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A computational model for studying coupled processes in wound healing for arbitrary wound geometries

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ABSTRACT

Healing of cutaneous wounds, when it occurs, proceeds by a cascade of interdependent chemical and mechanical processes: bleeding and blood clotting preventing the entry of infectious matter from the exterior, removal of bacteria and debris by phagocytosis, re-epithelialization or wound closure by cell mitosis and migration towards the center of the wound, repair of the vascular network (angiogenesis), extracellular matrix synthesis and wound contraction normal to lines of equal tension, among many others. Having an accurate model for any of these processes already poses a challenge in this emerging field of research. Furthermore, the existing models focus only on one isolated process and only axisymmetric wound geometries are studied.

In the first part of this work, we extend a fairly simple model for wound closure [1] to complex wound geometries. This basic model considers an Epidermic Growth Factor (EGF) which is produced in the area surrounding the wound (the so-called active layer) and diffuses into the wound. This EGF is responsible for the increased cellular activity at the wound edge. Cell motility is taken dose-dependent with respect to the EGF, and the advancing front of cells closing the wound is identified with a curve moving in the course of time. Furthermore, the closure rate is taken proportional to the local curvature of the wound edge. Because of these phenomenologycal hypotheses, some parts of the wound are allowed to heal whereas other parts remain unhealed for longer periods. Hence, changes in the wound morphology migth be obtained as healing proceeds. Despite of its simplicity, this model is capable of predicting relevant biological and medical implications such as the necessary conditions for (un)successful healing. Further analysis of the model allows us to derive bounds for the incubation time, which is defined as the time elapsed between injury and initiation of the wound closure, and reveals a jerky motion of the wound edge. Further investigation shows quite different healing kinetics depending on the wound

morphology: fast healing for elongated wounds and prominent growth (under certain conditions) at the concave areas of the wound.

In the second part of the talk, we include angiogenesis [2] into the closure model. We couple the equations in such a way that the production of the EGF is only sustained under sufficient oxygen availability. Since the capillaries are the only source of oxygen, repair of the vascular network is necessary to achieve successful healing. The capillary restoration is triggered by the action of Macrophage Derived Growth Factors (MDGF) that appear at the wound site due to low levels of oxygen. This extended model allows us to investigate indirectly the effect of oxygenation in the closure kinetics, which reveals to be counterproductive in extreme cases.

Our model is mathematically formulated as a system of coupled diffusion-reaction equations with an embedded moving interface. The active layer, and hence the production of the EGF, is determined from the wound edge position. The Level Set Method [3] is used to track the position of the wound edge in time. A Finite Element method with piecewise linear basis functions is used in the solution of the diffusion-reaction equations. As a reference mesh we use a structured triangulation, which is locally refined at the wound edge each time step. After refinement, the computational grid resembles two nested Cartesian grids on which Finite Difference or Finite Volume schemes are applied to solve the advection of the wound edge.

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