Agent-based Computational Modeling Workflow

Specify biomedical context

e.g. drug induced liver injury (DILI); bone fracture healing

Describe broad biomedical issues/question/needs

e.g. treat/avoid DILI; reduce frequency of non-unions

Identify referent experimental systems

e.g. DILI: cell cultures, mice, and humans with and without acetaminophen treatments; fracture healing: mice

Identify (& document with citations) referent phenomena (typically published experiments and selected results)

e.g. patterns of cellular necrosis within hepatic lobules; acetaminophen pharmacokinetics; plasma biomarkers of toxicity; time course of hepatic GSH depletion

State scientific objectives (immediate, near-term, longer-term)

e.g. for DILI, improve explanatory multiscale mechanistic insight; model and simulations are easily reproducible

Detail planned & envisioned (immediate, near-term, longer-term) model usage patterns (pattern = similar use cases)

e.g. document quantitative and qualitative validity for multiple acetaminophen-induced injury attributes; explore precision medicine interventions; embed sufficient knowledge so that the model can be a stand-alone explanation of selected phenomena; generated details can be easily understood across multiple domains (e.g. clinicians, policy makers, and regulators); different individuals and teams reuse model and/or components to address completely different biomedical objectives

Can an available (external or internal) model be repurposed?

Determine if planned & envisioned usage patterns match those for existing models and/or standard formats for expressing those models.

List requirements (examples)

• In silico experiments map to wet-lab counterparts; model and components are robust to changes in referent
• Model components and spaces are concrete (enabling knowledge embodiment); components and spaces are biomimetic and easy to assemble (disassemble and reassemble) to 1) generate, test, validate or falsify alternative plausible explanatory

mechanisms; 2) simulate current, past, and future laboratory or clinical experiments; and longer term, 3) to construct multi-attribute models capable of becoming individualizable virtual patients.

- Simulation experiments are feasible in the presence and absence of multiple compound objects (map to acetaminophen; metabolites; toxicity cascade factors; etc.).
- Components recognize different compound objects and adjust responses accordingly
- Coarse grain (from the perspective of biomimetic organization) phenomena will derive mostly from local component interactions at a finer grain
- When required, finer grain mechanisms can respond to coarser grain phenomena.
- Assemble a diverse set of experimental observations—Targeted Attributes (TAs), static and dynamic, that characterize multiple key aspects of interest at different scales and that future versions of the current implementation (*model v0*) should ultimately mimic.

Describe near-term milestones

Decide on model structures to actualize the above descriptions and usages.

> To meet the above example requirements a mathematical structure is inadequate: we must use an agent-based structure constructed using, for example, the MASON framework and toolkit.

> Verify implementations

Design and conduct experiments utilizing the Iterative Refinement Protocol (IRP)

> e.g. challenge a particular mechanism hypothesis that may explain a particular phenomenon
> 1. Use version control to identify *model v0,* decision made within each of the following steps, code changes made, along with observations made and recorded.
> 2. Prioritize and detail a subset TAs, initially small; they are the validation targets for the current IRP cycle.
> 3. (Re)Specify measurements & measurements granularity
> 4. (Re)Specify mechanism granularity; minimize reengineering
>   - Partition state information and expose each partition as a physiomimetic parametric container (within *model v0*).
>   - (Re)Specify *model v0* mechanisms to be modularized, mechanism users (within *model v0*), and relevant mechanism state information.
>   - When appropriate, encapsulate mechanism behavior as a physiomimetic mechanism module.
> 5. (Re)Specify Similarity Criteria (SC) & their target values.

6. Revise or posit *model v0* scenarios & mechanisms. Implement analog counterparts to mechanistic scenario and follow parsimony guideline by using as few different components as is reasonable.
7. Provide specifications. Create component logic. Instantiate, compose and parameterize components.
8. Conduct and measure many simulation experiments that predict TAs & achieve SC.
9. Tune to achieve Step 4 SM. Effort fails: return to Step 6 or 7. Effort successful: a degree of validation for *model v0* has been achieved; study sensitivity analysis results; stop or return to step 5 when SC stringency should be increased. When additional attributes remain to be achieved, return to Step 3. Otherwise, go to Step 10.
10. Expand TAs until *model v0* is falsified. Return to step 3.

Evaluate and archive IRP cycle results; when needed revise *model* structure and components, and return to IRP.

Milestone achieved: document workflow; revisit (rethink; revise when required) workflow steps from the start.

Upload documentation, example results, and code used to generate those results to a publically accessible site such as https://simtk.org/.