A Hybrid Simulation Model for Studying the Acute Inflammatory Response

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Systemic Inflammatory Response Syndrome/Multiple Organ Failure (SIRS/MOF)

- “Sepsis”
- A Leading Cause of death in the ICU
- Disease of the ICU => “Unexplored State”
- Pathologic state of Acute Inflammation
- Physiologic manifestations result from endogenous mediators => Disorder of Homeostasis

Acute Inflammatory Response (AIR)

- Initial defense and repair mechanism
- Specialized cellular/molecular pathways
- Diffusely distributed/Tissue Nonspecific
- Activation is non-specific to insult
- Precedes Adaptive Immune response (self/non-self distinction=>Antibodies)

Basic Sequence of Events

- Initial Insult (bacteria, tissue damage)
- Activating mediators
- Activation of inflammatory cells
- Cellular functions/Mediator Effects
  - Positive feedback
  - Negative feedback
- Clearance of damaged tissue/Healing

SIRS/MOF cont.

- Pathologic manifestation of inflammation, BUT *no pre-existing abnormality of inflammatory system!*
- Dependent on initial degree of perturbation/insult
- SIRS/MOF represents a phase transition of dynamics beyond "design parameters" of the AIR

Treatment of SIRS/MOF

- Physiologic support
- Molecular/mediator manipulation
  - Anti-inflammatory drugs
  - Anti-cytokine/Anti-mediator drugs
- Except for Activated Protein C attempts at mediator manipulation have been unsuccessful, even detrimental

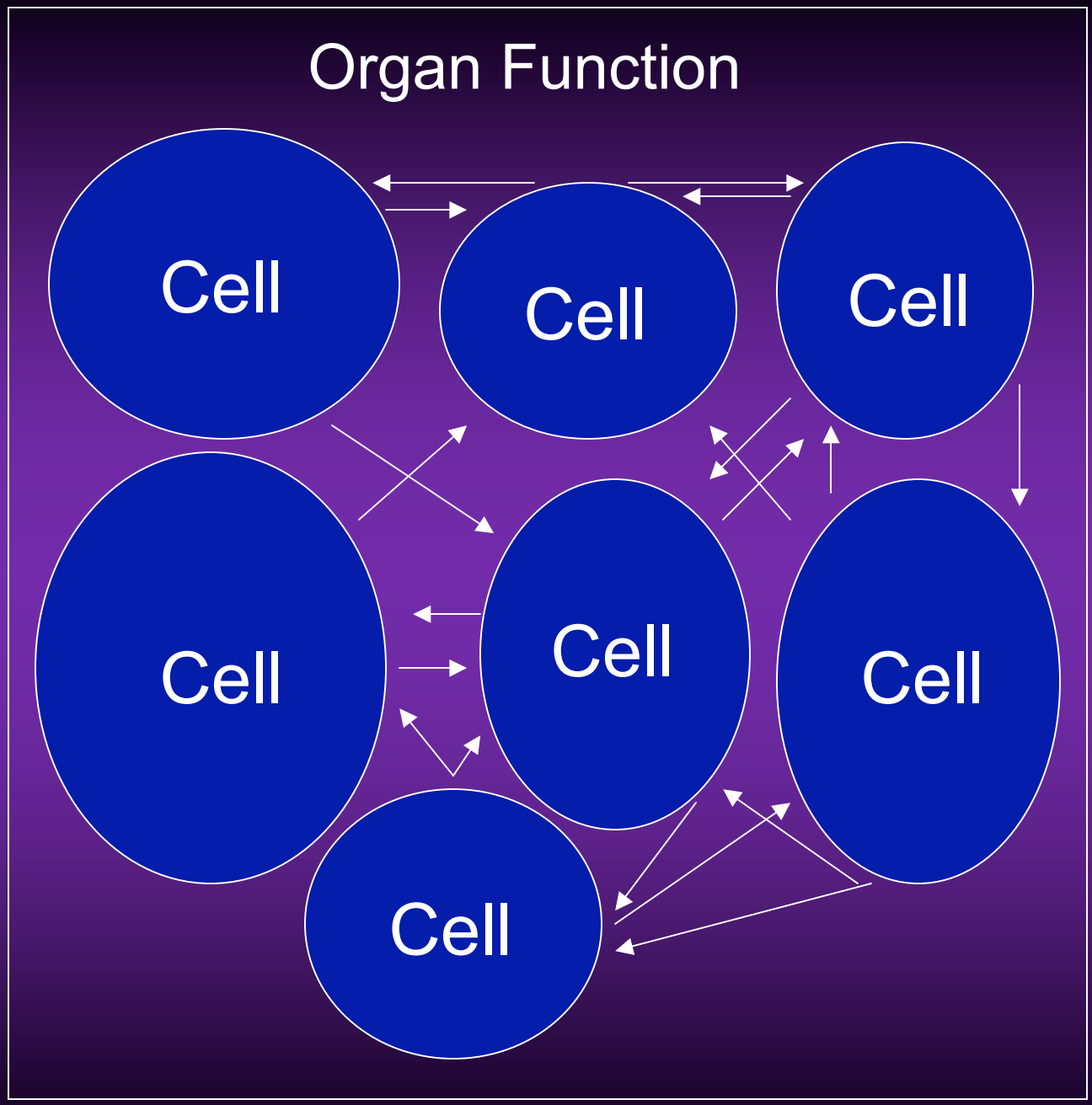
Challenge of SIRS/MOF

- Gap between Pathophysiology and Diagnosis
- Gap between Mechanisms and Treatment
- Gap between Basic Science and Clinical Implementation

