Corneal Relaxation Time estimation as Function Tear Oxygen Tension in Human Cornea During Contact Lens Wear.

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ABSTRACT

PURPOSE: Calculate the true relaxation time of the cornea in function of the oxygen tension at the interface cornea-tears with the intention to know the behaviour which follows the oxygen diffusion and chemical reactions to produce adenosine triphosphate (ATP).

METHODS: From oxygen tension measurements in vivo for human cornea-tears, under a wide range conventional Hydrogels (Hy) and Silicone-Hydrogel (Si-Hy) contact lenses, the transitory and stationary state of oxygen tension under open eyes conditions was obtained. We here separate the Fick diffusion behaviour given by the passive CL and tears from the active cornea by subtraction of the time-lags of both CL and tears, changing the origin times. The true cornea relaxation time was obtained by this procedure.

RESULTS: The relaxation time should be of 8 s, however our results shown that the corneal relaxation time follows a Non Fickean behaviour. Below this value (8 s), the behaviour is super-diffusive, and for high ones the corneal response behaviour is sub-diffusive.

CONCLUSION: The oxygen tension distribution in the corneal tears interface, is separated in two different zones. One, for conventional hydrogels, that is located between 6 and 75 mmHg, with a relaxation time compressed between 9 and 19 seconds; and the other zone where Silicone-Hydrogel CLs, which are situated at high oxygen tensions, between 95 and 140 mmHg, with a relaxation time in the interval of 1.5 to 8 seconds. We attribute this behaviour quantitatively to the coupling formalism between Fick oxygen diffusion and biochemical reactions which evolved to produce adenosine triphosphate (ATP).

Key words: Corneal hypoxia, relaxation time, oxygen diffusion, ATP, lens trasmisibility

Introduction

The cornea is an avascular tissue which requires oxygen for normal metabolic function. Oxygen reaches the cornea primarily from atmospheric air and secondarily from the anterior chamber (aqueous humor) under open eye conditions. During the closed eye situation (ie sleep), the oxygen is provided from both exposure to the tarsal palpebral conjuntiva and from the aqueous humor[1,2]. When variably oxygen permeable CLs are worn on the cornea, any induced hypoxia would result in may lead several complications.[3,4] Some researchers have reported that wear of low oxygen transmissible CLs limit normal oxygen supply to the anterior cornea leading to: corneal swelling, corneal acidosis, epithelial punctate staining, limbal hyperemia, loss of corneal transparency, and endothelial polymegethism.[5-8]

Others researchers[9-13] observed that hydrogel CL wear induces acidosis,[8,14-16] which then secondarily increases the corneal oxygen consumption rate by up to 1.8 times that found at normal pH; it is thought that such acidosis leads to activation of pH-regulatory mechanisms.[7] Accordingly, increasing oxygen consumption increases energy demand to produce additional ATP molecules via oxidative phosphorylation. On the other hand, when anterior corneal oxygen partial pressure is low, corneal oxygen consumption falls with the increase in glucose concentration because of anaerobic respiration. Frahm et al.,[17] explained that only excess glucose is independent of glucose concentration in respiration. Compañ et al[18] observed, using oxygen tension from *in vivo* estimations provided by Bonanno et al.,[8,19,20] that the Monod kinetics model for oxygen consumption reaction with glucose describes a maximum as a transition from aerobic to anaerobic metabolism. That is, when lowering oxygen tension, the maximum oxygen consumption rate initially increases depending on the intensity of pressure change. This could be related to variation in pH, where this parameter decreases for greater reductions in oxygen pressure, possibly due to changes in the concentration of glucose associated with anaerobic respiration.[18]

Transient relaxation time is generally considered as time-constant for a system to return to equilibrium after a disturbance or dysfunctions. Using the previous results of Bonanno et al.,[8,19,20] for corneal stress under exposure to a

CL wear in closed eye conditions (see Figs 2 & 3 of Bonanno et al.,[20]), we calculate here the time required for the partial pressure of oxygen at the cornea-tears film interfase, in a cornea under the presence of a CL, to return to its normal state under open-eye conditions, after being stressed.. This time is named the relaxation time for this transitory behavior. From the procedure followed by Bonnano et al.,[19] the data collected after eye opening was fit to a exponential function derived from transitory experimental data using a parameter which is the inverse of relaxation time. This parameter was considered for both the complete system including the passive CL and tears and the active cornea, which consumes oxygen.

