

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

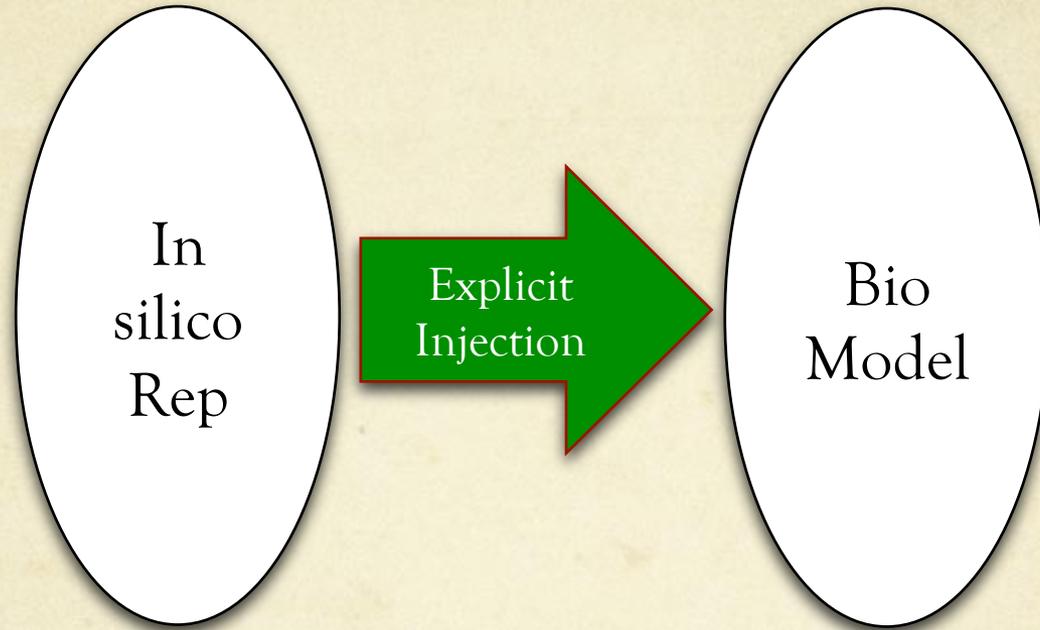


Gary An, MD  
University of Chicago  
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Bethesda, MD

# 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

*An, Shock Oct, 2001 and An, Critical Care Medicine Oct, 2004*

- 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

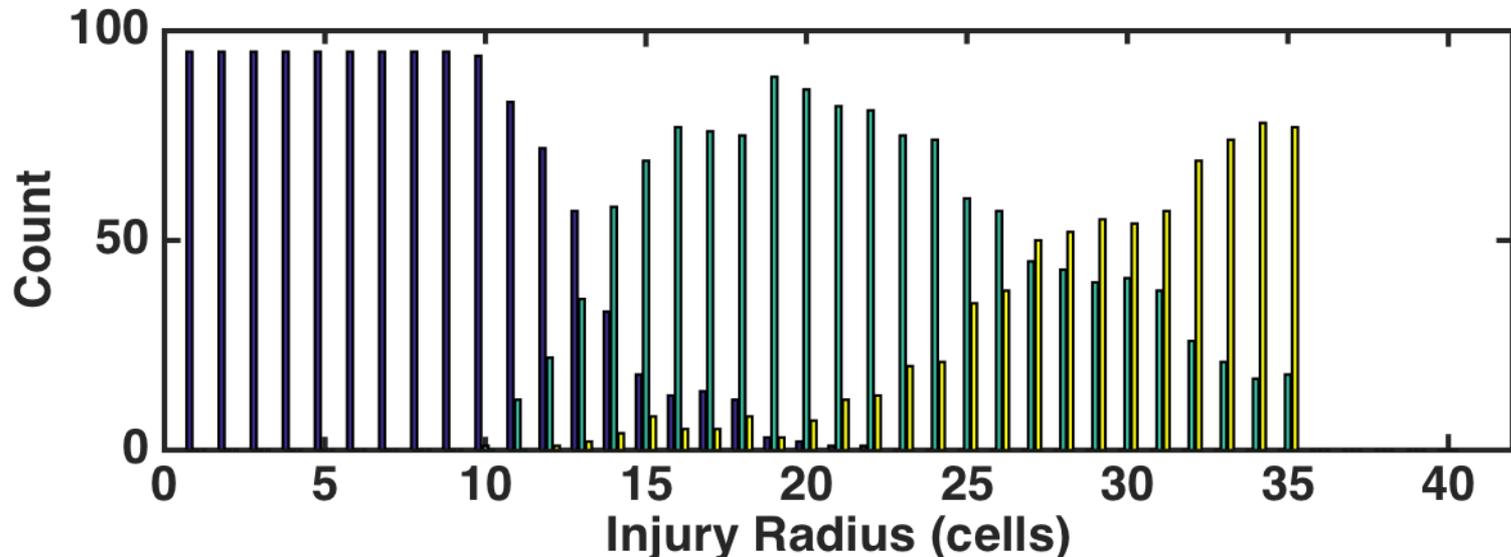
- Host Resilience: Cardiorespiratory Reserve
- Microbial Factors:
  - “Invasiveness”: Spread to adjacent areas
  - “Toxigenesis”: Ability to harm host tissue
- Environmental Contamination: Infection Control
- Question: What is the behavior space of the Sepsis ABM in terms of generating “realistic” population 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:

