Proofreading Corrections

1. FORMATTING

All the mathematical symbols throughout the text need to be written inside a Word equation, as for example , , and . In this way we can be consistent between formulas and symbols in the text.

2. FORMATTING

The resolution of Table 1, Figure 1-7 is low, I uploaded online the high resolution corresponding image.

3. FORMATTING

The equations enumeration (like (1), (2), etc.) should be aligned with the right margin of the page.

**Authors**

4. CHANGE...

Einar Stefansson

TO...

Einar Stefánsson

5. CHANGE...

School of Medicine, Indianapolis, IN,USA;

TO...

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6. CHANGE...

LABEX Institut de rechercheenmathématiques, interactions et applications,

TO...

LABEX Institut de Recherche en Mathématiques, Interactions et Applications,

7. CHANGE...

KatholiekeUniversiteit

TO...

Katholieke Universiteit

8. CHANGE...

HospitalarLisboa

TO...

Hospitalar Lisboa

**Abstract**

9. CHANGE...

In this study,a theoretical mathematical model

TO...

In this study, a theoretical mathematical model

10. CHANGE...

glaucoma patientsand is used to propose possible

TO...

glaucoma patients and is used to propose possible

11. CHANGE...

primary open angle glaucoma (POAG, IOP > 21mmHg) patientsand advanced normal tension glaucoma (NTG, IOP ≤ 21mmHg)

TO...

primary open angle glaucoma (POAG, IOP > 21 mmHg) patients and advanced normal tension glaucoma (NTG, IOP ≤ 21 mmHg)

12. CHANGE...

or a decrease in Krogh cylindertissue width(d)

TO...

or a decrease in Krogh cylinder tissue width ()

13. CHANGE...

or a decrease in dis more likely to yieldthe increased venous saturation levels observed in POAG patients,

TO...

or a decrease in is more likely to yield the increased venous saturation levels observed in POAG patients,

14. CHANGE...

dis more likely to yield the increased venous saturation levels observed in NTG patients.

TO...

is more likely to yield the increased venous saturation levels observed in NTG patients.

15. CHANGE...

The model predictions are used to hypothesize that a decrease in oxygen demand might be more relevant to explain the increase in venous saturation observed in advanced POAG, while impairment in autoregulation mechanisms might be more relevant to explain the increase in venous saturation observed in advanced NTG.

TO...

The model predictions are used to hypothesize that a decrease in oxygen demand might be more relevant to the increase in venous saturation observed in advanced POAG, while impairment in autoregulation mechanisms might be more relevant to the increase in venous saturation observed in advanced NTG.

**1 Introduction**

16. CHANGE...

however, alterations inthe retinal blood oxygen saturation levels of glaucomatous patients have been observed.3-6Also, blood flow

TO...

however, alterations in the retinal blood oxygen saturation levels of glaucomatous patients have been observed.3-6 Also, blood flow

17. CHANGE...

topropose possible explanations for the increases

TO...

to propose possible explanations for the increases

18. CHANGE...

patient-specific levels of tissue oxygen demand orKrogh tissue width (herein referred to as “tissue width”)that

TO...

patient-specific levels of tissue oxygen demand or Krogh tissue width (herein referred to as “tissue width”) that

19. CHANGE...

(MAP = (2\*DBP+SBP)/3), where DBP is diastolic blood pressure and SBP is systolic blood pressure)

TO...

(MAP = (2\*DBP+SBP)/3, where DBP is diastolic blood pressure and SBP is systolic blood pressure)

**2 Methods**

**2.1 Experimental data**

20. CHANGE...

74 glaucoma patientsof age 40 years or older were collected

TO...

74 glaucoma patients of age 40 years or older were collected

21. CHANGE...

using a Goldmannapplanationtonometry mounted

TO...

using a Goldmann applanation tonometry mounted

**2.2 Mathematical model**

22. IN FIGURE 1 CAPTION CHANGE...

central retinal vein (CRV):Large arterioles/arteries (LA),

TO...

central retinal vein (CRV): Large arterioles/arteries (LA),

23. CHANGE...

The subscriptsused in Table 1 indicate if the quantity

TO...