In this work, we separate the Fick diffusion behaviour given by the passive CL and tears from the active cornea by subtraction of the time-lags of both CL and tears, changing the origin of the times. The transient cornea relaxation time obtained by this procedure have been calculated for ten soft CLs worn on human corneas described by Bonanno et al.[19,20] We have analysed these results according to different oxygen partial pressures measured at the cornea-tears interface with the intention to study the behaviour between the oxygen diffusion and corneal response behaviour respect the transient relaxation times of the cornea. From our study, we could see a qualitative behaviour of coupling formalism between oxygen diffusion and chemical reaction, which is involved to produce adenosine triphosphate (ATP). For this, we first, however, separate CL and tears time-lags to obtain solely the transient relaxation time of the cornea. This information might be useful to determine the time required for the corneal physiology return to the stationary state after a perturbation of hypoxic stress caused by a contact lens wear depending on the contact lens transmissibility. It is known that contact lens wear causes corneal acidosis which, in turn, increases the corneal oxygen consumption and in consequence the pH-regulatory mechanism.[6]

So that, the determination of this parameter might also be relevant to design studies in which the same cornea is subjected to repeated tests with different lenses or hypoxic conditions, increasing oxygen consumption and making the cells, basically from the epithelium, in a limited hypoxic state over a limit pH range and therefore, resulting in more lactate production and lower oxygen availability for glucose oxidation[15-17, 20-24].

Materials and methods

Materials

For this study, we are selected ten contact lenses CLs (five hydrogel (Hy) and six siloxane-hydrogel (Si-Hy)) currently available on the world market. This selection was done because tear oxygen tension under hydrogel and silicone hydrogel contact lenses in humans were studied previously by Bonanno et al.,[19,20] using the phosphorescence decay methodology, with the aim to correlate the lens transmissibility and the oxygen tension and flux into the central cornea. Chhabra et al. have reported a polarographic method for measuring oxygen diffusivity and solubility of soft CL separately[23]. Technical details of CLs, reported by the manufacturer, such as average central thickness, permeability, and transmissibility through each CL are displayed with asterisks in Table 1. Data without asterisks were measured in our laboratory.

INSERT HERE TABLE 1

Methods

The values of apparent diffusion coefficient and permeability given in Table 1 were obtained following the procedure described previously[23,25-29] In brief, apparent oxygen diffusion and permeability of these CLs were determined from the measurement of electric current generated at the electrode as consequence of the reduction process of oxygen that passed through each CL. In the steady state conditions, apparent permeability (*P*) is obtained from equation,[25]

$$P = I_\infty \frac{L}{n \cdot A \cdot F \cdot \Delta p} \qquad (1)$$

where I_∞ represents current intensity at steady state conditions ($t \rightarrow \infty$), L is the central thickness of the CL, n is the number of electrons exchanged in the cathodic reaction (n=4), F, the Faraday constant, A, the area of the cathode and

Δp is the oxygen partial pressure difference across the lens at sea level (~155 mmHg). Transmissibility (T), is given by

$$T = \frac{P}{L} = \frac{Dk}{L} = \frac{I_\infty}{n \cdot A \cdot F \cdot \Delta p} \qquad (2)$$

The apparent oxygen diffusion has been calculated as[29]

$$D = \frac{I_\infty \cdot L^2}{6(I_\infty \cdot t - Q(t))} \qquad (3)$$

where Q(t) is the total charge transferred to the cathode as consequence of the oxygen reduction process from t=0 until the system reaches the stationary state and t the total elapsed time. The values of P and D are apparent because in the experimental procedure for the determination are included the boundary layers. Therefrore, the values of P and D, are the estimations for the total system: water layer//contact lens//water layer.

