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[Continued on next page]

(54) Title: IN VIVO CORNEAL MODELING

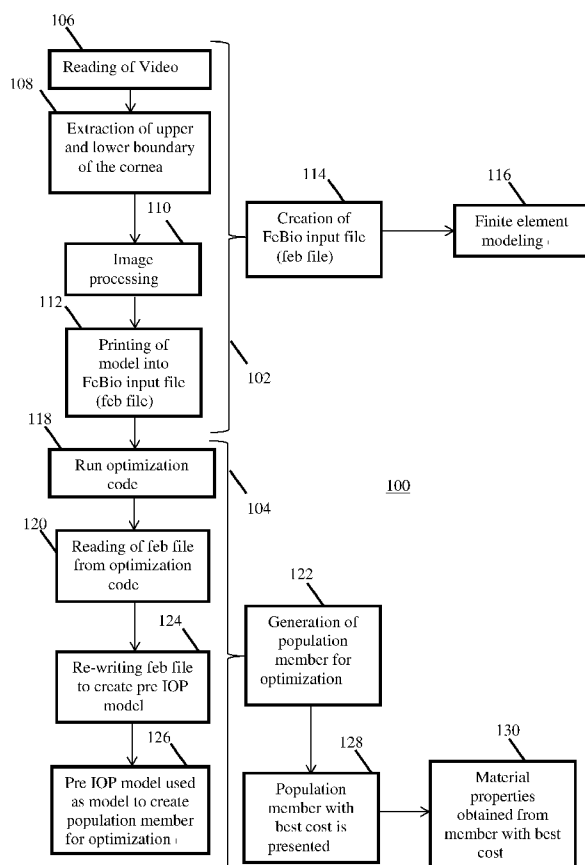


FIG. 1

(57) Abstract: A method for corneal diagnosis of a patient is provided. The method includes the steps of deforming a cornea of the patient by applying predetermined pressure to the cornea of the patient and recording images of the cornea of the patient in vivo when deforming the cornea until a time the cornea resumes its non-deformed shape.





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## **IN VIVO CORNEAL MODELING**

### **PRIORITY CLAIM**

**[0001]** This application claims priority from United States Provisional Patent Application No. 62/124,872 filed on January 5, 2015.

### **TECHNICAL FIELD**

**[0002]** The present invention generally relates to methods for in vivo corneal modeling, and more particularly relates to methods for three-dimensional in vivo corneal modeling.

### **BACKGROUND OF THE DISCLOSURE**

**[0003]** Evaluating corneal biomechanical properties can provide insights into understanding disease process and treatment modalities for blinding conditions such as glaucoma and corneal ectasias such as keratoconus. The cornea remains one of the most easily accessible tissues for mechanical testing in vivo. Similar to most collagenous tissues, it exhibits complex mechanical characteristics such as viscoelasticity (varying stiffness with rate of loading), anisotropy (varying stiffness with orientation), nonlinearity (varying stiffness with load), and heterogeneity (varying stiffness with location).

**[0004]** The Ocular Response Analyzer (ORA) is currently the only commercially available technology to provide some measure of corneal biomechanics in vivo. Although being available for clinical use, the ORA suffers from serious limitations. For example, it measures load-induced deformation at only a single site (i.e., the apex) of the cornea. In addition, the ORA only evaluates corneal viscoelasticity (indicated by the corneal hysteresis) and corneal rigidity (indicated by the corneal

resistance factor) by a single-value parameter which only grossly approximates the bulk tissue behavior. Even though it has been suggested that ORA parameters could become predictors of glaucomatous severity or other pathologies, it is clear that the information of corneal biomechanics provided by the ORA is incomplete.

**[0005]** Thus, what is needed is a method for in vivo corneal modeling which at least partially overcomes the drawbacks of present approaches and provides an improved measure of corneal biomechanics. Furthermore, other desirable features and characteristics will become apparent from the subsequent detailed description and the appended claims, taken in conjunction with the accompanying drawings and this background of the disclosure.

## SUMMARY

**[0006]** According to at least one embodiment of the present invention a method for corneal diagnosis of a patient is provided. The method includes the steps of deforming a cornea of the patient by applying predetermined pressure to the cornea of the patient and recording images of the cornea of the patient in vivo when deforming the cornea until a time the cornea resumes its non-deformed shape. The method also includes analyzing the images using image processing segmentation techniques to locate an upper boundary of the cornea and a lower boundary of the cornea, generating finite element nodes in response to the upper boundary and the lower boundary of the cornea, and rotating the finite element nodes across multiple angles to generate a three-dimensional corneal mesh. And the method further includes generating a three-dimensional model of the cornea in response to the three-dimensional corneal mesh and identifying material properties at various locations on

the cornea in order to treat the various locations on the cornea in response to the material properties identified at those locations.

### **BRIEF DESCRIPTION OF THE DRAWINGS**

[0007] The accompanying figures, where like reference numerals refer to identical or functionally similar elements throughout the separate views and which together with the detailed description below are incorporated in and form part of the specification, serve to illustrate various embodiments and to explain various principles and advantages in accordance with a present embodiment.

[0008] FIG. 1 illustrates a process flow for corneal biomechanical property determination in accordance with a present embodiment.

[0009] FIG. 2 illustrates a graphical user interface for corneal boundary identification during the process of FIG. 1 in accordance with the present embodiment.

[0010] FIG. 3 illustrates upper and lower corneal boundary determination during the process of FIG. 1 in accordance with the present embodiment.

[0011] FIG. 4 illustrates a graph of finite element node generation for the upper and lower corneal boundaries during the process of FIG. 1 in accordance with the present embodiment.

[0012] FIG. 5 illustrates a three-dimensional axisymmetric corneal mesh generated during the process of FIG. 1 in accordance with the present embodiment.

[0013] FIG. 6 illustrates three-dimensional model of the corneal generated by finite element analysis during the process of FIG. 1 in accordance with the present embodiment.

**[0014]** FIG. 7, comprising FIGs. 7A and 7B, illustrates an optimized model of the cornea during a first deformation phase generated by the process of FIG. 1 in accordance with the present embodiment, where FIG. 7A illustrates corneal deformation recorded at the first deformation phase during the process of FIG. 1 and FIG. 7B illustrates corresponding deformation at the first deformation phase of the optimized model of the cornea.

**[0015]** FIG. 8, comprising FIGs. 8A and 8B, illustrates an optimized model of the cornea during a second deformation phase generated by the process of FIG. 1 in accordance with the present embodiment, where FIG. 8A illustrates corneal deformation recorded at the second deformation phase during the process of FIG. 1 and FIG. 8B illustrates corresponding deformation at the second deformation phase of the optimized model of the cornea.

**[0016]** FIG. 9 illustrates a model of different layers of the cornea generated by the process of FIG. 1 in accordance with the present embodiment to allow description of the heterogeneous biomechanical behavior of the cornea.

**[0017]** FIG. 10 illustrates initial video recorded corneal images and resultant corneal modelling obtained by the process of FIG. 1 in accordance with the present embodiment.

**[0018]** And FIG. 11 illustrates a block diagram of a system for performing the process of FIG. 1 in accordance with the present embodiment.

**[0019]** Skilled artisans will appreciate that elements in the figures are illustrated for simplicity and clarity and have not necessarily been depicted to scale.

## DETAILED DESCRIPTION

[0020] The following detailed description is merely exemplary in nature and is not intended to limit the invention or the application and uses of the invention. Furthermore, there is no intention to be bound by any theory presented in the preceding background of the invention or the following detailed description. It is the intent of the present embodiment to present a method for corneal diagnosis of a patient by evaluating corneal biomechanical properties to understand disease process and treatment modalities for blinding conditions such as glaucoma and corneal ectasias such as keratoconus.