Basic Science Paradigm

- Examines a system via reduction and isolation of its components
- “Good” experiment=>solves for one variable=>linear analysis
- Reconstructs system behavior by summing the results of the linear experiments

Organ Function


Organ Function
Cell
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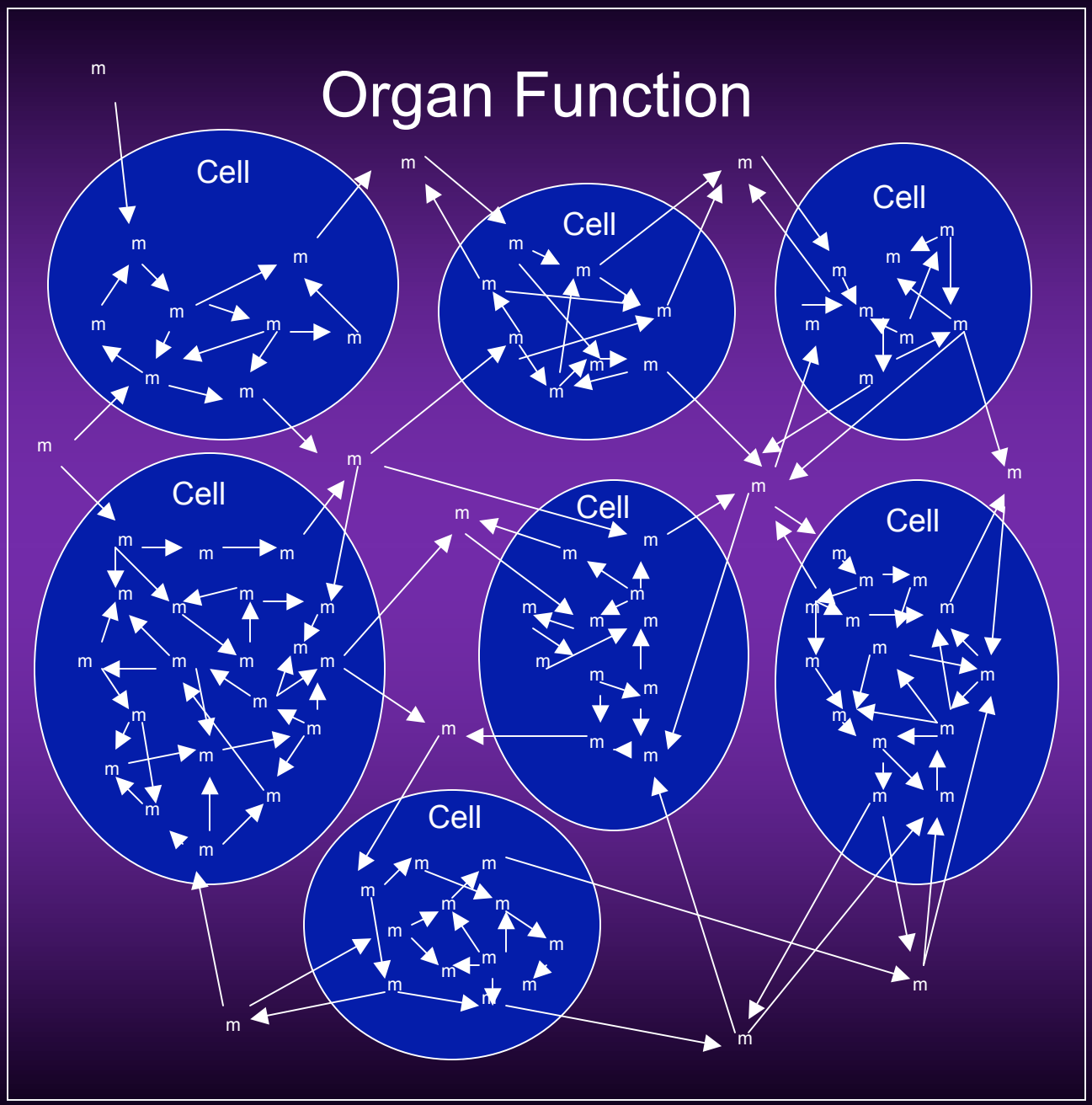
Organ Function



Basic Science Research is…

- Reductionist Paradigm
- Distributed
- Compartmentalized
- *Reductionism Necessary! => The only way we can know what things do => Mechanisms!*

Revisiting Reductionism: Analysis vs. Synthesis

- Analysis
  - Reductionist Scientific Method
  - Identifies Mechanism through Experiment
- Synthesis
  - Not well formalized=>”Intuitive”
  - Hypothesis Formation = Modeling
  - Intuition inadequate for Complex Systems

Formalizing Synthesis with Mathematical Modeling

- Common Framework for Integrating Hypotheses
  - Formal Rules
  - Explicit
  - Transparent
- Re-establish lost interconnections => System-level Behavior

What is Modeling (to me)?