From the apparent oxygen permeability and oxygen diffusivity we are calculated the apparent solubility as $k_l = \left({}^{P}\!/_{D}\right)_l$. The values obtained are given in table 1.

The values of time lag for oxygen diffusion through the CL displayed in the last column in table 1 was determined, from the oxygen diffusion coefficient through the CL given in third column and known thickness of the CL (tabulated in second column of table 1), by mean of $\tau_l = \frac{L_l^2}{6D_l}$, (see eq.(10) of reference[26]).

On the other hand, to calculate the time-lag for oxygen diffusion through the tears, we considered the oxygen diffusion coefficient of water which is around $3\text{x}10^{-6}$ cm^2/s [30]. Taking this value, and considering that a typical value for the thickness of the tears is at most 10 μm,[31,32] with both hydrogel and silicone-hydrogel CLs, we have estimate the time-lag of tears from $\tau_{tears} = \frac{L_{tears}^2}{6D_{water}}$ =0.33 s.

Results and discussion

Estimation of the transient-relaxation time for the cornea.

The steady-state values of tear oxygen partial pressures under the CLs for open eye conditions were obtained with a time-domain phosphorimeter as previously described from Bonanno et al.,[19,20,33,] are listed in Table 1. From the graphs of the Bonano et al.,[19,20,33] experimental data, we obtained stationary state oxygen tensions for open eye conditions. We then fit the transitory oxygen tension (P_{O2}) after eye opening data collected to a first-order exponential model as:

$$P_{O2} = SS - (SS - IN)e^{-\kappa t} \qquad (4)$$

where SS is the stationary value of oxygen partial pressure for a given CL, IN is the initial value of P_{O2}, κ represents the inverse of transient-relaxation time of the system, and t is time.

Given that corneas wear CLs in the Bonanno et al.[19,20,33] experimental procedure, the time data collected corresponds to the response of the total system. Therefore, in first approximation, the system is corneas, tears, and CLs. This response is "in-series," wherein oxygen diffuses first through the CL, then interposed tears, and thereafter diffuses into the underlying cornea.

The relaxation response of the cornea alone can be separated infitting of the experimental data. In fact, The Bonano et al.,[19,20,33] experimental data for oxygen tension at the cornea entrance (the interface cornea-tears film) can be changed from their time origen, taking into account the time lags of the lens and tears, respectively, according to the equation.

$$P_{O2} = SS - (SS - IN)e^{-\kappa_c(t-\tau_l-\tau_{tears})} \qquad (5)$$

Where κ_c is the inverse of the transient time of the cornea alone.

The variation of oxygen partial pressure in the cornea-postlens tear film interface as a function of time in open eye conditions, was measured using a phosphorescence dye technique[19,20,33]. Experimental transitory data, in combination with equation (5), allowed calculating the value of transient-relaxation time for different situations corresponding to a cornea wearing a contact lens. Figure 1 show the fit of experimental data for four lenses (2 hydrogel conventional and 2 Si-Hy contact lenses). Similar fitting has been made for the other lenses analyzed in this study. From the adjust of eq.(5) to experimental data we are obtained the transient-relaxation time for the cornea for each situation. Figure 2 show the plot of relaxation times for all CLs studied. A straight line is obtained of correlation coefficient r^2= 0.95. To carry out this analysis, the data of the figures of Bonanno corresponding to the transitory of P_{O2} versus time for all the CLs studied were taken. The procedure followed consists to load the data into the software "tracker", in which the coordinates of the points of the plot were obtained. Using the software "Wolfram Mathematica" the corneal relaxation time was obtained from the data adjusted.

INSERT HERE FIGURE 1

A close observation of figure 2 permit us conclude that conventional hydrogel CLs with relaxation times bigger than 8 seconds are displayed on the left side of Figure 2, while the cohort of silicone-hydrogel CLs, where relaxation time is below than 8 seconds, are on right side of this figure.