[0021] The cornea remains one of the most easily accessible tissues for mechanical testing in vivo. Similar to most collagenous tissues, it exhibits complex mechanical characteristics such as viscoelasticity (varying stiffness with rate of loading), anisotropy (varying stiffness with orientation), nonlinearity (varying stiffness with load), and heterogeneity (varying stiffness with location). In accordance with the present embodiment, measures of such mechanical characteristics for a given subject's cornea are provided. Two-dimensional and three-dimensional dynamic images of the cornea (transverse or sagittal plane) under deformation are recorded in vivo for a given human subject (i.e. a patient). Deformations are applied either with an air jet or a specific indenter (of known applied pressure and dimension).

[0022] Referring to FIG. 1, a process flow 100 illustrates the complete process in which the cornea's biomechanical properties can be derived in accordance with the present embodiment after two-dimensional cross-sectional images of the cornea (e.g., transverse plane images) are recorded. Prior to the illustrated process flow 100, a cornea of the patient is deformed by applying a predetermined pressure to the cornea

of the patient and an image of the cornea of the patient in vivo is recorded of the deforming of the cornea until a time the cornea resumes its non-deformed shape.

**[0023]** The process is split into two parts, a first part 102 dedicated to generation of a finite element model and a second part 104 comprising the optimization process. For the first part 102, a finite element software was used. An example of such software is FeBio software produced by the Musculoskeletal Research Laboratories, University of Utah, Salt Lake City, Utah, USA. Those skilled in the art will realize that this finite element software is not unique and that any other finite element software that uses syntax to code its input file would equally suffice.

**[0024]** In the second part 104, the optimization technique utilized was a differential evolution method, however those skilled in the art will realize that any other optimization technique (e.g. Genetic Algorithm) would also suffice. Furthermore, to aid the process in cornea boundary identification, a graphical user interface (GUI) was created on MATLAB obtainable from The MathWorks, Inc. of Massachusetts, U.S.A. A sample of the MATLAB GUI is shown as illustration 200 in FIG 2.

**[0025]** Through the use of a Corvis ST tonometer manufactured by Corvis ST, OCULUS of Wetzlar, Germany on the subject's cornea, a video of the deformation process is generated. The video is then analyzed at step 106 in MATLAB through the use of image processing segmentation techniques and, at step 108, an upper boundary 302 and a lower boundary 304 are identified from the video as shown in the illustration 300 of FIG. 3. Referring to FIG. 4, a graph 400 depicts the generation of finite element nodes 402 from the upper and lower boundaries. Specific image processing is done at step 110 (FIG. 1) to ensure that the cornea is centered, and the scale is correct. Nodes generation for finite element modelling can be either evenly spaced or spaced using a specific algorithm and the nodes 402 are generated from the



identified upper and lower boundaries. The three-dimensional graph 500 of FIG 5 shows the rotation of the nodes 402 across multiple angles to generate a three-dimensional axisymmetric corneal mesh. At steps 112 and 114, the three-dimensional corneal mesh is generated in a finite element software such as PreView or FeBio and a three-dimensional model is generated at step 116. The three-dimensional model 602 is depicted in the illustration 600 of FIG 6.

**[0026]** In the inverse finite element steps in the second part 104 of the process 100, differential evolution (DE) is used to optimize the cornea model. Following on from the finite element model generation at step 112, processing assumes that the material property of the cornea is assumed to fit the viscoelastic Veronda-Westmann model and runs a cost function as an optimization code 118. In the case of the cornea, the Veronda-Westmann model is especially applicable as it properly describes the nonlinear mechanical behavior of the cornea. Viscoelastic properties of the cornea can also be modeled by combining the Veronda-Westmann model with a quasi-linear viscoelastic description suitable for ocular soft tissues. This would add two additional parameters to be fitted to the experimental data, bringing a total of six parameters to fully describe the nonlinear, viscoelastic properties of the cornea. Those skilled in the art will realize that this constitutive model (Veronda-Westmann with or without a quasi-linear viscoelastic description suitable for ocular soft tissues) is not unique and that any other constitutive model capable of describing viscoelastic material properties would equally suffice. The generated results are c1 (first Veronda-Westmann coefficient), c2 (second Veronda-Westmann coefficient), K (bulk modulus),  $\gamma$  (viscoelastic coefficient) and  $\tau$  (relaxation times) and the cost function is shown in equation (1) below:

$$\varepsilon = \sum_{n_t} \sqrt{(x_m - x_v)^2 + (y_m - y_v)^2 + (z_m - z_v)^2} \quad (1)$$

where  $\varepsilon$  equals total error;  $n_t$  equals total number of nodes;  $x, y, z$  equal x position, y position and z position;  $m$  equals model and  $v$  equals video.

**[0027]** This cost function compares the positional error of each individual node between the model and the video generated from the Corvis ST tonometer. An error value is then given for each individual model. In differential evolution, each individual cornea model that is generated serves as a population member to be optimized at step 122. Each population member would hence possess five optimization parameters (i.e. the biomechanical properties) and a corresponding error value. The step 122 for population generation would repeat infinitely until either the minimum error cost that is required is reached or the maximum number of iteration steps has been attained. In the example used above, the scaling factor is  $F=0.5$ , the crossover constant  $CR=0.9$  and the population size  $NP=20$ . The range of value chosen for each parameter to be optimized is as follows,  $0 \leq c1 \leq 1 \times 10^5 \text{ Pa}$ ,  $0 \leq c2 \leq 1 \times 10^5 \text{ Pa}$  and  $0 \leq K \leq 1 \times 10^8$ ,  $0 \leq \gamma \leq 100$ ,  $0 \leq \tau \leq 1$ .

**[0028]** Prior to the generation of each population member at step 122, an additional step 124 is needed to ensure the accuracy of the model. Before acquiring deformational data of the cornea by recording images on the video, the intraocular pressure (IOP – the pressure within the eye) is already deforming the cornea. To increase accuracy, it is necessary to determine the pre-deformed cornea's shape before IOP is applied. This is done at step 124 through the use of a simple optimization step where a pre-deformed cornea shape is generated for each population member used in the differential evolution.

**[0029]** Step 126 would then generate population members and eventually evaluate each member to identify the member with the lowest cost ( $\varepsilon$ ) at step 128. FIG. 7 and FIG. 8 show two examples of the best model of the cornea that has the least cost

during the optimization process. Referring to FIGs. 7A and 8A, an image 700 and an image 800 respectively show the cornea 702 in the video at the 20/138 frame and the cornea 802 in the video at the 60/138 frame during deformation. Referring to FIGs. 7B and 8B, the images 720 and 820 respectively depict generated images of the cornea 722 and 822 at the exact same frames. The material properties of the cornea can then be obtained from the population member with the best cost at step 130. The material properties are obtained for the cornea as well as for various locations within the three-dimensional model of the cornea. Thus, if three-dimensional images of corneal deformations can be obtained, an anisotropic description of the mechanical properties using a formulation suitable for ocular soft tissues can be included.

**[0030]** Referring to FIG. 9, an illustration 900 shows the different layers 902, 904 of the cornea, and these layers can be modeled individually with a different constitutive model and its own sets parameter if required, thus allowing description of the heterogeneous biomechanical behavior of the cornea.

**[0031]** Referring to FIG. 10, results obtained from the method in accordance with the present embodiment are depicted in the table 1000. Each column contains four result sets, each result set including a Corvis ST tonometer video matched with a strain model and a stress model generated from the FeBio file. Column 1002 depicts four result sets from corneas of patients having open angle glaucoma. Column 1004 depicts four result sets from corneas of patients having angle closure glaucoma. Column 1006 depicts four result sets from corneas of patients having ocular hypertension. And column 1008 depicts four result sets from corneas of normal patients. The stress and strain of the models are shown depicting the difference between biomechanical properties of a diseased eye versus that of a healthy eye.

