# Bio-Energy: Muscle work and breathing in the cornea

## Bio-Energía: Trabajo muscular y respiración en la córnea

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## Abstract

In this review article, we present two cases of the bioenergy area in relation to the production of energy via the decomposition of adenosine triphosphate (ATP). The first is the work done by the human body due to the contraction of the skeletal muscle and the second the process of oxygen diffusion in the cornea. The chemical-physical background of the production and use of the energy molecule par excellence of the ATP is exposed. The generation of bioenergetic molecules in aerobic respiration and in anaerobic glycolysis are analyzed from the thermodynamic point of view. In this sense, the processes of biosynthesis for the use of the energy stored by the ATP molecules are presented and the active transport of molecules against concentration gradients is described. The vesicular transport of proteins, the permeability of ions through the enveloping membranes to the cell walls by means of the so-called sodium-potassium pumps. Subsequently, some details are established about the mechanisms by which muscle contraction occurs, with reference to the structure of muscle fibers. In the second case, the study of the physiology of the cornea is shown, where chemical work is also generated to maintain its transparency to light, coming from outside the eye. This leads to the conservation of the proper structure of the endothelial cells, stroma, and epithelium. Likewise, the osmotic work requirement is illustrated to maintain the pH balance in the cornea, when it encounters an oxygen deficiency. In such circumstances, an osmotic flow is generated from the aqueous humor towards the stroma which tends to counteract the increase in acidity.

***Keywords:*** muscle contraction; cornea; adenosine triphosphate (TPA); adenosine diphosphate (DPA); oxygen consumption; porphyrin.

## Resumen

En este artículo de revisión se presentan dos casos del área de bioenergía en relación con la producción de energía vía descomposición del trifosfato de adenosina (ATP). El primero, es el trabajo que realiza el cuerpo humano debido a la contracción del músculo esquelético y el segundo el proceso de difusión

de oxígeno en la córnea. Se exponen los antecedentes químico-físicos de la producción y utilización de la molécula energética por excelencia del ATP. Se analizan desde el punto de vista termodinámico, la generación de moléculas bioenergéticas tanto en la respiración aeróbica como en glicólisis anaeróbico. En este sentido, se presentan los procesos de biosíntesis para la utilización de la energía que almacenan las moléculas de ATP y se describe el transporte activo de moléculas en contra de gradientes de concentración. El transporte vesicular de proteínas, la permeabilidad de iones a través de las membranas envolventes a las paredes celulares por medio de las denominadas bombas de sodio-potasio. Posteriormente, se establecen algunos detalles acerca de los mecanismos por medio de los cuales se da la contracción muscular, haciendo referencia a la estructura de las fibras musculares. En el segundo caso, se muestra el estudio de la fisiología de la córnea, donde también se genera trabajo químico para mantener su transparencia a la luz, proveniente del exterior del ojo. Lo que conlleva a la conservación de la estructura adecuada de las células del endotelio, estroma y epitelio. Así mismo, se ilustra el requerimiento de trabajo osmótico para mantener el balance del pH en la córnea, cuando se encuentra con una deficiencia de oxígeno. En tal circunstancia se genera un flujo contra osmótico desde el humor acuoso hacia el estroma que tiende a contrarrestar el aumento de acidez.

***Palabras clave:*** contracción muscular; córnea; trifosfato de adenosina (TPA); difosfato de adenosina (DPA); consumo de oxígeno; porfirina.

## Introduction

The specialized molecule capable of producing movement from chemical energy, as a result of the work generated is the molecule of adenosine triphosphate (ATP). The conversion of chemical energy into muscular work is one of the most extraordinary mechanisms known in biological nature (Lodish *et al*., 1995). In addition, it is the mechanism responsible for motility and muscular efforts (Kushmerick and Davies, 1969). The essential thing is the production of direct work of the free energy that is contained in the molecular bonds. In contrast, engineering devices produce work from the energy trapped in fuels, using an intermediate step between the conversion of chemical energy and work (Cavagna, Heglund, and Taylor, 1977). This process generates a volumetric expansion that leads to the realization of work. This mechanism is used in external combustion engines (steam engines) and internal combustion engines (automotive machines). In the case of muscular motility, the violent rupture of the ATP molecule is carried out in two parts: one of lower molecular weight that corresponds to the phosphate group, and another of higher molecular weight that corresponds to the adenosine diphosphate ADP (Bennett, 1981).

In relation to the motility and tension originated in the skeletal muscles, the special arrangement presented by the muscle fibers is described, in order to perform a retro charge produced by the decomposition of the ATP in which a thin filament slides in relation to another thick one, giving rise to the muscle contraction effect.

On the other hand, in terms of the physiology of the cornea (Leung, Bonanno, and Radke, 2011), the work of ATP is used to establish active transport channels of the sodium-potassium pump type, to move bicarbonate ions, regulate pH in the cornea and transfer glucose from the vitreous (Baum, Maurice and McCarey, 1984). All this, in this work, will be indicated in terms of experimental analysis describing the oxygen consumption, in each one of the parts of the cornea (endothelium, stroma, and epithelium), and the associated effect of said consumption with the partial pressure of oxygen existing in the cornea-tear/lens interface generated as a function of the transmissibility of the contact lens used (Takatori *et al*., 2012; Bonanno *et al*., 2002; Bonanno, Clark, Pruitt, and Alvord, 2009). The measurement of the pressure is obtained experimentally from the analysis of the fluorescence produced by a porphyrin located between the cornea and the contact lens (Takahashi, Fatt, and Goldstick, 1966). Finally, the result of the numerical analysis obtained by computational simulation will be discussed, to quantify the oxygen consumption in different points of the cornea: epithelium, stroma, and endothelium (Del Castillo, 2015; Compañ, Aguilella-Arzo, Del Castillo, Hernández, and Gonzalez-Meijome, 2017).

From the study of the partial pressure of oxygen on the cornea-contact lens interface, the need for the production of ATP in the cornea is shown and the details of the respiration of the cornea cells are described. For this, we describe the experiments that quantify the partial pressure of oxygen at the entrance of the cornea (cornea-tear-contact lens interface), and the simulations that allowed predicting the profiles of the oxygen distribution in each of its internal parts. (epithelium, stroma, endothelium). The model for determining oxygen consumption is based on the kinetics of enzymatic reactions. Finally, the predictions of oxygen consumption in the cornea on which different contact lenses are disposed are exposed, using the metabolic model, and the presence of a discontinuity that is currently the subject of debate and investigation is shown.