To give a more general and complete evaluation, we must also include the following two cases in the plot: 1) the open eye cornea where the anterior tear surface is in contact with the ambient atmosphere at sea level (oxygen tension ≅155 mmHg) and the transient -relaxation time τ is about 1 sec. This value represents the aerobic response of the cornea where six moles of carbon dioxide and water are produced for each mole of glucose consumed, and 36 moles of adenosine triphosfate (ATP) are produced. We also need to consider 2) the opposite case, where the anterior tear surface over the cornea is exposed to a oxygen partial pressure of zero where the relaxation time will be equal to 21.5 sec. This value represents the rate of production of ATP by glycolysis. In such situation the anaerobic breakdown of glucose requires consumption of 1 mole of glucose to produce two moles of lactic acid, and only two moles of ATP are produced.[20,30] The result is a rate equal to 36/2. Comparing these two extreme values with the ten experimental values of CL generated data obtained from the Bonnano et al.,[19,20,33] we found the resulting straight line as shown (see Figure 2); where the percentage of participation of oxygen rules out the transient-relaxation time of the cornea. The characteristic time limit for p_c equal to zero obtained here is valid and representative, although it has been difficult to produce truly anoxic conditions at the ocular surface.[34]

Considering the cornea as a one-dimensional homogenous tissue, the oxygen pressure as a function of time and position is given by the equation[22,35,36]

$$D_c \frac{\partial^2 p_c}{\partial x^2} - \frac{Q(p_c)}{k_c} = \frac{\partial p_c}{\partial t} \qquad (6)$$

where $p_c(x,t)$ is the oxygen tension in the cornea in mmHg, D_c the oxygen diffusion coefficient into the cornea, k_c the oxygen solubility coefficient in the corneal tissue (cm^3 of O_2/cm^3 of tissue/mmHg), x is the distance perpendicular to the surface (cm) , $Q(p_c)$ is the oxygen consumption rate (ml of O_2/ cm^3 of tissue layer/s), and t is time (s). The subscript c refers to the quantities measured at the cornea.

The solutions of eq.(6) in the cornea are functions of Q(pc) which is a result of the aerobic and anaerobic metabolisms.[22,36-38] To determine the solution of eq.(6) we have considered the Monod kinetics model given by[22,24,35,36]

$$Q(p_c) = \frac{Q_{c,\max}\, p_c(x)}{k_m + p_c(x)} \qquad (7)$$

where k_m is the Monod dissociation equilibrium constant (k_m=2.2 mmHg) and $Q_{c,max}$ represent the maximum oxygen consumption.[24] Inserting the eq (7) into eq.(6) we have numerically calculated the variation of the oxygen tension versus time at the interface corneas-tears film when a CLs is wearing. The results obtained for the lenses Polymacon, Acuvue2, Optix and Oasys can be seen in figure 1, as a continuous solid line fitting to Bonanno experimental data. From this fit we also have calculated the transient-relaxation time of the cornea, for each one of the system cornea-tears/ CLs. The values obtained are shown in the inset of figure 2. In the Inset we can see that a straight line is obtained with a correlation coefficient r^2= 0.90. To carry out this analysis, the data of the figures of Bonanno corresponding to the transitory of P_{O2} versus time for all the CLs studied were taken. A comparison between the two procedures show a good agreement between the values of transient- relaxation time of the cornea obtained. On the other hand, we can observe that the tendency of the straight-line in the region of high oxygen tension (nearly to 155 mmHg) change its slope in order to avoid negative values for the transient -relaxation time of the cornea. This asymptotic change tends to the value of 1.2 sec for the fit of eq. (5) and of 1.36 sec in case of the fit using eq.(6). The values of 1.2 sec has been determined from the relation Intercept at Pc=0, as 21.6/18. The value of 18 is obtained from the relation between 36 moles of ATP when the cornea is found below maximum amount of oxygen and 2 moles that is established for an cornea below the absence of oxygenOn the other hand, the transient-relaxation time of the cornea, taking into account that it is a passive homogeneous tissue, is around of τ=8s. This value is obtained considering a corneal thickness of L=532 µm and a corneal diffusion coefficient of $6x10^{-5}$ cm^2/sec. The last value is the mean value of cornea oxygen diffusion coefficient obtained for a cornea wearing Balafilcon and Polymacon lenses.[37] A close inspection of this value in Figure 2 corresponds to a value approximately in abscissa axis equal to 90 mmHg. Which is around of limit of low pressure to avoid hypoxia given by Compañ and Weissman[37] and little below the value of 105 mmHg postulated by Compañ et al.[38] Note that, for pressures higher than this value, the cornea behaves as super-diffusive phase, since it present lower transient-relaxation times, and for low pressure behaves as sub-diffusive one, since it present lower transient-relaxation times. These conclusions are explained considering that the diffusive process is coupled to the oxygen chemical reaction that produces ATP. In the case of super-diffusion, enhanced velocity of oxygen molecules could be given by replacement of molecules consumed and its transit produces a sequence of jumps-line, in which oxygen molecules move faster than Brownian diffusion in the cornea.