**[0032]** Referring to FIG. 11, a block diagram 1100 depicts a system in accordance with the present embodiment. A video camera 1102 acts as a recording device for recording images of an eye 1104 of a subject 1106 (e.g., a human patient) in vivo while deforming a cornea of the eye 1104 by applying predetermined pressure to the cornea, the video camera 1102 recording the images of the cornea while deforming the cornea until a time the cornea resumes its non-deformed shape. The images are provided from the video camera 1102 to a processor 1108 which performs the methodology as described above. Results of the biomechanical modeling can be displayed on a display 1110 or output in some other methods (e.g., printed on a printer).

**[0033]** Thus it can be seen that the methodology in accordance with the present embodiment has strong potential to help diagnose numerous ophthalmic pathologies in which biomechanics plays a critical role (e.g. glaucoma, keratoconus) through the determination of patient-specific corneal material properties and by identifying the material properties provide treatment. More specifically, the material properties identified at various locations on the cornea allows for patient-specific treatment at those various locations. For example, it is known that focusing ultraviolet light on the collagen of the cornea can increase the stiffness of the cornea. The methodology in accordance with the present embodiment can identify the material properties including stiffness properties at various locations on the cornea allowing for patient-specific ultraviolet treatment to stiffen only those locations of the cornea identified as having soft stiffness properties. In addition, knowledge of corneal biomechanics could guide surgical procedures (corneal transplants), and could help identify patients at risk for complications following refractive surgery. Further, the methodology in accordance with the present embodiment can identify a relationship between stress

and strain at various locations of the cornea, can identify corneal ectasias of the cornea, can identify glaucoma properties of the cornea and can identify lasik surgery suitability properties of the cornea, all of which can lead to development of patient-specific treatment plans in response to the identified material properties of the cornea.

**[0034]** The present methodology is translational in nature and could quickly be applied to corneal clinical practice. It could either be packaged as a user-friendly software for clinicians that have already acquired corneal deformation data and need corneal biomechanics estimates, or combined with a new device that can deform the cornea by air jet or other indentation and simultaneously image the resulting deformations in two dimensions or in three dimensions (e.g. with optical coherence tomography).

**[0035]** Thus, it can be seen that the present embodiment can provide an improved robust method for identifying material properties of a patient's cornea which overcomes the problems of prior methodologies. The present embodiment provides a novel system that is capable of determining biomechanical material properties of the cornea using various constitutive models (nonlinear, viscoelastic, anisotropic, heterogeneous constitutive models). It provides an invaluable research tool for understanding many common blinding conditions such as glaucoma and corneal diseases such as keratoconus and other corneal ectasias. The present embodiment can also provide an accurate and validated model of the cornea with minimal assumptions. Performing the method in accordance with the present embodiment generates a corneal FEM model that is patient-specific and created independently. Thus the biomechanical parameters can be used to monitor disease process over time and predict treatment efficacy.

[0036] While exemplary embodiments have been presented in the foregoing detailed description of the invention, it should be appreciated that a vast number of variations exist. It should further be appreciated that the exemplary embodiments are only examples, and are not intended to limit the scope, applicability, operation, or configuration of the invention in any way. Rather, the foregoing detailed description will provide those skilled in the art with a convenient road map for implementing an exemplary embodiment of the invention, it being understood that various changes may be made in the function and arrangement of steps and method of operation described in the exemplary embodiment without departing from the scope of the invention as set forth in the appended claims.

## CLAIMS

What is claimed is:

1. A method for corneal diagnosis of a patient comprising:
  - deforming a cornea of the patient by applying predetermined pressure to the cornea of the patient;
  - recording images of the cornea of the patient in vivo when deforming the cornea until a time the cornea resumes its non-deformed shape;
  - analyzing the images using image processing segmentation techniques to locate an upper boundary of the cornea and a lower boundary of the cornea;
  - generating finite element nodes in response to the upper boundary and the lower boundary of the cornea;
  - rotating the finite element nodes across multiple angles to generate a three-dimensional corneal mesh;
  - generating a three-dimensional model of the cornea in response to the three-dimensional corneal mesh; and
  - identifying material properties at various locations on the cornea in order to treat the various locations on the cornea in response to the material properties identified at those locations.
2. The method in accordance with Claim 1 wherein the recording step comprises recording a two-dimensional cross-sectional image of the cornea in vivo when deforming the cornea.

3. The method in accordance with either Claim 1 or Claim 2 wherein the generating finite element nodes step comprises generating evenly spaced finite element nodes in response to the upper boundary and the lower boundary of the cornea.

4. The method in accordance with either Claim 1 or Claim 2 wherein the generating finite element nodes step comprises generating finite element nodes in response to the upper boundary and the lower boundary of the cornea, the finite element nodes spaced apart in accordance with a predefined algorithm.

5. The method in accordance with any of Claims 1 to 4 wherein the identifying material properties step comprises identifying stiffness properties at various locations on the cornea in order to treat the cornea to increase a stiffness property of the cornea by focusing ultraviolet light on collagen at ones of the various locations determined to have soft stiffness properties.

6. The method in accordance with any of Claims 1 to 4 wherein the identifying material properties step comprises identifying a relationship of stress and strain at various locations on the cornea

7. The method in accordance with any of Claims 1 to 4 wherein the identifying material properties step comprises identifying corneal ectasias of the cornea.



8. The method in accordance with any of Claims 1 to 4 wherein the identifying material properties step comprises identifying glaucoma properties of the patient in response to the material properties of the cornea.

9. The method in accordance with any of Claims 1 to 4 wherein the identifying material properties step comprises identifying lasik surgery suitability properties of the cornea.

10. The method in accordance with any of Claims 1 to 4 wherein the identifying material properties step comprises identifying corneal complications following refractive surgery in response to the material properties identified at the various locations.

11. The method in accordance with any of Claims 1 to 4 wherein the identifying material properties step comprises identifying steps for corneal transplant surgery in response to the material properties identified at the various locations.

12. The method in accordance with any of Claims 1 to 11 wherein the step of generating the three-dimensional model of the cornea comprises:

generating a three-dimensional model of the cornea in response to the three-dimensional corneal mesh; and

optimizing the three-dimensional model.

13. The method in accordance with Claim 12 wherein the step of optimizing the three-dimensional model comprises optimizing the three-dimensional model by a differential evolution algorithm.

14. The method in accordance with either of Claim 12 or Claim 13 wherein the step of optimizing the three-dimensional model comprises optimizing the three-dimensional model in response to intraocular pressure.

15. A system for corneal diagnosis of a patient comprising:

a recording device for recording images of the cornea of the patient in vivo when deforming the cornea by applying predetermined pressure to the cornea of the patient until a time the cornea resumes its non-deformed shape;

a processor for analyzing the images using image processing segmentation techniques to locate an upper boundary of the cornea and a lower boundary of the cornea, generating finite element nodes in response to the upper boundary and the lower boundary of the cornea, rotating the finite element nodes across multiple angles to generate a three-dimensional corneal mesh, generating a three-dimensional model of the cornea in response to the three-dimensional corneal mesh, and identifying material properties at various locations on the cornea in order to treat the various locations on the cornea in response to the material properties identified at those locations.

