# Modeling of the contribution of a possible intra-muscular lactate shuttle to aerobic metabolism. A volumetric model.

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***Abstract:*** *The possibility of an intra-cellular lactate shuttle has been proposed by GA Brooks. However, this hypothesis is contested. A numerical simulation of the diffusions and reactions of the different molecules (lactate, pyruvate, $H^+$, $NAD^+$, NADH, Glucose-1P…) would be difficult. In the present study, the contribution of a possible lactate shuttle to aerobic metabolism was computed with a volumetric model. Indeed, the double integral of a positive function of two variables corresponds to the volume of the region between the surface defined by the function and the plane which contains its domain D. The positive function corresponded to the production of ATP by glycolysis which is equal to 9.68 % of the total ATP production during an aerobic exercise and domain D corresponded to the cross-section of a muscle fiber. Different solids of revolution (cones and a cylinder) whose volumes were equal to 9.68% of the fiber volume were computed and the surface of these solids corresponded to the glycolytic-ATP production in function of the distance from the center. The results of this model suggest that the maximal contribution of a possible lactate shuttle would be lower than 10 % of the aerobic metabolism of the whole muscle fiber. However, the local contribution of a lactate shuttle would be much higher especially for the local metabolism in the center of the fiber.*

***Key words:*** *endurance, lactate, pyruvate, shuttle.*

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## I.    INTRODUCTION

At high metabolic rates, oxygen diffusion can be critical. A myoglobin-facilitated oxygen diffusion, (i.e., reversible combination of myoglobin with oxygen and translational diffusion of oxymyoglobin molecules) was assumed to contribute to 50% of the oxygen diffusion in muscle fibers [1, 2]. However, in more recent studies, the directly measured diffusivity of myoglobin in skeletal muscle cells was 2–10 times lower than previously assumed and the myoglobin-facilitated diffusion has been largely overestimated [3, 4].Many mitochondria are close to the sarcolemma (subsarcolemmal mitochondria, SS). Moreover, the subsarcolemmal mitochondria are located in front of the capillaries, which decreases the distance between blood and mitochondrial membranes. The other mitochondria are located between myofibrils and are called intermyofibrillar mitochondria (IMF).However, a subsarcolemmal aerobic metabolism increases the distance between aerobic ATP production and ATP consumption by the myofibrils in the core of the muscle fibers. The coupling of ATP hydrolysis-synthesis with the phosphocreatine-creatine shuttle [5, 6] enables the transfer of high energy phosphates with low ATP-ADP gradients, which limits the lowering of $|\Delta G_{ATP}|$.
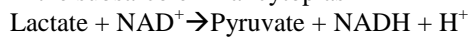
A lactate shuttle within the same fiber has been suggested [7-10]: mitochondria in the periphery of the fibre oxidises the lactate produced in the centre of the same fibre, which would enables a global alactic ATP production in spite of lactate production in the fiber center (Fig 1.).The presence of a monocarboxylic transporter (MCT) in the internal membrane of the mitochondria facilitates the input of pyruvate or lactate in the mitochondria [11, 12]. More recently [13, 14], mitochondrial pyruvate carriers (MPC) have been found. Moreover, there is a mitochondrial lactate dehydrogenase (mLDH)[15-16] that consists mainly of the heart (H4, LDH-1) isoform. The presence of MPC, MCT and mLDH facilitates the entry of pyruvate and lactate into mitochondria and their oxidation.
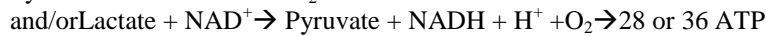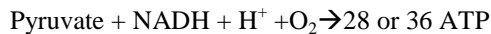
In the core cytoplasm:

Glycogen + $P_i$➔Glusose-1 P

Glusose-1 P + 3 ADP➔ 2 Pyruvate + 2 NADH + 2 $H^+$ + 3 ATP ➔ 2 Lactate + 2 $NAD^+$ + 3 ATP

in the subsarcolemmal cytoplasm
Lactate + NAD$^+$→Pyruvate + NADH + H$^+$
and within the subsarcolemmal mitochondria:
Pyruvate + NADH + H$^+$ +O$_2$→28 or 36 ATP
and/orLactate + NAD$^+$→ Pyruvate + NADH + H$^+$ +O$_2$→28 or 36 ATP

In most of biochemistry books it is assumed that the passage of two electrons from NADH to O$_2$ drives the formation of 3 ATP and the passage of two electrons from FADH2 to 0$_2$ yields 2 ATP. However, it is likely that the passage of two electrons to O$_2$ yields 2.5 ATP for NADH and 1.5 ATP for FADH2, only [18]. Moreover, the ATP production by mitochondria also depends on the relative contributions of the malate-aspartate shuttle and α-glycerol phosphate shuttle to the transfer of hydrogen from cytoplasmic NADH to the matrix of the mitochondria. Therefore, it is likely that the ATP production by pyruvate oxidation yields 28 ATP instead of 36 ATP [17]. In this case, the total ATP production of glucose-1P catabolism is 31 ATP instead of 39 ATP. The ratio of the ATP production by the fermentation of glucose-1P to pyruvate on the total ATP production would be 0.09677 (3/31) instead of 0.077 (3/39).

