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RBC-ATP Theory of Regulation for Tissue Oxygenation-ATP Concentration Model

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1. Introduction

It is known that red blood cells release ATP when blood oxygen tension decreases. ATP has an effect on microvascular endothelial cells to form a retrospective conducted vasodilation to the upstream arteriole. Local metabolic control of coronary blood flow due to vasodilation in microvascular units where myocardial oxygen extraction is relatively high occurs due to ATP.[5] Arterioles dilate or constrict in response to changing intravascular pressure.[6]

"It is well known that myogenic responses, flow-dependent vasodilation, local metabolic effects, and propagation all contribute to blood flow regulation. Primarily responsible for carrying oxygen in blood, red blood cells (RBCs) may also act as oxygen sensors and thus play a role in the communication of metabolic demand" [3,7]. The mechanisms for release of ATP from the RBC in response to lowered oxygen saturation have been studied. [8]. Jagger et al. [9] measured the ATP release at low O₂ levels in the presence and absence of CO to demonstrate that the release of ATP from RBCs may be connected to the change of the hemoglobin molecule from its relaxed state to its deoxygenated state. Upon release, ATP binds to P2Y purinergic receptors on the luminal surface of the endothelium, starting the conducted response [10]. An in vitro microfluidic experimental study to investigate the dynamics of shear-induced ATP release from human RBCs with millisecond resolution was conducted by Wan et al. [11]. Conclusively it was shown that there is a sizable delay time between the onset of increased shear stress and the release of ATP. "It was seen that this response time decreases with shear stress, but does not depend significantly on membrane rigidity. It was shown that even though the RBCs deform significantly in short constrictions (duration of increased stress <3 ms), no measurable ATP is released." [11]

ATP is short for adenosine triphosphate, which is a “currency” of biological energy. There exists an adenosine group with 3 phosphate groups attached to it. Hydrolizing this bond detaches one of the phosphate groups and produces ADP, which is adenosine di-phosphate plus a phosphate group and energy. Through chemical reaction if you pop off a phosphate group of ATP, energy will be generated for general heat or one can couple this reaction with other reactions that require energy. This chemical reaction of ATP to ADP involves going from stored energy to used energy. ADP can be recharged back to ATP by processes in the mitochondria.

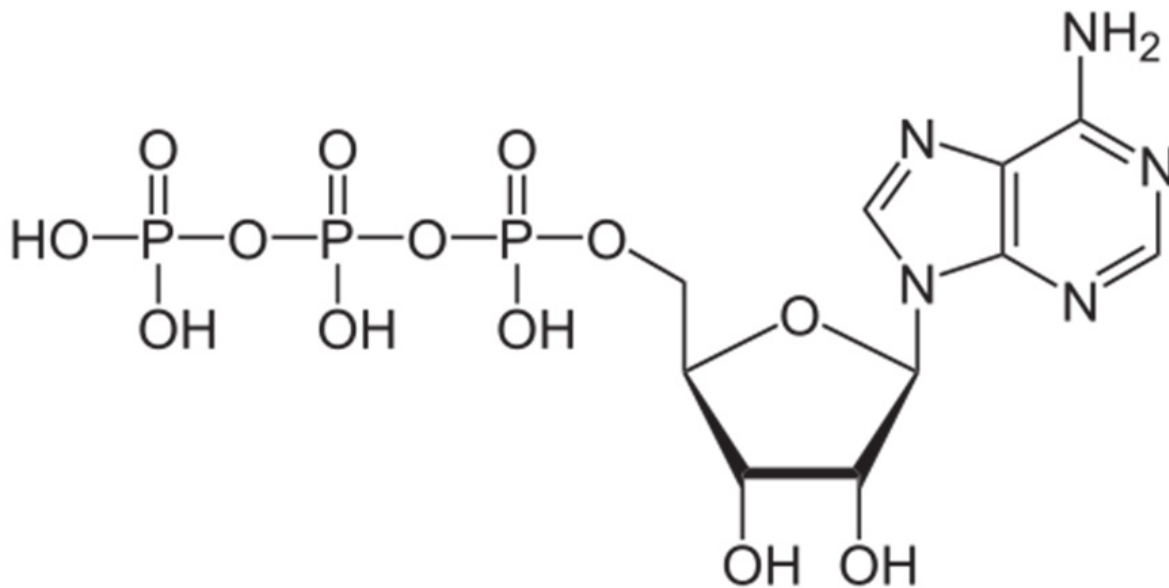


Figure 1. Adenosine Triphosphate[12]