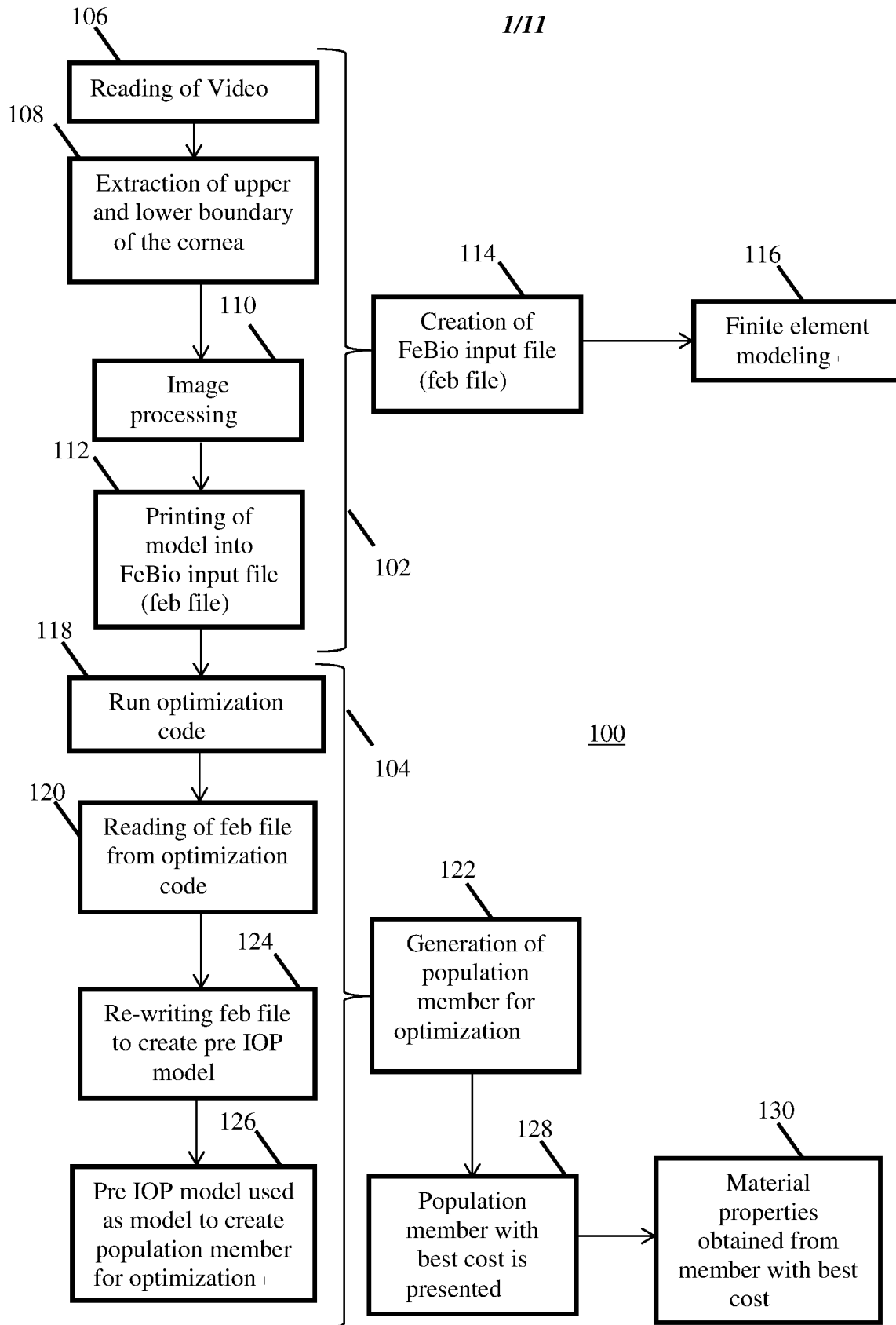
16. The system in accordance with Claim 15 wherein the recording device records a two-dimensional cross-sectional image of the cornea in vivo when deforming the cornea.

17. The system in accordance with either Claim 15 or Claim 16 wherein the processor generates evenly spaced finite element nodes in response to the upper boundary and the lower boundary of the cornea.

18. The system in accordance with either Claim 15 or Claim 16 wherein the processor generates finite element nodes in response to the upper boundary and the lower boundary of the cornea, the finite element nodes spaced apart in accordance with a predefined algorithm.

19. The system in accordance with any of Claims 15 to 18 further comprising an output device for outputting information identifying the material properties at various locations on the cornea.

20. The system in accordance with Claim 19 wherein the processor identifies a relationship of stress and strain at various locations on the cornea and wherein the output device outputs information identifying the relationship of the stress and the strain at various locations on the cornea.

**FIG. 1**

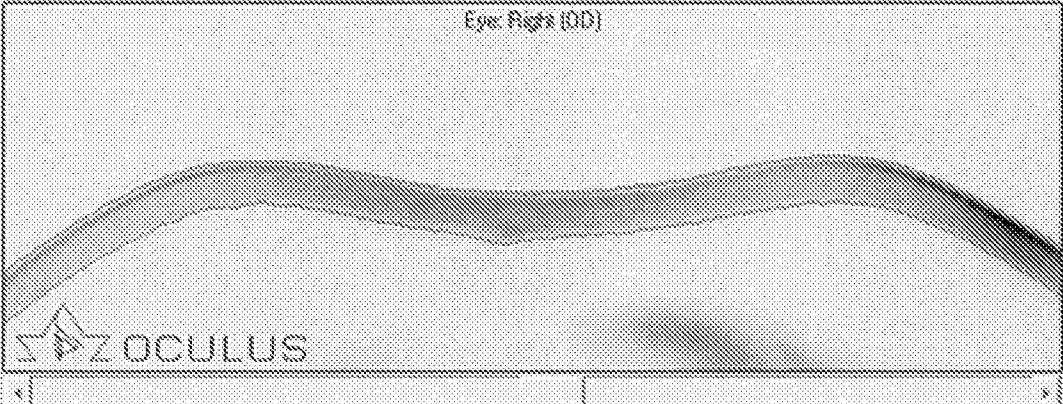
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**Initial Inputs**

| Required Inputs           |     | Viscoelastic Parameters |               |
|---------------------------|-----|-------------------------|---------------|
| Intraocular Pressure      | 8   | Viscoelasticity         | Yes           |
| Central Corneal Thickness | 0.5 | Gamma                   | $2.405039e-4$ |
| Chosen Name               | 13  | Tau S                   | $1.984552e2$  |
| Chosen Video              |     | Tau L                   | $2.081906e3$  |

Video Frame: 73      Magnetize: Yes

Eye: Right (OD)



Choose Boundary: Bottom      Fitted Boundary Plot: Yes

Fitting Options: Smoothing Spline      Smoothing Parameter [0-1]: 0.55

Automated Algorithm: Otsu Method      Automated Algorithm Plot: No

**Default Inputs**

|                    |           |                     |           |
|--------------------|-----------|---------------------|-----------|
| PESu Version       | 1.8       | Time step size      | 0.031878  |
| Run PESu           | Yes       | Density             | 1000      |
| Analysis Method    | Dynamic   | Radius of Apert     | $1.53e-3$ |
| Meshing Method     | Semi-Dome | Apert Pressure      | 8000      |
| Generate .xpt file | No        | Smoothing Parameter | 0.000001  |
| Density of x mesh  | 30        |                     |           |
| Density of y mesh  | 4         |                     |           |
| Density of z mesh  | 32        |                     |           |
| Mesh multiplier    | 1         |                     |           |
| Auto time stepper  | Yes       |                     |           |
| Model time step    | 1         |                     |           |
| Initial time step  | 1         |                     |           |

