Abstract:
There is a growing number of studies that model immunological processes in the artery wall that lead to the development of atherosclerotic plaques. However, few of these models use parameters that are obtained from experimental data even though data-driven models are vital if mathematical models are to become clinically relevant. We present the development and analysis of a quantitative mathematical model for the coupled inflammatory, lipid and macrophage dynamics in early atherosclerotic plaques. Our modeling approach is similar to the biologists' experimental approach where the bigger picture of atherosclerosis is put together from many smaller observations and findings from in vitro experiments. We first develop a series of three simpler submodels which are least-squares fitted to various in vitro experimental results from literature. Subsequently, we use these three submodels to construct a quantitative model of the development of early atherosclerotic plaques. We perform a local sensitivity analysis of the model with respect to its parameters that identifies critical parameters and processes. Further, we present a systematic analysis of the long-term outcome of the model which produces a characterization of the stability of model plaques based on the rates of recruitment of low-density lipoproteins, high density lipoproteins and macrophages. The analysis of
the model suggests that further experimental work quantifying the different fates of macrophages as a function of cholesterol load and the balance between free cholesterol and cholesterol ester inside macrophages may give valuable insight into long-term atherosclerotic plaque outcomes. This model is an important step towards models applicable in a clinical setting.

Stichworte:
atherosclerosis, plaque development, quantitative model, parameter estimation, metabolic control analysis, stability analysis

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