In Silico Construction of a Host/Pathogen Patient Cohort Using HPC Parameter Sweeps on an Agent Based Model of Sepsis

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Abstract

Current predictive models for sepsis generally use correlative methods, and as such are limited in their individual precision due to patient heterogeneity and data sparseness. The use of computational modeling and simulation can aid in the process of contextualizing data generated by complex systems in order to describe their behavior. Towards this end, we have performed a multi-dimensional parameter sweep on a previously validated model of sepsis. Data from this parameter sweep has been used to construct an *in silico* cohort of patients, defined by parameters representing host health and microbial virulence, upon which further studies and simulations can be performed to both understand the septic process and design putative interventions.

Model and Simulation Details

We use a previously validated **Agent Based Model** of sepsis that reproduces the overall dynamics of systemic inflammation seen in a clincal population. Our simulations consisted of:

- 8800 parameter sets (invasiveness, toxigenesis, host resilience, environmental toxicity)
- 40 initial injury/infection sizes
- 100 random number seeds (to account for model stochasticity)
- **35.2 million** simulations
- Three clinically relevant outcomes: **Survival, Death with Overwhelming Infection, Death from Sepsis**
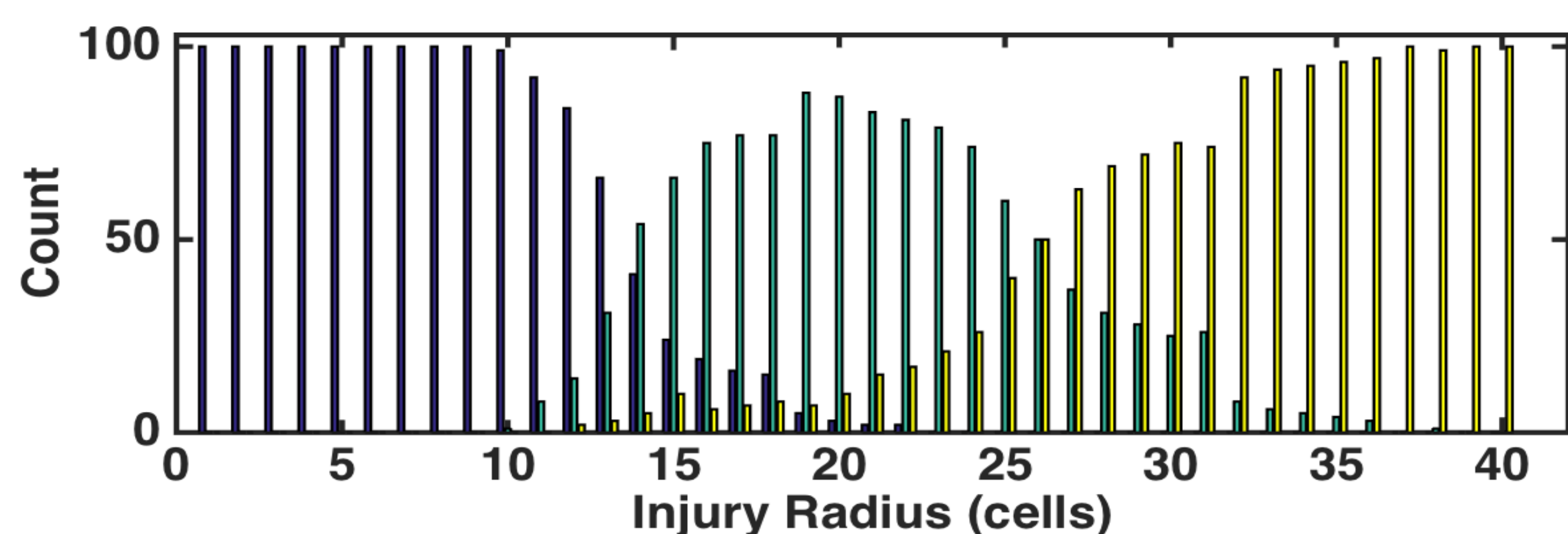
- Single parameter set aggregate output visualization
- Survival (dark blue), death from sepsis without infection (light blue), overwhelming infection (yellow)
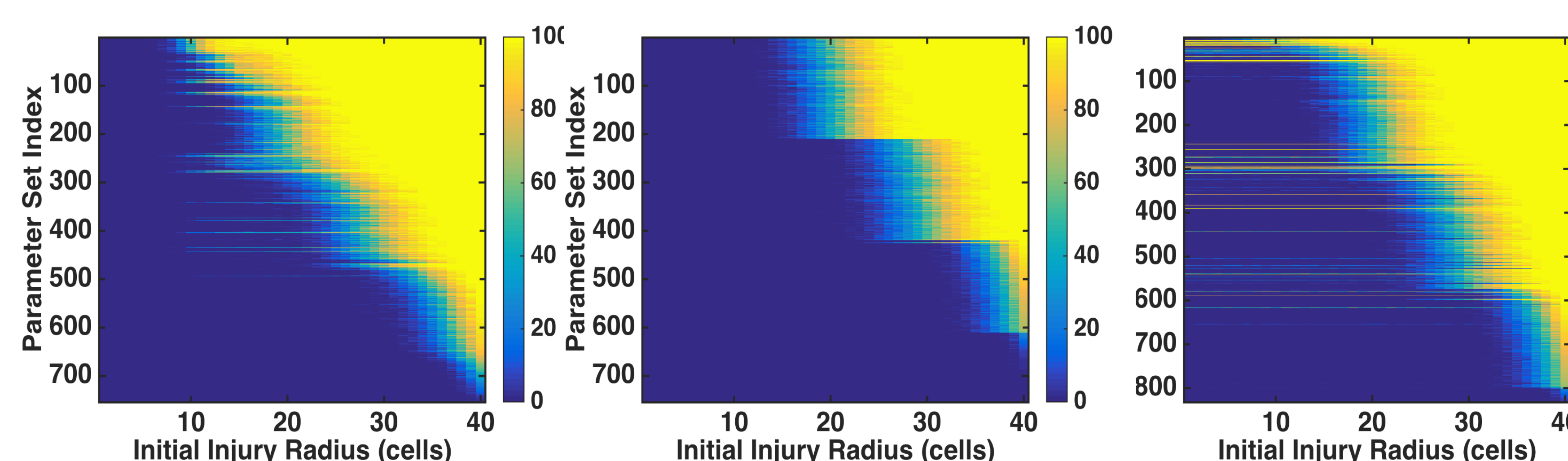
Total Parameter Space Visualization