The same part(adenine) that makes up DNA is that which makes up these energy currency molecules known as ATP molecules. Adenine makes part of adenosine which makes part of ATP. The other part of ATP is known as ribose from RNA, which is a five carbon sugar. ATP drives biological reactions. In terms of electrons when one pops off the phosphate group the electrons enter a lower energy state between phosphate and oxygen atoms which generates energy.

RBC's have no nucleus or mitochondria. As a result RBC's obtain their energy using glycolysis to produce ATP. There are both advantages and disadvantages to this. An advantage is due to the biconcave disk shape which optimizes the cell for the exchange of oxygen with its surroundings and optimizes space for the hemoglobin. The RBC's are deformable and flexible so that they can move through the tiny capillaries where oxygen is released. The disadvantage is that because of the absence of nuclei and organelles, mature RBC's do not contain DNA and cannot synthesize any RNA, and cannot divide or repair themselves. The Mitochondria enables cells to produce 15 times more ATP than usual. Lack of mitochondria means that the cells use none of the oxygen they transport. Instead they produce the energy carrier ATP by means of fermentation, via glycolysis of glucose and by lactic acid production.

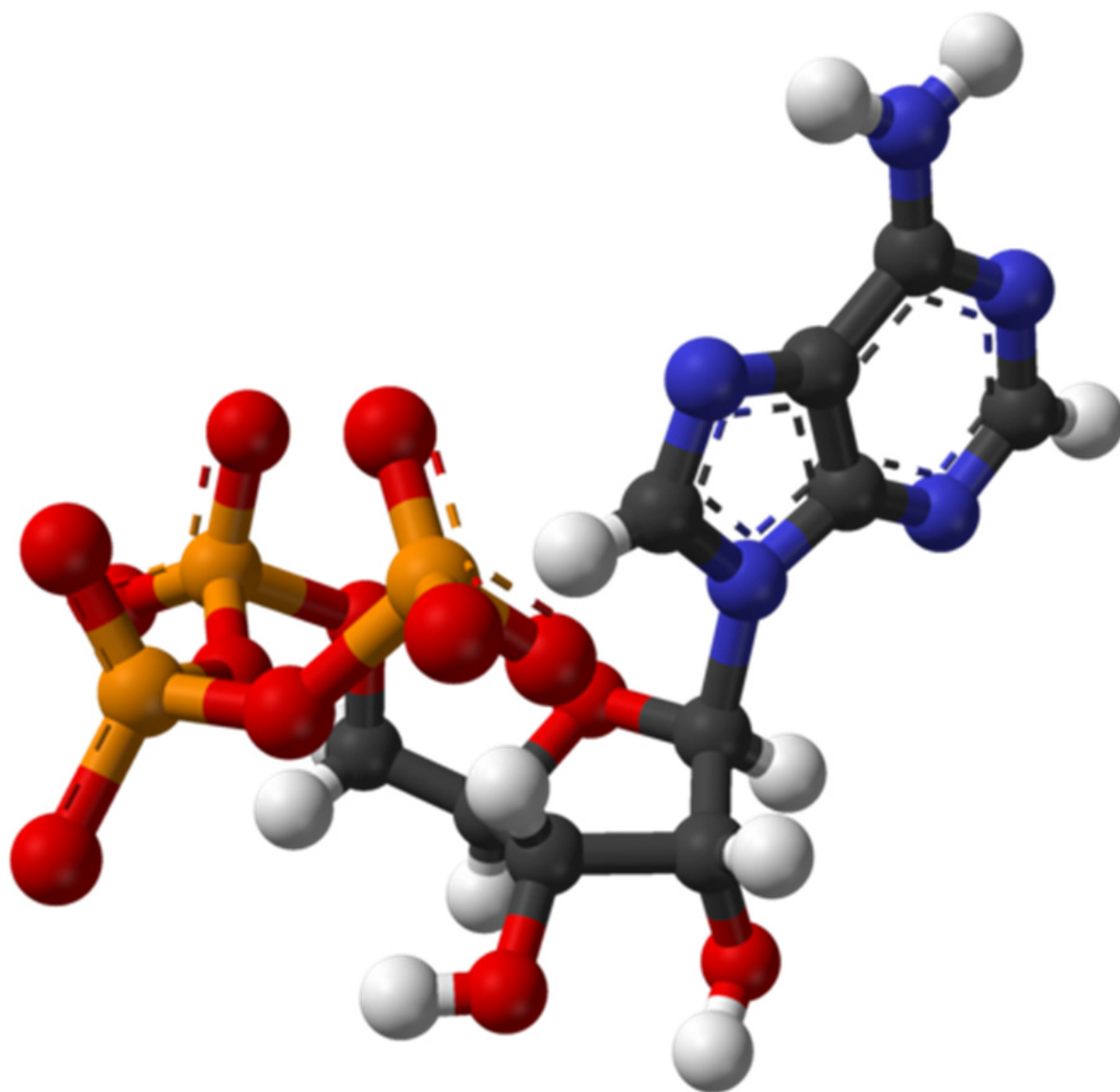


Figure 2. Ball and Stick Model of ATP based x-ray diffraction data[13]