## Thermodynamic fundamentals of the conversion of chemical energy into muscular work

In the thermodynamic formalism, the work (W) obtained in any of the processes mentioned above is detailed by means of equation 1, which expresses the maximum work theorem.

$$W \leq -\Delta G^{0\prime} \qquad (1)$$

The symbol Δ represents the change of Gibbs free energy ($G^{0\prime}$). The zero superscripts indicate that this function is evaluated under standard conditions (a pressure atmosphere, $20^0$C and a pH of 7.0). The premium superscript indicates that this amount is molar.

According to the previous equation, the equal sign describes the work obtained in quasi-static reversible conditions, corresponds to the maximum work that could be obtained, since in real conditions some amount of energy is not used for the production of work and becomes heat *Q*. Under this situation, we can express the inequality in the equation where equality can be expressed in equation 2.

$$W + Q = -\Delta G^{0\prime} \qquad (2)$$

According to equations (2) and (3) we can express that an increase in entropy ($\Delta S^{0\prime}$) indicates that the conversion of free energy into work is an incomplete process.

$$Q = T\Delta S^{0\prime} \geq 0 \qquad (3)$$

## Biofuels from organic molecules

The way in which the chemical energy is conserved and transported is in the molecule called adenosine triphosphate or ATP, whose chemical structure is represented in Figure 1. A close observation of the figure indicates that its molecular structure reveals the approach of charges of the same sign so that it resembles a compressed spring ready to jump and therefore with power production capacity when any of the links are broken.

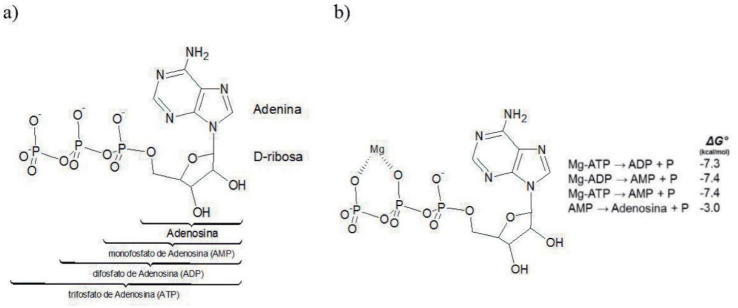



*Figure 1.* a) Structure of the ATP molecule. b) Structure of the ATP complex with $Mg^{2+}$, which is coordinately linked with beta (β) and gamma (γ) phosphates (Lenhinger, 1970)
Source: the authors.

In a series of chemical reactions staggered in different strata, one of the most energetic molecules known is formed. The ATP molecule is obtained in the respiration of the heterotrophs, involving a chemical cycle called Krebs, where oxygen is consumed and 36 molecules of ATP are produced. This represents a high performance compared to the fermentation of glucose, where two molecules of ATP are produced. In the latter case, energy in the form of adenosine triphosphate (ATP) is generated by the decomposition of 1 mole of glucose in water and carbon dioxide, first through the Embden-Meyerhof pathway (anaerobic glycolysis) producing 2 moles of ATP. In the absence of oxygen, this process ends here in pyruvic acid, which is then converted to lactic acid. If oxygen is available (Lodish *et al*., 1995), the conventional cycle of the tricarboxylic acid (TCA) or Krebs (aerobic glycolysis) usually follows, transforming pyruvic acid to $CO_2$ and water to produce 36 additional moles of ATP, as illustrated in Figure 2.

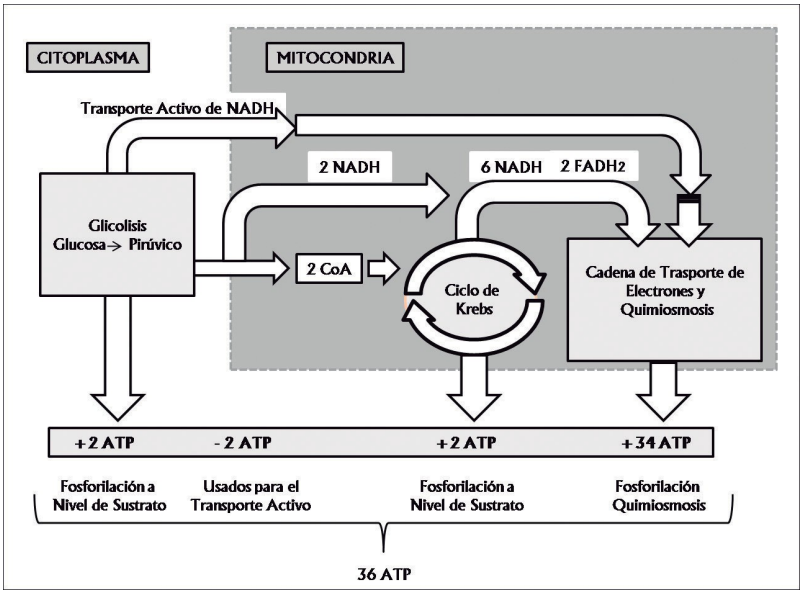



*Figure 2.* Firstly, the production of ATP by the glycolysis process produces 2 molecules of ATP with a yield of 31 %. In contrast, the oxidation of glucose produces in the Krebs cycle 2 ATP molecules and through the transport of electrons through the chains 34 molecules of ATP giving a total of 36 molecules of ATP with a yield of 38 %
Source: the authors.

The use of the ATP is divided into 3 ways:

a) Chemical work.

b) Osmotic work.

c) Mechanical work.

In the first case, we have the so-called biosynthesis in which ATP intervenes in the production of complex products of animal metabolism, such as in the production of polysaccharides, porphyrins, phosphates, proteins, nucleic acids, lipids, among others. In the second case, we have the concentration of substances that raise the chemical potential (against the *Fickian* diffusion) of the compartments of the cell and generate osmotic flux. In particular, this flow follows the direction of the gradient of the chemical potential and the ATP manages to raise the electrochemical potentials by working to concentrate substances, ions, and compounds of vital importance within the metabolic consumption of the cell, such as glucose. The way to achieve the concentration of substances is through active transport, in the form of sodium-potassium pumps, through facilitated transport and by means of vesicles. Specifically, a sodium-potassium pump is characterized by being a structure at the

interface of the cell membrane and operates by means of a change in the absorption sites to trap $Na^+$ and $K^+$ ions, modifying their configurational form by means of a decomposition of the ATP.

