A Tale of Two Methods—Agent-based Simulation and System Dynamics—Applied in a Biomedical Context: Acute Inflammatory Response

BIOMEDICAL SIGNAL PROCESSING LABORATORY
bsp.pdx.edu

W. Wakeland[1,2] J. Fusion[1] B. Goldstein[2,3]

[1]Systems Science Ph.D. Program, Portland State University

[2]Complex Systems Laboratory, Oregon Health & Science University

[3]Biomedical Signal Processing Laboratory, Portland State University

PORTLAND STATE UNIVERSITY

ELECTRICAL & COMPUTER ENGINEERING

System Science Ph.D. Program

Oregon Health & Science Univ. Complex Systems Laboratory

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- Research questions
- Brief description of published agent-based and differential equation-based models of SIRS
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Motivation

- Systemic inflammatory response syndrome (SIRS) is an important clinical problem
  - ➔Proximal infection/damage is eradicated, but the organs do not recover from the collateral damage
  - ➔Complex, poorly understood processes
  - ➔Poor prognosis for 1000's of patients
- Multiple computer models published recently
  - ➔Used to simulate clinical trials *in silico*
- How well do these models/methods work?
  - ➔How do they compare?

A Systems Problem

- Multiple "level" phenomena
  - → Organ, tissue, cell, molecule
- Very complex interactions of factors or agents
  - → Even highly simplified models have dozens of interacting effects
- Tipping points
  - → Very different behavior modes
  - → Clearly defined "region of interest"
- Multiple potential approaches
  - → Spatial /Agent-based simulation (ABS)
  - → Differential equation-based (DE)

Research Questions

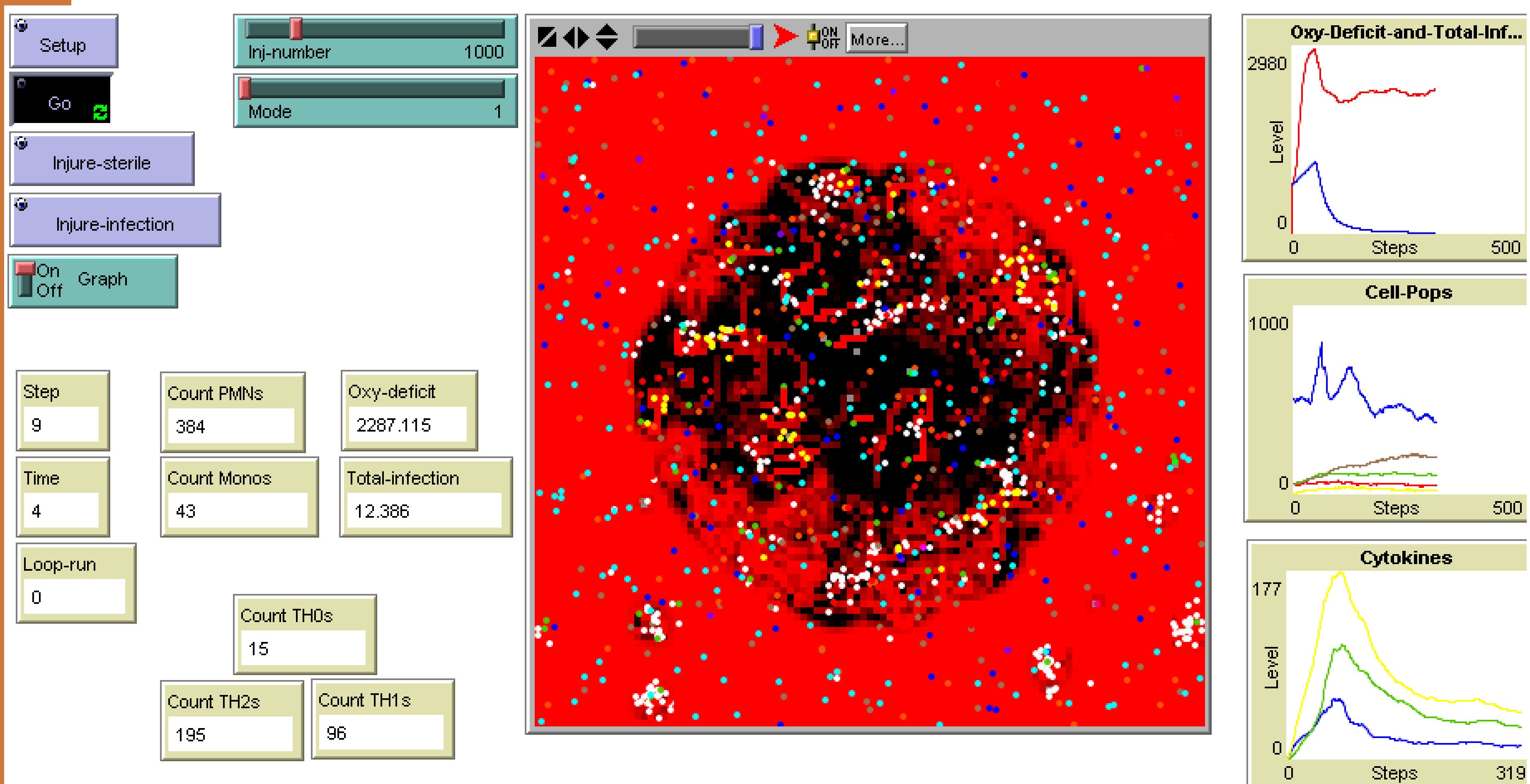
- How do ABS and DE models compare in this particular biomedical context?
  - ➔Are they complementary as suggested by others?
  - ➔Do they lead to different kinds of insights?
  - ➔What are their relative strengths & weaknesses?
- Could a much simpler DE model using the system dynamics (SD) modeling approach capture the essence of the more complex models?
- Is the notion of an *in silico* clinical trial an idea whose time has come?