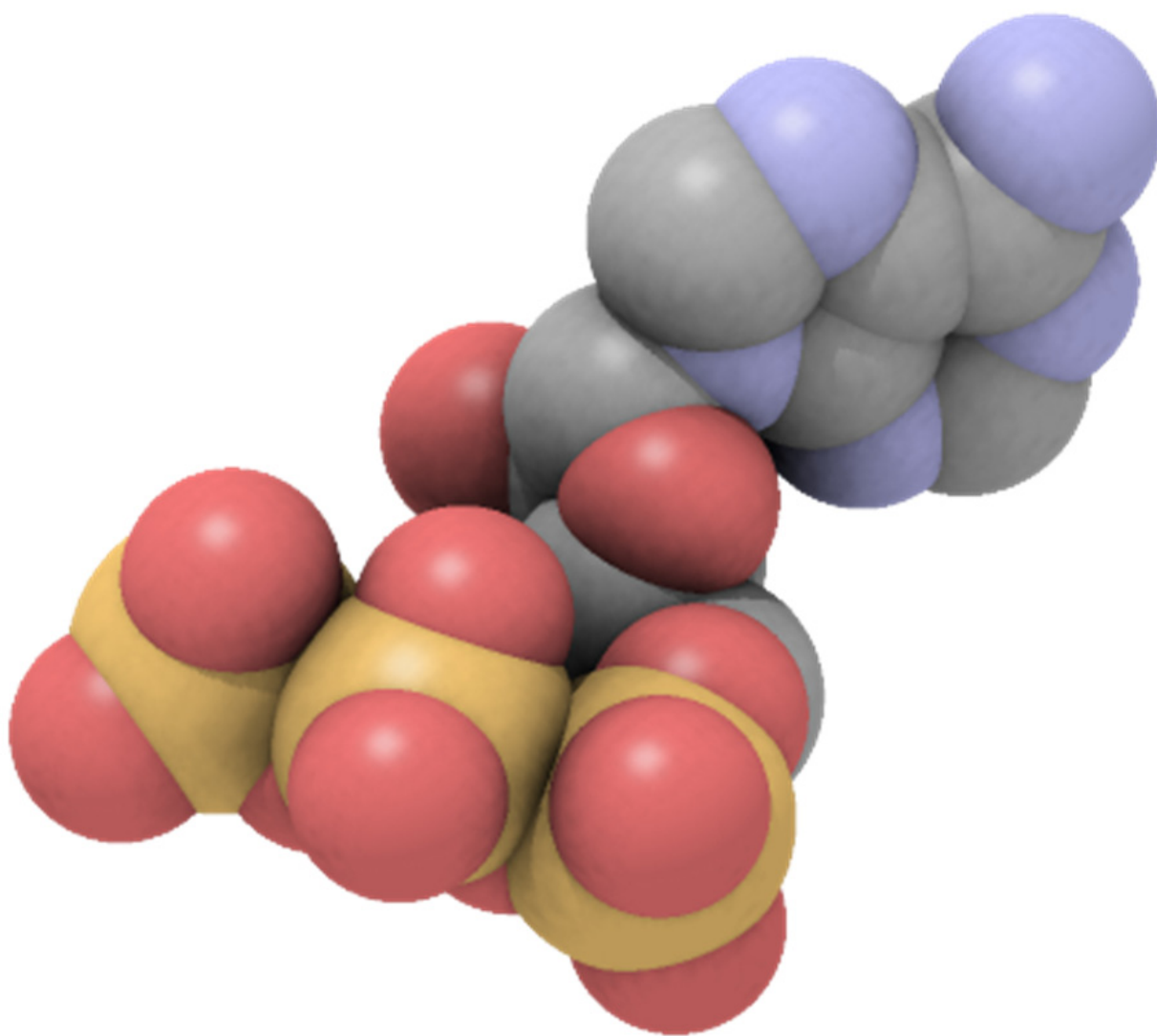


Figure 3. Space-Fill Representation of ATP[14]

2. Structural features erythrocyte and the erythrocyte membrane

Lacking organelles as nucleus, mitochondria, or ribosomes, the red cell does not synthesize new proteins, carrying out the oxidative reactions associated with mitochondria, or undergo mitosis.

The RBC consists of a membrane surrounding a solution of protein and electrolytes. About 95% of the protein is the oxygen-transport protein, hemoglobin. The remainder of the protein includes enzymes required for energy production and for maintenance of hemoglobin.

3. Shape of RBC

In immobile state, the normal human RBC is shaped as a biconcave disc. The disc shape is important to erythrocyte function. The ratio of surface to volume is optimized so that oxygen transfer is possible. Also the biconcave disc is more deformable than a sphere and undergoes the change in shape necessary for optimal movement in microvasculature.

The four possible forces to maintain the shape described are (1) elastic forces within the membrane, (2) surface tension, (3) electrical forces on the membrane surface, and (4) osmotic or hydrostatic pressures. The maintenance of RBC shape is dependent on the structure of the cell as well as in the external environment. If these are changed, the cell may become spherical.

When RBC's are suspended in hypotonic solutions and osmotic swelling occurs. This can make the cell spherical. These changes are associated with an increase in volume while the cell surface area remains the same or changes only slightly. When spherical shape is attained, the cell diameter decreases, and this shows the elastic properties of the membrane.

Discocyte-echinocyte transformation takes place when ATP is depleted, when intracellular calcium is increased, when the cell is exposed to plasma, anionic detergents, high pH, lysolecithin or fatty acids.

4. Dimensions of RBC

Photomicrographs are used to measure the dimensions of RBC's. Average values for the mean cellular volume in normal subjects are from approximately 85 to 91 fl. Ninety-five percent of normal red cells are between about 60 and 120 fl in volume. Various results have yielded an average normal value for red cell diameter of 7.2 to 7.4 microns.

5. Present objective

In this work we model the time delay of release of ATP as supporting work shows by Wan et al. [11] for shear-induced ATP release from red blood cells. A release rate which is a function of time and introduces a delay mechanism is introduced to show how the concentration of ATP is thus affected.