In the third case, we have the realization of work by means of the fibers of the skeletal muscles. Obtaining the contraction force of the muscle fibers provides the mobility of the animals.

## Model to explain muscle contraction

To better understand the muscle contraction model, the anatomical structure of the skeletal muscular system, that is, the components that make up the striated muscle is addressed first. In the second instance, the microfibrils that make up the striated muscle are divided into a series of longitudinally repeated units called sarcomeres, which is shown in Figure 3A. The sarcomere is the basic and functional unit of the muscle, and it is delimited by the Z disks. The intercalated disposition of these filaments gives rise to the appearance of the bands A that alternate with the bands I. Likewise, the fine myofilaments are formed by a protein called actin, which is a globular protein. These molecules polymerize to form fibrillar actin. Other proteins that make up the filaments are tropomyosin and troponin (Figure 3B).

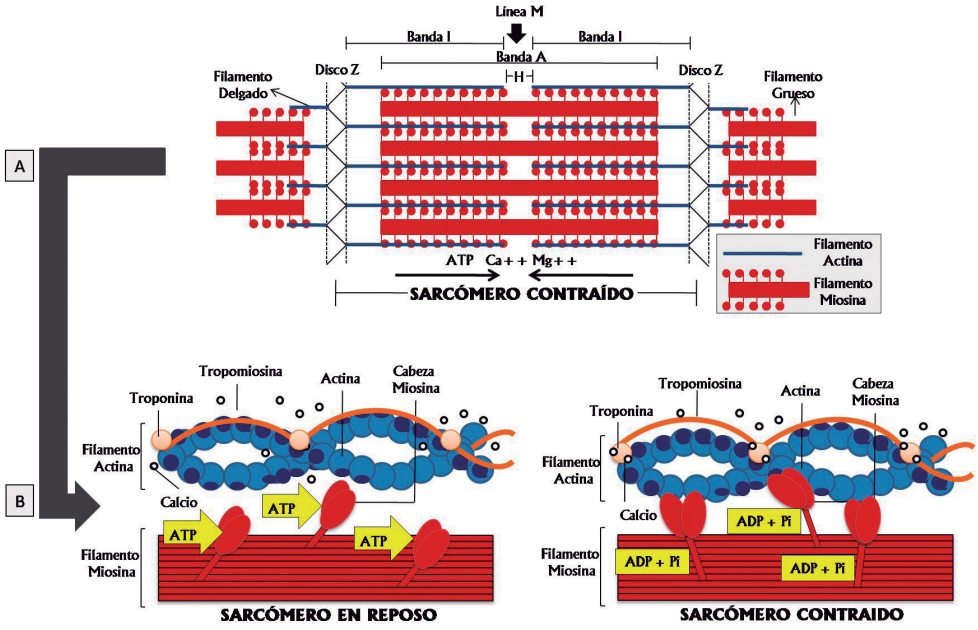



*Figure 3*. a) Sarcomere Distribution: Band A, Bands I, Z Disks, Thin Filaments, Thick Filaments, Space H and Line M. b) Distribution of calcium ions in the intermuscular spaces, by approach, the ATP molecule triggers the decomposition in two molecules, the ADP and the phosphate group. The latter is bound to myosin which has adhered to the thin fibers of actin
Source: the authors.

According to Figure 3, there are special structures in the skeletal muscle fibers that coordinate muscle contraction. The sarcomere of the endoplasm of the cell is highlighted. When calcium ions are released from the sarcomere and reach the fibrils, muscle contraction is triggered.

Although the mechanism of muscle contraction is currently under discussion (Morel, 2015), a tentative image is established considering the relative slip of the actin or thin filament, with respect to thick filaments (myosin), the contraction occurs when a lattice breaks given by crosslinks of fine strands with birth in the thick filaments and termination in the head of the myosin (Huxley, and Simmons, 1971). The lattice occurs when the

end where the myosin is attached to the thin filaments. A molecule of ATP binds to myosin. When the calcium ion approaches the ATP molecule, due to the effect of the Colombian repulsion carried out between the charges of the calcium ions ($Ca^{2+}$) with the magnesium ion ($Mg^{2+}$) (Muňiz *et al*., 1996) the group is separated phosphate from the other part the ATP molecule, which is adenosine diphosphate (ADP). The head of the myosin attached to the thin filaments moves this filament through the backload produced by the firing of the ADP (see part B of Figure 3).

According to the concentration of calcium in the intramuscular solution of the number of myosin heads, which are involved in the simultaneous action of ATP, the required intensity of muscular force is produced, as schematically visualized in Figure 3A. In the regulation of the activity of muscular work, millions of nerve terminals participate by means of the injection of neurotransmitters on the nerve-muscle interfaces. When the muscle is inactive, calcium ions are isolated in intramuscular compartments. However, by the time the cells receive the electrical signal of action, calcium is released and the actin and myosin filaments slide together resulting in muscle contraction. The metro recharge of the phosphate group to the firing impulse of the ADP makes the muscle recede. The joint action of other simultaneous shots gives the intensity and tone of the muscle contraction (Rayment *et al*., 1993).

## *Effect of the partial pressure of oxygen on the oxygen consumption in the cornea*

The cornea is avascular tissue and osmotic work is required for the transport of glucose and other substances necessary for ocular physiology. In each of its parts, endothelium, epithelium, and stroma, active transport is carried out to move carbonate ions, regulate the *pH* of the cornea and prevent the resulting edema. For this, a supply of oxygen necessary for the formation of ATP, which reflects the activity of the cornea, is needed. Said supply comes mostly via aerobic respiration from the ambient atmosphere, in the case of open eyes, while it is carried out by diffusion from the capillaries of the palpebral conjunctiva and the anterior chamber (aqueous humor) under closed eyes conditions. Experimentally, it is complex to quantify the pressure gradient and oxygen consumption in the different parts of the cornea (epithelium, stroma, and endothelium) (Nicholls, and King-Smith, 2003, Weissman, 1984). The studies are carried out by means of theoretical simulations from experimental data, which are known at the ends of the cornea, both under the situation of open eye and closed eye (Papas, 2003, Pérez, Méijome, Jalbert, Sweeney and Erickson, 2003; Alvord, Hall, Keyes, Morgan, and Winterton, 2007).