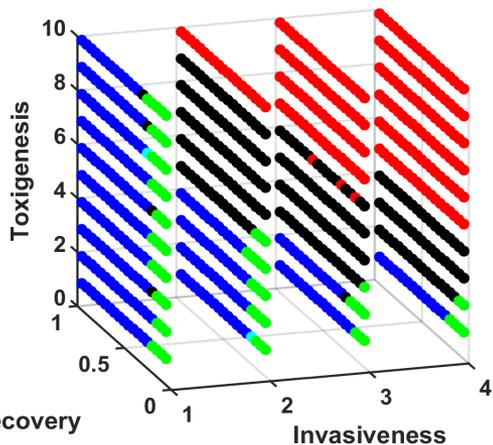


# Parameter Space Characterization

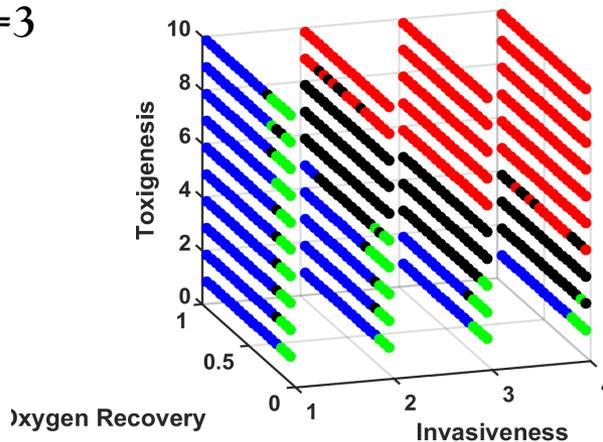
- 11,428 parameter sets evaluated
- 799,960 conditions (35 levels of perturbation, with and without antibiotics)
- 79,996,000 (~ 80 million) simulated patients
- Patterns Targeted: Population distribution of outcomes (combinations of recovery, overwhelming infection, non-recovery w/o residual infection)
- Implemented on “Beagle” (Cray XE6 Supercomputer) => Run-time = 20K node hours