The subscripts used in Table 1 indicate if the quantity

24. CHANGE...

For a complete description of the model we refer to a previous study by Arciero *et al..*23

TO...

For a complete description of the model we refer to a previous study by Arciero *et al.*23

25. IN TABLE 1 CAPTION CHANGE...

Summary of model23 variables and equations (sections b – f), including input (section a) and output (section g) data.

TO...

Summary of model23 variables and equations (sections b – f), including input (section a) and output (section g) data.

26. IN TABLE 2, LEFT PART 3nd LINE 1stCOLUMN, CHANGE...

TO...

27. IN TABLE 2, LEFT PART 5th LINE 1st COLUMN, CHANGE...

TO...

28. IN TABLE 2, LEFT PART 6th LINE 1st COLUMN, CHANGE...

TO...

29. IN TABLE 2, LEFT PART 7th LINE 1st COLUMN, CHANGE...

[]

TO...

[]

30. IN TABLE 2, RIGHT PART 5th LINE 1st COLUMN, CHANGE...

TO...

31. IN TABLE 2, RIGHT PART 5th LINE 2nd COLUMN, CHANGE...

8

TO...

8

AND 5th LINE 3rd COLUMN CHANGE...

1.31

TO...

1.31

32. IN TABLE 2, RIGHT PART 6th LINE 1st COLUMN, CHANGE...

TO...

33. FORMATTING

In Table 2, the left and the right part need to be divided by an empty column, with no lines and no color.

34. IN TABLE 3, 5th LINE 1st COLUMN, CHANGE...

discharge hematocrit,

TO...

discharge hematocrit,

35. IN TABLE 3, 6th LINE 1st COLUMN, CHANGE...

rate of ATP degradation,

TO...

rate of ATP degradation,

36. IN TABLE 3, 7th LINE 3rd COLUMN, CHANGE...

[]

TO...

[]

37. IN TABLE 3, 8th LINE 1st COLUMN, CHANGE...

effect of oxygen saturation on ATP release,

TO...

effect of oxygen saturation on ATP release,

38. IN TABLE 3, 9th LINE 1st COLUMN, CHANGE...

oxygen capacity of red blood cells,

TO...

oxygen capacity of red blood cells,

39. IN TABLE 3, LAST LINE 1st COLUMN, CHANGE...

length constant for , ,

TO...

length constant for ,

40. IN TABLE 4, 2nd LINE 1st COLUMN, CHANGE...

number of segments,

TO...

number of segments,

41. IN TABLE 4, 3rd LINE 1st COLUMN, CHANGE...

segment length,

TO...

segment length,

42. IN TABLE 4, 4th LINE 1st COLUMN, CHANGE...

viscosity,

TO...

viscosity,

43. CHANGE...

viscosity μ to vessels in each compartment according to an experimental in vivo relationship24(Table 4)

TO...

viscosity to vessels in each compartment according to an experimental in vivo relationship24 (Table 4)

44. CHANGE...

generated in the vessel

TO...

generated in the vessel

45. CHANGE...

function which results from a linear

TO...

function which results from a linear

46. FORMATTING

In page 8 there is an empty line before the enumerated list in page 8, but there is no empty line after the list.

47. CHANGE...

Details are provided inTable 1(c), where

TO...

Details are provided in Table 1(c), where

48. CHANGE...

drop along each segment of the ith compartment

TO...

drop along each segment of the th compartment

49. CHANGE...

blood flow in each segment of the ith compartment,

TO...

blood flow in each segment of the th compartment,

50. CHANGE...

resistance to flow offered by a single segment of the ith compartment.

TO...

resistance to flow offered by a single segment of the th compartment.

51. CHANGE...

*shearstressmechanism*,relatedtothewallshearstressτicomputedaccordingto

TO...

*shear stress mechanism*, related to the wall shear stress computed according to

52. CHANGE...

ATP concentration at each position x along the network TO...