The experimental techniques only manage to measure the partial pressure of oxygen that we have in the tear layer in contact with the cornea, both in the open eye (approximately 155 mmHg at sea level) (Smelser and Ozanics, 1952) and in the closed eye (approximately 61.5 mmHg) from the palpebral conjunctiva (Brennan, 2005, Chhabra, 2009, Compañ *et al*., 2014). The entry of oxygen occurs in the region called epithelium. On the other hand, in the posterior part of the cornea, the endothelium, receives oxygen from the aqueous humor whose oxygen tension is approximately 24.1 mmHg. (Polse and Mandell, 1970). We can take these data as boundary conditions, and apply a numerical analysis to know the profile of oxygen pressures in the different points of the cornea, estimating the oxygen consumption ratio. The procedure is proposed in the solution of the second law of Fick, with a term of consumption under the limiting conditions to the border (Leach and Treacher, 1998).

The experimental data of the partial pressure of oxygen are measured by means of a phosphorimager before the reaction of porphyrin placed between the cornea and the contact lens, as has been reported by Bonanno et al. (Bonanno et al., 2002; Bonanno, *et al*., 2009). For this, the patient is prepared with a contact lens placed on the cornea for five minutes under the condition of closed eyes. After this time (zero time), the cornea-tear-lens system is exposed to the ambient atmosphere and the transient of the pressure change is measured over time, as indicated in Figure 4.

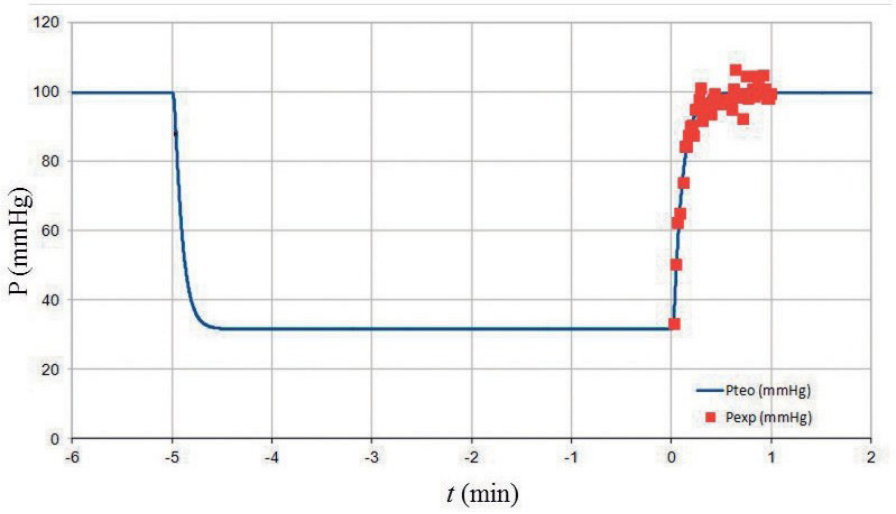



*Figure 4.* Evolution of the partial pressure of oxygen at the entrance of the cornea
Source: Larrea *et al.*, 2009.

In Figure 4, we observe that after a time depending on the disposed of the lens, a state is obtained where the pressure is practically constant with time (Chhabra, 2009, Larrea and Büchler, 2009). This pressure is called stationary pressure and is what the patient will have in the cornea-tear interface when using the lens uninterrupted (stationary conditions) (Lee, Nguyen, Edrington, and Weissman, 2015).

The solid line in Figure 4 represents the evolution of the oxygen pressure gradient in the cornea. Therefore, it is necessary to determine the solution of the following differential equation (Guyer, Wheeler, and Warren, 2009), equation 4.

$$\frac{\partial^2 p_c}{\partial x^2} - \left(\frac{Q}{Dk}\right)_c = \frac{1}{D_c}\frac{\partial p_c}{\partial t} \qquad (4)$$

where $p_c(x,t)$ is the partial pressure of oxygen in *mmHg*, $D_c$ is the diffusion coefficient in the corneal tissue, assumed, homogeneous, in $cm^2/s$, $k_c$ is the solubility coefficient of the cornea tissue in cm3 of $O_2/cm^3$ of *tissue/mm of Hg*, $x$ is the distance in the normal direction to the surface of the cornea in *cm*, $Q_c$ is the variation of the oxygen consumption in *mL of* $O_2/cm^3$ of *tissue layer/s*, and t the time in *s*. The sub-index c refers to the quantities measured in the cornea. When the steady-state is reached, equation (5) is reduced to:

$$\frac{\partial^2 p_c}{\partial x^2} = \left(\frac{Q}{Dk}\right)_c \qquad 0 \le x \le x_c, \qquad (5)$$

In accordance with the Dirichlet boundary conditions

$$p(x_c = 0) = p_0 = 24.1 \ mmHg$$
$$p(x_c) = p_{xc}$$

Where xc is the thickness of the cornea, that is, the distance from the aqueous humor to the cornea-tear interface, $p_0$ is the oxygen tension in the aqueous humor $(x_c=0)$, and $p_{xc}$ the oxygen tension in the cornea interface- tear that in the case of open eyes without a lens will be 155 mmHg, and in the case of closed eyes without a lens it is given by the partial pressure of oxygen that comes from the palpebral conjunctiva and equal to 61. 5mmHg. In the case of a contact lens placed on the cornea, the oxygen tension will depend on its transmissibility, this being defined as the quotient between the permeability (P) and the thickness of the lens (L),

(ie Transmissibility=Permeability/L), (Weissman, 1986; Compañ, Andrio, López-Alemany, Riande and Refojo, 2002). For the tear layer and the lens, the equations are given, respectively, by means of equations (6) and (7).

$$\frac{\partial^2 p_{tear}}{\partial x^2} = 0 \qquad x_c \le x \le x_c + x_{tear} \qquad (6)$$

$$\frac{\partial^2 p_{lens}}{\partial x^2} = 0 \qquad x_c + x_{tear} \le x \le x_c + x_{tear} + x_{lens} \qquad (7)$$

Where $x_{tear}$ and $x_{lens}$ are the thicknesses of the tear layer and the lens, respectively. $p_{tear}$, $p_{lens}$, and $p_c\,(x)$ are the partial pressures of oxygen in the tear, the lens and the cornea (the variable to be determined punctually), respectively. In first approach, to determine the oxygen consumption, we consider the cornea as a homogeneous system where each of the parameters, diffusivity, solubility, and oxygen permeability are average values of the whole system composed of the epithelium, stroma, and endothelium (Wang, Fonn and Simpson, 2003).