The hypothesis of lactate-shuttle within muscle fibers has been contested [18-20]. However, in two microscopy studies[21, 22] on the depletion of glycogen after exhaustive long distance running, the glycogen particles just beneath the sarcolemma seem to remain chiefly unaffected in type I muscle fiber (slow fibers) whereas there was a few or no glycogen particles in the core of these same fibers. This pattern of glycogenolysis could be the result of a lactate shuttle but it could also be the consequence of the oxidation of fatty acids in the periphery of the muscle fibers during these submaximal exercises.

It would be very difficult to study the contribution of the lactate shuttle to the metabolism in the core and periphery of muscle fibers by a simulation of the diffusions and the reactions of the different particles (lactate, pyruvate, H$^+$, NAD$^+$, NADH, Glucose-1P, O$_2$, oxymyoglobine, myoglobine, ATP, ADP, creatine, creatine-phosphate…) in such an anisotropic compartment.

The aim of the present study is not to prove the possibility of a lactate shuttle within a muscle fiber but to estimate the limits of its contribution if an intra-cellular lactate shuttle is possible during exercise. The importance of the contribution of a possible lactate shuttle to aerobic metabolism has been studied with a volumetric model [23] at maximal oxygen uptake when glucose is the only substrate of the oxidative metabolism.
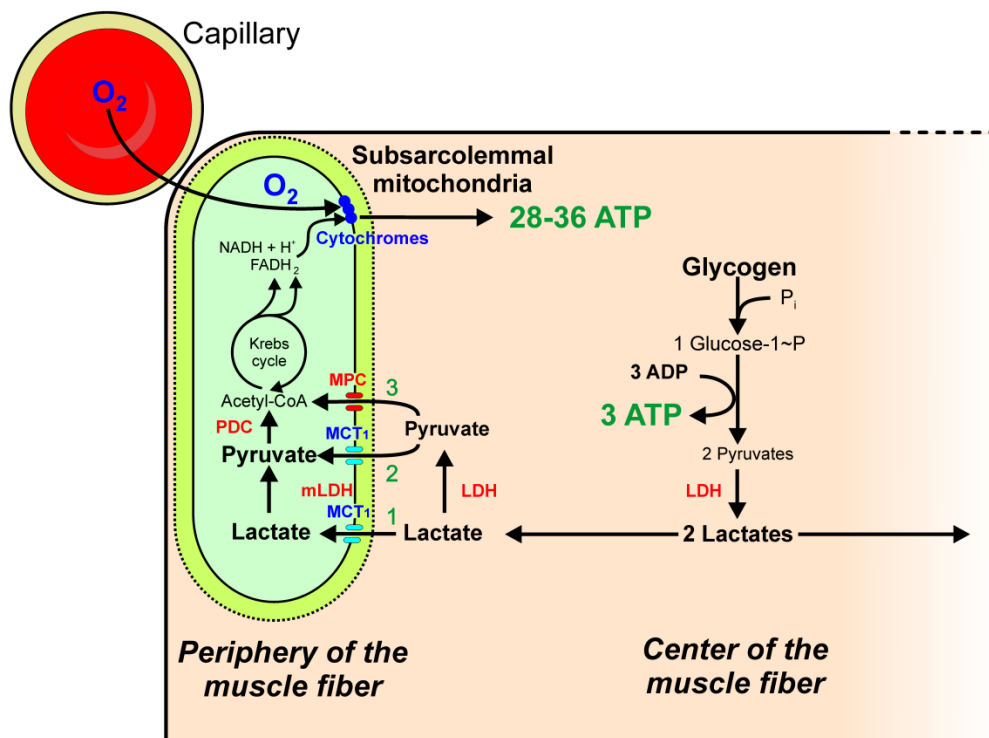


**Fig. 1**: Description of the lactate shuttle between the center and the periphery of a muscle fiber.MPC, mitochondrial pyruvate carrier; LDH lactate-dehydrogenase; mLDH mitochondrial lactate-dehydrogenase; MCT monocarboxylate transporter, PDC Pyruvate Dehydrogenase Complex.

## II.  METHODS

### 2.1 Double integral of positive function and volume

The double integral of a positive function of two variables ($z = f(x, y)$) corresponds to the volume of the region between the surface defined by the function (on the three-dimensional Cartesian plane where $z = f(x, y)$) and the plane which contains its domain D (Fig.2A). If z corresponds to the fraction $F_G$ of the Total ATP production by the glycolysis at a point P and D corresponds to a circle, the sum of this ATP production by all the points inside the circle is equal to the volume of the region between the surface defined by the function $F_G = f(x, y)$ and the plane which contains this circle. In Fig. 2B, f(x,y) corresponds to a cone.
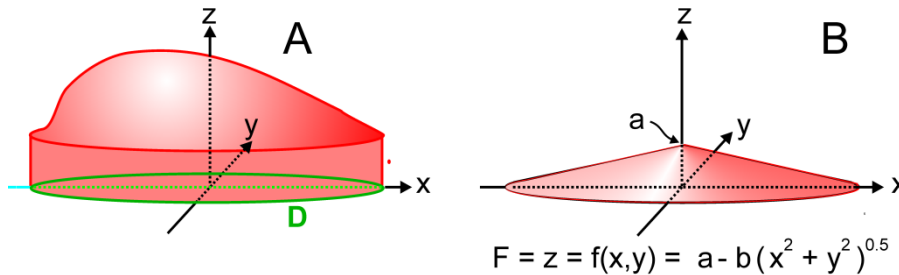


$$F = z = f(x,y) = a - b(x^2 + y^2)^{0.5}$$

**Fig. 2**: in A, volume corresponding to the double integral of the positive function Z of two variables x and y in domain D. In B, the volume corresponding to the double integral of function Z is a cone.

