.*, vol. 7, no. May, pp. 1–10, 2019, doi: 10.3389/fbioe.2019.00105.
- [6] S. M. Rahmati, R. Razaghi, and A. Karimi, "Biomechanics of the keratoconic cornea: Theory, segmentation, pressure distribution, and coupled FE-optimization algorithm," *J. Mech. Behav. Biomed. Mater.*, vol. 113, no. September 2020, p. 104155, 2021, doi: 10.1016/j.jmbbm.2020.104155.
- [7] S. Muench, M. Roellig, E. Spoerl, and D. Balzani, "Numerical and Experimental Study of the Spatial Stress Distribution on the Cornea Surface During a Non-Contact Tonometry Examination," *Exp. Mech.*, vol. 59, no. 9, pp. 1285–1297, 2019, doi: 10.1007/s11340-018-00449-0.
- [8] B. A. Nguyen, C. J. Roberts, and M. A. Reilly, "Biomechanical impact of the sclera on corneal deformation response to an air-puff: A finite-element study," *Front. Bioeng. Biotechnol.*, vol. 6, no. JAN, pp. 1–8, 2019, doi: 10.3389/fbioe.2018.00210.
- [9] L. Huang, M. Shen, T. Liu, Y. Zhang, and Y. Wang, "Inverse solution of corneal material

parameters based on non-contact tonometry: A comparative study of different constitutive models," *J. Biomech.*, vol. 112, p. 110055, 2020, doi: 10.1016/j.jbiomech.2020.110055.

- [10] M. Á. Ariza-Gracia, W. Wu, B. Calvo, M. Malvè, P. Büchler, and J. F. Rodriguez Matas, "Fluidstructure simulation of a general non-contact tonometry. A required complexity?," *Comput. Methods Appl. Mech. Eng.*, vol. 340, pp. 202–215, 2018, doi: 10.1016/j.cma.2018.05.031.
- [11] O. Maklad, A. Eliasy, K. J. Chen, V. Theofilis, and A. Elsheikh, "Simulation of air puff tonometry test using arbitrary lagrangian–eulerian (ALE) deforming mesh for corneal material characterisation," *Int. J. Environ. Res. Public Health*, vol. 17, no. 1, 2020, doi: 10.3390/ijerph17010054.
- [12] I. Issarti, C. Koppen, and J. J. Rozema, "Influence of the eye globe design on biomechanical analysis," *Comput. Biol. Med.*, vol. 135, no. March, p. 104612, 2021, doi: 10.1016/j.compbiomed.2021.104612.
- [13] E. Redaelli, J. Grasa, B. Calvo, J. F. Rodriguez Matas, and G. Luraghi, "A detailed methodology to model the Non Contact Tonometry: a Fluid Structure Interaction study," *Front. Bioeng. Biotechnol.*, vol. 10, no. October, pp. 1–12, 2022, doi: 10.3389/fbioe.2022.981665.
- [14] J. Wang *et al.*, "Accuracy and reliability of orthogonal polynomials in representing corneal topography," *Med. Nov. Technol. Devices*, vol. 15, no. 270, p. 100133, 2022, doi: 10.1016/j.medntd.2022.100133.
- [15] G. A. Holzapfel, T. C. Gasser, and R. W. Ogden, "A new constitutive framework for arterial wall mechanics and a comparative study of material models," *J. Elast.*, vol. 61, no. 1–3, pp. 1–48, 2000, doi: 10.1023/A:1010835316564.
- [16] M. Á. Ariza-Gracia, S. Redondo, D. Piñero Llorens, B. Calvo, and J. F. Rodriguez Matas, "A predictive tool for determining patient-specific mechanical properties of human corneal tissue," *Comput. Methods Appl. Mech. Eng.*, vol. 317, pp. 226–247, 2017, doi: 10.1016/j.cma.2016.12.013.
- [17] V. S. De Stefano and W. J. Dupps, "Biomechanical diagnostics of the cornea," *Int. Ophthalmol. Clin.*, vol. 57, no. 3, pp. 75–86, 2017, doi: 10.1097/IIO.00000000000172.
- [18] O. Maklad *et al.*, "Fluid-Structure Interaction Based Algorithms for IOP and Corneal Material Behavior," *Front. Bioeng. Biotechnol.*, vol. 8, no. August, pp. 1–11, 2020, doi: 10.3389/fbioe.2020.00970.