Finding the Most Influential Factors in the Healing Process of Diabetic Foot Ulcers Using Parameter Space Geometry

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The treatment of chronic wounds has long been a challenge to wound care professionals and presents a substantial economic burden to healthcare systems globally. Over $50 billion is spent on the treatment of chronic wounds each year, with the annual cost rising as chronic wounds are becoming more prevalent and difficult to treat. To combat this issue, a mathematical model describing the interactions between matrix metalloproteinases (MMPs), their regulators (TIMPs), fibroblasts, and the extracellular matrix (ECM), which is the primary measure for the healing response in the wound, was developed and analyzed to find the most influential factors, or parameters, in the healing process of diabetic foot ulcers. Using the differential equation model with de-identified patient data, the three-dimensional geometry of parameter space was visualized for all combinations of the twelve parameters in the model to more precisely see how these parameters affect the biological system. Knowledge of the identifiability of parameters can, in turn, streamline treatment by allowing us to individualize treatment for each patient. This approach plots two parameters against the sum of squared errors to generate a three-dimensional graph. By analyzing the minimum of the graph, we can conclude if a parameter is able to be uniquely determined, or identified. The identifiability of a parameter signifies its importance in the healing response. This research shows that the regulators of MMPs (TIMPs) are the most influential parameters in a wound-healing model. With this knowledge we can better illuminate the unpredictable nature of wound healing.

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