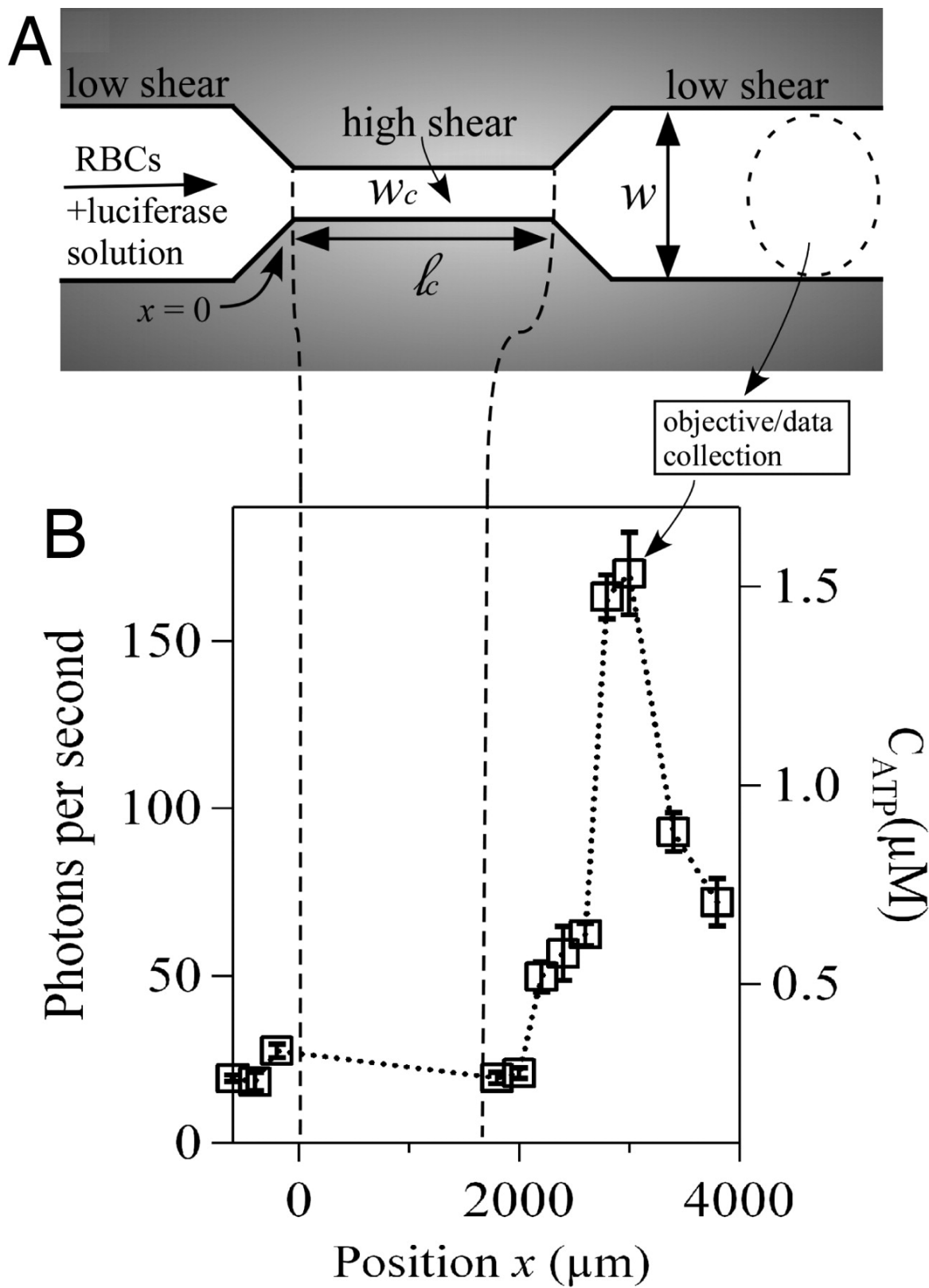


Figure 4. [11]

6. Method of solution

By conservation of mass, the decline in oxygen flux must equal the rate of oxygen consumption, giving the following equation for the change in oxygen saturation, $S(x)$, with distance, x , along each arteriole:

$$\frac{d}{dx}[Qc_oH_D S(x)] = -q \quad (1)$$

where Q is volume flow rate in an individual vessel, c_o is the carrying capacity of RBCs at 100% saturation. H_D is the discharge hematocrit, and $q = \pi M_0(r_{1,j}^2 - r_j^2) [3]$.

The release rate of ATP from an RBC, $R[S(x)]$, is defined by a decreasing linear function of oxyhemoglobin saturation based on experimental data. ATP release from human erythrocytes in response to normoxia and hypoxia was observed in in vitro experiments.[3].