- Modeling = Formalization
- Modeling = Abstraction
- Modeling = Synthesis
- Modeling = Hypothesis Generation
- ***Models = Formalized Knowledge Representation***

Modelling Techniques

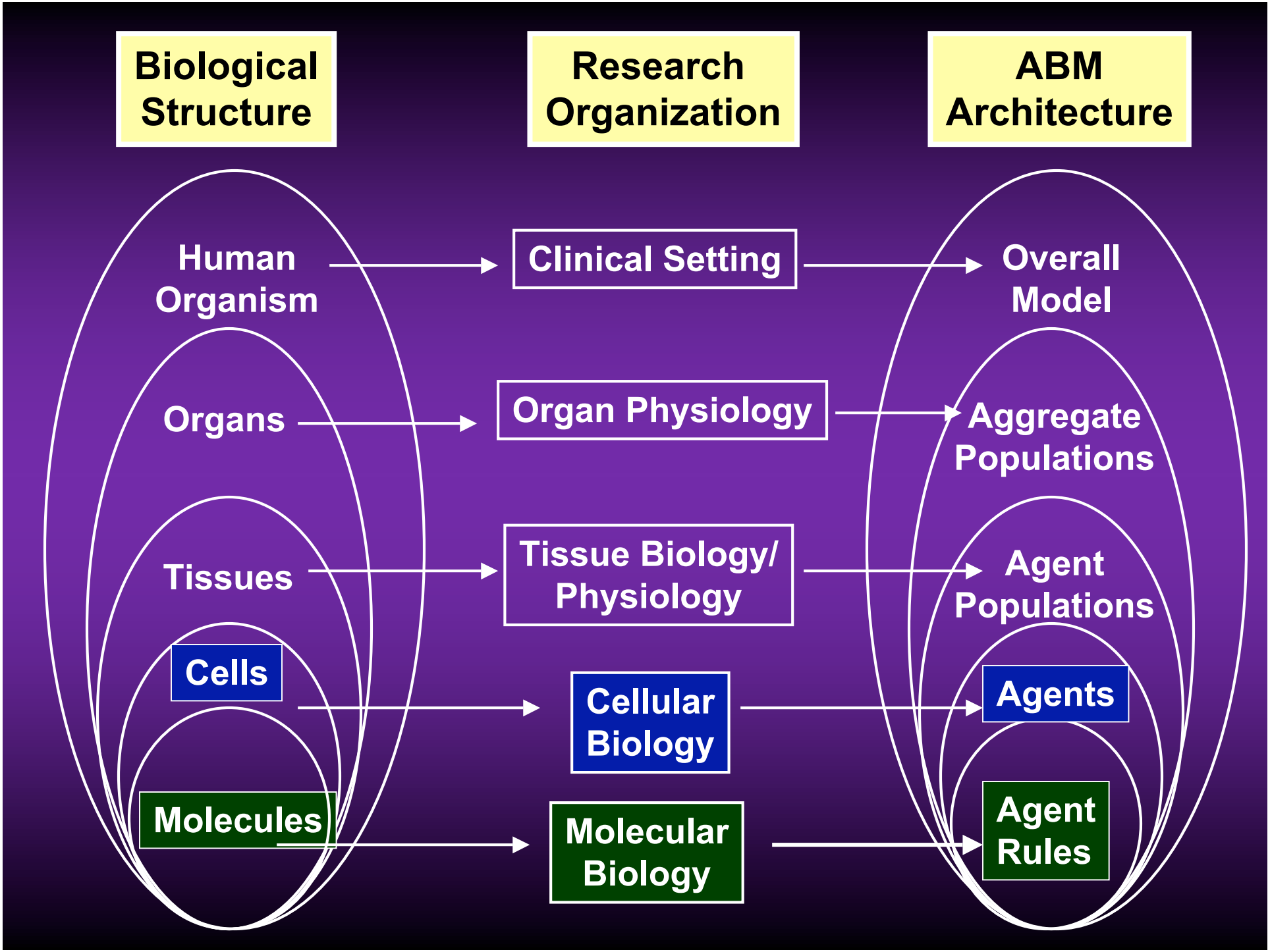
- "Population Down"
  - Equation Based (EBMs)
  - Differential Equations (Ordinary and Partial)
  - Systems Dynamics (SD)
- "Component Up"
  - Object/Event Based
  - Agent Based Models (ABMs)

Why use ABM to model AIR/SIRS/MOF?

- Lots of information about potential agents (cells and molecules)
- Process is driven by *local* interactions
- Dynamics *may* be too complex for top-down modeling
- Multiple possible levels of model validation
- Integration of Models => Total System

Why use EBM/SD to model AIR/SIRS/MOF?