# Parameter Space Characterization: No Antibiotics

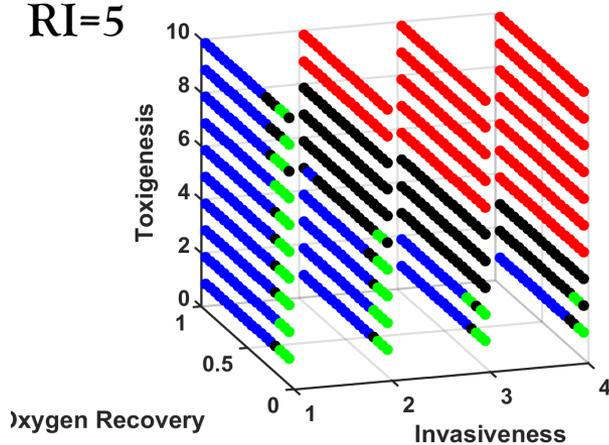
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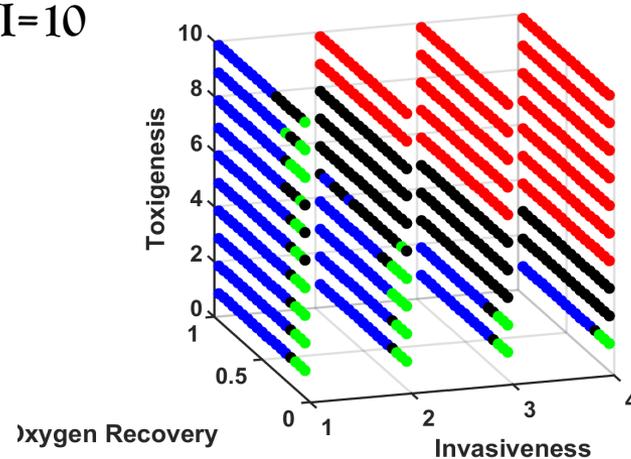
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RI=5



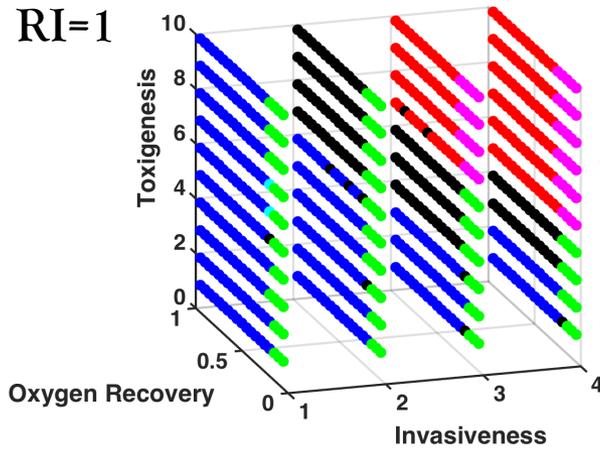
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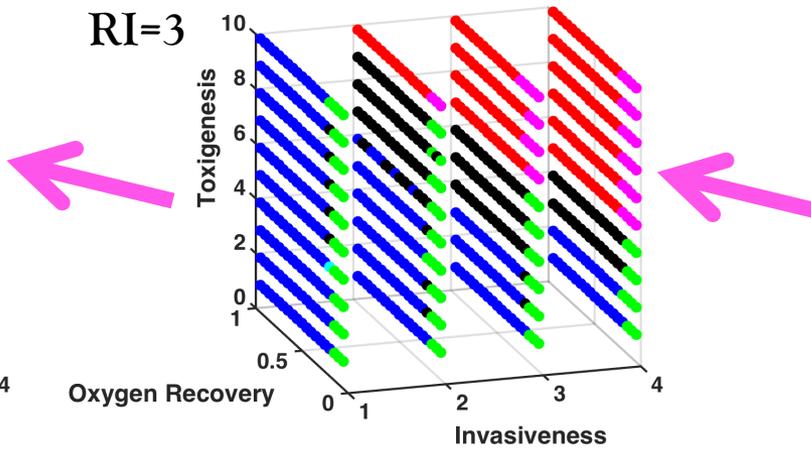
- Alive
- Overwhelming Infection
- 3 Outcomes
- Recovery/Infection
- Recovery/Hyperinflammatory System Failure
- Infection/Hyperinflammatory System Failure