- Single parameter set leads to 1 of 6 classifications
- Injury/Infection without treatment (top); Injury/Infection with antibiotic intervention (bottom); Environmental Toxicity (left to right) values: 1,3,5,10
- Least sensitivity to environmental toxicity parameter
- Clinically relevant parameter sets (those that lead to all three clinical outcomes) are shown in green
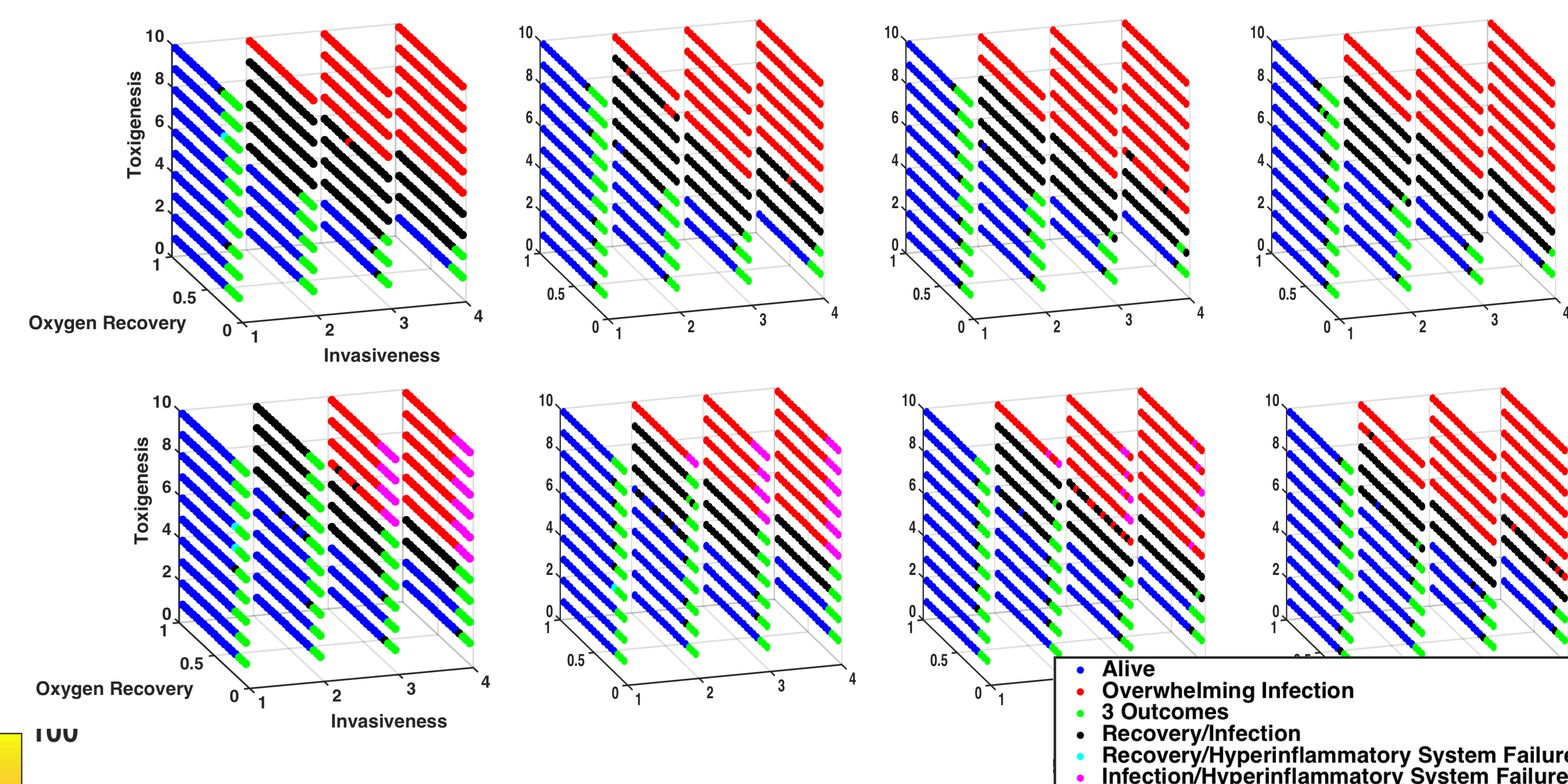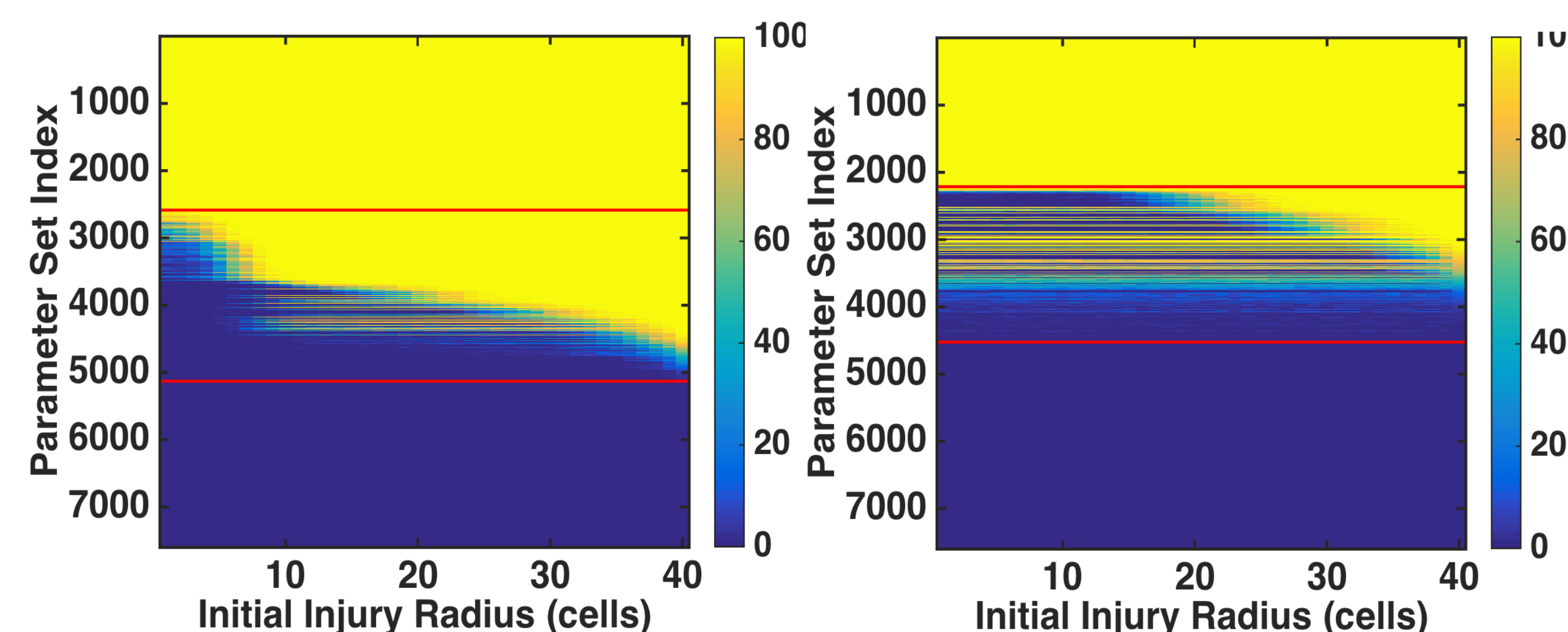

