**Mathematical Modeling of Intracellular Diffusion and Reaction of Nitric Oxide, Superoxide, and Peroxynitrite**

by

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Submitted to the Department of Chemical Engineering
on May 5, 2000 in Partial Fulfillment of
the Requirements for the Degree of
Master of Science in Chemical Engineering

## Abstract

During the immune response activated macrophages release nitric oxide and superoxide, and these molecules react to form peroxynitrite. While macrophage activation has the desired effect of destroying microorganisms, tumor cells, and damaged tissue, prolonged activation may have the undesirable side effects of destroying healthy tissue and causing cancer. Indeed in vitro studies of nitric oxide, superoxide, and peroxynitrite have implicated each of these free radicals in cytotoxicity and mutagenesis. Under physiological conditions, these molecules, particularly superoxide and peroxynitrite, are highly recative and present only in small amounts, so direct measurement of their concentrations is technically infeasible. However concentrations of chemical species are determined by a competition between chemical reaction and physical diffusion, and mathematical modeling of these processes allows quantitative evaluation of concentration profiles. Although a few reaction-diffusion models of these species exist, none has considered the intracellular region. We created an intracellular model for a single activated macrophage, or generator cell, and for a single cell exposed to the chemicals produced by the generator, the target cell. For each model we determined the intracellular concentration profiles of nitric oxide, superoxide, and peroxynitrite. We also used these models to answer two important questions: Is the superoxide released by activated macrophages the product of basal mitochondrial respiration and other intracellular processes? Does peroxynitrite inside the cell originate primarily from diffusion of extracellular peroxynitrite into the cell or from intracellular generation? We found that basal intracellular superoxide production is not large enough to account for the observed extracellular flux of superoxide from activated macrophages. This implies that a membrane-associated enzyme or enhanced intracellular production plays a role in superoxide release from activated macrophages. In addition, we determined that intracellular peroxynitrite exposure is primarily due to intracellular generation. This was true for both generator and target cells, for intracellular superoxide generation rates greater than one-tenth the basal generation rate determined from the literature.

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