Our modeling and simulation efforts are intended to advance science on two biomedical research fronts: quantitative pharmacology and epithelial morphogenesis. Advances in biomedical science require more explanatory mechanistic models, and our goal is to develop, instantiate, and challenge such models in silico. Having explanatory mechanistic biological models is a precondition to having predictive biological models. I will argue that (validated) mechanistic models that are more explanatory must employ relational rather than metric and absolute grounding. Grounding: units, dimensions, and/or objects to which a variable or model constituent refers; absolute grounding: variables, parameters, and I/O are in real-world units like seconds and meters; relational grounding: variables, parameters, and I/O are in units defined by other components of the model. I will also argue that models that employ relational grounding and have achieved a degree of validation can become suitable objects of experimentation (analogous to in vitro models used in biomedical research): they enable posing and testing biologically relevant mechanistic questions. Developing such models requires adhering to an Iterative Refinement Protocol, which I will describe. I will draw on examples from our recent research, including exploration of plausible mechanisms involved in drug transport through and metabolism by epithelial monolayers, and in MDCK cell cystogenesis.

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