A linear fit of experimental values defines the ATP release function of saturation :

$$R[S(x)] = R_0[1 - R_1 S(x)] \quad (2)$$

In general, the rate of change in plasma ATP concentration, $C(x,t)$, is given by the difference between the rates of ATP release and degradation:

$$\frac{\partial}{\partial t}[\pi R^2 \cdot (1 - H_T)C] + \frac{\partial}{\partial x}[(1 - H_D)QC(x)] = \pi R^2 H_T R[S(x,t)] - 2k_d \pi RC(x,t) \quad (3)$$

where H_T is tube hematocrit, R is radius of vessel and k_d is a concentration rate constant.([3])

We assume that there is no convection in the vessel and there is no x -dependence. Equation (3) simplifies to the following equation:

$$\frac{dC}{dt} = \frac{H_T}{1 - H_T} R(S(t)) - \frac{2}{R} \frac{k_d}{1 - H_T} C$$

In this chapter a model is developed which predicts tissue ATP concentrations as a variation of time and depth into the tissue due to changing oxygen tensions.

The ATP concentration within plasma as a variation of time due to changes in oxygen tension at the tissue surface is related to the release and degradation of ATP, by the following equation:

$$\frac{dC}{dt} = \eta \cdot R_{ATP}(t) - \delta C \quad (4)$$

where δ is some constant of degradation. $\delta = \frac{2}{R} \frac{k_d}{1-H_T}$ [Related to the RBC fraction], R is the release of ATP from the RBC and C is ATP concentration.

In this model the ATP concentration maximizes at some constant value, depending on the oxygen saturation. This model can be used to predict the plasma ATP concentration based on different oxygen saturations.

7. Discussion

From Equation (4), with varying degradation constant, related to the RBC fraction, and release rate, $R_{ATP}(t) = H(t-3)$ where H is the Heaviside function as a function of t, we show results in Figure 5 for concentration of ATP, (μM), versus time (ms). The value in the shifted Heaviside function corresponds to the experimental results of Wan et al [11] for time $t < 3$ ms. This is the time interval where there is no ATP release and can be confirmed in Figure 4 where there is no ATP release before and throughout the stenosis of the microfluidic device. In fact there is ATP release in the low shear expansion on the right of the microfluidic device. This can be seen in the increase in concentration of ATP released by RBC as shown in Figure 4. The parameter η represents the rate of increase of ATP release and for large η , the concentration of ATP increases rather steeply, whereas for smaller η the concentration of ATP increases less steeply as can be seen in Figure 6 for varying values of degradation constant. Also our model is consistent with the experimental results of Wan et al.[11] in that the greatest increase in ATP occurs approximately 29 ms after the onset of increased shear stress.

(See Figure 6 for $\delta = 0.1$ at time $t=30$ ms.) It is noteworthy to see that these results for shear-induced ATP release can also be extended to ATP release due to a decrease in saturation.

