COMPUTATIONAL INSIGHTS INTO MECHANICAL CHANGES IN BACTERIALLY INFECTED CELL MONOLAYERS

Raúl Aparicio-Yuste (1,2), Marie Muenkel (2), María Teresa Sánchez (3), Effie E. Bastounis (2), María José Gómez-Benito* (1)

1. Multiscale in Mechanical and Biological Engineering (M2BE), University of Zaragoza, Spain; 2. Interfaculty Institute of Microbiology and Infection Medicine, Cluster of Excellence "Controlling Microbes to Fight Infections" (CMFI, EXC 2124), University of Tübingen, Germany; 3. Centro Universitario de la Defensa de Zaragoza, Zaragoza, 50090, Spain

Introduction

Listeria monocytogenes (*Lm*) is a food-borne facultative intracellular bacterial pathogen that mainly affects individuals with a weakened immune system [1]. The gold standard for studying *Lm* infection is through *in vitro* models of infected epithelial or endothelial cell monolayers [2]. It has been observed that in these *in vitro* models, intracellular *Lm* infection alters the mechanical behavior of infected as opposed to neighboring uninfected cells. *Lm* infection affects not only the cellular mechanical properties through cytoskeletal reorganization but also their mechano-sensing mechanism [3]. Infected cells get less stiff while uninfected cells surrounding the infection domains become stiffer compared to cells never exposed to infection [1]. Moreover, *Lm* infection also alters the active behavior of cells which contract or protrude in a different manner. Our study develops a hybrid *in silico* model of *Lm*-infected cell monolayers to understand infection's impact on cell mechanics.

Materials and Methods

We implement a hybrid model of epithelial cell monolayers that combines an agent-based model (ABM) and a finite element model (FEM). The ABM simulates cells as discrete entities, accounting for example for cell-cell interaction forces and cell contraction, while the FEM retrieves the intracellular mechanical stimuli [4]. The ABM's cell movement serves as input for the FEM, which considers the different mechanical properties of the cells. The FEM calculates intracellular stresses, which are thought to drive the cell's new active response through its mechano-sensing mechanism [3]. This calculation results in the determination of new cell forces in the FEM, which then serve as input for the ABM.

Results

Our simulation results are validated using *in vitro* data. Cell movement in the ABM is compared with *in vitro* cell nucleus movement and additionally, the intracellular stress distribution in the FEM is compared with the stresses obtained through monolayer stress microscopy [5] (Figure 1).

Our results showed that varying levels of bacterial replication inside the monolayer affect its mechanical behavior, altering both the movement and dynamics of cells within the monolayer.
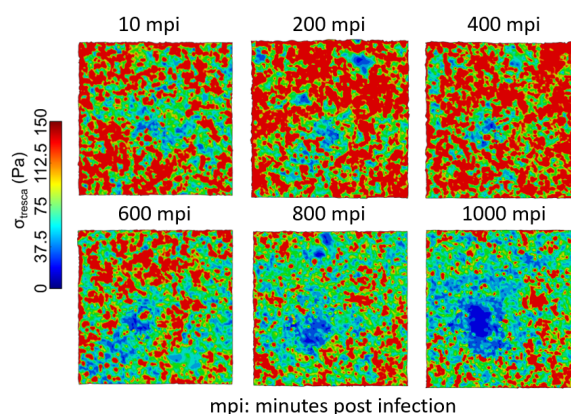

Figure 1. Maximum cell tangential stresses (Pa) within the monolayer plane as infection spread progresses.

Discussion and Conclusions

The hybrid model developed in this work is a first step in understanding the mechanical alterations in cell monolayers during bacterial infections.

By using our proposed model, we have been able to test different hypotheses regarding the altered mechanical behavior of infected cell monolayers, including changes in cellular contractility and in intercellular force transduction. Our results point that this hybrid model could be a valuable tool to unravel the mechanical alterations occurring in host cells during infection. It could assist us in the design of new experiments to test in the laboratory which can reveal novel virulence mechanisms employed by bacteria and lend key insight into basic host cell mechanobiology.

References

1. OrtegaFE et al, eLife, 8:e40032, 2019.
2. Bastounis EE et al., Developmental Cell, 56:443–460, 2021.
3. Aparicio-Yuste R et al., Comput Methods in Appl Mech Engrg, 401, 115477, 2022.
4. González-Valverde I and Garcia-Aznar JM. Comp. Part. Mech, 337: 246-262, 2019.
5. Aparicio-Yuste R et al., Front. Cell Dev. Biol., 10, 2022

Acknowledgements