ABS Model of SIRS/MOF (An 2004*)

- Spatial, 2-D grid of simulated tissue cells
  - ➜18 classes of agents, each with their own rules (code)
  - ➜~500 lines of Netlogo™ code → 3 control parameters
  - ➜14 global variables →16 agent vars. → 23 grid vars.
- Although highly abstracted, the model produced behavior similar to clinical observations
- Dr. An used the model to run *in silico* versions of several clinical trials
  - ➜100 subjects per treatment group
  - ➜Results mirror the actual clinical trials

* An, Gary (2004) "*In silico* experiments of existing and hypothetical Cytokine-directed clinical trials using agent based modeling" *Crit Care Med 32*(10):2050-2060

Screenshot of the Netlogo™ Interface



DE Model of Sepsis (Clermont et al 2004*)

- **Model was used to study immunomodulatory strategies for treating cases of severe sepsis**
  - ➔ **18 state variables**
  - ➔ **80+ parameters, estimates based on experience**
  - ➔ **Strives to reflect the underlying physiology**
- **A population of 1000 patients was simulated by varying 11 parameters**
- **Results were consistent with actual clinical trials**

*** Clermont, G., J. Bartels, K. Kumar, G. Constantine, Y. Vodovotz, C. Chow (2004) "*In silico* design of clinical trials: A method coming of age" *Crit Care Med 32*(10):2061-2070**

DE Model Equations

$$P' = k_{pg} \cdot P \cdot (1 - k_{ps} \cdot P) \cdot heav(P - P0) - (k_{pm} \cdot MA + k_{pno} \cdot NO + k_{po2} \cdot O2 + k_{ab} \cdot heav(t - tab)) \cdot P$$

$$PE' = k_{pp} \cdot P + k_{pg} \cdot P \cdot (1 - k_{ps} \cdot P) \cdot heav(P - P0) - (k_{pm} \cdot MA + k_{pno} \cdot NO + k_{po2} \cdot O2 + k_{ab} \cdot heav(t - ta - k_{pe} \cdot PE$$

$$MR' = -(k_{mp} \cdot P + k_{mpe} \cdot PE + k_{md} \cdot D) \cdot (S_m + f2(TNF, x_{tnf}) \cdot k_{m6} \cdot f2(IL6, x_{il6}) \cdot fs2(CA, x_{ca})) \cdot MR + k_{mm} \cdot f(s_{noa} \cdot TNF + s_{noa} \cdot PE + NO, x_t) - k_{mr} \cdot MR + S_m$$

$$MA' = (k_{mp} \cdot P + k_{mpe} \cdot PE + k_{md} \cdot D) \cdot (S_m + f2(TNF, x_{tnf}) \cdot k_{m6} \cdot f2(IL6, x_{il6}) \cdot fs2(CA, x_{ca})) \cdot MR - k_{ma} \cdot MA$$

$$NA' = (k_{np} \cdot f(P, x_{t2}) + k_{npe} \cdot f(PE, x_{t2}) + k_{ntnf} \cdot f(TNF, x_{tnf}) + k_{n6} \cdot f(IL6, x_{il6}) + k_{nd} \cdot f(D, x_{t2})) \cdot NA \cdot (1 - k_{ns} \cdot NA) - ((k_{nno} \cdot NO/s_{noa} + k_{no2} \cdot O2) \cdot NA - k_n \cdot (fs(TNF, x_{tnf})$$
$$+ fs(IL6, x_{il6})) \cdot NA + S_n$$

$$NOD' = (k_{non} \cdot NA + k_{nom} \cdot MA) \cdot fca(CA, x_{ca}) \cdot (f(TNF, x_{tnf}) + f(IL6, x_{il6})) - k_{nod} \cdot NOD$$