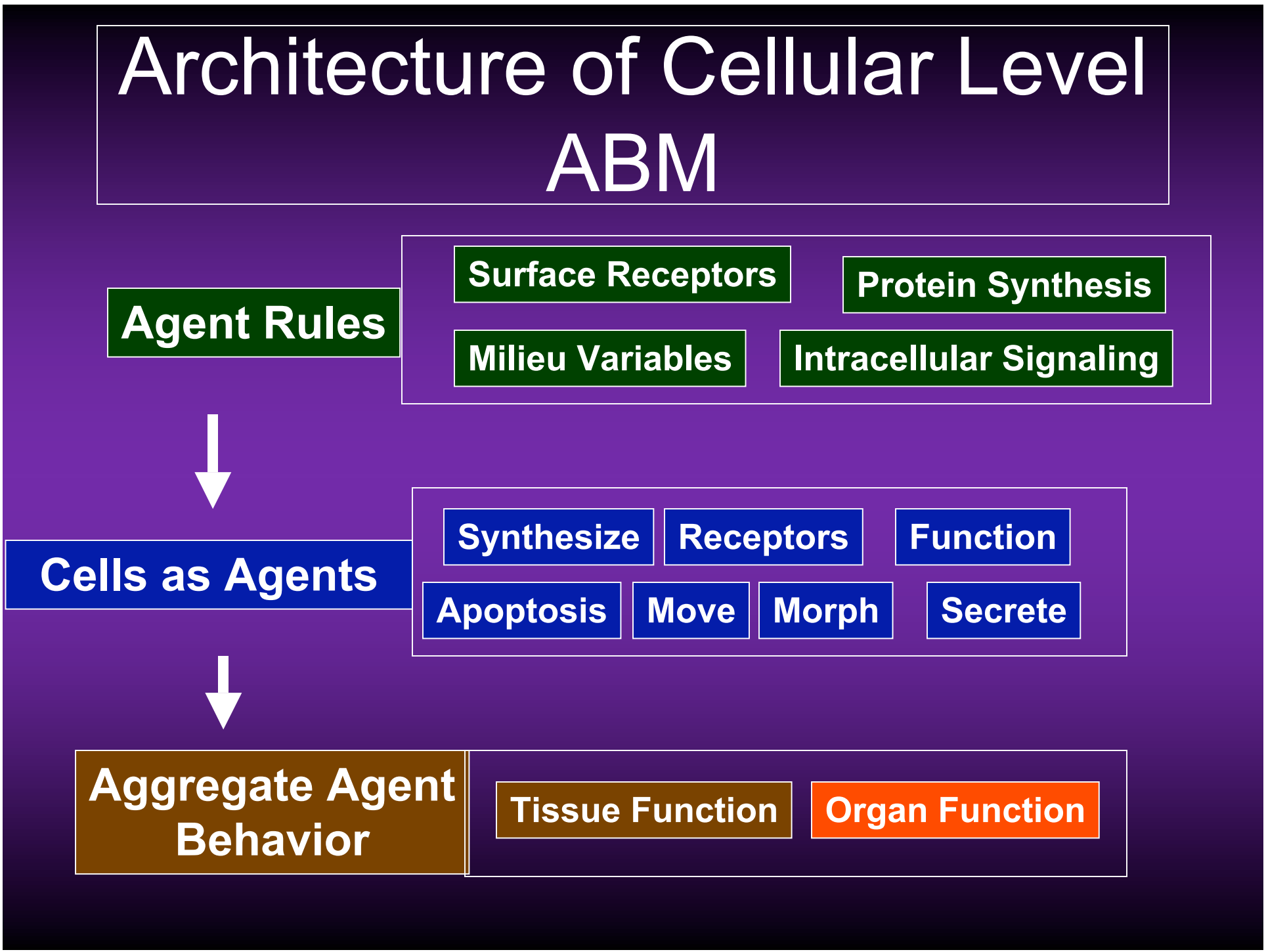
- Lots of information about populations of cells and levels of mediators => Fluxes
- These can be measured at multiple time points => Validation and Calibration
- Global Dynamics *may* be adequate to describe system
- Integration of Models => Total System


Biological Structure
Research Organization
ABM Architecture
Human Organism
Organs
Tissues
Cells
Molecules
Clinical Setting
Organ Physiology
Tissue Biology/ Physiology
Cellular Biology
Molecular Biology
Overall Model
Aggregate Populations
Agent Populations
Agents
Agent Rules

Why focus on Cells?

- Border Between Chemistry and Biology
- “Wrapper” for Biochemical Processes
- Stochastic Objects
- Heterogeneous Population Behavior
- Aggregate Behavior Determines Physiology and Pathophysiology

Architecture of Cellular Level ABM



Doing Science with ABM

- *In-Silico Experiments* => Virtual control and experimental populations
  - Apply standard statistical tools
  - Use *Pattern Oriented Analysis*
- Formalize mental model building/testing hypotheses
- Develop Theories

How Much Detail Needed?

- Level of Potential Manipulation determines Resolution of Model
- But difficult to determine a priori the levels of effects
- Therefore need capacity to be inclusive in modeling structure
- ***Emulation vs. Simulation***

Hierarchies of ABMs of Acute Inflammation

- Single Cell model
  - Intracellular Processes
  - “Back Validated”
- Tissue Model
  - In-vitro Wet Lab
- Multi-tissue Model
  - Ex-vivo Wet Lab
- Global Model of Inflammation
  - In-silico Clinical trials

ABM of Global Systemic Inflammation

- Endothelial/Blood interface
- Activation/Propagation of Inflammation
- Endothelial Cells and White Blood Cells
- Dynamics of Pathophysiology
- Proto-Testing Platform for Systemic Therapies
- *Very Abstract!*

Current Model of Global Inflammation

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

Validation Strategies

- Agent Rules=>Transparency wrt code
- Pattern Oriented Analysis/Modeling
  - Behavior of Individual wrt global response to injury=>*Individual Dynamics*
  - Behavior of Population wrt cytokine patterns=>*Population Dynamics*
  - Behavior of Population wrt outcome to intervention=>*Population Response*

Simulating Anti-inflammatory Interventions

- Any mediator represented as a variable can be manipulated
- Modified based on published effects
- No other modifications of the ABM other than simulated intervention
- *Results all generated prospectively*

List of In-Silico Experiments

Phase III Clinical Trials	3 day anti-TNF (Reinhart) 3 day rhIL-1ra (Opal) 7 day GCSF (Root)
Smaller Clinical Trials	1 dose anti-CD18 (Rhee)
Animal Studies	3 day combination anti-TNF and IL-1ra (Remick)
Hypothetical Multi-modal Regimes	anti-CD-18/anti-TNF/IL-1ra GCSF/anti-TNF/IL-1ra

Problems with ABMs

- Computationally Intensive
- Requires extensive mechanistic information (may not be available)
- “Unnecessarily” Complex/Complicated
- Difficult to Calibrate
- Less ability to formally analyze