# Parameter Space Characterization: With Antibiotics

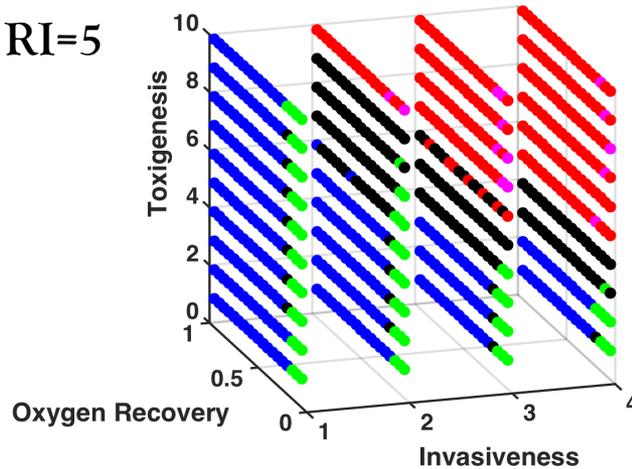
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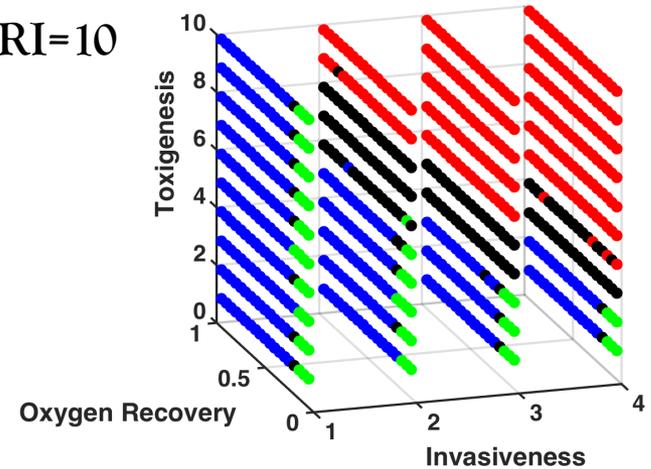
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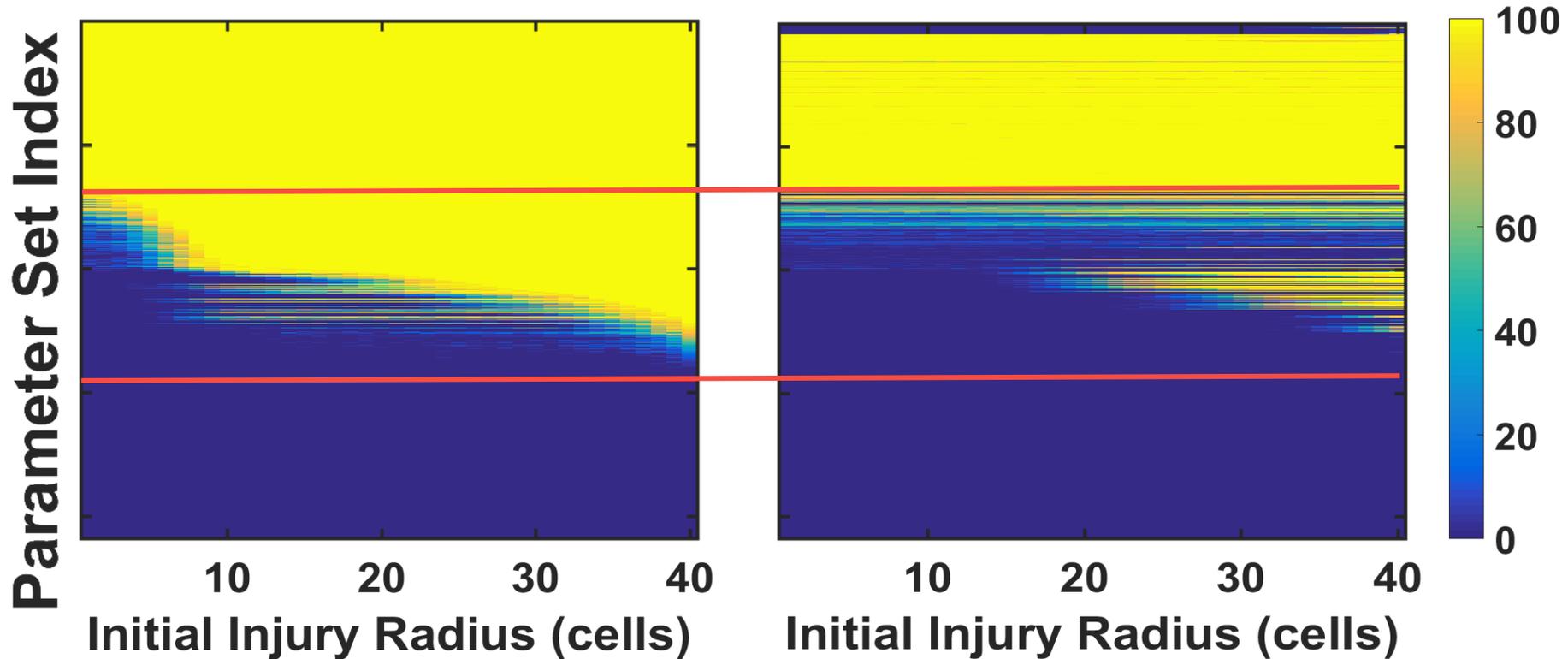
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- Alive
- Overwhelming Infection
- 3 Outcomes
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# Plausible Landscapes

