Supplement 2.

Functions $f_1(C_O)$ and $f_2(C_O)$, and the appropriate constants

The function $f_1(C_O)$ is chosen such that it gives a reduction in glucose and oxygen consumption in the hypoxic region, while $f_2(C_O)$ shifts the metabolism in the hypoxic region towards glycolysis. We use the non-unique form $f_i(C_O) = (1 - a_i C_O^{0.02} \exp(-100(C_O - 0.01)^4))$ with $i = 1,2$, where $a_1 = 2/3$ and $a_2 = 1/2$ (C_O is in the unit of 10^{-2} mM). $p_g = p_o/6 = 1.9\times10^{-3}$ mM/s (10) is the consumption rate of glucose under normoxic conditions, and k_O and k_G are the Michaelis constants for oxygen and glucose, respectively, with $k_O = 2\times10^{-4}$ mM and $k_G = 5\times10^{-2}$ mM. The parameter r is the ratio of oxygen to glucose consumption under normoxic conditions. The values of k_O and k_G and the functional form of $f_1(C_O)$ and $f_2(C_O)$ are chosen such that they give the proposed pattern for consumption rates of oxygen and glucose. A plot of these functions are depicted in Fig 1A.

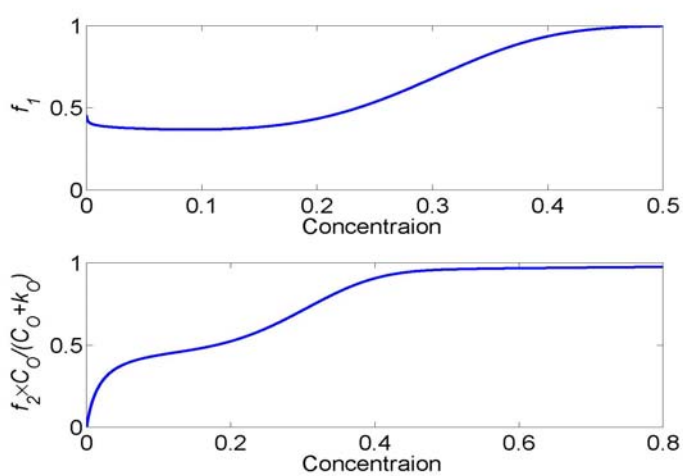

Fig. 1A: $f_1(C_O)$, $f_2(C_O)\times C_O/(C_O + k_O)$, as a function of concentration (concentration is in the unit of 10^{-2} mM) . Based on these functions the hypoxic region is a region where concentration is less than 0.44

($f_2(C_O)\times C_O/(C_O+k_O)=1$) and we choose the anoxic region as a region where concentration is less than 0.002.

Variation of pH as a function of *r*

The influence of the parameter *r* on pH is illustrated in Fig. 1A, which shows pH as a function of distance for different values of *r*. By decreasing the value of r (i.e. shifting the metabolism to glycolysis), the plateau in the hypoxic region disappears and we see a monotonic drop of pH as a function of distance. These results suggest that in order to see the plateau observed in the *in vivo* experiments of Helmlinger *et al.* (11), the cell metabolism in the presence of oxygen should be a combination of respiration and glycolysis.

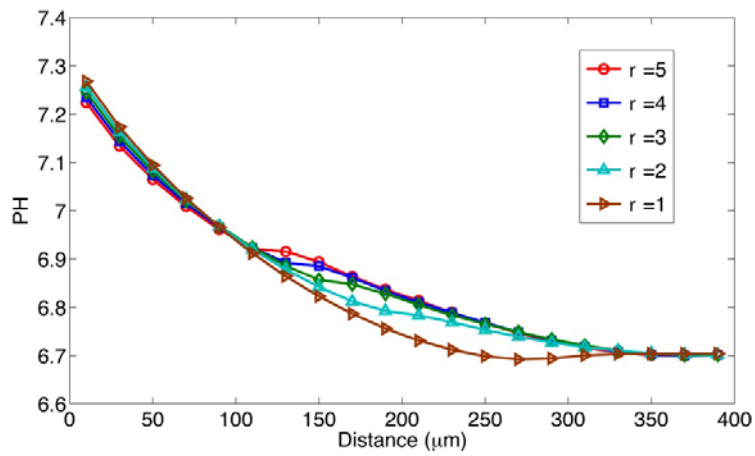

Fig. 2A: pH as a function of distance for different values of r. By decreasing *r*, there is a shift in the metabolism from respiration to glycolysis and the plateau disappears.

pH and pO_2 for *r*=1

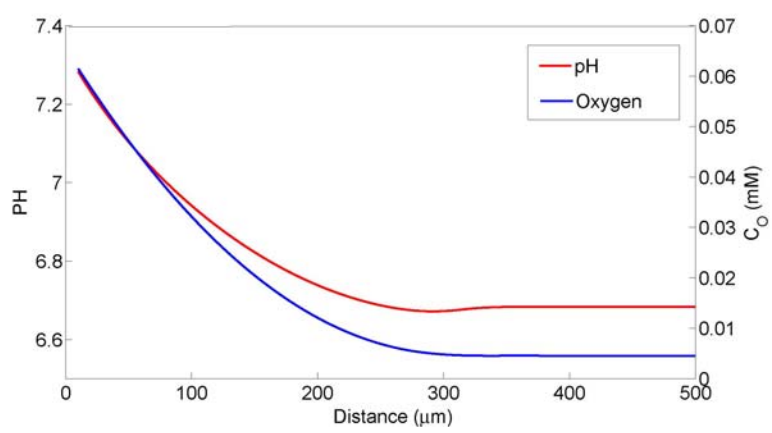

Fig. 4A: pH and pO_2 as a function of distance for glycolysis-dominated metabolism (*r*=1).