The solution of equation (8) for the cornea is a function of $Q_c\,(p_c)$ as a result of aerobic metabolism, more specifically of the Krebs cycle, where one mole of glucose reacts with 6 moles of oxygen to form 6 moles of dioxide carbon and water; producing an energy in the form of 36 moles of ATP. During the last few years (Hill and Fatt, 1964), different $Q_c\,(p_c)$ functions have emerged to determine the profile of pressures and oxygen consumption in the cornea. The most used is a non-linear function based on a functional hypothesis of oxygen consumption, according to the enzymatic reaction depending on the concentration of oxygen, as is the expression given for metabolic functioning, where consumption varies with blood pressure. means of expression:

$$Q_c(p_c) = \frac{Q_{c,\max} \cdot p_c(x)}{(K_m + p_c(x))} \qquad (8)$$

Where $Q_{c,max}$, is an unknown amount that depends on other variables such as pH and glucose concentration. The value of the $K_m$ parameter is modeled according to the respiration reaction of biological species called heterotrophs that consume oxygen, with a value of $K_m$=2. 2. This value corresponds to $Q_c / Q_{c,\,max}$=0. 9, and pressure in the cornea-tear interface of 20 mmHg (Chhabra *et al*., 2009).

Equation (8) describes the variation of the consumption $Q_c\,(p_c)$ as a function of the pressure $p_c$, from a minimum value equal to zero when the oxygen tension is zero $Q_c\,(p_c) = 0$, up to a maximum value $Q_{c,\,max}$ and an oxygen tension $p_c$ = 155 mmHg, corresponding to the partial pressure of oxygen in the cornea-tear interface under the condition of open eyes, which represents the equilibrium condition of a cornea exposed to atmospheric pressure at sea level. These conditions, for the aerobic metabolism of glucose with oxygen (Krebs cycle), are saturated, leading the system to consumption that is independent of pressure (Holden, Sweeney, Vannas, Nilsson, and Efron, 1985). This model reproduces individual experiments for each lens (Fonn, Sweeney, Holden and Cavanagh, 2005).

Figure 5A shows the variation of the oxygen tension in the cornea-tear interface, as a function of time using a Biomedics contact lens. The points represent the experimental data obtained by Bonanno and collaborators (Bonanno *et al*., 2002) using the technique "Dye" and the solid line corresponds to the theoretical curve obtained, by taking the equations (5) to (8), with the boundary conditions established for open eye and closed eye (Graham, Fusaro, Polse, Lin, and Giasson, 2001), respectively. Obtained the parameter $Q_{c,\,max}$ has determined the pressure gradient in the cornea, as shown in Figure 5B for the cornea/teardrop/Biomedics lens system. For this, the tear has been considered as a layer of water with solubility values and oxygen diffusion coefficient of 3.3 x$10^{-5}$mL of $O_2$ (sTP)/$cm^3$ of tissue / mmHg and 3x$10^{-5}$ $cm^2$/s, respectively. The parameters of the Biomedics lens are the thickness of the central part of the lens, L=115 μm, and oxygen permeability P=19. 7 b. As we can see from Figure 5A, the theoretical adjustment tends to behave in the same way as the experimental values. The value of oxygen consumption in the cornea obtained for this type of lens was 5x$10^{-5}$ $cm^2$ of $O_2$ /$cm^3$ of tissue/s.

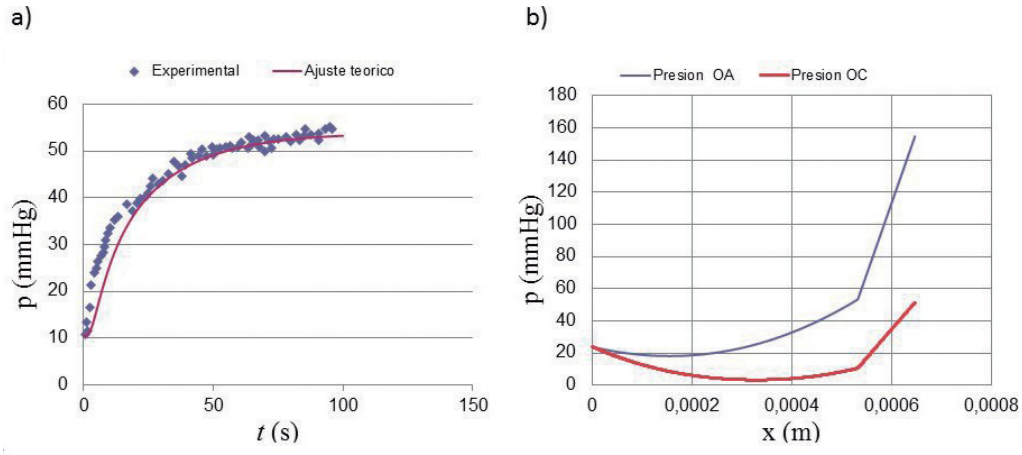



*Figure 5.* In Figure (a) the adjustment to the experimental data is established by means of the metabolic model for a Biomedics lens. Figure (b) shows the profile of the partial pressure of oxygen at each point of the cornea, for the same lens, calculated by means of the PDE differential equation using FiPy. The solution can be obtained through Python with the indicated boundary conditions. Each curve corresponds to different conditions:
OA: open eyes and OC: closed eyes
Source: Bonanno *et al*., 2002.