ATP concentration at each position along the network

53. CHANGE...

*carbon dioxide mechanism*, related to the signal .

TO...

*carbon dioxide mechanism*, related to the signal .

54. CHANGE...

where the signal is given by the nonlinear function f of the partial pressure

TO...

where the signal is given by the nonlinear function of the partial pressure

55. CHANGE...

represented by the function g.

TO...

represented by the function .

56. CHANGE...

effect of endothelium-1 released by endothelial cells1 is not modeled explicitly.

TO...

effect of endothelin-1 released by endothelial cells1 is not modeled explicitly.

57. FORMATTING

On page 9, the sentence that starts with “By the conservation of mass” identify a new paragraph.

58. FORMATTING

The line after equation (1) should not be indented.

59. CHANGE...

wherex is the distance along the network,Qi is the blood flow

TO...

where is the distance along the network, is the blood flow

60. IN FIGURE 2 CAPTION CHANGE...

where r is the radial coordinate, x is the distance along the network, rt is the radius of the tissue region, rv is the radius of the vessel, d is the tissue width and L is the vessel length.

TO...

where is the radial coordinate, is the distance along the network, is the radius of the tissue region, is the radius of the vessel, is the tissue width and is the vessel length.

61. FORMATTING

In Figure 2 caption, numbers and units should not be written in italic.

62. IN FIGURE 2 CAPTION CHANGE...

pressure of oxygen in the tissue surrounding the small arterioles in the radial direction at two fixed positions and , , ,

TO...

pressure of oxygen in the tissue surrounding the small arterioles in the radial direction at two fixed positions cm and cm, mmHg, mmHg,

63. CHANGE...

Oxygen consumption in the tissue is calculated usinga Krogh cylinder model

TO...

Oxygen consumption in the tissue is calculated using a Krogh cylinder model

64. CHANGE...

In the present model,oxygen is assumed to be delivered bythe large and small arterioles and capillaries; no oxygen exchangeis assumed in the venules.

TO...

In the present model, oxygen is assumed to be delivered by the large and small arterioles and

capillaries; no oxygen exchange is assumed in the venules.

65. FORMATTING

In equation (2) the parenthesis after d/dr are smaller than the fraction inside the parenthesis, they should be bigger.

66. FORMATTING

The line after equation (2) should not be indented.

67. CHANGE...

it is important to note that the defined here is primarily

TO...

it is important to note that the defined here is primarily

68. FORMATTING

In page 10 there are empty lines between different paragraphs. This is not consistent with the other sections.

69. CHANGE...

The partial pressure of oxygenin the tissue along

TO...

The partial pressure of oxygen in the tissue along

70. FORMATTING

The line after equation (3) should not be indented.

71. CHANGE...

denotes the vessel radius, as depictedin Fig. 2B.

TO...

denotes the vessel radius, as depicted in Fig. 2B.

72. CHANGE...

two positions cm (blue curve) and cm(black curve) in the small arterioles for, ,

TO...

two positions m (blue curve) and (black curve) in the small arterioles for, ,

73. FORMATTING

In equation (4) and are inside the integral instead they should be on the top and bottom of the integral symbol.

74. FORMATTING

The line after equation (4) should not be indented.

75. CHANGE...

equal to the same value d for each oxygen-delivering vessel

TO...

equal to the same value for each oxygen-delivering vessel

76. CHANGE...

oxygen consumption rate q will induce changes in the oxygen

TO...

oxygen consumption rate will induce changes in the oxygen

77. CHANGE...

ordinary differential equationinTable 1(b) until equilibrium

TO...

ordinary differential equation in Table 1(b) until equilibrium

78. CHANGE...

Theuse of a steady state model is justified since the variation in the clinical measurements of oxygen saturation due to the cardiac cycle are not large.29

TO...

The use of a steady state model is justified since the variation in the clinical measurements of oxygen saturation due to the cardiac cycle is not large.29

**2.3 Model reference state**

79. CHANGE...

spaceof .30 Inthe reference state, the proportion of the tissue occupied by capillary lumensis about 2.7%,

TO...