In the present study, the positive function corresponds to the production of ATP by glycolysis which corresponds to the 9.677 % of the total ATP production during an aerobic exercise and domain D corresponds to the cross-section of a muscle fiber. Different solids of revolution (cones and a cylinder) whose volumes are equal to 9.677% of the fiber volume are computed and the surfaces of these solids correspond to the glycolytic ATP production in function of the distance from the center.

The application of the volume corresponding to a double integral to the concept of lactate shuttle within a muscle fiber is illustrated in Fig.3. If there is a lactate shuttle, glycolysis is maximal in the core of the muscle fiber. In Fig. 3A, the columns within the muscle fiber that are the darkest correspond to the columns whose production of ATP by glycolysis are the highest.  In Fig. 3B, all the columns are dark but those whose glycolytic ATP productions are the lowest, are the smallest columns. The glycolytic ATP production in each column depends on the volume of the column. Therefore, the total glycolytic ATP in the whole muscle fiber depends on the sum of the volumes of all the columns in the muscle fiber.
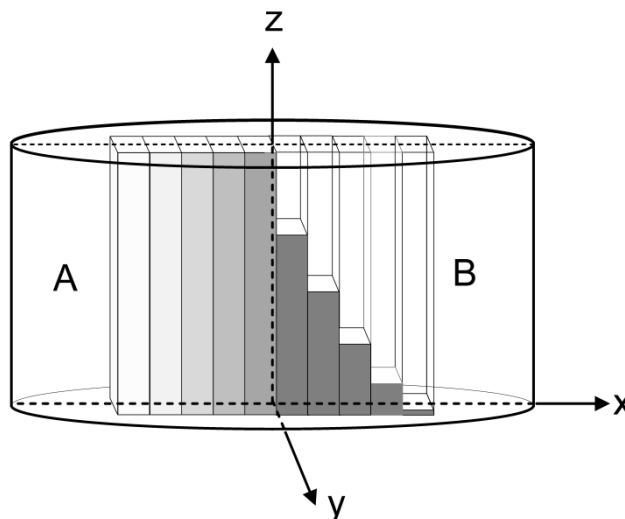


**Fig. 3**: In A, the darkest columns correspond to the columns whose glycolytic ATP productions are the highest; in B, the columns whose glycolytic ATP productions are the lowest, are the smallest.

In the present study, it is assumed that the need of ATP is the same in all the parts of the muscle fiber and is equal to 31 ATP for the same time unit. In the case of glucose metabolism, 3 ATP originate from glycolysis and 28 ATP from mitochondrial oxidation of pyruvate [18]. Therefore, glycolysis provides 9.677% of the total ATP produced during aerobic glucose metabolism. Similarly, the volume of the sum of all the columns

is equal to 9.677% of the volume of the muscle fiber ($V_m$). In the present study, the muscle fiber is assumed to be a cylinder whose height and radius were equal to H and R, respectively and, therefore, the value of $V_m$ is equal to $\pi*H*R^2$

**2.2 Computation of radius (r) and height (h) of a cone whose volume is equal to 0.09677 $V_m$**

A cone is a solid of revolution corresponding to a right triangle T rotating around an axis of revolution that lies on the same plane. For a cone whose radius and height are respectively equal to r and h, its volume $V_C$ is equal to:

$V_C = \pi*h*r^2/3$.

If the volumes of a cone $V_C$ is equal to 0.09677 $V_m$, its radius r and height h are equal to:

$V_C = \pi*h*r^2/3 = 0.09677 \, V_m = 0.09677*H*R^2$

$h*r^2/3 = 0.09677*H*R^2$    and    $h = 0.2903*H*(R/r)^2$

$r^2 = 3*0.09677*H*R^2/h$   and    $r = 0.5388*R*(H/h)^{0.5}$

if H = R = 1

$h = 0.2903/r^2$                                               Equation 1

$r = 0.5388/(h)^{0.5}$                                             Equation 2

For a cylinder whose height is equal to H and volume $V_{CY}$ is equal to 0.09677 Vm, the radius r is:

$V_{CY} = \pi*H*r^2 = 0.09677 \, Vm = 0.097*\pi*H*R^2$         and $r^2 = 0.09677*R^2 = 0.09677$
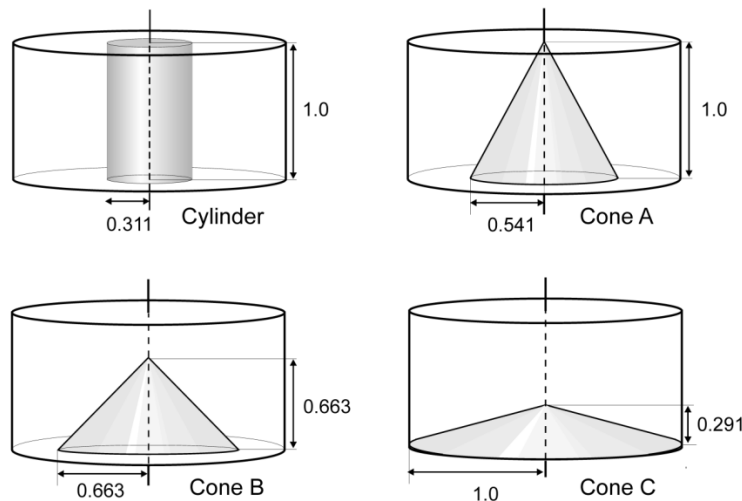
$r = 0.311$ (Fig. 4)