$$NO' = k_{no} \cdot (NOD \cdot s_{noa} - NO)$$

$$O2' = ((k_{o2n} \cdot N + k_{o2m} \cdot MA) \cdot (f(TNF, x_{TNF}) + k_{o26} \cdot f(IL6, x_{il6})) + k_{O2np} \cdot NA \cdot f(P, x_t)) \cdot fs2(CA, x_{ca}) - k_{o2} \cdot O2$$

$$TNF' = (k_{tnfn} \cdot NA + k_{tnfmr} \cdot MR + k_{tnfma} \cdot MA) \cdot fs2(CA, x_{tnfca}) \cdot (1 + k_{tnftnf} \cdot f(TNF, x_{tnf}) - k_{tnf} \cdot TNF - k_{atnf} \cdot square(tiatnf, tiatnf + dur) \cdot TNF$$

$$IL6' = k_{6m} \cdot MA \cdot (1 + k_{6th} \cdot f(TH, x_t) \cdot fs2(CA, x_{t2}) - k_6 \cdot IL6$$

$$CAR' = (k_{can} \cdot N + k_{cam} \cdot MA) \cdot (k_{catnf} \cdot f(TNF, x_{tnf}) + k_{ca6} \cdot f(IL6, x_{il6}) + k_{cano} \cdot f(NO, x_t) + k_{cao2} \cdot f(O2, x_t)) - k_{car} \cdot CAR$$

$$CAI' = CAR - k_{ca} \cdot CAI$$

$$CA = CAI \cdot k_{capc} \cdot PC$$

$$TF' = (k_{tfpe} \cdot PE + k_{tftnf} \cdot TNF + k_{tf6} \cdot IL6) \cdot fs(PC, x_t) - k_{tf} \cdot TF$$

$$TH' = (k_{th1} + k_{thn} \cdot TH) \cdot TF - k_{th} \cdot TH$$

$$PC' = k_{pcth} \cdot TH - k_{pc} \cdot PC$$

$$B' = k_b \cdot (B_a - B) - ((k_{bno}/s_{noa}) \cdot NO \cdot fs(O2, x_t) + k_{btnf} \cdot TNF + k_{bth} \cdot TH) \cdot B$$

$$D' = k_{db} \cdot (1 - (B/B_a)) + k_{dtnf} \cdot TNF + k_{do2} \cdot O2 + (k_{dno}/s_{noa}) \cdot NO \cdot fs(NO, x_{t2} \cdot s_{noa})/s_{noa} + k_{dth} \cdot TH + k_{deg} \cdot O2 \cdot e^{-10 \cdot (NO - s_{noa} \cdot O2)^2 / s_{noa}^2} - k_d \cdot D$$

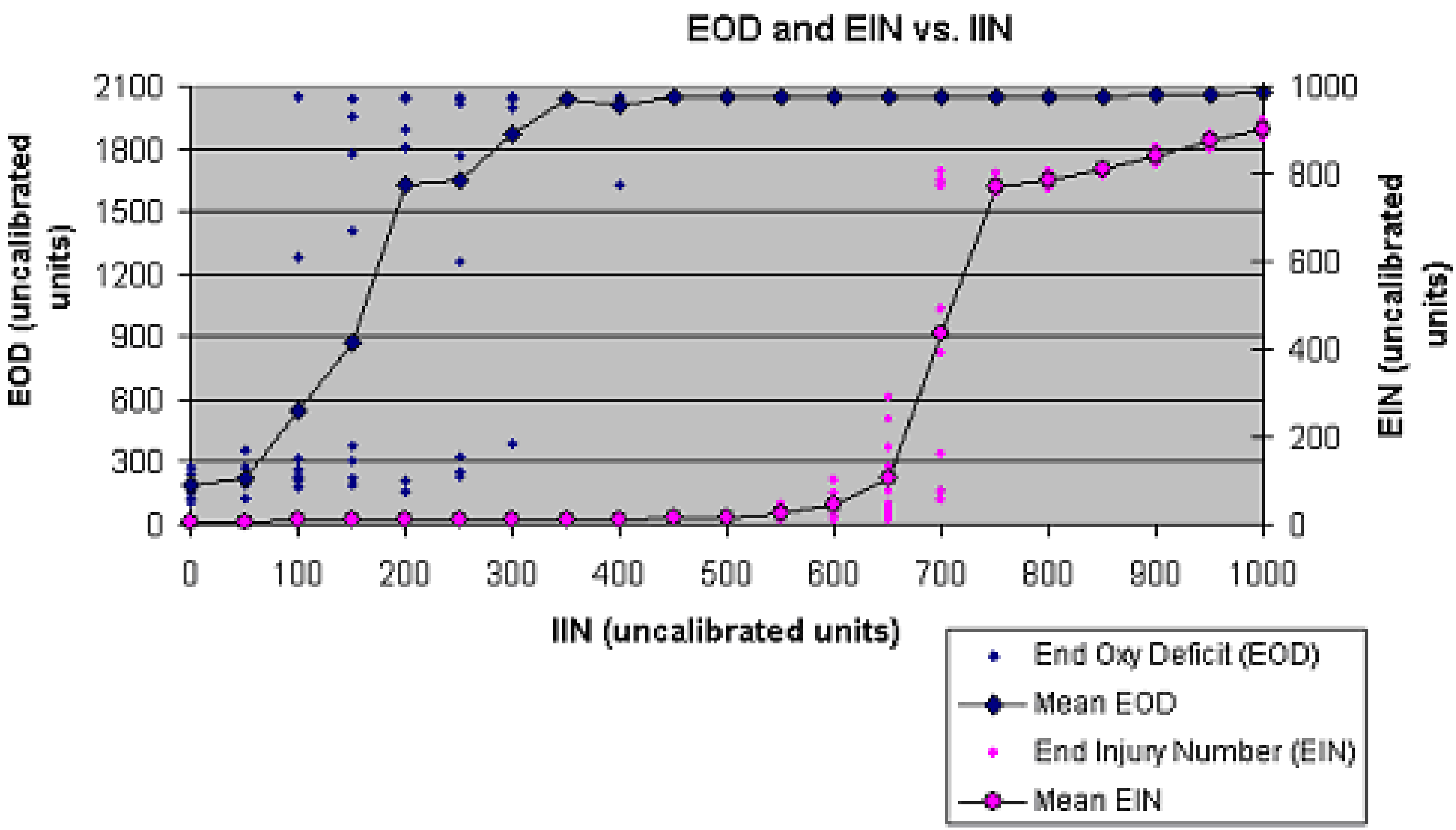
Exploratory (subjective) Research Method