A study similar to the one done on the Biomedics lens (conventional hydrogel) has been carried out by placing a silicone hydrogel lens (Si-Hy) on the cornea. This lens, unlike conventional hydrogels, has high transmissibility (Figure 6). As was the case with the Biomedics lens, the theoretical adjustment follows a behavior consistent with the experimental data, with a maximum oxygen consumption of 2x10-4 cm2 of O2/ cm3 of tissue/s. That is, four times greater than that observed with the Biomedics hydrogel lens. Which implies a modification in the aerobic metabolic model.

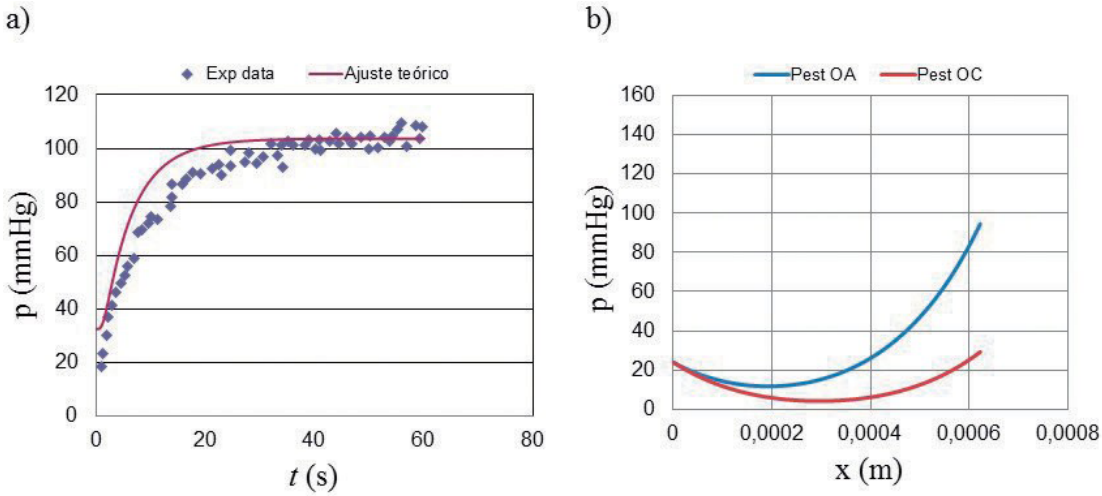



*Figure 6.* a) Transient state of the measurement of oxygen tension in the cornea-lens interface using the fluorescence technique "Dye" performed by Bonanno (Bonanno *et al*., 2002 and Bonanno *et al*., 2009). b) Profile of the oxygen partial pressure at each point of the cornea. Both studies have been performed for the system: Cornea-lagrima-lens PureVision
Source: Bonanno *et al*., 2002 and Bonanno *et al*., 2009.

The parameters of the PureVision lens are thickness of the central part of the lens, L= 90 μm, and oxygen permeability, P=112 b. Note that in both Figure 5a and Figure 6a the pressure profile reaches a minimum when the oxygen flow is zero between the endothelium and the epithelium according to Fick's first law (Sweeney, 1992, Sweeney, 2003).

In the simulation of oxygen consumption for eleven contact lenses presented in the reference of Compañ *et al*., (2017) it is established that as the partial pressure of oxygen decreases at the entrance of the cornea, the value of the oxygen consumption ratio (see equation 8) increases with acidity and decreases with increasing concentration of glucose (Holden et al., 1985), see Figure 7.

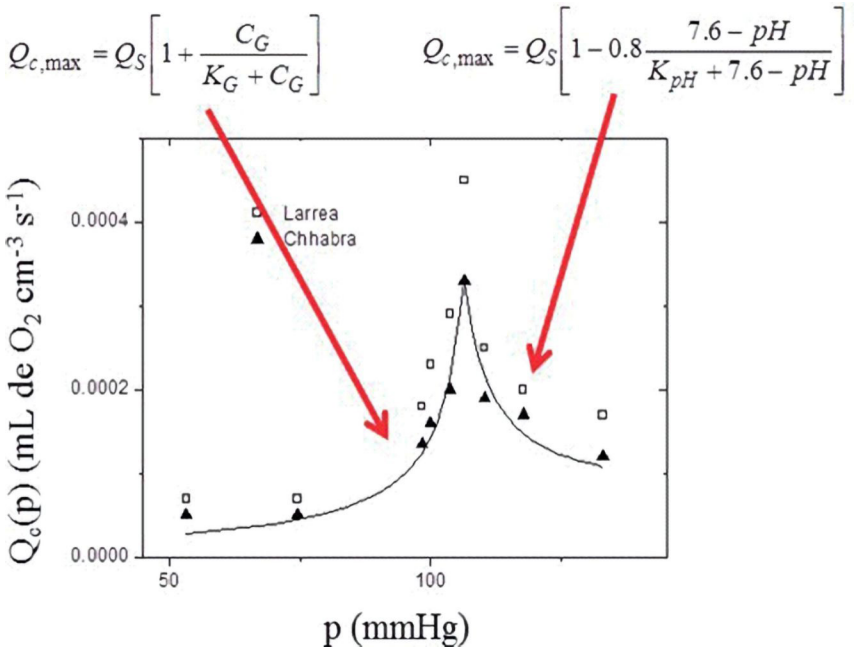



*Figure 7*. Values of the rate of oxygen consumption, based on its partial pressure at the entrance of the cornea
Source: Compañ *et al*., (2017)

It has been previously reported by Harvit and Bonanno (1998;1999) that the oxygen consumption increases due to the acidosis produced by the unbalance in the production of ATP, which occurs when the partial pressure of oxygen decreases and the proportion of the oxygen increases. anaerobic contribution. The maximum ratio of oxygen consumption is increased by the demands of metabolism when there is a decrease in oxygen partial pressure (see Figure 7). In fact, the simulation reported (Compañ *et al*., 2017), presents an oxygen consumption that increases with partial pressure, below 140 mmHg decreases. Consequently, when the stromal cells do not receive enough oxygen (Lin, Graham, Polse, McNamara and Tieu, 2000) to perform the aerobic metabolism (insufficient production of ATP by this means) the glucose consumption is increased by glycolysis and produces an increase in acidity (by lactic acid). The response is an electro-osmotic flow, which originates in the aqueous humor and starts in the endothelium and ends in the stroma to compensate for the increase in pH. This causes inflammation of the cornea (Sarver, Baggett, Harris, and Louie, 1981), known as corneal edema (Mandell and Farrell, 1980), and is caused by an increase in acidity by the formation of lactic acid.