**Fig. 4:** computed cylinder and cones whose volumes are equal to 0.09677 $V_m$.

For cone A (Fig.4) whose height h is equal to H, its radius r is:

$r = 0.5388/(1)^{0.5} = 0.5388$

For cone B (Fig. 4) whose height h is equal to its radius r, its height h is:

$h = 0.2903/h^2 = 0.663$

For cone C (Fig. 4) whose radius is equal to R, its height h is:

$h = 0.2903/(1)^2 = 0.2903$

**2.3 Production of ATP by glycolysis and oxidation of pyruvate (or lactate)**

In the present study, the ratio $F_G$ is equal to the local glycolytic ATP production on the local total production of ATP.

$F_G$ = local glycolytic ATP production/local total ATP production

When all the local ATP production is derived from local glycolysis, $F_G = 1$.

When pyruvate and lactate originate only from local glycolysis and do not diffuse into other parts of the muscle fiber, the value of $F_G$ is 0.09677.

When part of the locally produced pyruvate (or lactate) diffuses to other regions of the fiber, the value of $F_G$ is between 0.09677 and 1.

When the pyruvate (or lactate) produced by local glycolysisis inferior to pyruvate (or, lactate) oxidation, the value of $F_G$ is between 0 and 0.0967.

In the case of a cone, $F_G$ is equal to zero when the distance from the axis (x) is equal to r. On the other hand, $F_G$ is equal to h when x = 0. Therefore, the relationship between $F_G$ and x is:

$F_G = h - (h/r)*x = h*(1 - x/r)$                    Equation 3

For cone A: $F_{G\,A} = 1 - 1.8560*x$

For cone B: $F_{G\,B} = 0.6621 - x$

For cone C: $F_{G\,C} = 0.2903*(1 - x)$

The ratio $F_{Ox}$ concerns the amount of ATP corresponding to the glycolysis necessary to the production of pyruvate (or lactate) locally oxidized.

$F_{Ox}$ = glycolytic ATP production corresponding to the amount of pyruvate (or lactate) locally oxidized/local total ATP production

When there is not a local glycolysis, the whole ATP production is derived from the oxidation of pyruvate or lactate produced in another part of the muscle fiber. Therefore, the oxidation of pyruvate (or lactate) provides 31 instead of 28 ATP, which corresponds to $F_{Ox}$ equal to 0.1071. When part of the oxidized pyruvate (or lactate) originates from other regions of the fiber, the value of $F_{Ox}$ is between 0.09677 and 0.107. In the present study, the relationship between $F_{Ox}$ and $F_G$ is:

$F_{Ox} = (1 - F_G)*0.107$

### 2.4 Center and periphery of the muscle fiber

In the present study, it assumed that the pyruvate (or lactate) that diffuses to other regions of the fiber, is produced in the center of the fiber and is oxidized in the periphery of the fiber. At $F_G = 0.09677$, the production of lactate is equal to lactate oxidation. Therefore, the limit of the center and periphery of the muscle fiber corresponds to the distance $x_{0.097}$ where the value of $F_G$ is equal to 0.0967.
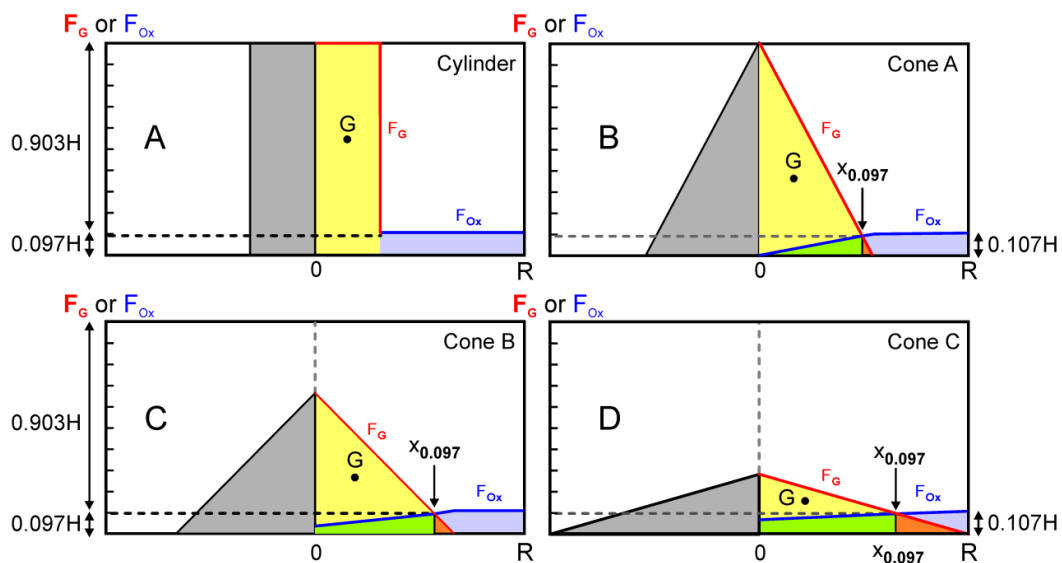


**Fig. 5**: relationships between the distance x from the center of the muscle fiber (0) and $F_G$ (red line) or $F_{Ox}$ (blue line) for the cylinder and cones A, B and C whose volumes are equal to $0.0967\ V_m$. The distances $x_{0.097}$ correspond to the distances where $F_G$ and $F_{Ox}$ are equal. Explanations of the different colored areas in the text. G: centroids of the yellow areas.