- Phase I: Ran experiments with ABS model
  - ➜Reproduced the reported results
  - ➜Recorded insights and learning
- Phase II: Built a simplified System Dynamics model of the core phenomena
  - ➜Recorded insights and learning
- Phase III: Implemented the DE model
  - ➜Attempted to reproduce reported results
  - ➜Recorded insights and learning
- Phase IV: Compared and contrasted results

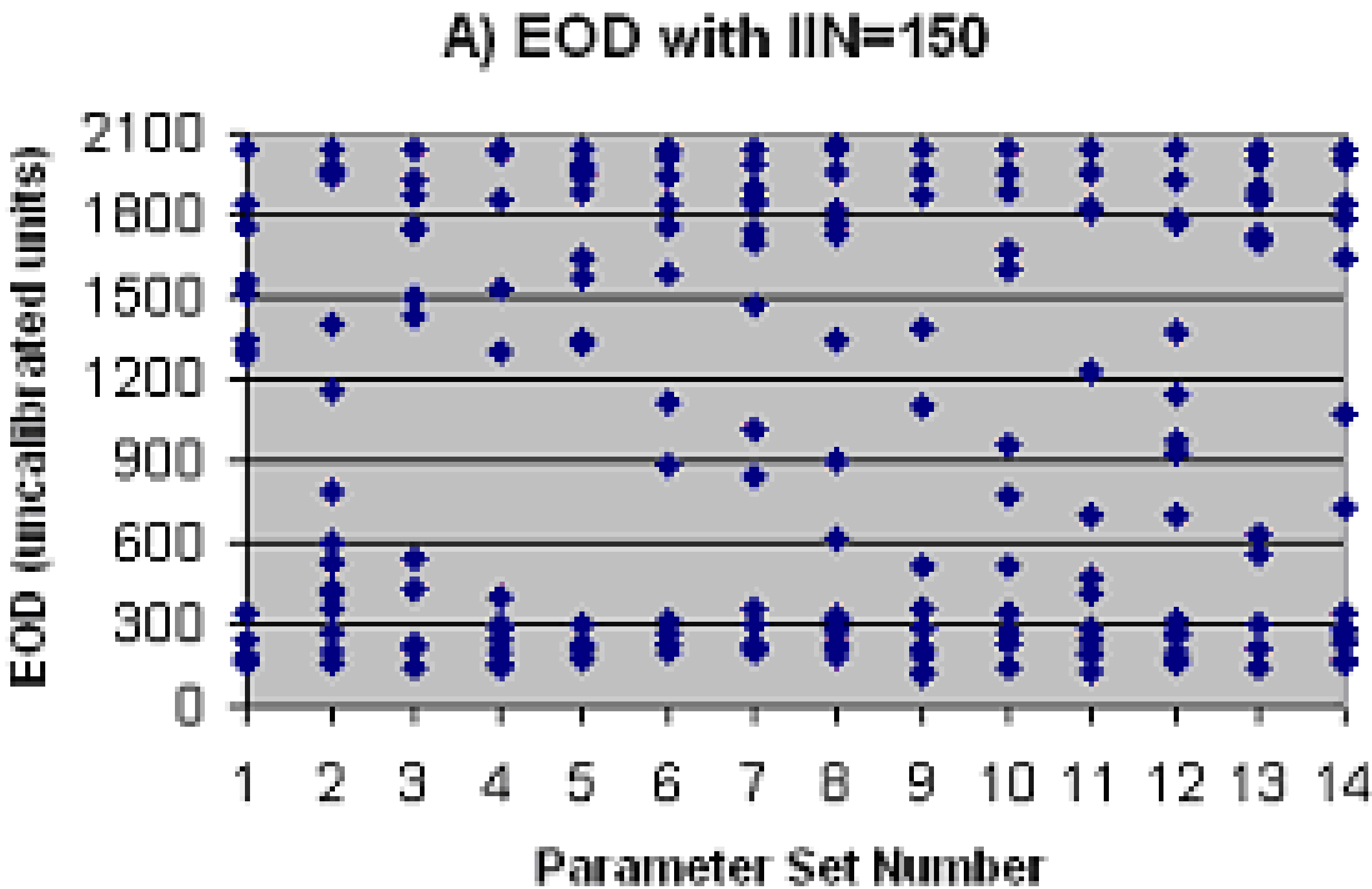
Results: Phase I

- Reproduced reported results (region of interest)