Figure 7 shows that the variation of oxygen consumption is a function of the tension in the two cases: the metabolic model with the parameters of Chhabra (2009a) and Larrea and Büchler (2009). A detailed observation of the figure shows an apparent discontinuity inherent in both models due to the fact that oxygen consumption increases with acidosis and decreases with the anaerobic transition (Harvitt and Bonanno, 1999). To include these effects (acidosis and lack of oxygen) in the oxygen distribution model, this must be modified based on the actual behavior of the cornea.

For consumption between 105 and 135 mmHg of oxygen pressure is considered in equation 9 (Compañ *et al*., 2017).

$$Q_{c,\max} = Q_S\left[1 - 0.8\frac{7.6 - pH}{K_{pH} + 7.6 - pH}\right] \qquad (9)$$

Being Qs the consumption in the discontinuity where $p_c$=$p_s$, and being $pH$ and $K_{pH}$, two parameters that characterize the acidosis.

The minus sign in Eq. (9) reflects that oxygen consumption decreases.

On the other hand, if the pressure range is considered below the maximum pressure $p_s$ ($p_s$ values between 50 and 105 mmHg), it is possible to analyze this variation as a consequence of the change in glucose concentration. This variation can be described by equation 10:

$$Q_{c,\max} = Q_S\left[1 + \frac{C_G}{K_G + C_G}\right] \qquad (10)$$

$C_G$ is the concentration of glucose and $K_G$ the constant of the reaction model, (Leung *et al*., 2011).

For all the above described, the non-linear function of the pressure generates a discontinuity associated with other metabolic reactions that occur in the cornea as a result of the Krebs cycle as well as other reactions that occur in the cornea when a lack of oxygen it is present as corneal swelling, acidosis, limbal hyperemia, neovascularization, keratitis, lack of transparency, (Sweene and, 2003, Fonn *et al*., 2005, Brennan, 2005a).

On the other hand Bonnano *et al*., (2002); Bonanno *et al*., (2009); Giasson and Bonanno (1994), observed that hydrogel contact lenses placed on a cornea can induce acidosis. Harvitty Bonanno (1998) concluded that an acidosis increases 1.8 times the oxygen consumption in the cornea, with respect to a normal pH. The increase in energy demand for these processes causes an increase in oxygen consumption, which generates additional ATP molecules through the oxidized pathway of phosphorylation. The maximum point present in Figure 7 is explained in biochemical terms. The behavior at low pressures in Figure 7, could be explained following the work of Frahm *et al*., (2003), where a decrease in oxygen consumption is observed because the concentration of glucose decreases due to respiration. A factor describing the transition as a function of the oxygen partial pressure is included in equations 9 and 10.

## Oxygen detector systems in the cornea

The porphyrins, Figure 8, present a basic nucleus: macrocycle of four pyrrole rings joined by four methine bridges. The existence of alternating double bonds in the 16 internal carbon atoms of the tetrapyrrolic ring stabilizes a flat molecule, resonant and highly resistant to chemical modifications. The four pyrrole rings are named A, B, C and D, and the methyl bridges are σ, α, β and γ. In this rigid planar structure, there are eight lateral chains joined in positions 1 to 8, which determine the physical characteristics of the porphyrins, Figure 8.

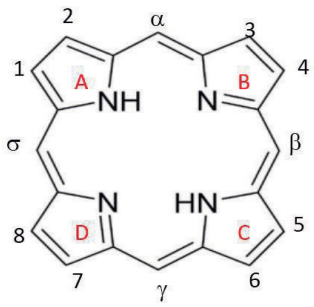
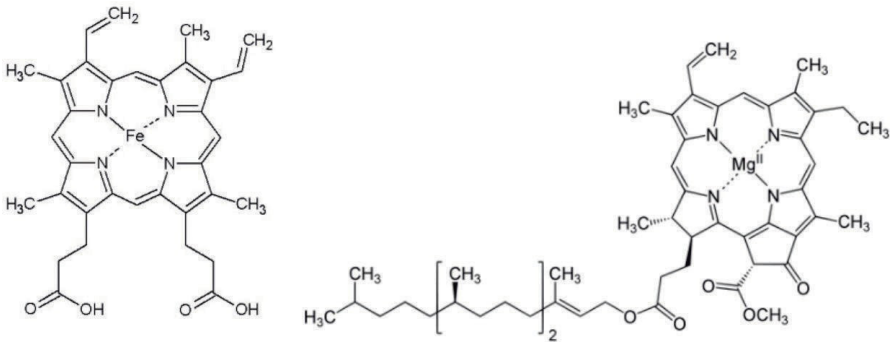



*Figure 8.* Porphyrin ring
Source: the authors.

Porphyrins are easily combined with transition metals forming chelate rings, which are part of the structure of compounds of great biological importance, for example: Hemoglobin and myoglobin (Smith, Raven, and Chernova, 2011), which contain iron in state of oxidation $2^+$ and Chlorophyll that possesses the magnesium ion $2^+$ in its structure, Figure 9.




a) b)

*Figure 9.* Structure of systems with porphyrin: a). hemoglobin, and b). chlorophyll
Source: the authors.

In the biosynthesis of porphyrins intervenes the intracellular concentration of ATP, there is a significant effect in the synthesis of tetrapyrroles (Rouault and Tong, 2005); for organisms with porphyria induced by certain porphyrinogenic agents, ATP levels are diminished (Briggs and Christie, 2002).

At an electronic level, biological molecules tend to absorb energy in the UV-Vis regions. Molecular systems with conjugated double bonds absorb at wavelengths in the visible region, as a consequence of the electronic resonance effect (Awschalom and Flatté, 2007). The tetrapyrrolic structure of the porphyrins presents electronic spectra in the region of the visible spectrum. An intense Soret band close to 400 nm and four additional absorption peaks of lower intensity are generally observed, between 500 and 650 nm for non-chelated porphyrins with metals (Kan, Li, Yang and Hou 2008). Once the electronic excitation process is carried out, the molecules can present two states: singlet, with a short half-life and ability to relax to more stable states and a triplet state with a much longer half-life (Chen *et al.*, 2010 ). The excited states tend to pass to stable basal configurations dissipating the absorbed energy, either by emitting light observing fluorescent effects, heat, or transferring the energy to another molecule.

