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Sensitivity and Bifurcation Analysis of Tuberculosis Progression

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An Investigation of Tuberculosis Progression Revealing the Role of Macrophages Apoptosis via Sensitivity and Bifurcation Analysis

Short title: Sensitivity and Bifurcation Analysis of Tuberculosis Progression

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Mycobacterium tuberculosis infection features various disease outcomes: clearance, latency, active disease, and latent tuberculosis infection (LTBI) reactivation. Identifying the decisive factors for disease outcomes and progression is crucial to elucidate the macrophages-tuberculosis interaction and provide insights into therapeutic strategies. To achieve this goal, we first model the disease progression as a dynamical shift among different disease outcomes, which are characterized by various steady states of bacterial concentration. The causal mechanisms of steady-state transitions can be the occurrence of transcritical and saddle-node bifurcations, which are induced by slowly changing parameters. Transcritical bifurcation, occurring when the basic reproduction number equals to one, determines whether the infection clears or spreads. Saddle-node bifurcation is the key mechanism to create and destroy steady states. Based on these two steady-state transition mechanisms, we carry out two sample-based sensitivity analyses on transcritical bifurcation conditions and saddle-node bifurcation conditions. The sensitivity analysis results suggest that the macrophage apoptosis rate is the most significant factor affecting the transition in disease outcomes. This result agrees with the discovery that the programmed cell death (apoptosis) plays a unique role in the complex microorganism-host interplay. Sensitivity analysis narrows down the parameters of interest, but cannot answer how these parameters influence the model outcomes. To do this, we employ bifurcation analysis and numerical simulation to unfold various disease outcomes induced by the variation of macrophage apoptosis rate. Our findings support the hypothesis that the regulation mechanism of macrophage apoptosis affects the host immunity against tuberculosis infection and tuberculosis virulence. Moreover, our mathematical results suggest that new treatments and/or vaccines that regulate macrophage apoptosis in combination with weakening bacillary viability and/or promoting adaptive immunity could have therapeutic value.

Reference: Zhang, Wenjing, et al. "An investigation of tuberculosis progression revealing the role of macrophages apoptosis via sensitivity and bifurcation analysis." Journal of mathematical biology 83.3 (2021): 1-32.