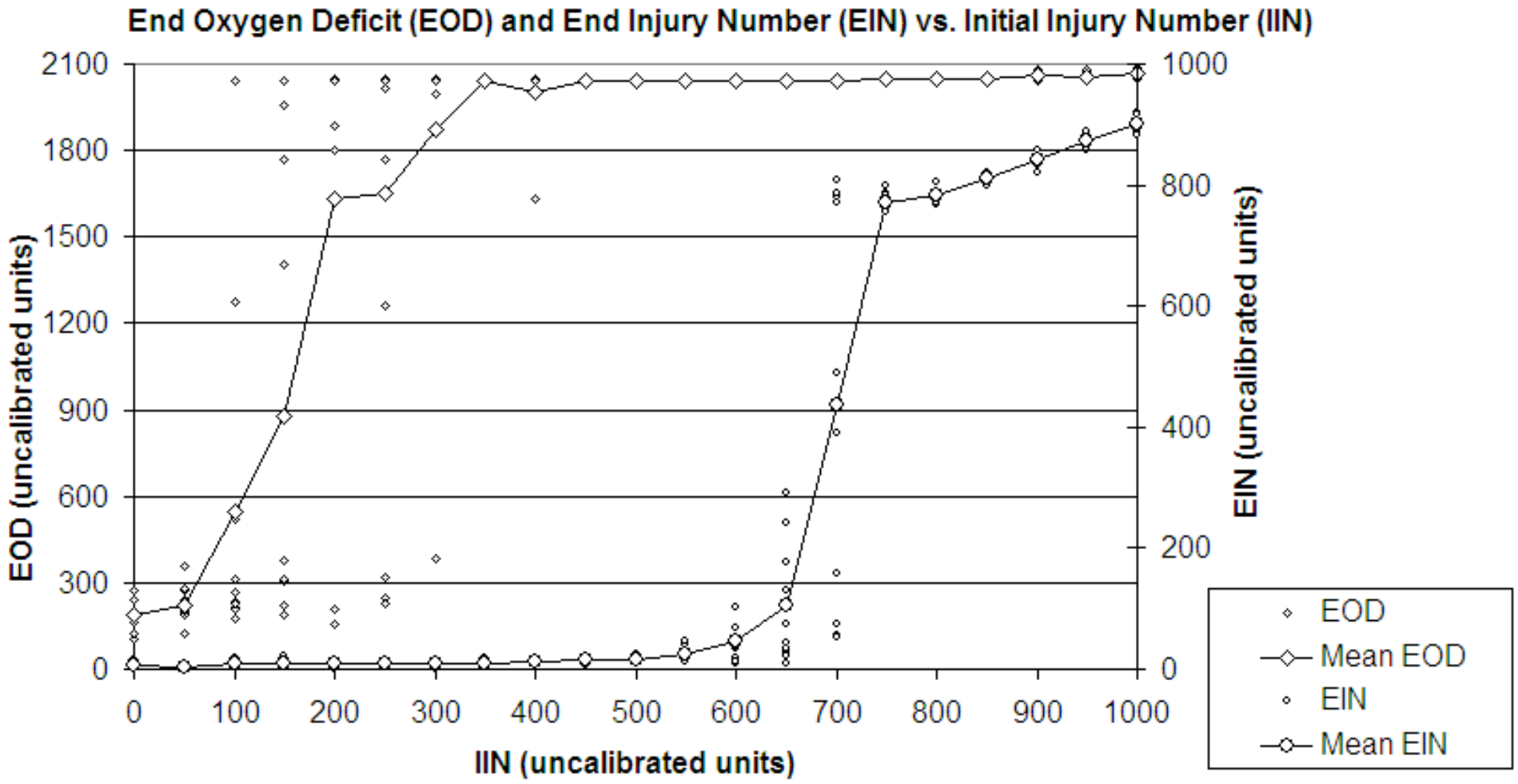
Improving Computational Efficiency

- Code Optimization
- Decreasing the Number of Agents
- Removing “Unnecessary” Complexity*
- Parameter Sensitivity Analysis
- * Don’t know what is “Unnecessary” until you do this step => *Need to have component first to remove it!*