  - ➜ Discrepancies between paper and code
  - ➜ Model ran very slowly!
    - ✓ Scaled down: a) model area by 4x, b) number of cases from 100 to 10, and c) run duration by 4x
  - ➜ Still required over 30 hours of computer time
- Optimized model code to improve speed
- Ran additional experiments
  - ➜ Varied 5 parameters to create 14 parameter sets
  - ➜ Increased cases from 10 to 20
  - ➜ Variation within vs. across parameter sets

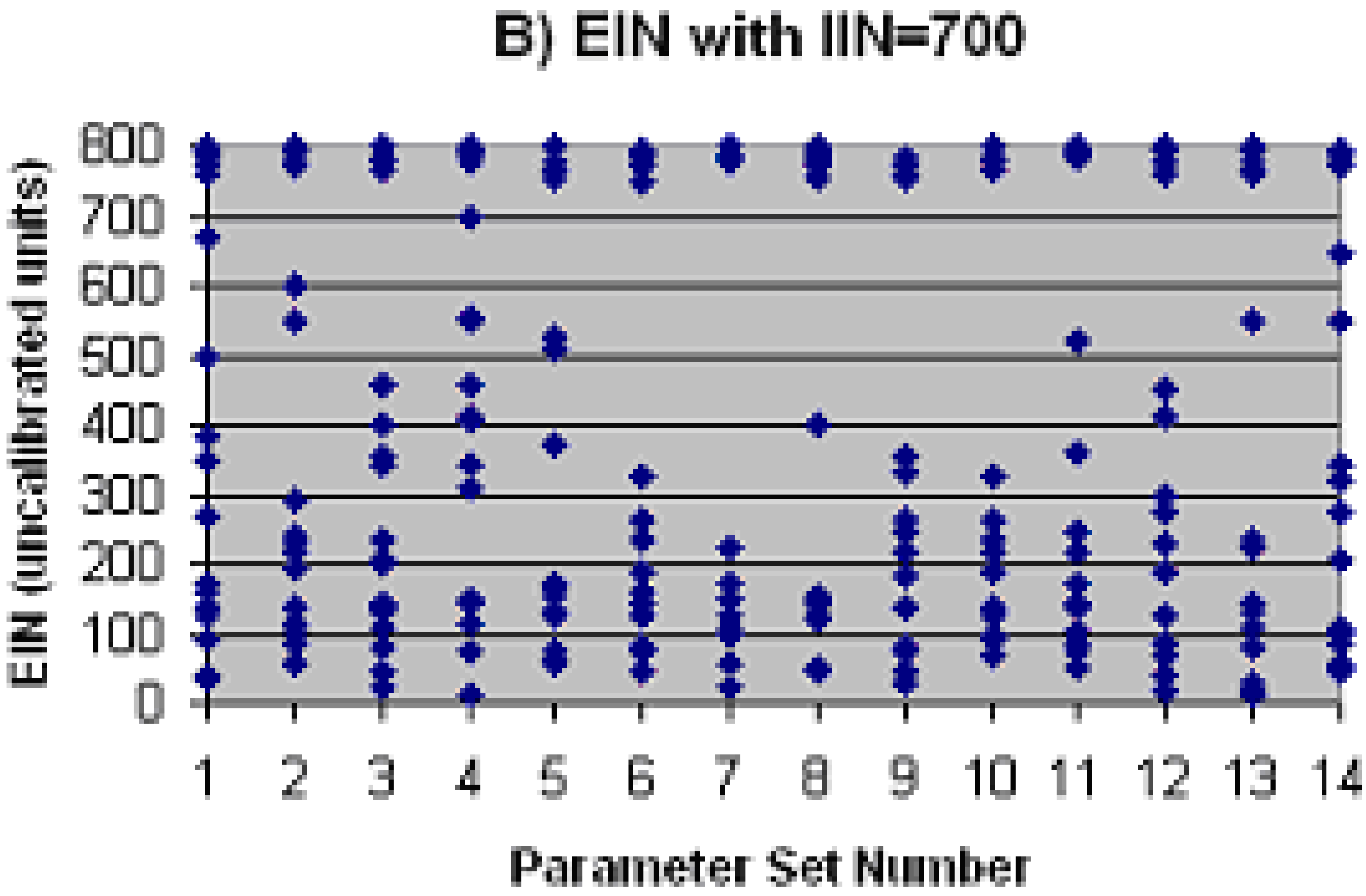
The "Region of Interest" (ROI): ABS Model



