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Virtual whole-blood infection assays

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Background

- Opportunistic human-pathogenic fungi: *Candida albicans*, *C. glabrata*
- Enter the bloodstream via the intestinal gut or medical devices (e.g. catheters)
- Cause systemic infections like sepsis in immunocompromised patients
- High mortality rates

Whole-blood infection assays (WBIA)

during 4 hours: flow cytometry and killing assays

General design

Blood Samples (healthy donors and patients) → WBIA Experiments (various pathogens and treatment strategies) → Virtual Infection Model (migration parameters and reaction rates)

characterization of WBIA to quantitatively compare treatment outcomes

Bottom-up approach

Input: WBIA → Models: SBM, ABM, HABM → Output: transition rates, migration parameters, chemotactic parameters → Readout: quantification of immune response, impact of spatial aspects, impact of chemotactic signaling

State-based model (SBM)

SBM: M - monocytes, N - neutrophils, P - pathogens

Rules:

- ϕ_{MN} - phagocytosis by monocytes
- ϕ_{NP} - killing by neutrophils
- ϕ_{NP} - killing by neutrophils
- μ - immune reaction by pathogens
- κP - activity of antimicrobial peptides
- γ - decay of antimicrobial activity

Parameter Fitting:

- Least-Squares Error (LSE): $LSE = \sum_{i=1}^n (f_i^{(exp)} - f_i^{(sim)})^2$
- SBM: Simulated Annealing based on the Metropolis Monte Carlo Scheme
- ABM: Adaptive regular grid search

Agent-based model (ABM)

Environment: three-dimensional, continuous

Agents: Candida cells, Neutrophil, Monocyte

Rules:

- Interactions: ϕ_{MN} , ϕ_{NP} , μ , κP , γ
- Migration: Random Walk

Boundary Conditions: Periodic

Molecule Diffusion and Cell-Molecule Interaction:

isotropic reaction-diffusion equation with cells as source/sink:

$$\frac{dC(x,t)}{dt} = D \cdot \Delta C(x,t) - \lambda C(x,t) + \rho C(x,t)$$

- periodic boundary condition
- Time discretization using the explicit Euler scheme: $C_{i,j,t+1} = A_{i,j} + \Delta t C_{i,j,t}$
- Δ : three-dimensional second order finite difference matrix
- $\rho C(x,t)$: discretized cell-molecule interaction

Applications:

- Cytokine secretion of neutrophils
- Ligand-Receptor binding of chemokines
- Complement opsonization of pathogens

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