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# THEORETICAL SIMULATION OF TUMOUR HYPOXIA MEASUREMENTS

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## 1. INTRODUCTION

Tumour oxygenation is one of the most important factors that influence the treatment response and several techniques have been developed to characterise it. Among the experimental methods, the polarographic oxygen sensor has been widely used for *in vivo* measurements of oxygen and has been considered a sort of gold standard for measuring tumour hypoxia. Several studies have indeed shown that there is a general correlation between polarographic measurements and the treatment outcome[1-7]. Like many other experimental methods, however, the polarographic technique is quite invasive because it involves the physical insertion of the probe into the tissue and the consumption of oxygen thus perturbing the natural steady state. It would therefore be interesting to investigate the relationship between the electrode measurements and the real tissue oxygenation.

Our previous modelling on tissues with regular blood vessel networks[8-10] has shown that the electrode measurement is inevitably modified by the averaging of the $pO_2$ values in the measurement volume. In fact, given a certain distribution of oxygen values in the tissue, this averaging process determines the removal from the measured distribution of the extreme values especially if these values appear in regions smaller than the electrode measurement volume. Based on this observation we have concluded that generally it is not possible to use a polarographic electrode to measure hypoxia appearing in small rims, one or two cells wide, surrounding a blood vessel. In the light of these findings, the next step of the study was to expand the simulation for measurements in tissues with realistic vascular configurations in order to investigate the influence of the supposedly large regions of perfusion limited hypoxia caused by the temporary closure of some tumour blood vessels.

The aim of this article is to study the ability of the electrode to measure tumour hypoxia in various tissues having all or only a fraction of the blood vessels open and in particular the influence on the electrode measurements of the two types of hypoxia known to appear in tumours.

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## 2. MATERIALS AND METHODS

The investigation was performed as a computer simulation of both the oxygen diffusion into the tissue and the individual electrode measurements. The oxygen distribution into tissue was calculated from the basic processes of diffusion from the blood capillaries and consumption at the cells. A Monte Carlo method was used to generate tissues with blood vessels placed according to distributions that were in agreement with the experimental measurements of Konerding and his co-workers[11]. A numerical method was then employed to calculate the oxygen distributions around the blood vessels. The $pO_2$ value in the blood vessels was set to 40 mmHg as most tumour vasculature comes from the venous side[12]. The oxygenation map thus obtained reflected only the distribution of diffusion limited hypoxia throughout the tissue. The effects of perfusion limited hypoxia were modelled by the random closure of some of the blood vessels in the simulated tissue and the recalculation of the tissue oxygenation. The details are described elsewhere[13]. We were thus able to control the amount and pattern of hypoxia in the tissue and therefore to investigate the influence of the two types of hypoxia on the electrode measured distributions of $pO_2$ values.

Electrode measurements were simulated according to the method described previously[8-9], where the probe was placed in a random point in the tissue and each individual measurement was calculated as the weighted average of oxygen tensions in the measuring volume according to the response function of the electrode. As it has been shown elsewhere[14], this approach closely mimics the clinical measurements. Simulations were performed for a large number of tumours covering a whole range of situations that may be encountered in practice. The results of the simulations (both real and measured oxygenations) were presented as discrete distributions of $pO_2$ values grouped in 2.5 mmHg intervals.

The theoretical approach used for this study avoided the artefacts that characterise most of the experimental measuring methods, thus allowing the determination of the tumour oxygenation in the least invasive manner. It was therefore possible to compare the results of the simulated measurements with the actual oxygenation of the tissue. This direct comparison also minimised the importance of the input parameters, and hence the use of higher or lower $pO_2$ values in the blood vessels would not have changed the concepts illustrated by the results in this paper. Furthermore, the controlled distribution of tumour hypoxia between diffusion limited and perfusion limited compartments allowed the investigation of the effects of each of them on the measurements.

## 3. RESULTS AND DISCUSSION

In practice, the electrode is placed and the oxygenation is measured in a limited number of more or less random points, chosen according to the tumour size. Thus, one important question that may arise regarding the use of a polarographic electrode for measurements of tissue oxygenation is the relevance of the measured sample for the whole tissue. In order to investigate how the process of sampling influences the result of the measurement, we have calculated the oxygen distribution in a tissue and then we have extracted the $pO_2$ values in a limited number of random points (50-1000), thus simulating the random placing of the electrode in the tissue but without including the averaging effect of the electrode measurement.

Figure 1 shows the distributions of $pO_2$ values in the whole tissue (grey bars) and the distributions of values in samples containing a limited number of points (black bars). Our