**Material Properties**

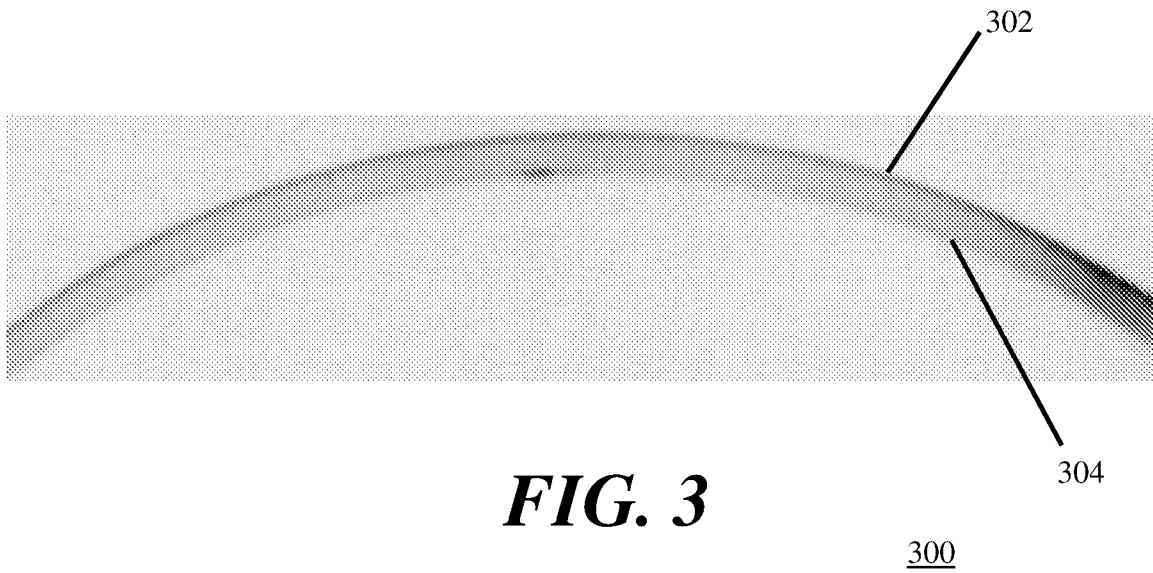
|              |                  |
|--------------|------------------|
| Material     | Veronda-Wastmann |
| C1           | 7438.923         |
| C2           | 9.17921          |
| Bulk Modulus | 13582290         |

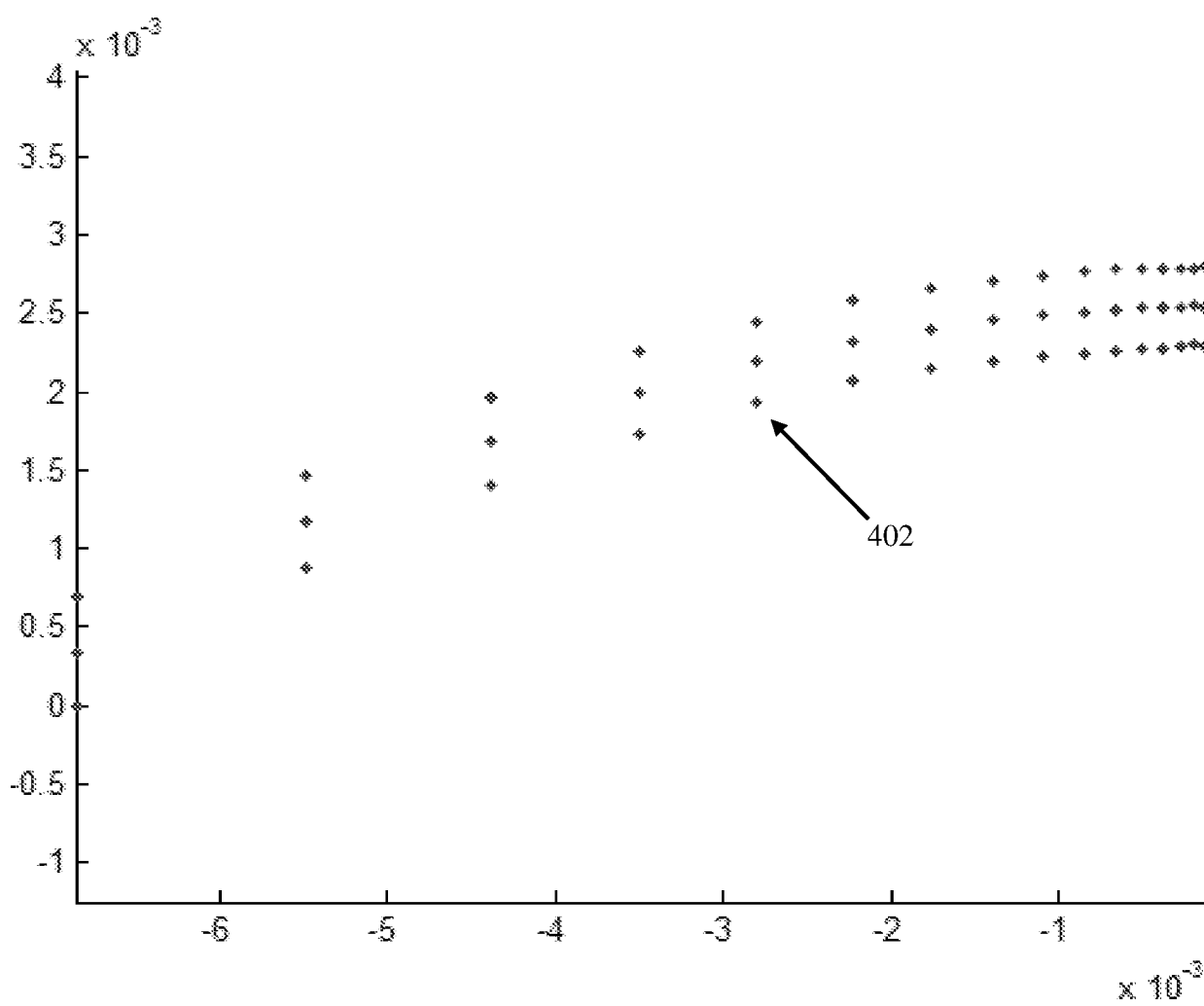
Run DE      Import data      Export data