INSERT HERE FIGURE 2

On the other hand, anaerobic conditions do not involve oxygen molecules by definition; several chemical reactions occur which take more time than does usual respiration. In that condition, when the few oxygen of aerobic metabolism produces additional ATP, the transient is not finished until the present reactions in the cornea are relaxed, exceeding the time of Brownian diffusion.

It is well known that CLs (daily disposable wear, extended wear, flexible wear or conventional wear) are a popular alternative for correction of refractive error. Reductions of CL tolerance have been associated with both limited oxygen availability and lens movement on the eyes.[39,40] Contact lens oxygen transmissibilities and corneal oxygen consumption are the key performance characteristics which permit us to understand many changes occurring in corneal physiology while CLs are worn. The latest generation of soft CLs (silicone-hydrogel or “Si-Hy”) are much more oxygen permeable than conventional hydrogel CLs (Hy) and therefore expected to be much better tolerated in vivo. Enhanced oxygen diffusivity in Silicone hydrogel materials occurs through two co-continuous phases: 1) the ion/water permeable (ionoperm and waterperm) hydrogel phase, and 2) the oxygen permeable (oxyperm) phase, but oxygen permeability is more through the xerogel phase than the hydrogel phase.[39-40] These characteristics induce different transient-relaxation times of the cornea, which should be associated with production of different values (moles) of ATP for each mole of consumed glucose. We observed that corneal oxygen consumption rate increases with the acidosis and decreases with the anaerobic transition. This kinetic transition can be understood not only as the result of the metabolic reactions that occur in the Krebs cycle, but also of the other observed corneal reactions.[41]

Therefore, it has to be commented that our concern is with short transient relaxation in experiments with close and open eyes. This case should be separated when a prolonged hypoxia effect is present. Then others phenomena appears, such as corneal swelling, corneal acidosis, loss of corneal transparency, keratitis, neovascularization and limbal hyperemia, among others. All of them may not be related with the transient-relaxation time. Particularly, the cornea deswells upon waking over a period of about one hour.[41,42] Therefore, these studies are not related with the present approach. Nevertheless, before these phenomena could be produced, an estimation of the transient-relaxation time can give us information on the lens transmissibility requirements to avoid corneal hypoxia, because knowing the value of transient-relaxation time of the cornea we can estimate the apparent oxygen tension at the interface cornea-tears-CLs and calculate which transmissibility have to have a CL to be use to avoid hypoxia.[7,12,43,44]

Therefore, this study suggests that current scleral gas permeable and hydrogel contact lenses should produce some levels of cornea hypoxia under open eye conditions. Only lenses producing an oxygen tension greater than 90 mmHg can prevent different abnormalities, which, with an insufficient oxygen supply could be produced. This information will be prudent that clinicians to prescribe contact lenses manufactured for higher oxygen transmissibility.