Space of .30 In the reference state, the proportion of the tissue occupied by capillary lumens is about 2.7%,

80. IN TABLE 5 CAPTION CHANGE...

(OPP MAP – IOP, in mmHg)

TO...

(OPP MAP – IOP, in mmHg)

81. IN TABLE 5 CAPTION CHANGE...

(visual field MD10 dB)

TO...

(visual field MD≥10 dB)

82. IN TABLE 5 CAPTION CHANGE...

(POAG, IOP 21 mmHg)

TO...

(POAG, IOP>21 mmHg)

83. IN TABLE 5 CAPTION CHANGE...

(NTG, IOP21 mmHg)

TO...

(NTG, IOP≤21 mmHg)

84. FORMATTING

In Table 5 caption there is an extra empty line between “Reference state” and “parameter values are highlighted in bold.”

85. FORMATTING

In Table 5, in the Healthy column and in the last two rows, 1.65 and 15 are not in bold.

86. IN TABLE 5, 2nd COLUMN AND 7th ROW, CHANGE...

TO...

**2.4 Model Simulations**

87. CHANGE...

The model is used to predictthe theoretical effect of the artificial variation of the model inputs (Table 1(a))on

TO...

The model is used to predict the theoretical effect of the artificial variation of the model inputs (Table 1(a)) on

88. FORMATTING

In the section 2.3 there are empty lines between the different paragraphs. This is not consistent with the previous sections.

89. CHANGE...

and (Table 1(a)) given the clinical measurements of MAP,IOP and arterial oxygen saturation

TO...

and (Table 1(a)) given the clinical measurements of MAP, IOP and arterial oxygen saturation

90. CHANGE...

set the initial guess for the input oxygen demand to M\_0^0 (Table 1(a)), for

TO...

set the initial guess for the input oxygen demand to (Table 1(a)), then for

91. FORMATTING

In Algorithm 2A the point iii.d. is extra ( the d. needs to be deleted), moreover the lines overlap.

92. CHANGE...

otherwise set〖M\_0^(k+1)=M〖\_0^k+ δ\_M

TO...

otherwise set

93. CHANGE...

set the input oxygen demand equal to the reference state value M\_0^ref (Table 1(a));

TO...

set the input oxygen demand equal to the reference state value (Table 1(a));

94. CHANGE...

set the initial guess for the input tissue depth to (Table 1(a)), for

TO...

set the initial guess for the input tissue depth to (Table 1(a)), then for

95. FORMATTING

In Algorithm 2B point iii.c. the first and the second line overlap.

96. CHANGE...

are determined viathe MATLAB algorithm fsolve

TO...

are determined via the MATLAB algorithm fsolve

97. FORMATTING

Figure 3 is not complete, the right part is missing.

98. IN FIGURE 3 CAMPTION CHANGE...

advanced NTG patients (n=8) 4 (blue dots)

TO...

advanced NTG patients (n=8)4 (blue dots)

**3 Results**

**3.1 Experimental data**

99. CHANGE...

Four healthy individuals and one advancedNTG patient were excluded

TO...

Four healthy individuals and one advanced NTG patient were excluded

100. CHANGE...

not included in the figure since Olafsdottirand Vandewalle et

TO...

not included in the figure since Olafsdottir and Vandewalle et

101. CHANGE...

the average value of venous oxygen saturationis higher than in healthy individuals, and the average value ofarteriovenous difference is lower than in healthy individuals

TO...

the average value of venous oxygen saturation is higher than in healthy individuals, and the average value of arteriovenous difference is lower than in healthy individuals

**3.2 Theoretical investigation**

102. CHANGE...

The clinical data (blue dots) are compared to themathematical model prediction (solid curve) of venous saturation as OPP isvaried

TO...

The clinical data (blue dots) are compared to the mathematical model prediction (solid curve) of venous saturation as OPP is varied

103. CHANGE...

arterial oxygen saturation, 〖M\_0〖^ref and are used to produce

TO...

arterial oxygen saturation, and are used to produce

104. CHANGE...

Since the clinical data 4 show an increase in venous

TO...