The yellow areas in Fig 5 concern the glycolytic ATP production corresponding to the pyruvate and lactate produced in the center and diffusing into the periphery of the fiber (lactate shuttle). The green areas concern the glycolytic-ATP production corresponding to the pyruvate and lactate produced and oxidized in the center of the fiber. The orange areas concern the glycolytic ATP production corresponding to the pyruvate and lactate produced and oxidized in the periphery. The blue areas concern the glycolytic ATP production corresponding to the pyruvate and lactate produced in the center and oxidized in the periphery of the fiber (lactate shuttle). The solids of revolution, whose rotating surfaces correspond to yellow and blue areas, have the same volumes.

**2.5 Combination of different cone volumes**

Different profiles of lactate shuttle can be obtained by combining different geometric shapes (for example cones A, B, C) with different values of parameters a, b, c (for example, 0.333 or 0.5).Let 2 cones A and B whose volumes $V_A$ and $V_B$ are equal to $0.09677V_m$. These cones are solids of revolution whose rotating surfaces are right triangles $T_A$ and $T_B$. Let a solid $S_{AB}$ of revolution whose volume $V_{AB}$ is equal to $a*V_A + b*V_B$

$V_{AB} = (a + b)*0.09677*V_m$

$V_{AB}$ is also equal to $0.09677\ V_m$ if a + b = 1.

$S_{AB}$ is a solid of revolution whose rotating surface is equal to the sum of the surfaces $a*T_A$ and $b*T_B$. The combination of two cones A and B and solid $S_{AB}$ is presented in Fig. 6. The parameters a and b of both cones A and B are equal to 0.5. Therefore, each volume of cones A or B is equal to $0.0\ 4838*V_m$ ($0.09677\ *V_m/2$) and the sum of these volumes is equal to $0.09677\ *V_m$. Oblique triangle $T_A$, has the same surface as right triangle $T_A$. Moreover, the distance $r_G$, between the centroid of $T_A$, and the rotation axis is the same as the distance $r_G$. Therefore, according to the second theorem of Pappus, the volumes of the solids of revolution corresponding to $T_A$ and $T_A$, are the same. Consequently, the volumes of the solids of revolution $S_{A'B}$ and $S_{AB}$ are equal. For $S_{A'B}$, the relationship between $F_G$ and x is:

$F_{G\ A'B} = a*F_{G\ A'} + b*F_{G\ B}$

$F_{G\ A'B} = a*h_A*(1 - x/r_A) + b*h_B*(1 - x/r_B)$                    Equation 4

with $F_{G\ A'} = 0$ when $x > r_A$ and $F_{G\ B} = 0$ when $x > r_B$

Let a third cone (cone C) whose volumes $V_C$ is equal to $0.09677\ V_m$. Let a solid $S_{ABC}$ of revolution whose volume $V_{ABC}$ is equal to $a*V_A + b*V_B + c*V_c$. Its volume $V_{ABC}$ is also equal to $0.09677\ V_m$ if a + b + c = 1. For $S_{ABC}$, the relationship between $F_G$ and x is:

$F_{G\ ABC} = a*F_{G\ A} + b*F_{G\ B} + c*F_{G\ C}$

$F_{G\ ABC} = a*h_A\ *(1 - x/r_A) + b*h_B*(1 - x/r_B) + c*h_C*(1\ x/r_C)$                    Equation 5

with $F_{G\ A} = 0$ when $x > r_A$; $F_{G\ B} = 0$ when $x > r_B$; $F_{G\ C} = 0$ when $x > r_C$
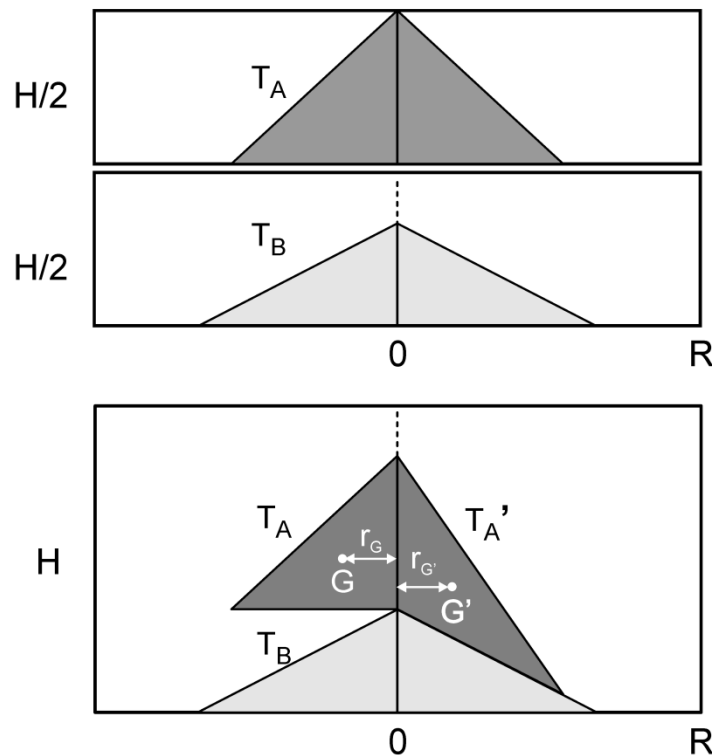