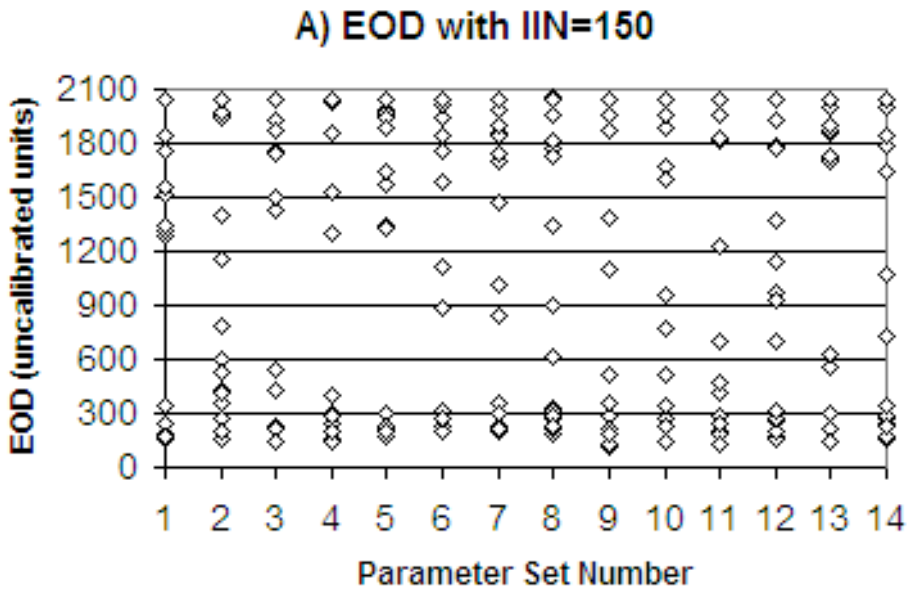
Reduced ABM of Global Inflammation

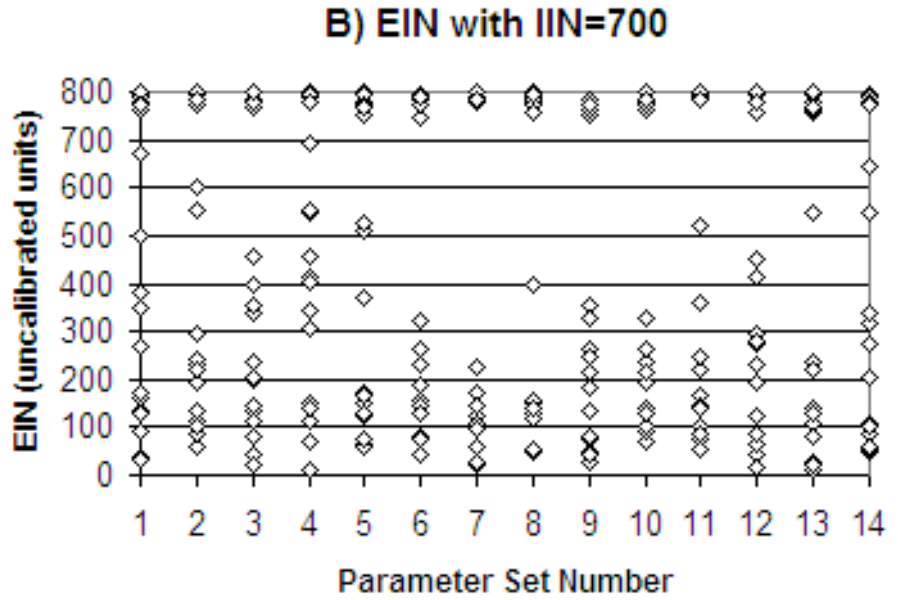
- Grid Space Reduced x 4
- N (“cases”) per experiment Reduced x 10
- Iterations per “case” Reduced x 4
- “Code Cleaned Up”
- Increased Efficiency ~ 5x Total Run Time
- Parameter Sensitivity Analysis
  - Varied/Removed T-cells

Identification of “Zone of Interest”



Parameter Sensitivity Analysis wrt Presence of T-Cells





- N = 10 for each Parameter Set Value
- No Statistical Difference between parameter sets ($p<0.05$)
- No influence by T-cells (either pro- or anti-)
- *May be suggested in literature (early effects)

Limitations of Reduced ABM

- Too Coarse Grained
  - Spatial
  - Components
- Abstracted to Homogeneous Populations
- Loss of Fidelity to “Real World”
  - Limits Potential Applications

Hybrid ABM/EBM

- Where do spatial considerations matter?
  - Cannot make Mean Field approximations
  - Don't want to use PDEs
  - Retain some benefits of ABM approach
- "Binding" of Multiple Components
- Improve Computational Efficiency
- Improve Calibration/Validation

