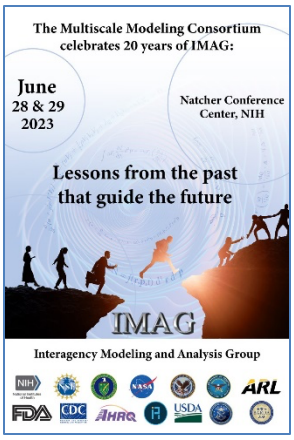

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Agent-based model predicts that layered structure and 3D movement work synergistically to reduce bacterial load in 3D *in vitro* models of TB granulomas

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BACKGROUND: Tuberculosis (TB) caused over 1.6 million deaths in 2021. TB is associated with granulomas, organized structures of immune cells that contain the causative bacteria. These structures are three-dimensional with an inner core of macrophages and an outer cuff of T cells. Advanced 3D cell cultures have been applied to emulate these clinical structures *in vitro.* One in vitro approach showed that 3D spheroid models have improved bacterial control compared to traditional in vitro infection models.

METHODS: We use hybrid modeling to simulate these spheroid models and traditional counterparts, with an agent-based model of immune cell and bacteria rules coupled to a partial differential equation model of chemokine diffusion. We calibrate our model to experimental data while enforcing shared parameters between the spheroid and traditional setups, only changing the initial structure and movement rules to reflect the experimental setups.

RESULTS: Lower bacterial load in spheroid simulations compared to traditional simulations is predicted to be due to increased proportions of activated macrophage killing of bacteria, either in tandem with increased proportions of CD8+ T cell activation or not. The spatial distribution of cells was found to be an important factor in macrophage and CD8+ T cell activation in spheroid simulations, with more activation being associated with increased proximity. Next, an *in silico* experiment was performed, where the initial structure and movement rules were uncoupled to see if either of these independently lead to bacterial control. Neither of the uncoupled mechanisms reduced bacterial load on its own, rather they worked together synergistically.

CONCLUSIONS: This work further emphasizes the impacts of spatial organization and dimension in biological processes, while highlighting the flexibility of in silico modeling and the perturbations it makes possible.