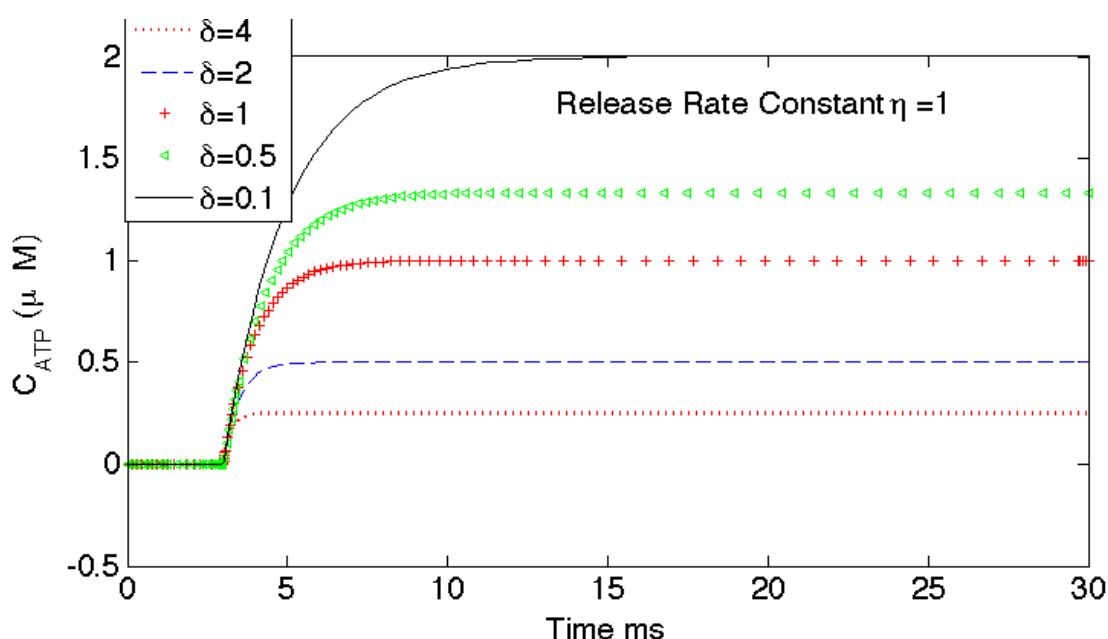


Figure 5.

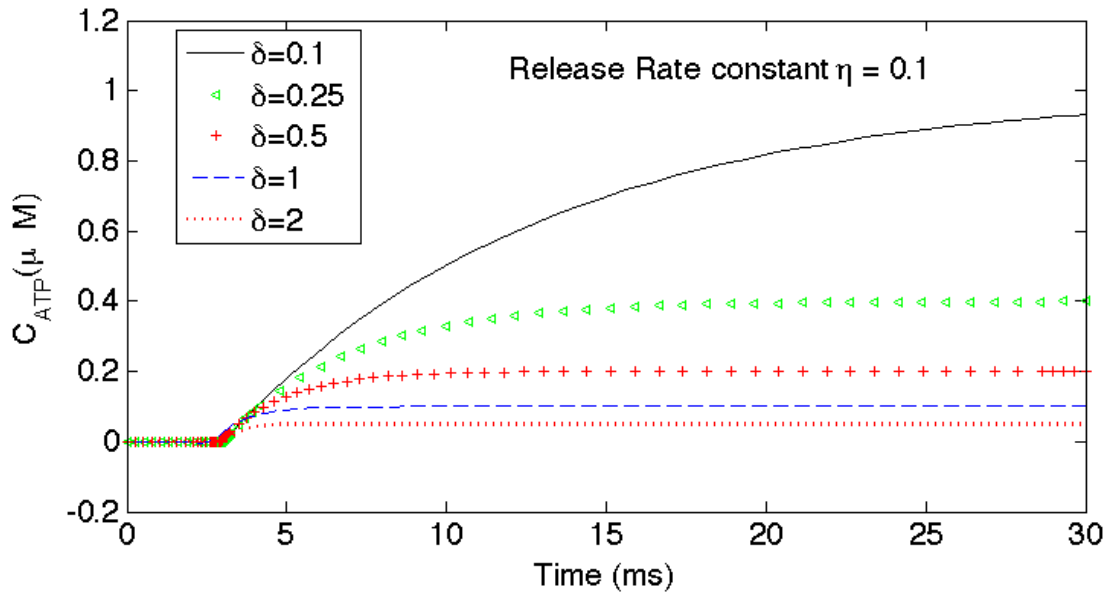


Figure 6.

8. Summary and conclusion

In this work we have outlined the importance of ATP as a signaling molecule in the microcirculation and have discussed the biochemical aspects of ATP and ADP as well as introduce a model for ATP release as used in microfluidic devices where RBC's are subject to compression and deform thus resulting in ATP release.

It is shown by Wan et al. [11] that even though the RBCs deform significantly in short constrictions (duration of increased stress <3 ms), no measurable ATP is released. This critical timescale is in proportion with a characteristic membrane relaxation time determined from observations of the cell deformation by using high-speed video[11]. "The results suggest a model wherein the retraction of the spectrin-actin cytoskeleton network triggers the mechano-sensitive ATP release and a shear-dependent membrane viscosity controls the rate of release".[11]

It is noteworthy to see that these results for shear-induced ATP release can also be extended to ATP release due to a decrease in saturation.[3]

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