**Fig. 6**: combination of two cones A and B whose parameters a and b are equal to 0.5. Triangle $T_A$, and $T_A$ have the same surface. The distances $r_G$ and $r_G$, correspond to the distances between the rotation axis and the centroids of $T_A$ and $T_A$,.

**2.6 Evaluation of the lactate shuttle**

The diffusion of pyruvate and lactate from the center ($x < x_{0.097}$) to the periphery ($x > x_{0.097}$) correspond to the yellow area ($A_Y$) in Fig.5 and 7 which correspond to the integral of the difference ($F$) between $F_G$ and $F_{Ox}$ for x between 0 and 0.09677:

$$F = F_G - F_{Ox} \quad \text{and} \quad A_Y = \int_0^{X0.0977} F \ dx$$

This integral was estimated by a numerical solution with $\Delta x$ equal to 0.0001. According to the second theorem of Pappus, the volume $V_Y$ of the solid of revolution corresponding to the plane area $A_Y$ rotating around an axis in the same plane is equal to:

$$V_Y = 2 \pi * r_G * A_Y$$

Where $r_G$ is the distance between the centroid of $A_Y$ and the rotation axis (the center of the muscle fiber). The centroid of $A_Y$ was computed in parallel with the calculus of the $A_Y$:

$$r_{G \ n+1} = (\Delta A_Y * (n*\Delta x + 0.00005) + r_{G \ n} * A_{Y \ n}) / (A_{Y \ n} + \Delta \ A_Y)$$

where $\Delta A_Y$ is equal to $F*\Delta x$.

Thereafter, the value of $V_Y$ was normalized to the volume of the muscle fiber ($V_m$). The ratio $V_Y/V_m$ corresponds to the fraction of lactate that is produced in the center ($x < x_{0.09677}$) and is oxidized in the periphery ($x > x_{0.09677}$) of the muscle. Therefore, $V_Y/V_m$ is an evaluation of the contribution of the lactate shuttle to the whole muscle metabolism.

The contribution of a lactate shuttle to the local metabolism in the center can be estimated by the normalization of $V_Y$ to the volume of the center of the fiber ($V_{0.097}$) which is equal to $\pi * H * x_{0.09677}^2$. Therefore, the ratio $V_Y/V_{0.097}$, equal to $(V_Y/V_m)/(x_{0.09677}^2)$, is all the higher when the $x_{0.09677}$ is small, i.e. for the cylinder and cone A in Fig. 5A and 5B.

On the other hand, the contribution of a lactate shuttle to the local metabolism in the periphery can be estimated by the normalization of $V_Y$ to the volume of the periphery of the fiber ($1 - V_{0.097}$). Therefore, the ratio $V_Y/(1 - V_{0.097})$, equal to $(V_Y/V_m)/(1 - x_{0.09677}^2)$, is all the lower when the $x_{0.09677}$ is small, i.e. for the cylinder and cone A in Fig. 5A and 5B.

## III. RESULTS

The combination of cones A',B' and C with parameters a, b and c equal to 0.3333 and the relationships between x and $F_G$ (red curve) and $F_{Ox}$ (blue curve) and the lactate shuttle (yellow and blue areas) are illustrated in Fig. 7.
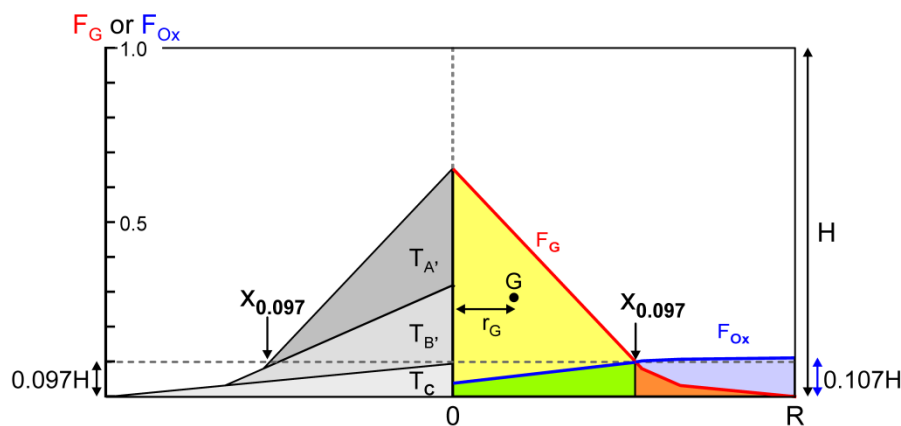


**Fig. 7**: Relationship between distance from the axis and $F_G$ (red curve) and $F_{Ox}$ (blue curve) in the case of the combination of cones A',B' and C with parameters a, b and c equal to 0.3333.