Variation Within and Between Parameter Sets

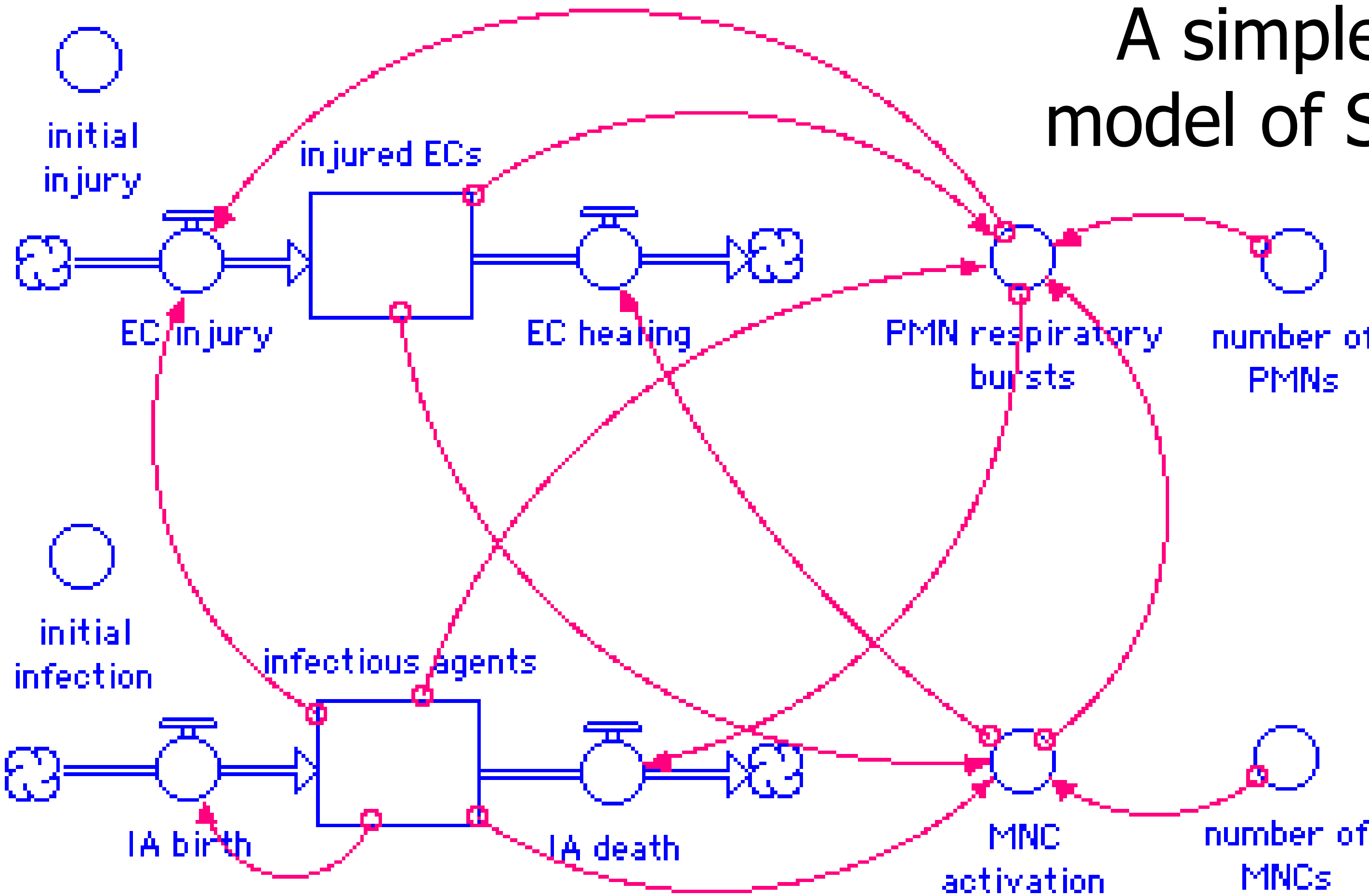


Variation Within and Between Parameter Sets 2

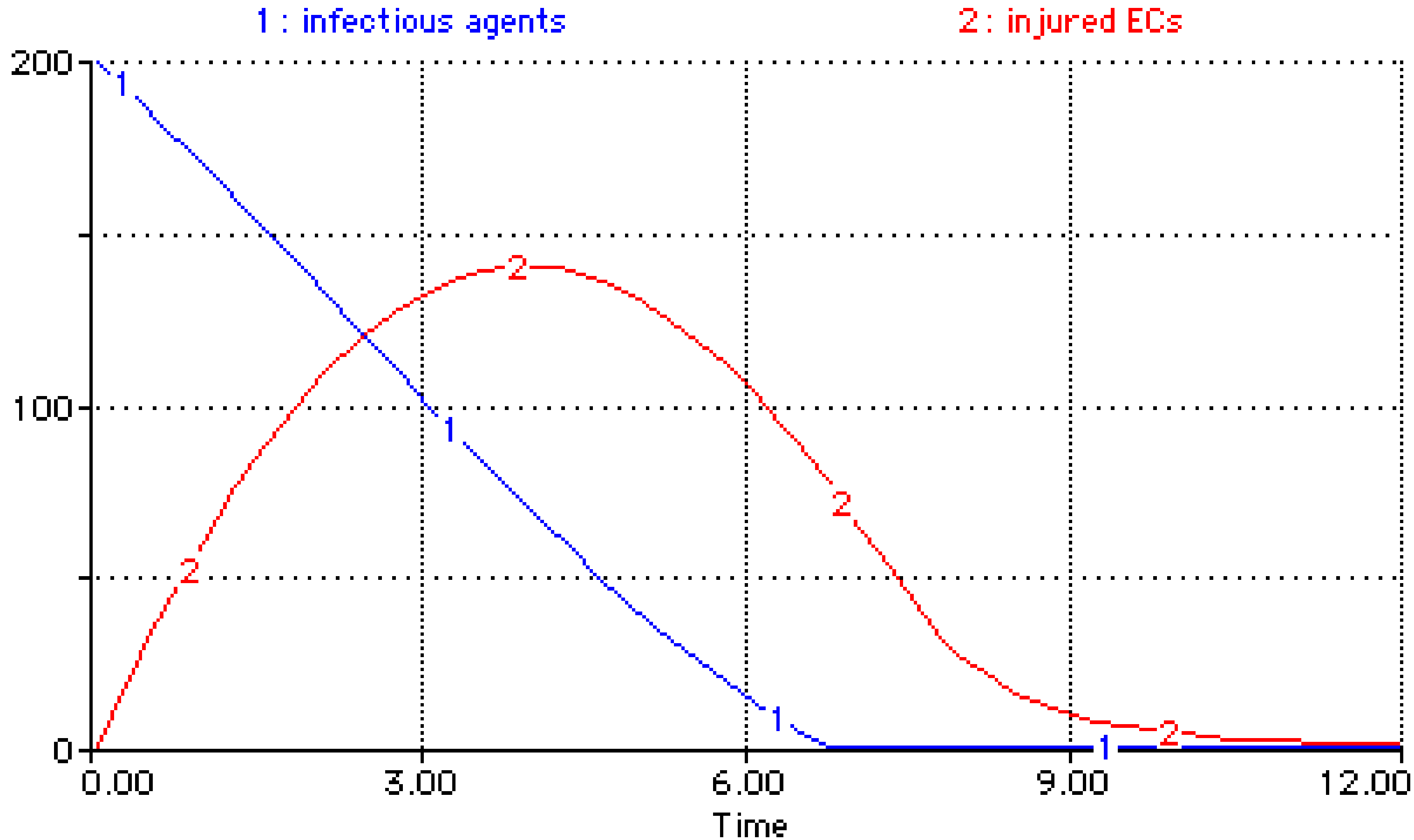


Results: Phase II

A simple SD model of SIRS

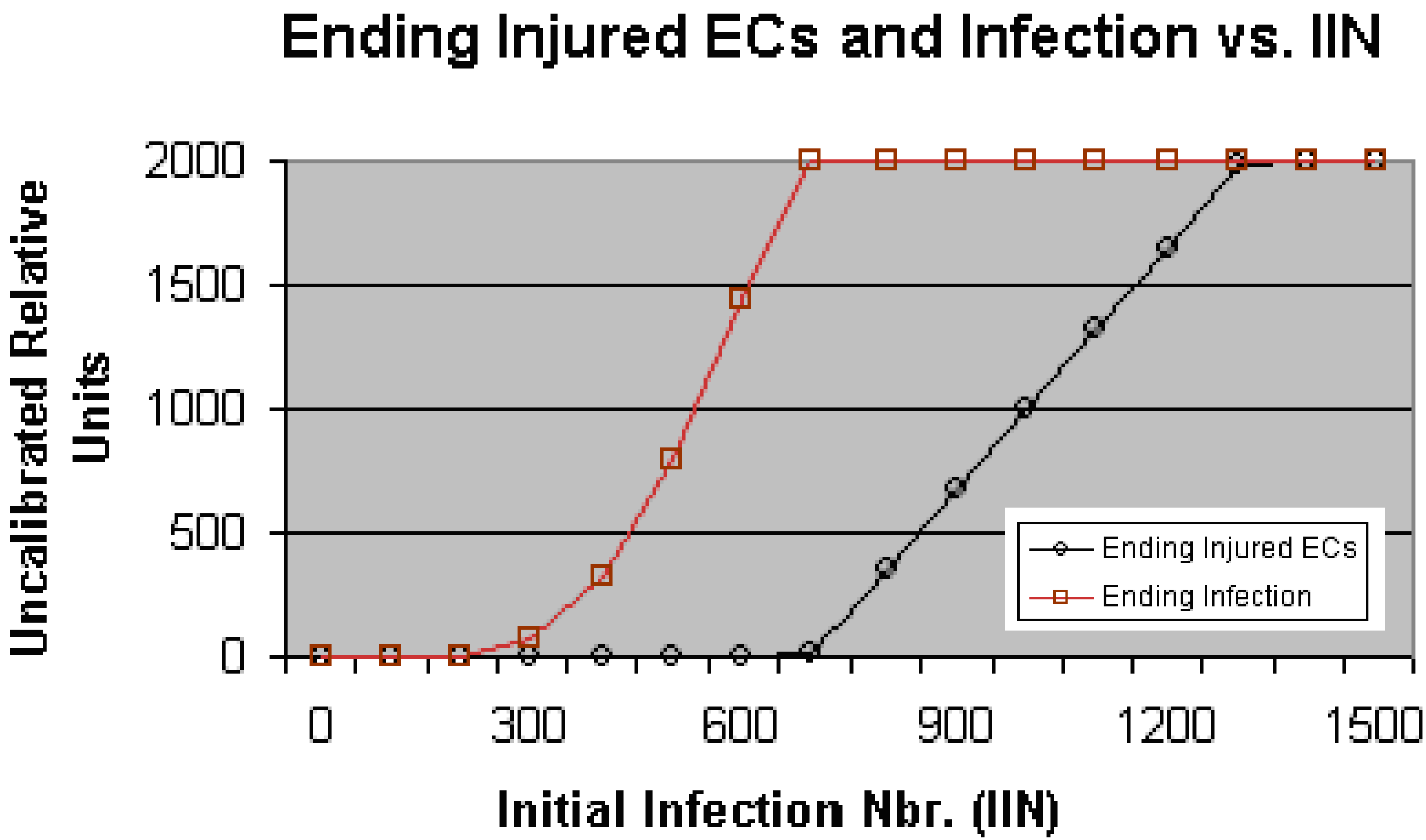


SD Model Behavior Over Time



Infectious Agents and Injured ECs over time

The "Region of Interest" (ROI): SD Model



Results: Phase III

- DE model equations & parameter values were entered into Matlab
  - ➔ Overcame discrepancies and missing values
  - ➔ Made & corrected inadvertent typographical errors
- Initial numerical solution attempts failed
  - ➔ Eventually found solver and criteria that worked
