The Meaning of Parameter Space in a Clinical Context: Lessons learned from the simulation of ~80 million sepsis patients

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Heterogeneity of Sepsis

- Kills more patients in U.S./year than AIDS, Breast and Prostate Cancer combined
- Gulf between phenotype description and mechanistic knowledge

Clinical Populations are heterogeneous
- Different Co-Morbidities, Individual/Time dependent

Q: What is similar, what is different?

A: Similar => All are human beings...same essential biological structure = model structure

A2: Difference => Different functional responsiveness => different parameters of that model
The Role of Modeling

- This Injective function is Explicitly Described (Model specification/structure)
- As a Dynamic Model, the In Silico Model produces range of behaviors => greater explanatory power => (t)heories/(n)atural (l)aws
- This is how the physical sciences work...
Dynamic Knowledge Representation of Sepsis with Agent-based Modeling


- ABMs of Global Systemic Inflammation, circa 1990
  - Endothelial/Blood interface
  - Activation/Propagation of Inflammation
  - Endothelial Cells and White Blood Cells

- Examine Overall Dynamics of Systemic Inflammation/Sepsis?

- What are the Clinical Phenotypes of Interest?
Model of Global Inflammation, circa 1990

| Cell types                                      | Endothelial cells, neutrophils, monocytes, TH0, TH1, TH2, bacteria, white blood cell generative cells |
| Cell Receptors and Functions                    | L-selectin, E/P-selectin, CD-11/18, ICAM, TNFr, IL-1r, adhesion, migration, respiratory burst, phagocytosis, apoptosis |
| Mediators                                       | Endotoxin, PAF, TNF, IL-1, IL-4, IL-8, IL-10, IL-12, IFN-g, sTNFr, IL-1ra, GCSF |
Clinical Heterogeneity = Parameter Landscape

- Functional differences => System Level Phenotypes
- Same genome/component structure, different state dependent on time
- Too much overlap in just state definition by component listing (biomarkers, -omics)
- Trajectories important, dynamic behavior important
- Question: What are the boundaries of parameter space corresponding to clinical sepsis?
4 “External” Variables

- Host Resilience: Cardiorespiratory Reserve
- Microbial Factors:
  - “Invasiveness”: Spread to adjacent areas
  - “Toxigenesis”: Ability to harm host tissue
- Environmental Contamination: Infection Control

Question: What is the behavior space of the Sepsis ABM in terms of generating “realistic” population patterns of sepsis?
“Plausible” Behaviors/Patterns

- Never always die
- Never never die

Population Dynamics:
- Heals, sometimes
- Effective clearing of infection, yet still die, sometimes
- Overwhelming infection, sometimes
Population Dynamics/Behavior

For each external parameter set, response across a range of perturbation (Initial Infection load)

N = 100, 28 days of simulated time

Example:
Parameter Space Characterization

- 11,428 parameter sets evaluated
- 799,960 conditions (35 levels of perturbation, with and without antibiotics)
- 79,996,000 (~80 million) simulated patients
- Patterns Targeted: Population distribution of outcomes (combinations of recovery, overwhelming infection, non-recovery w/o residual infection)
- Implemented on “Beagle” (Cray XE6 Supercomputer) => Run-time = 20K node hours
Parameter Space Characterization:
No Antibiotics

RI=1

RI=3

RI=5

RI=10

- Alive
- Overwhelming Infection
- 3 Outcomes
- Recovery/Infection
- Recovery/Hyperinflammatory System Failure
- Infection/Hyperinflammatory System Failure
Parameter Space Characterization: With Antibiotics

- **RI=1**
- **RI=3**
- **RI=5**
- **RI=10**

Legend:
- Alive
- Overwhelming Infection
- 3 Outcomes
- Recovery/Infection
- Recovery/Hyperinflammatory System Failure
- Infection/Hyperinflammatory System Failure
Plausible Landscapes

Identify Parameter Sets that met Plausibility Criteria (bounded survival)

No Antibiotics
Ordering Based on Onset 100% Mortality

With Antibiotics
Ordering Based on Onset 100% Mortality
Plausible Landscapes

1458 Parameter Sets that met Plausibility Criteria (bounded survival)

No Antibiotics
Ordering Based on Onset 100% Mortality

With Antibiotics
Ordering Based on Onset 100% Mortality
Beyond Big Data = REALLY Big Data (from Simulations)

- Quasi-mechanistic Simulations => Define Behavior
  Space across parameter sets => Clinical
  Heterogeneity

- Simulation data => fill in gaps in invariably data-
  poor observational data

- Different Role for Observational Data => No
  longer used to generate hypotheses (statistically
  limited), rather observational targets to define
  plausible hypotheses instantiated in simulations
  (Pattern Oriented Modeling)
Next Steps

- Are there patterns in parameter configurations that are associated with better outcome?

- Are there biomarker patterns associated with/predictive of behavioral trajectory (data-driven approach with Vodovotz, et al.)?

- Variability of “internal” parameters => reflect different genetic predispositions/functional states

- Use Adaptive Simulation => automated optimization workflow (simulated annealing, GA, etc) to identify behavior of parameter space (meta-parameters?), evolve model structures (Toolkit being developed...looking for alpha/beta testers)
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