Model Credibility - A modular approach to multiscale modeling of the innate immune response to invasive aspergillosis

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Summary

Core Principles

Accessibility
- Software that is hard to use is hard to test
- Model must be easy to use by a non-computer scientist
- Carefully identify system specifications, and guarantee functionality on systems meeting specs
- “Wet lab” team will be first testers/validators, community-based approach to post-release validation
- Strong visualization component and high performance essential in to facilitate engagement

Transparency
- All source published in whole as early as possible to allow anyone to inspect/challenge model
- Strict usage of version control to allow free inspection of past iterations and permit easy branching & modification

Standardization
- Agent-based model (tissue-level) specified by Overview, Design Concepts, Details (ODD) protocol
- Boolean network-based model and finite state machine (FSM) specified for intracellular level
- Source code strictly adherent to ISO standards - e.g. C99, Fortran 90, VHDL-93

Delegation
- Three main teams with domain experts:
  - Computation (UConn Health)
  - Experimentation/testing (UFHealth)
  - Visualization/UI (Kitware, Inc.)
- Each team performs detailed uncertainty & validation - e.g. precision estimates for computation, biological/technical replicates for wet lab, I/O functionality for visualization
- Teams work in parallel on design, test, iterate cycles with weekly discussions and shared digital lab notebook

Parallel Design Approach

Two sites: Experimental/Clinical & Mathematical/Computational

Experimental

In vitro infection
- Macrophages
- Dendritic Cells

Experiments
- RNA-seq - 5 time pts
- Western blot - 5 time pts

In vivo infection
- Wild-type BL6
- Transient neutropenic BL6

Experiments
- BAL - RNA seq & Western
- Histology & staining

UConn Health

Intracellular models
- Literature review
- Public data sets

Computational

ABM & PDE models
- Overview, Design, Details
- Diffusion solver

Reconciliation
- Statistical analysis

Competing Implementations

Two paths: High-level & Mid-level

Initial evaluations using previously published model

DBMS in Docker container

Memory model
- Statically allocated

Separate processes

Module Structure
- Shared objects

ParaView

Geometry & UI
- Unreal Engine 4

Compare model output

ABMs - Collisions/clipping & physics
PDEs - Conservation laws
Performance - Determine sufficient system specs, consider FPGA SoC if needed

Crossover validation

Lab team
- Test UI and physiological accuracy of model output

Comp team
- Statistical Analysis of experimental data, ensure sufficient replicates/powers

Visualization team
- Validate ABM physics & behavior