**3.1 lactate shuttle and aerobic metabolism of the whole muscle fiber**

As shown in Fig.8, the contribution ($V_Y/V_m$) of a possible lactate shuttle to the total aerobic metabolism of the muscle fiber is maximal for the cylinder and would be lower than 10 %. The higher the value of $r_G$ (or $x_{0.097}$), the lower $V_Y/V_m$ is.
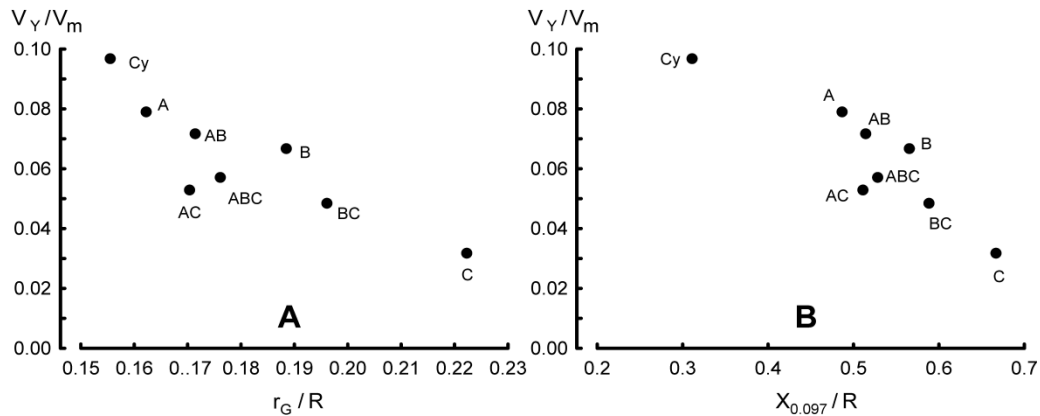
**Fig. 8**: relationships between the values of $r_G$ (A) or $x_{0.097}$ (B) and $V_Y/V_m$ for the cylinder and the different combination of cones. Cy: cylinder; A, B, C: cones A, B and C alone; AB, AC and BC: combinations of two cones with parameters a, b, and c equal to 0.5; ABC, combination of cones A, B and C with parameters a, b and c equal to 0.3333.

**3.2 lactate shuttle and local metabolism**

As expected, the estimation of local contribution of lactate shuttle is higher in the center ($x < x_{0.09677}$) or the periphery ($x > x_{0.09677}$) when the value of $V_Y$ is normalized to the central ($V_{0.097}$) or peripheric volume ($1 - V_{0.097}$) instead of $V_m$ (Fig. 9).
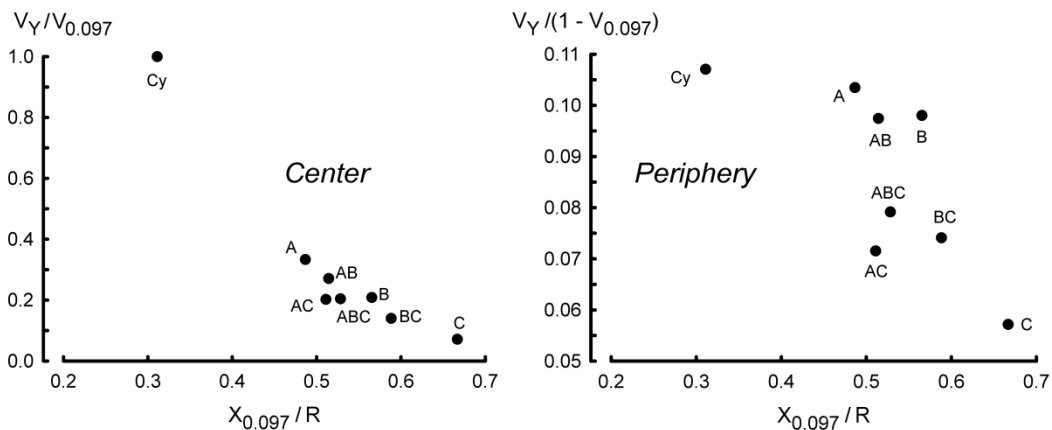


**Fig 9**: relationships between the values of $x_{0.097}$ and $V_Y/V_{0.097}$ (center) or $V_Y/(1 - V_{0.097})$ (periphery) for the cylinder and the different combinations of cones. Cy: cylinder; A, B, C: cones A, B and C alone; AB, AC and BC: combinations of two cones with parameters a, b, and c equal to 0.5; ABC, combination of the three cones A, B and C with parameters a, b and c equal to 0.3333.

