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Regulation of Tumour Intracellular pH: A Mathematical Model Examining the interplay between hydrogen ions and lactate

Non-invasive measurements of pH have shown that both tumour and normal cells have intracellular pH (pHi) that lies on the alkaline side of neutrality (7.1-7.2). However, extracellular pH (pHe) is reported to be more acidic in some tumours compared to normal tissues. Many cellular processes and therapeutic agents are known to be highly pH dependent which makes the study of intracellular pH regulation of paramount importance. We thus develop a mathematical model that examines the role of various membrane-based ion transporters in tumour pH regulation, in particular, with a focus on the interplay between lactate and H⁺ ions and whether the lactate/H⁺ symporter activity is sufficient to give rise to the observed reversed pH gradient. Using linear stability analysis and numerical methods, we are able to gain a clear understanding of the relationship between lactate and H⁺ ions. We extend this analysis using perturbation techniques to specifically examine a rapid change in the H⁺ ions concentrations relative to lactate. We finally perform a parameter sensitivity analysis to explore the solution robustness to parameter variations. An important result from our study is that a reversed pH gradient is possible but for unrealistic parameter estimates-pointing to the possible involvement of other mechanisms in this phenomenon such as acidic vesicles, lysosomes, golgi and endosomes.