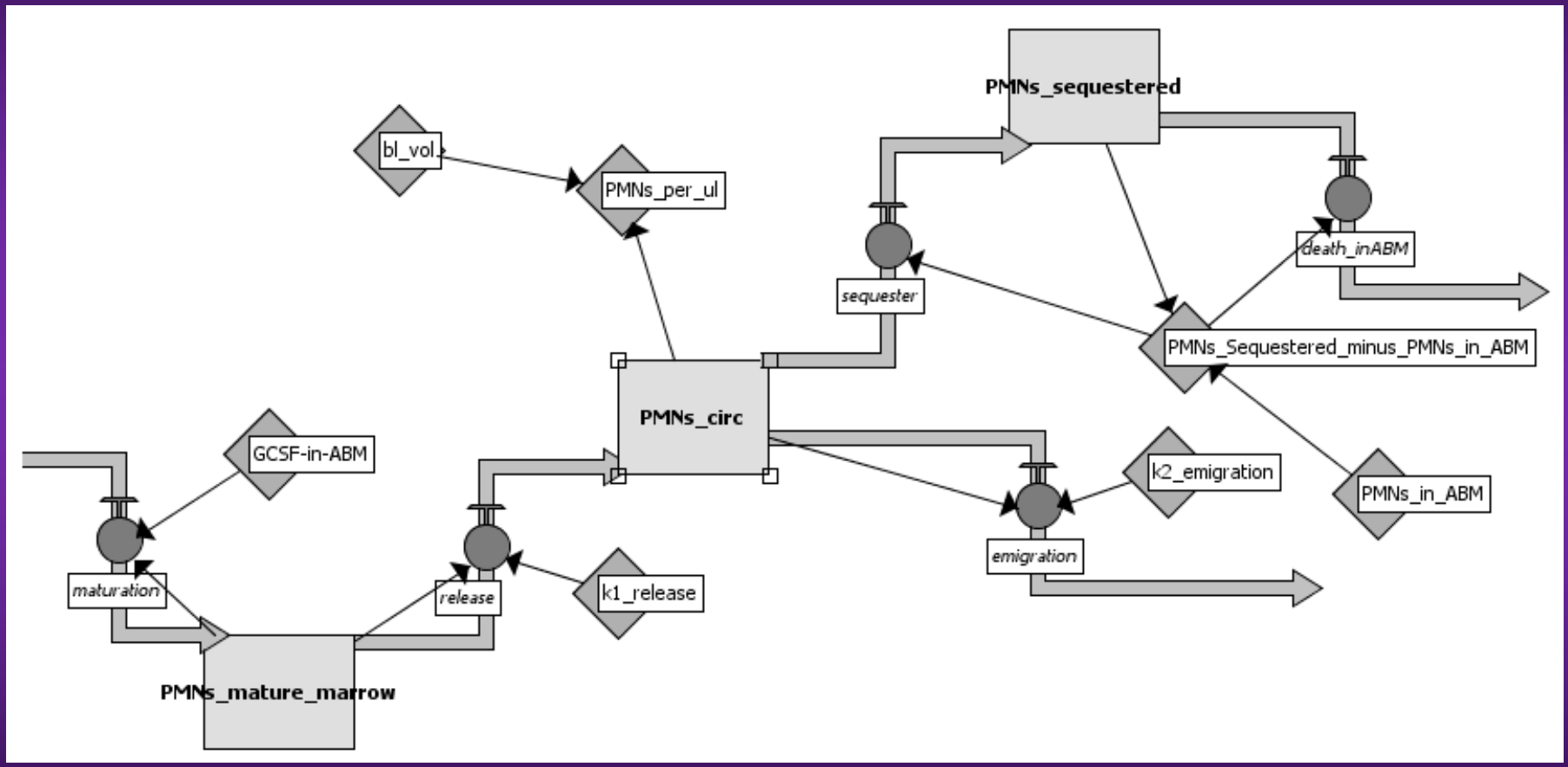
Hybrid ABM/EBM of AIR

- What the “Edge” between the two?
- Local Insult => ABM Component
  - Spatially discrete perturbation => Trauma or Infection
  - Focus on Cellular Mechanisms
- System-wide Dynamics => SD Component
  - Focus on Global Reponses
  - Circulating Mediators and their effects

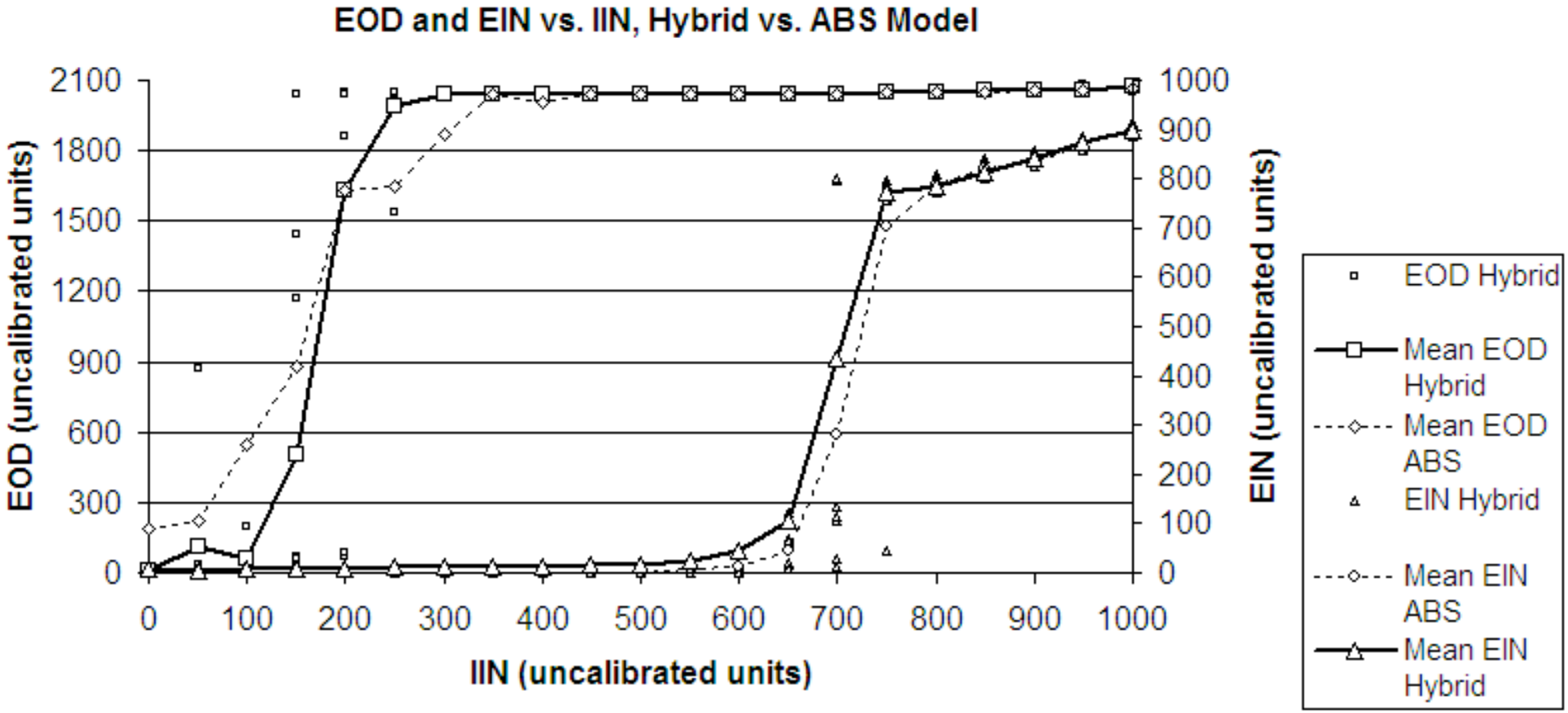
Hybrid ABM/EBM of AIR

- ABM Component =>
  - Reduced ABM
  - Retains area of Injury/Infection
  - Local Cellular Responses
  - Moved “Off screen Effects” to SD Component
- SD Component =>
  - Control of Circulating Populations of Inflammatory Cells (PMNs, Monocytes, T-cells)
  - Generation Determined by Maturation Mediators produced in ABM