200

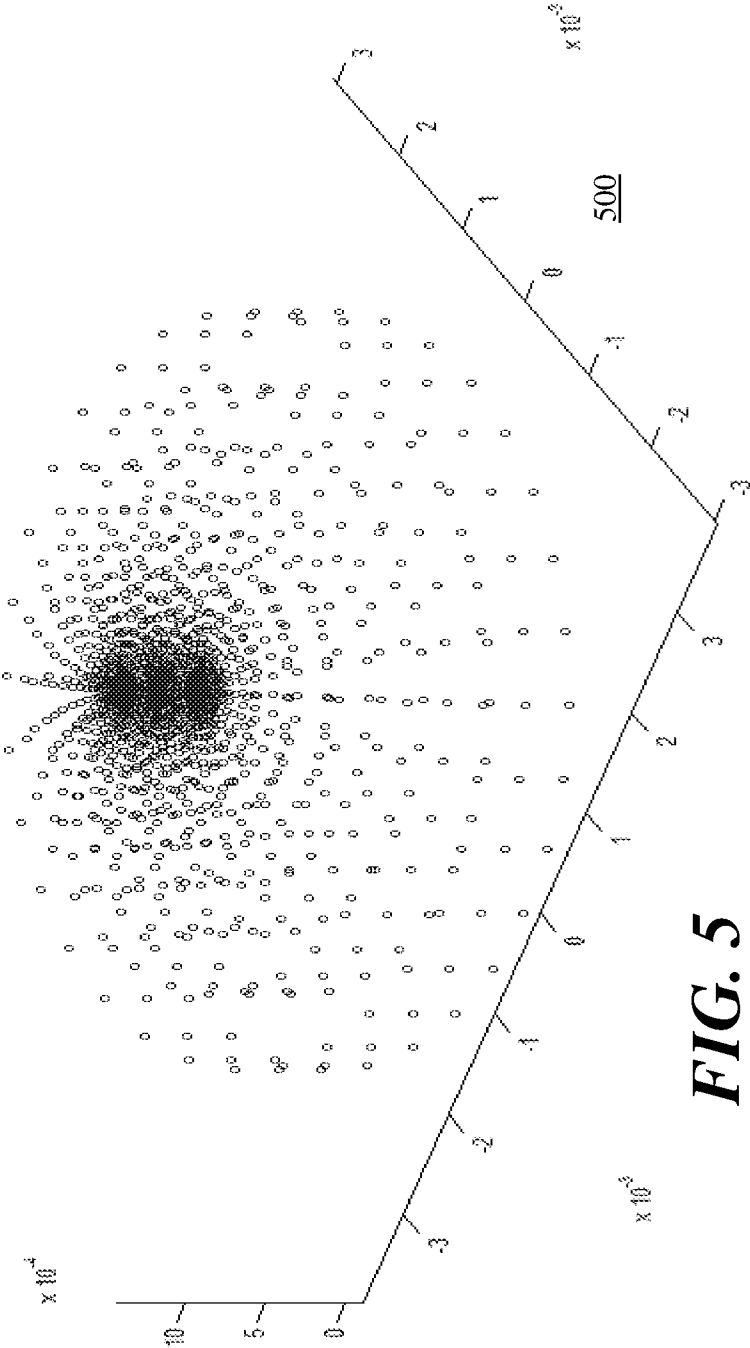
**FIG. 2**

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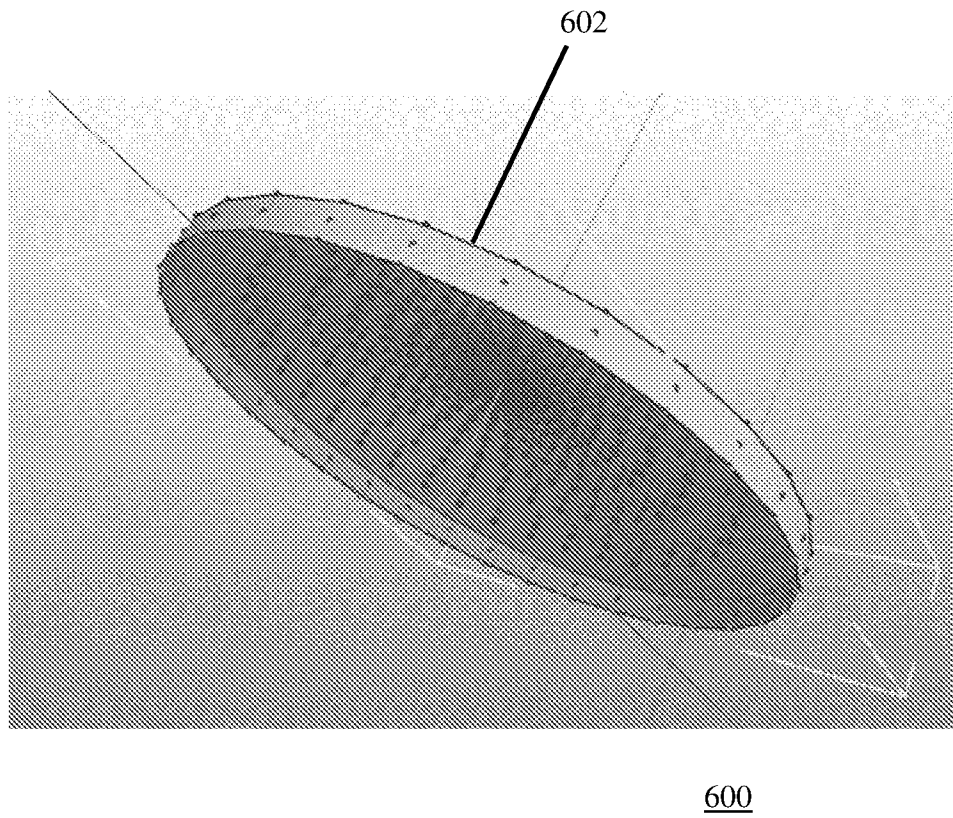


**FIG. 4** 400





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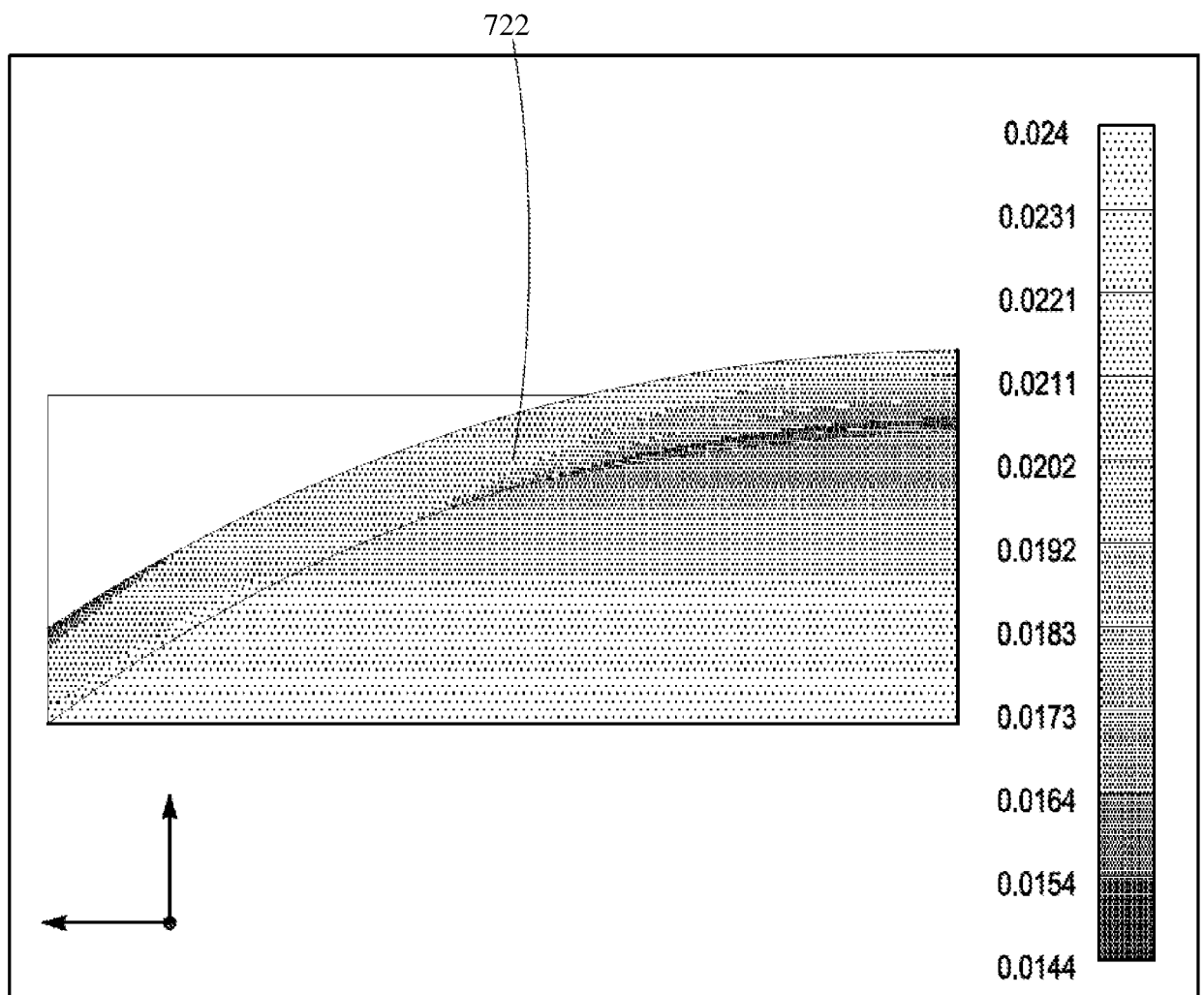


