

## For MSM Research Description

The research in Prof. Hunt's BioSystems Group is motivated by this question. What are the causal mechanisms that link induced changes in molecular level events to emergent changes in phenotype at the organism level? We need ways to answer that question. So doing will facilitate moving away from empirical approaches to biomedical research and reliance on correlational methods toward new approaches based on improving mechanistic knowledge and insight.

To begin addressing that question, we need ways to build and challenge experimentally (falsify) many alternative hierarchical mechanistic hypotheses. Doing so using established, bottom-up, computational mathematical models is problematic. New methods and new approaches are needed. The BioSystems's Group has developed and is demonstrating the scientific power of a fundamentally new class biomedical simulation models along with methods and protocols to challenge and iteratively improve plausible mechanisms. Concepts and advanced methods were adapted from several domains. The process is called the *synthetic method of modeling and simulation* (SM). It is called *synthetic* because standalone biomimetic components are plugged together in specific ways to form hierarchical, multiscale biomimetic mechanisms in software. The models are called *analogues* because even though they exist only in silico, their phenotypes can be made to increasingly overlap more of the referent, biological phenotype. They are designed to evolve to become embodiments of most of what we know (or think we know) about aspects of specific organisms and their components.

Current research projects focus on the liver (normal and diseased), its cellular components, and the consequences of xenobiotic interventions; epithelial cells and the organoids they form in cultures along with responses to xenobiotic interventions; leukocytes and their interactions with surfaces in vitro and in vivo; and abnormal and malignant cellular phenomena.