

Sensitivity Analysis of a Redox System Model to Understand the Initiation of Chronic Kidney Disease of Unknown Etiology Progression

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Identification of the most significant parameter set in a mathematical model is very important to understand the model behavior. Sensitivity analysis is carried out to accomplish this purpose. Chronic Kidney Disease of unknown etiology has been identified as a disease with very high death rates in many tropical countries around the world including Sri Lanka, India, Egypt, and some Mesoamerican countries. Heavy metal exposure is one of the identified evidential factors of this disease progression. Oxidative stress is the main pathological mechanism that leads the kidney tubular cells to cell death pathways with heavy metal exposure. Oxidative stress is raised due to the unbalanced production of reactive oxygen species inside the cells. In this study, a sensitivity analysis was carried out on an existing mathematical model of the Redox system of the body to identify the parameters which are significant in controlling the process of reactive oxygen generation. After simulating the existing mathematical model, a sensitivity analysis was carried out including a local sensitivity analysis which gives the individual effect followed by a global sensitivity analysis which gives the group effect of parameter perturbations. According to the study, five parameters out of sixteen parameters in the mathematical model were identified from the local sensitivity analysis as the most sensitive parameters. Global sensitivity analysis was used to rank them according to the P values of the KS test. A constant was identified which is related to superoxide variation in the system has the highest sensitivity. Also, most of the identified sensitive parameters are correlated with enzyme driven reactions. According to the researchers' perspective, heavy metal exposure also affects the enzymes in the redox system of the body. Therefore, when modeling heavy metal toxicity we can conclude that much consideration should be given to those reactions correlated with enzymes.

Keywords: CKDu, Oxidative stress, Mathematical modeling, Sensitivity analysis, Parameters