# IV.    DISCUSSION

The aim of the present study is not to prove that there is a lactate shuttle within the muscle fibers. As with any model, there are several simplifications of the anatomical, cytological and biochemical characteristics of muscle fibers: the fibers are assumed to be cylindrical; the shuttle is not studied for submaximal exercise when fat metabolism contributes to aerobic ATP production… The aim of the present study is to estimate the highest limits of the contribution of a possible lactate shuttle. Therefore it is assumed that all the pyruvate (or lactate) oxidized in periphery provided from the pyruvate (or lactate) produced in the center of the fiber. The highest limit of a possible lactate shuttle is relatively small (<10 %, Fig. 8) when expressed as fraction of the aerobic metabolism of the total muscle fiber. However, the importance of the lactate shuttle is much higher and not negligible when expressed as a fraction of the local metabolism in the center of the muscle fiber (Fig.9).
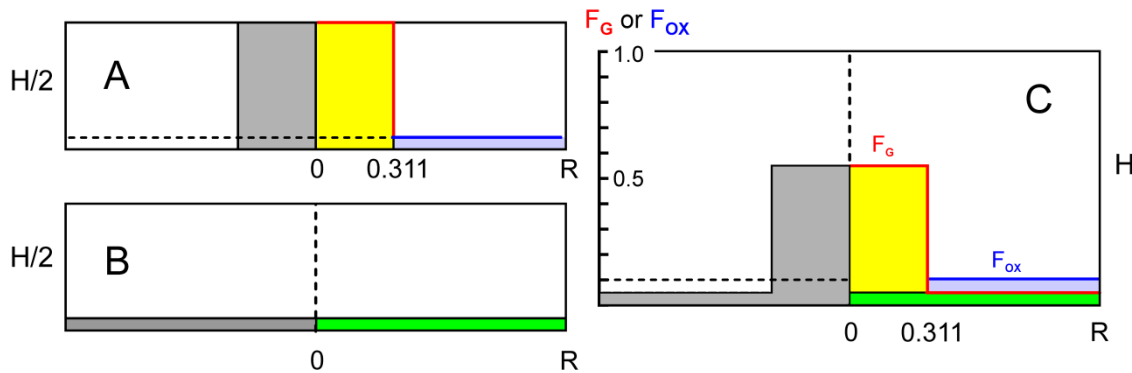
**Fig.10**: in A: the same cylinder as in Fig. 4 and 5; in B: a portion of muscle fiber without any lactate shuttle; in C: combination of A and B. Yellow areas concerns the glycolytic-ATP production corresponding to the amount of pyruvate and lactate diffusing from the center into the periphery of the fiber.

The small contribution of the lactate shuttle to the total aerobic metabolism would be even lower if a part of the pyruvate oxidized in periphery provide from glycolysis in periphery. The simplest example corresponds to Fig.10 that combines the same cylinder as in Fig. 4 and 5 (Fig. 10A) with a fiber of the same dimension but without any lactate shuttle (Fig.10B). If there is not a lactate shuttle, all the pyruvate locally produced is locally oxidized (green area in Fig 10B). In this combination (Fig.10C), the value of $V_Y/V_M$ would be equal to 0.0484 instead of 0.0967. However, the lactate shuttle in the center of the fiber would not be negligible in this case ($V_Y/V_{0.097} = 0.5$; i.e. 50%). The same result would be obtained with cones A, B or C: the values of $V_Y/V_{0.097}$ in Fig. 9 would be reduced by 50%.

The relationship between x and $F_G$ corresponding to the combination of cones A, B and C with parameters a, b and c equal to 0.3333 (Fig. 7, red curve) is probably more realistic than those of the cylinder and the cones in Fig.5. In this combination of cones A, B and C, the value of $V_Y/V_{0.097}$, equal to 0.2646 (ABC in Fig.9) is not negligible. When combined with a fiber of the same dimension but without any lactate shuttle as in Fig.10, the value of $V_Y/V_{0.097}$ would be equal to 0.1323, that is, a lactate shuttle corresponding to 13.23% of central aerobic metabolism.

The volume of the peripheric part of the muscle fiber ($x > x_{0.097}$) is much higher than the central volume ($x > x_{0.097}$) because the volume of a cylindric muscle fiber is proportional to the square of x. Consequently, the contribution of lactate shuttle to the mitochondrial oxidation in the periphery of the fiber is much lower than its contribution to the metabolism in the center of the fiber (Fig. 9).The difference between the contributions of a possible lactate shuttle to the metabolism in the center and the periphery would be even higher for a spheric cell because its volume would be proportional to the cube of x.

The cytosolic redox state depends on the ratio of the concentrations of lactate and pyruvate [24, 25] whereas the diffusions flux of lactate and pyruvate (J) depend on the gradient of their concentration (Fick's law):

Redox state = $[NADH]/[NAD^+]$= $K_{eq}$ [Lactate]/[Pyruvate]*$[H^+]$

where $K_{eq.} = 1.11*10^{-11}$ M

$J = - D_{Lac}*dC_{Lac}/dx$

where $D_{Lac}$ is the diffusion coefficient of lactate and $dC_{Lac}/dx$ the gradient of lactate concentration. Therefore, a lactate diffusion can increase without a large difference in redox state between the center and the periphery especially when both pyruvate and lactate concentrations largely increase as in the case of an exercise at maximal oxygen uptake.

## V.    CONCLUSIONS

The results of the volumetric model does not prove the existence of a lactate shuttle between the center and periphery of a muscle fiber but suggest that the highest limit of the contribution of a possible lactate shuttle to the aerobic metabolism of the whole muscle fiber would be lower than 10 %. Nonetheless, the contribution of a lactate shuttle to the local metabolism would be much higher especially for the local metabolism in the center of the fiber because the volume of the central part of the muscle fiber is much smaller than the peripheric volume.

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