Porphyrins act as efficient photosensitizers in biological systems. This interaction is due to the fact that structurally the amino acids formed by thiol groups appease the triplet state of these unsaturated systems. Important effects have been reported in the photochemical degradation of contact lenses as a consequence of photodynamic couplings. Roberts (1984) observed the marked photopolymerization and destruction of histidine in the protein of a photolyzed lens in the presence of different substitutions of the porphyrin ring. This suggests that porphyrin-type components allow possible photooxidative damage *in situ*. This is the case of Mesotetra (p-sulfonatophenyl) porphine (TPPS), which binds to the lens proteins. This feature increases the residence time of the sensitizer in the lens and, therefore, increases the likelihood of inducing photooxidative damage to the tissue in vivo. The binding of TPPS decreases the fluorescence of the lens proteins, causes a shift in the absorption-fluorescence spectrum of the ground state and an increase in the life of the triplet state of TPPS (Chen *et al*., 2010; Zhang, Wu, Guo and Zeng, 2010).

In the presence of oxygen, the porphyrin ring triggers photosensitizing singlet oxygen processes. The light is absorbed by the porphyrins which, when activated react with oxygen, produce reactive oxygen species. Peripheral porphyrin substitutions reflect changes in quantum yield, a lifetime of singlet and triplet states, and an effect on molecular singlet oxygen production, Figure 10 (Drain *et al*., 2002). The reactivity of molecular

oxygen and the different species caused by reduction are essential in biological systems. The inertia of molecular oxygen against organic substrates is a consequence of its triplet state in its most stable electronic configuration.

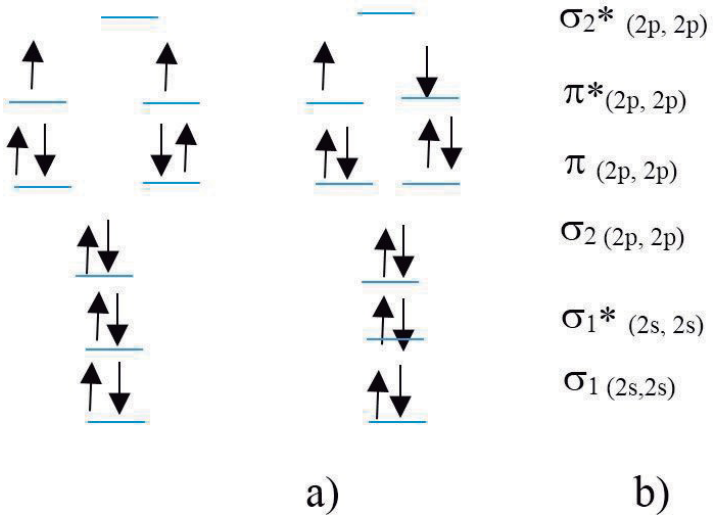



*Figure 10*. Basal electron states of the oxygen molecule: a) Triplet, b). Singlet
Source: the authors.

This effect is important in corneal hypoxia, extending a relationship between the amount of corneal oxygen and the blood staining thereof. This represents the deposition of hemoglobin and its decomposition products. Pathological evidence of these corneas have typically revealed degenerated endothelial cells and keratocytes. These degenerative changes have typically been attributed to the toxicity of erythrocyte waste. However, another possible mechanism for this lesion is photosensitivity induced by porphyrin. Examination of frozen sections of a human cornea with blood has shown fluorescence in all layers of the cornea, similar to that seen with the hematoporphyrin derivative. The production of cytotoxic oxygen species within the cornea stained with blood exposed to light may contribute to endothelial and keratocyte degeneration. Limiting light exposure to corneas with blood could theoretically reduce the toxicity induced by light and porphyrin.

Oxygen transport in the cornea leads to significant effects on its functionality and structure. It has been observed that during the wear process of contact lenses the $O_2$ consumption of the cornea is altered, which has implications for ion transport (Purrello, Monsu'Scolaro, Bellacchio, Gurrieri, and Romeo, 1998). This transport involves the mobility of ions such as H + protons. There is a significant effect of pH on the wear process. When the pH changes from 7.5 to 6, 7-7, 3, the $O_2$ consumption increases by a factor of 1.80 ± 0.11. This increase is secondary to the activation of pH-regulating mechanisms, including the exchange of $Na^+$ / $H^+$, which then stimulates $Na^+$ / $K^+$ - ATPase activity.

## Conclusions

Thermodynamics and chemical kinetics have been the two pillars on which the physicochemical description of aerobic and anaerobic respiration of physiological processes is based. Oxygen as a pathway in the production of ATP originates in heterotrophs, achieving greater efficiency in the metabolism of cells. The type of chemical reactions that in anaerobic and oxidative glycolysis support the physiology of the organs and tissues of animals has been pointed out in this review article. Especially mentioned is the use of ATP in the walls of cells to establish an intro-and extra-cellular exchange of active transport, such as the sodium-potassium pump and the mechanism of skeletal muscle motility. Likewise, oxygenation of the cornea has been highlighted, where an aerobic-anaerobic transition occurs when the partial pressure of oxygen is approximately 100 mmHg at the cornea-tear interface. Indeed, from the analysis of the experimental values shown in Figure 7, obtained

through the metabolic model, there are two processes that do not occur simultaneously. This is because when the oxygen pressure decreases (between 130 and 105 mmHg), the oxygen consumption in the cornea increases with acidosis, which leads to an anaerobic transition with a decrease in oxygen consumption. When the partial pressure of oxygen in the cornea-tear interface is in the range between 30 and 105 mmHg, approximately, the oxygen consumption is dependent on the glucose concentration. A singularity is observed as the dependence of oxygen consumption with respect to the tension in the cornea. At low and moderate pressures, other phenomena different from those already mentioned may occur, such as corneal swelling, acidosis, loss of transparency, keratitis, neovascularization, and limbal hyperemia, among others, which can be described by a non-linear function with the Pressure. At the molecular level, the wear process of contact lenses alters the $O_2$ consumption of the cornea, which has implications for ion transport. This transport involves the mobility of ions such as protons, which has a significant effect of pH on the wear process.

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