- Outcome visualization: survival (blue) vs. death (yellow) for simulation without (left) and with (right) antibiotic intervention
- Colored rows represent parameter sets ordered in terms of outcome severity.
- Antibiotics increase total survival, decrease total death

Clinically Relevant Patients

- Outcome visualization for clinically relevant parameter set without antibiotics (left), same parameter set with antibiotics (center), and larger parameter set leading to all outcomes with antibiotics
- 754 biologically plausible parameter sets without antibiotics; 832 parameter sets with antibiotics; 588 shared parameter sets
- Antibiotic unique parameter sets tend towards more severe injuries and weaker hosts – when simulations are run with these parameter sets without antibiotics, the only outcome is death (with or without infection).
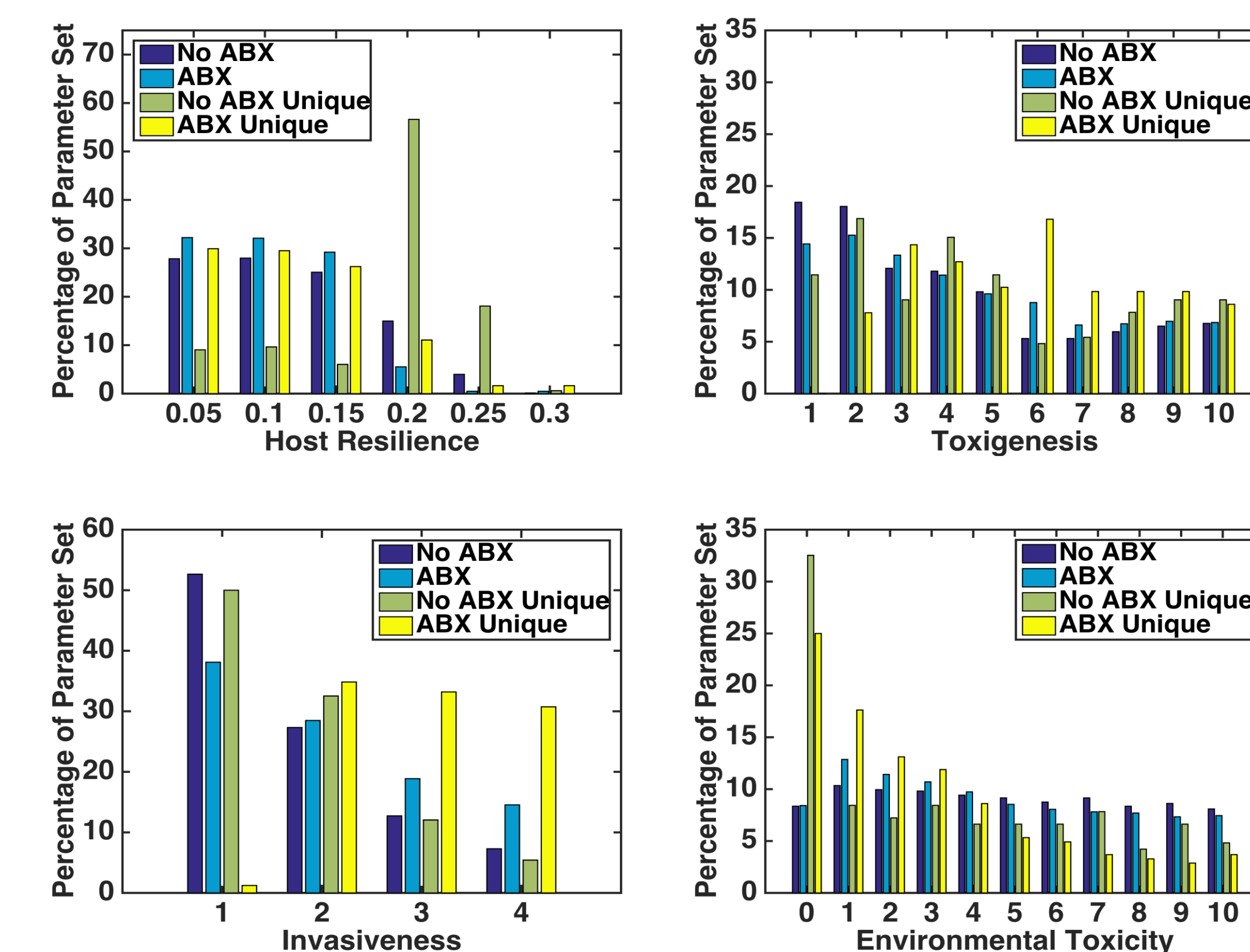
Parameter distribution for clinically relevant patients