Identify Parameter Sets that met  
Plausibility Criteria (bounded survival)

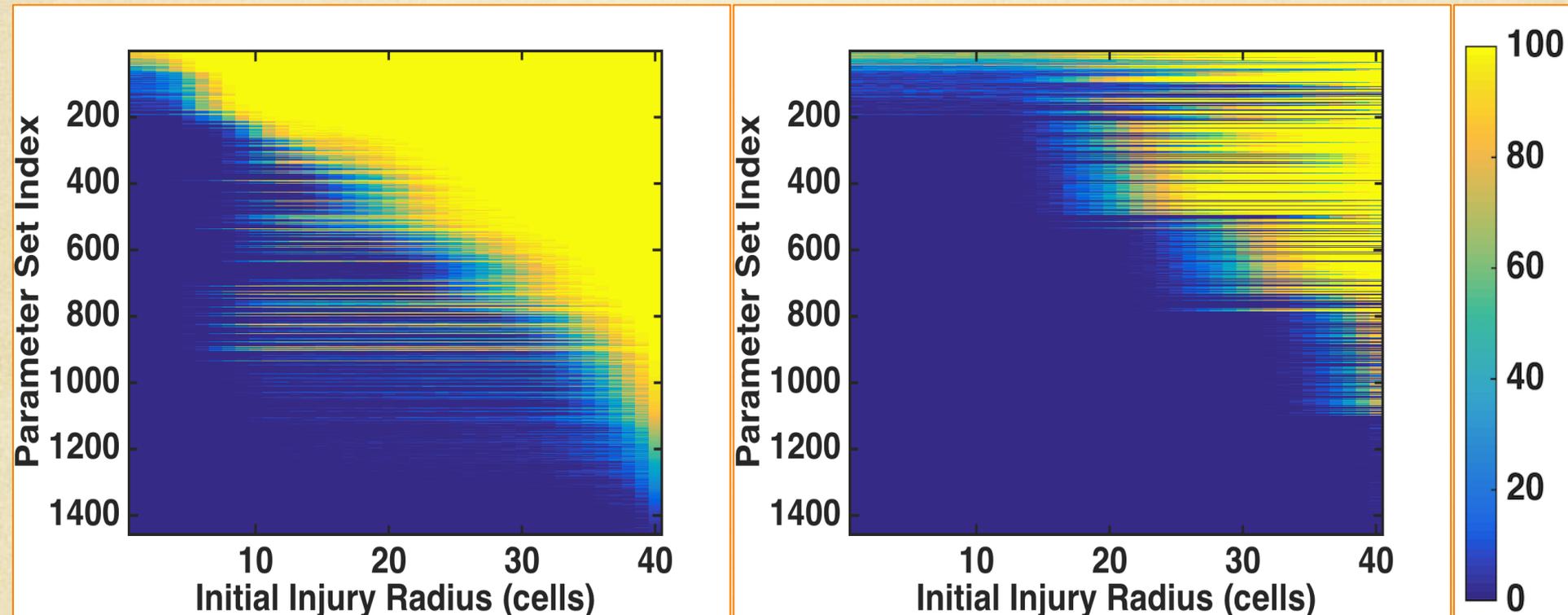


No Antibiotics  
Ordering Based on  
Onset 100% Mortality

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)

*Finis*