Conclusions

Two procedures to calculate transient-relaxation times of the cornea are reported. Both determinations give practically same results. We note a distribution correlated with cornea-tear interface oxygen partial pressure, from near zero to 155 mm Hg, as shown in both Table 1 and Figure 2. Our results show an oxygen tension distribution in two different zones: conventional hydrogels are located between 6 and 75 mmHg with a transient-relaxation time in the interval between 9 and 19 seconds, while Si-Hy CLs are situated at high oxygen tensions, between 95 and 140 mmHg, with a relaxation time in the interval of 3 to 8 seconds. These conditions allow us to verify different behavior of the cornea; namely, super-diffusive, Fickean, and sub-diffusive. Fick behavior occurs when the cornea is considered as a single homogenous tissue with a specified width and a given diffusion coefficient (it leads to a transient-relaxation time of 8 seconds). The super-diffusive regime accounts for faster responses due to the oxygen ballistic flow around the locality where the aerobic chemical reaction takes place to produce ATP (less than 8 seconds). Finally, longer characteristic times than 8 seconds are achieved when anaerobic chemical reaction controls the rate of total corneal relaxation. Contact lenses which transmissibility yield transient-relaxation time higher than 8 s will produce sub-diffusive processes into the cornea and if persist, induces different anomalies, such as corneal swelling, corneal acidosis, loss of corneal transparency, keratitis, neovascularization and limbal hyperemia, among others. However CLs with higher transmissibility yielding a relaxation times lower than 8 seconds maintain to the cornea with a good oxygenation and transparency, and only in certain cases a moderate acidosis could be observed.

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Figure captions

Figure 1. Variation of oxygen tension versus time at the interface cornea-tears-CLs. a) Symbols represent the experimental data obtained from Bonanno et al.[20] b) Dashed line correspond to the experimental data fit by means of eq.(5). c) Solid line has been obtained fitting the data using eq.(6).

Figure 2. Variation of the relaxation time of the cornea versus oxygen tension at the cornea-tears-lens interface for each one of the lenses considered in this study. The inset show the corneal time relaxation versus oxygen tension at the interface cornea-tears film using the solution of eq.(6).

Table 1. Parameters of the lenses used in this study. The asterisks indicate that these parameters have been measured by manufacturer. Values without asterisks have been measured experimentally by us.

Lens	Thickness L_1 (μm)	D_l (cm^2/s)	k_l cm^3 of O_2 /cm^3 mmHg)	$(Dk)_l$ (Barrer)	$(Dk/t)_l$ (Barrer/cm)	$\tau_l = \frac{L_l^2}{6D_l}$ (s)
Polymacon2	200*	6.8×10^{-6}	1.5×10^{-5}	10.2 (8.4*)	5.1 (4.2*)	11.1
Biomedics	115*	8×10^{-6}	2.4×10^{-5}	19.2 (19.7*)	16.7 (17.1*)	2.8
Acuvue2	105*	6×10^{-6}	4.7×10^{-5}	28.2 (28*)	26.9 (27*)	3.1
Advance	71*	4.5×10^{-6}	13.2×10^{-5}	59.4 (60*)	83.7 (85+)	1.9
Balafilcon	100*	1.5×10^{-5}	6.7×10^{-5}	100.5 (99*)	100 (99*)	1.1
Purevision	90*	5.5×10^{-6}	19.3×10^{-5}	107.0 (112*)	119 (124*)	2.3
Optix	80*	5.1×10^{-6}	21.1×10^{-4}	106.8 (110*)	133.5 (138*)	2.1
Oasys	62*	4.4×10^{-6}	2.3×10^{-4}	101.5 (103*)	163.7 (166*)	1.4
N&D	80*	7.1×10^{-6}	2×10^{-4}	141.8 (140*)	177.3 (175*)	1.5
N&D UT	55*	6.6×10^{-6}	2.15×10^{-4}	141.8 (140*)	257.8 (255*)	0.8