Since the clinical data4 show an increase in venous

105. FORMATTING

In page 15 there are empty lines before and after the

enumerated list. This is not consistent with the previous sections.

106. CHANGE...

**An impairment of blood flowautoregulation**:

TO...

**An impairment of blood flow autoregulation**:

107. CHANGE...

**Adecreaseintissuewidth(d):**Ifthevolumeoftissuesuppliedbyeachcapillary or arteriole is decreased,higher levels

TO...

**A decrease in tissue width ():** If the volume of tissue supplied by each capillary or arteriole is decreased, higher levels

108. CHANGE...

all other factors (MAP,IOP, d, arterial blood

TO...

all other factors (MAP, IOP, , arterial blood

109. CHANGE...

variable increasesinvenous oxygen saturationdepending on the value of OPP.

TO...

variable increases in venous oxygen saturation depending on the value of OPP.

110. CHANGE...

are impaired (i.e., absent)in theblack dashed curve.

TO...

are impaired (i.e., absent) in the black dashed curve.

111. CHANGE...

Fig. 5D shows that adecrease in tissue width

TO...

Fig. 5D shows that a decrease in tissue width

112. IN FIGURE 5 CAMPTION CHANGE...

Figure 5. A) Decrease

TO...

Fig. 5. A) Decrease

113. IN FIGURE 5 CAMPTION CHANGE...

oxygen demand (M0) is increased

TO...

oxygen demand () is increased

114. IN FIGURE 5 CAMPTION CHANGE...

oxygen saturation.The remaining panels

TO...

oxygen saturation. The remaining panels

115. IN FIGURE 5 CAMPTION CHANGE...

D) tissue width (d) on model

TO...

D) tissue width () on model

116. IN FIGURE 5 CAMPTION CHANGE...

OPP is varied.Each scenario

TO...

OPP is varied. Each scenario

117. CHANGE...

tissue width from (blue curve) to d=13 μm (green curve)

TO...

tissue width from (blue curve) to (green curve)

118. FORMATTING

Caption of Figure 5 is repeated and included in the text as a paragraph at the end of page 16.

**3.3 Theoretical interpretation of clinical data**

119. IN FIGURE 6 CAMPTION CHANGE...

tissue oxygen demand (M0) and tissue width (d)

TO...

tissue oxygen demand () and tissue width ()

120. IN FIGURE 6 CAMPTION CHANGE...

advanced POAG and advanced NTG populations 4

TO...

advanced POAG and advanced NTG populations4

121. IN FIGURE 6 CAMPTION CHANGE...

NTG patients.Black bars represent

TO...

NTG patients. Black bars represent

**3.3 Theoretical interpretation of clinical data**

122. CHANGE...

oxygen demand(gray) or tissue width (blue)that willyield the clinically observed venous saturation levels(Fig. 3)

TO...

oxygen demand (gray) or tissue width (blue) that will yield the clinically observed venous saturation levels (Fig. 3)

123. CHANGE...

oxygen demand ispredicted in advanced NTG patients. A slightlylower tissue

TO...

oxygen demand is predicted in advanced NTG patients. A slightly lower tissue

124. CHANGE...

Table 6lists the mean and standard deviation

TO...

Table 6 lists the mean and standard deviation

125. FORMATTING

Table 6 is missing and the caption of Table 6 is included in the text as a paragraph.

126. IN TABLE 6 CAPTION CHANGE...

and tissue width () that yield the

TO...

and tissue width () that yield the

127. IN TABLE 6 CAPTION CHANGE...

POAG and advanced NTG patients 4.

TO...