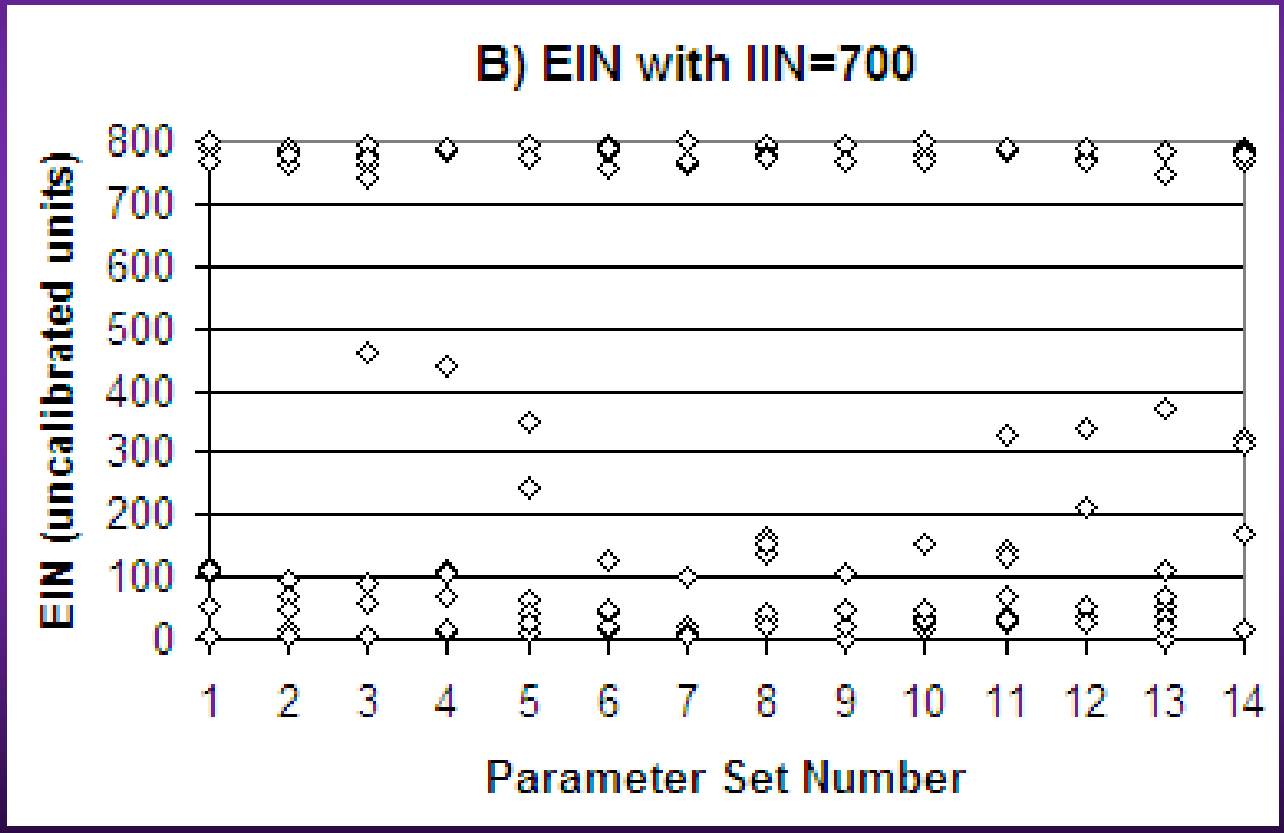
Flow Diagram of SD Submodel



Behavior Comparison: Hybrid vs. ABM



Parameter Sensitivity Analysis wrt T-cells in Hybrid Model



Another Option

- Dynamic Agent Compression
  - Wendel and Dibble at University of Maryland
  - “Compressed” agents are internally homogeneous groupings within a heterogeneous population
  - Determination of “compression” is updated per step
  - Lossless Method (lossy methods also exist

Eventual Goals

- Multiple aspects of Biomedical Systems maybe modeled with different methods (ABM/SD/Stochastic)
- Common Means of Communicating between and Integrating Models => “Articulated” Models
- Functional Unit Representation Method (FURM) => Hunt at UCSF

Eventual Goals, cont.

- Create simplified models that maintain behavioral richness => high detail and then deconstruct
- Use SD as a “wrapper” for ABM submodels => organ-organ crosstalk / multi-hierarchies
- Identification of different “edges” between SD and ABM to best utilize respective strengths
- Dynamic “shifting” of edges between SD and ABM to optimize computational efficiency

Eventual Goals, cont.

- Develop Multi-scale, Multi-hierarchical Modeling Framework
- Multiple Models of same processes/level
- “Fertile” Hypothesis Environment => Competition and Concatenation
- “Ecology”of Ideas
- Use Natural Selection to refine Community Knowledge

SCAI

Society for Complexity in Acute Illness

http://www.scai-med.com