***FIG. 6***

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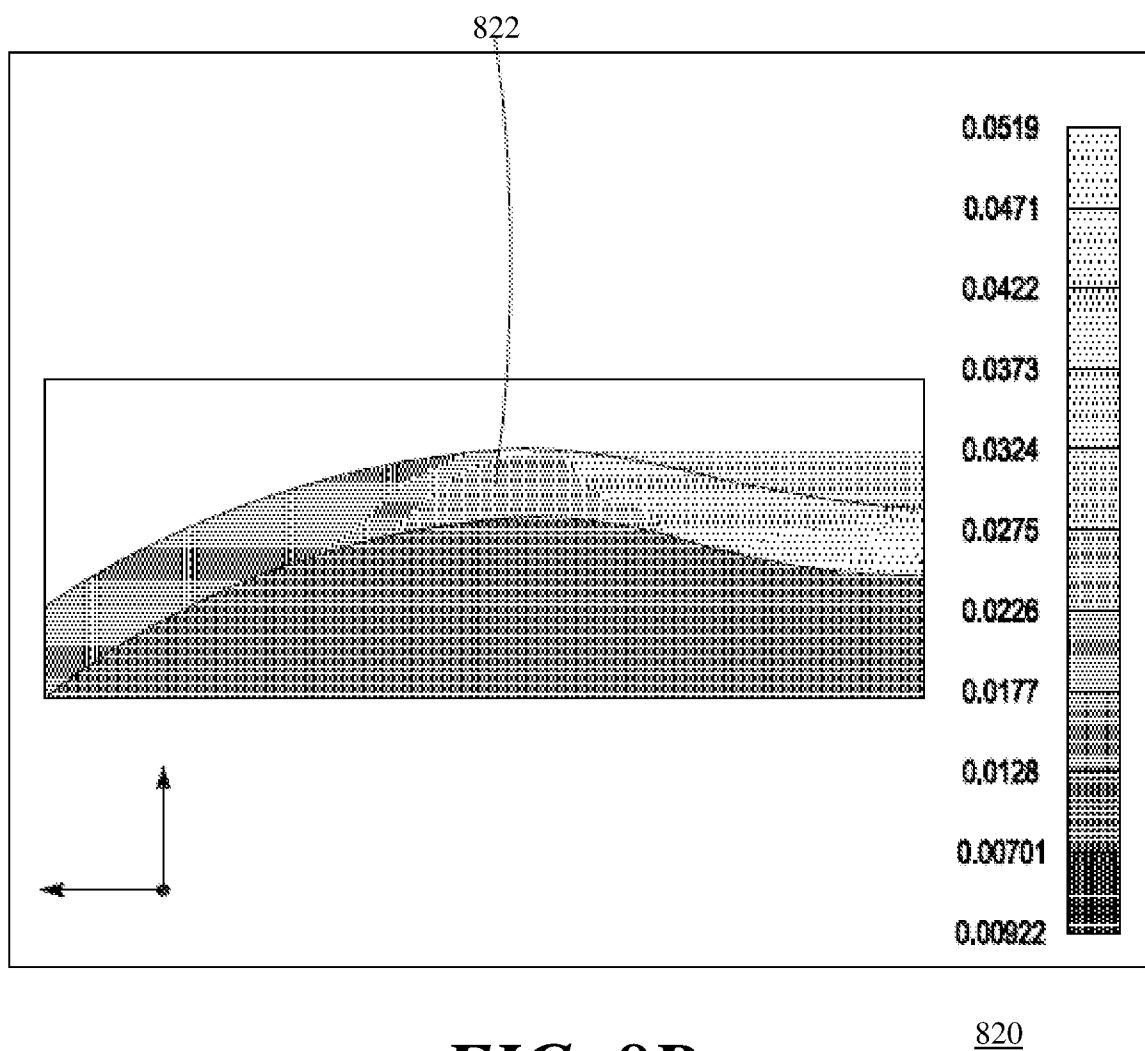
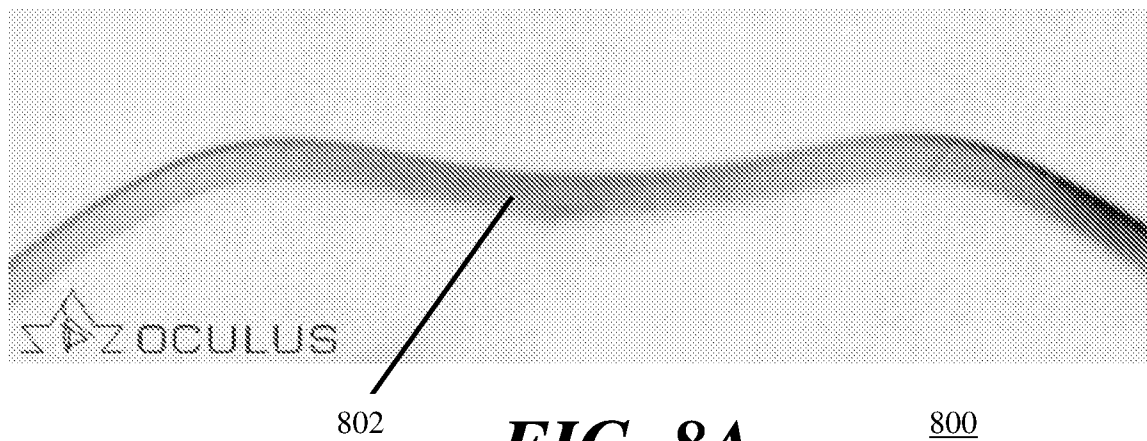
**FIG. 7A**