POAG and advanced NTG patients.4

128. CHANGE...

oxygen demand and tissue widthcalculated for the healthy population

TO...

oxygen demand and tissue width calculated for the healthy population

129. CHANGE...

the values of and d are computed using the MAP, IOP

TO...

the values of and are computed using the MAP, IOP

130. CHANGE...

as well as the average clinicalvalues of venous saturation

TO...

as well as the average clinical values of venous saturation

131. CHANGE...

autoregulation is assumed to be impaired for the blackdashed curve

TO...

autoregulation is assumed to be impaired for the black dashed curve

132. FORMATTING

Figure 7 is not in page 18, where is cited, but in page 19. It would be possible to move it to the end of page 18, or at most at the top of page 19?

133. IN FIGURE 7 CAPTION CHANGE...

OPP measured clinically.A) The observed increase

TO...

OPP measured clinically. A) The observed increase

134. IN FIGURE 7 CAPTION CHANGE...

POAG patients (blacksquare)

TO...

POAG patients (black square)

135. IN FIGURE 7 CAPTION CHANGE...

tissue demand.B) The observed

TO...

tissue demand. B) The observed

**4 Discussion**

**4.1 Experimental data**

136. CHANGE...

Other studies 21, 22 have confirmed these findings

TO...

Other studies21,22 have confirmed these findings

**4.2 Theoretical investigation**

137. CHANGE...

to enhance themodel in the current study to include a more realistic

TO...

to enhance the model in the current study to include a more realistic

**4.3 Theoretical interpretation of clinical data**

138. CHANGE...

autoregulation or adecrease in tissue width can all lead to increased venous saturation levels

TO...

autoregulation or a decrease in tissue width can all lead to increased venous saturation levels

139. CHANGE...

However, the interconnectionof tissue width

TO...

However, the interconnection of tissue width

140. CHANGE...

a decrease in oxygen demandmay be more relevant to the

TO...

a decrease in oxygen demand may be more relevant to the

141. CHANGE...

Importantly, impairedblood flow autoregulation

TO...

Importantly, impaired blood flow autoregulation

142. CHANGE...

as suggested by Fig.6. Additional theoretical

TO...

as suggested by Fig. 6. Additional theoretical

143. CHANGE...

on a wider set of glaucoma patients,are needed to

TO...

on a wider set of glaucoma patients, are needed to

**Acknowledgments**

144. CHANGE...

thankSien Boons, AsbjorgGeirsdottir andJonaValgerdurKristjansdottir for

TO...

Thank Sien Boons, Asbjorg Geirsdottir and Jona Valgerdur Kristjansdottir for

145. CHANGE...

The authors acknowledge support from:National

TO...

The authors acknowledge support from: National

146. CHANGE...

Prevent Blindness, Inc.(AH,BAS),

TO...

Prevent Blindness, Inc. (AH,BAS),

147. CHANGE...

the FondsWetenschappelijkOnderzoek - Vlaanderen and unrestricted grant from Merck Sharp and Dohme (no. B322201010013)(EV).

TO...

the Fonds Wetenschappelijk Onderzoek – Vlaanderen and unrestricted grant from Merck Sharp and Dohme (no. B322201010013) (EV).

**References**

148. IN REFERNCE 1 CHANGE ...

Clin Ophthalmol

TO...

Journal of Clinical Ophthalmology

149. IN REFERNCE 4 CHANGE ...

Abegao Pinto L,,,,, , Geirsdottir A, Clerck, E. De,,,, , Stalmans P,

TO...

Abegao Pinto L, Geirsdottir A, Clerck, E. De, Stalmans P,

150. IN REFERNCE 22 CHANGE ...

Graefes Arch Clin Exp Ophthalmol

TO...

Graefe's Archive for Clinical and Experimental Ophthalmology

151. IN REFERNCE 25 CHANGE ...

Ann Biomed Eng

TO...

Annals of Biomedical Engineering

152. IN REFERNCE 28 CHANGE ...

Biomech Model Mechanobiol

TO...

Biomechanics and Modeling in Mechanobiology

153. IN REFERNCE 34 CHANGE ...

Arch Ophthalmol

TO...

Archives of Ophthalmology

154. IN REFERNCE 37 CHANGE ...

Ann Biomed Eng

TO...

Annals of Biomedical Engineering