1Barrer=10^{-11} (cm^2/s)(mL STp O_2/(ml.mmHg)) or 1 Fatt Dk units

1 Barrer/cm= 10^{-9} (cm/s)(mL STp O_2/(ml.mmHg)) or 1 Fatt Dk/t units

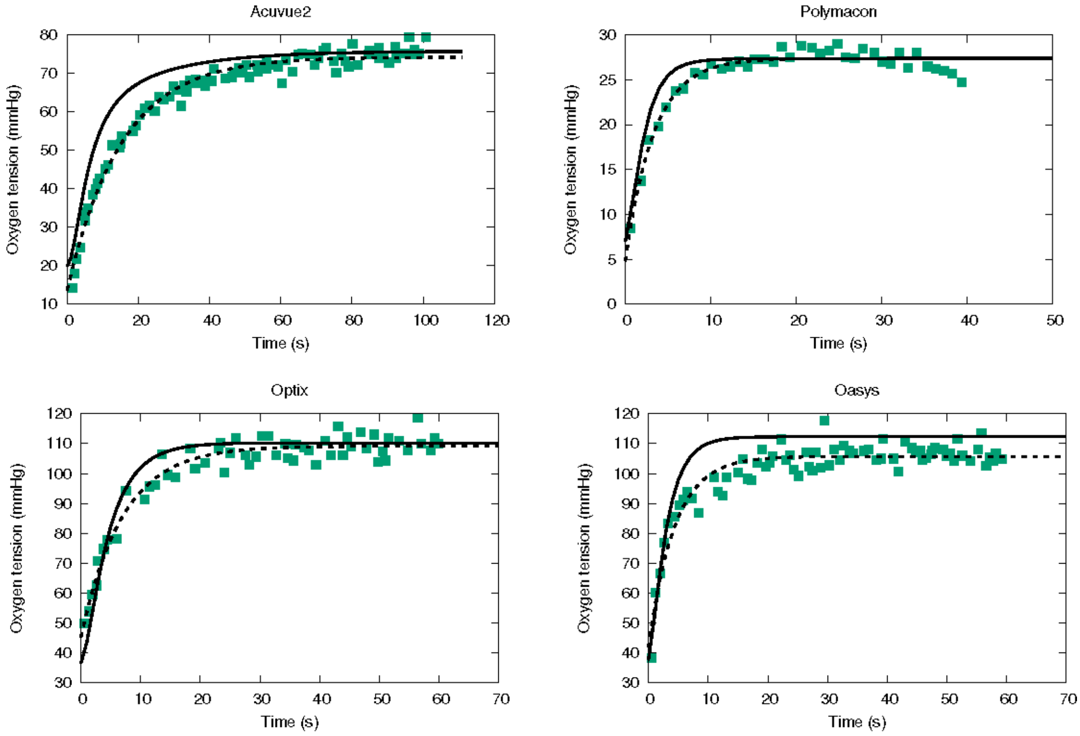

Figure 1.

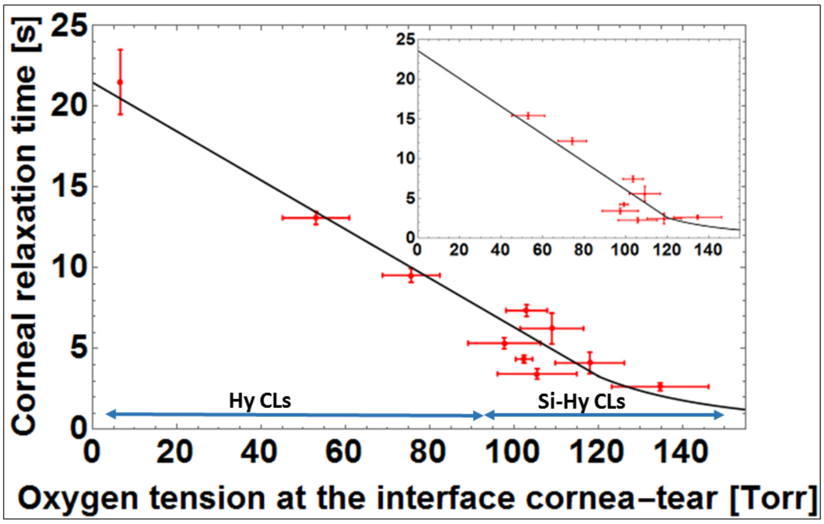

Figure 2.