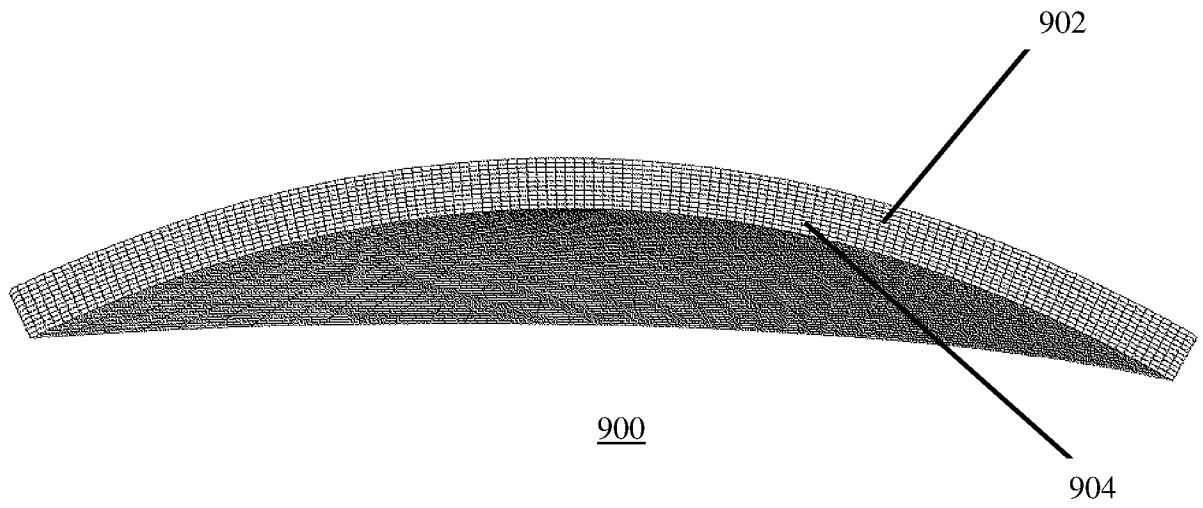
**FIG. 7B**

720

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***FIG. 9***

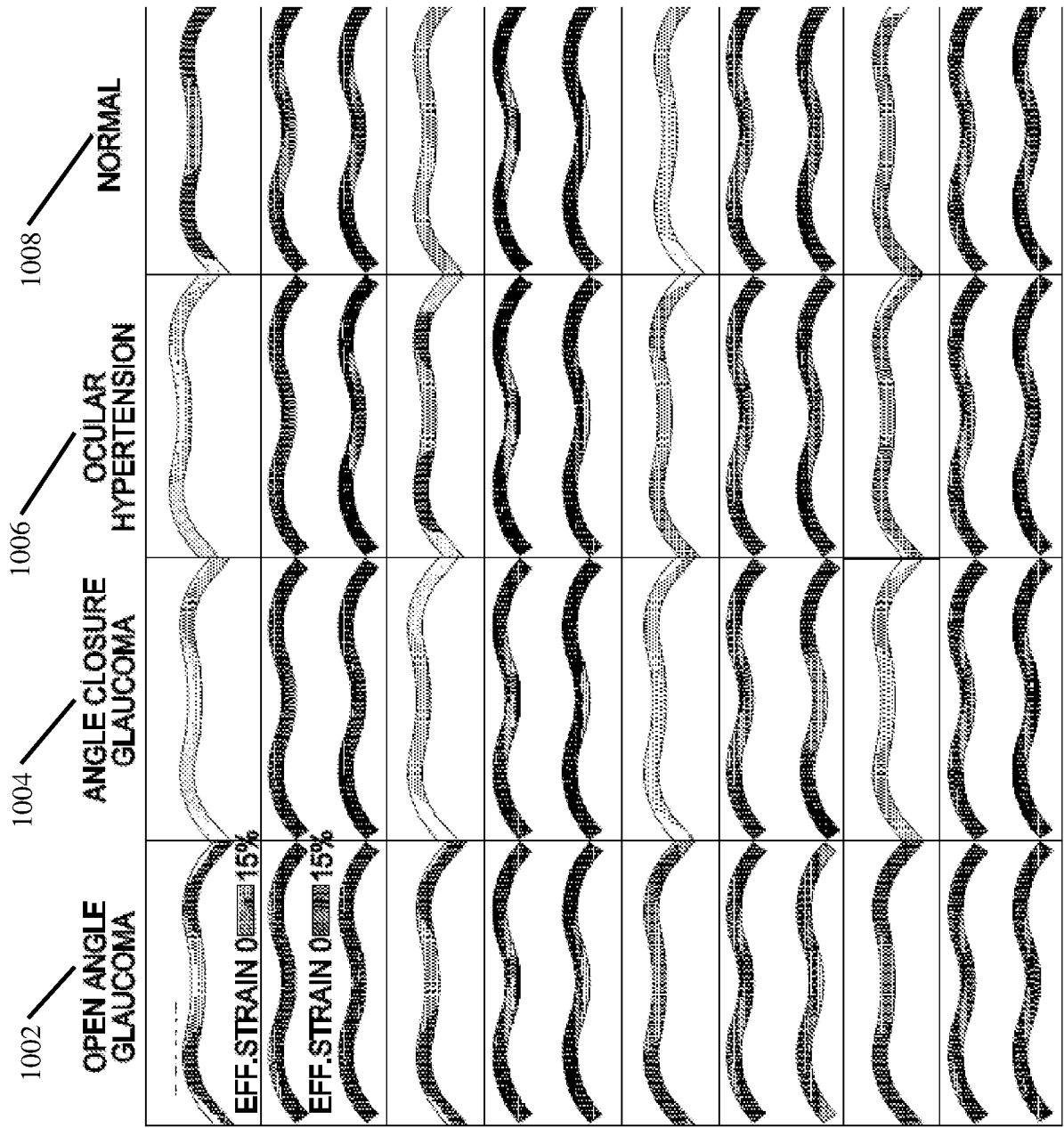
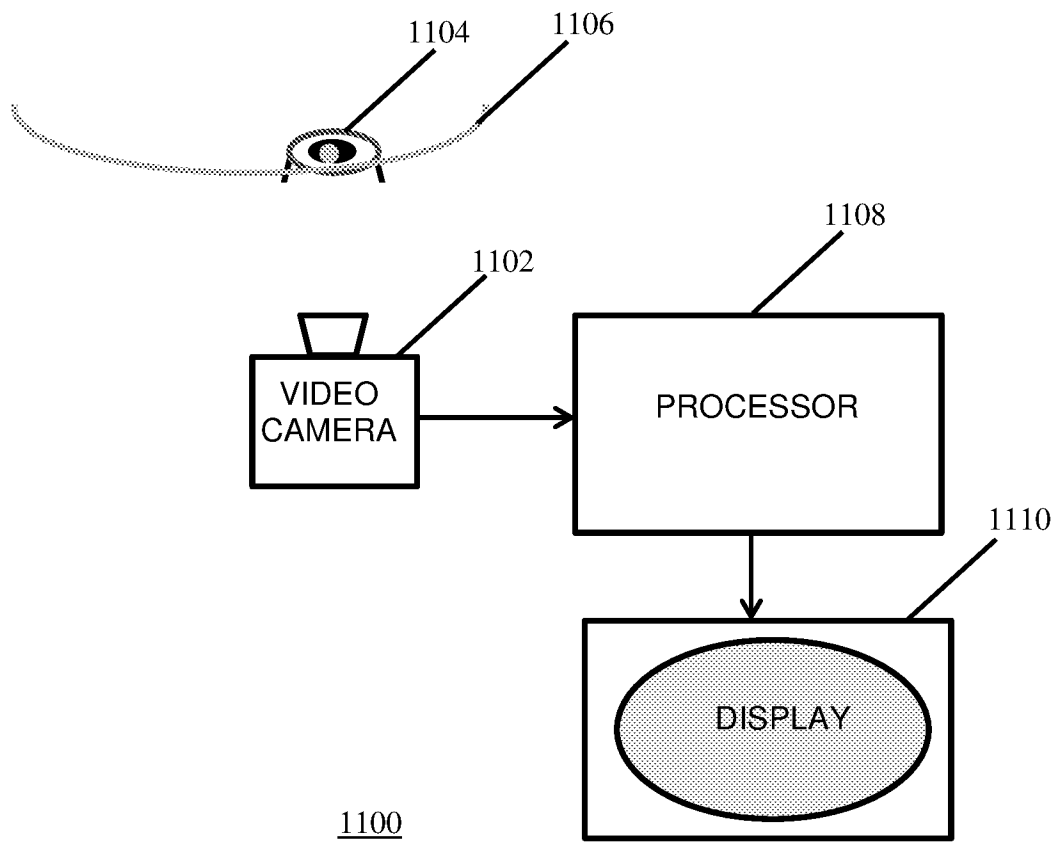


FIG. 10

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*11/11****FIG. 11***

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2016/050002

## A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. A61B3/16(2006.01) i, A61B3/14(2006.01) i

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl. A61B3/16, A61B3/14

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Published examined utility model applications of Japan 1922-1996  
 Published unexamined utility model applications of Japan 1971-2016  
 Registered utility model specifications of Japan 1996-2016  
 Published registered utility model applications of Japan 1994-2016

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                              | Relevant to claim No. |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | YAMADA, Kenji, et al., Dynamic Sensing of Cornea Deformation during an Air Puff, Journal of Control, Measurement, and System Integration, 2009.10.31, Vol.45 No.10, Page.495-501, ISSN0453-4654 | 1-20                  |
| A         | JP 2009-273715 A (ISII, koutarou) 2009.11.26, full text, all figs & US 2011/0118585 A1                                                                                                          | 1-20                  |



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

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Date of the actual completion of the international search

14.03.2016

Date of mailing of the international search report

22.03.2016

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