- Could not reproduce the reported results
  - ➔ Unable to verify correctness of model runs
    - ✓ Lacked specific test cases to verify against
    - ✓ Hampered by model complexity & our lack of understanding

Results: Phase IV…Compare & Contrast

Characteristic	The ABS model	The SD model	The DE model
Variables in the model	14 agent types 500 lines of code 53 state variables 3 varied parms. 60+ implicit const.	2 state vars. 2 varied parms. 5 constants	18 state variables 11 varied parms. 80+ constants
Computational demands	High	Low	High
Time to run non-trivial experiments	Days	Hours	Hours to days
Technical skills required to operate the model	Medium	Low	High
Degree of physio-logical realism	Medium	Low	High
Potential clarity for clinicians	High	High	Low
Ability to replicate results	Medium	High	Low

Discussion: Conclusions

- **Models /methods are quite different**
- **Methods nonetheless *are* complementary**
- **Model complexity leads to discrepancies and creates challenges**
  - → **Bookkeeping**
  - → **Computational (time, algorithm selection, design)**
  - → **Comprehension**
- **ABS models "have yet to predict anything*"**
- **SD model, though overly simple, is intriguing**

*** Marshall, John C (2004) "Through the glass darkly: The brave new world of *in silico* modeling" *Crit Care Med* *32*(10):2157-2158.**

Discussion: Implications

- For researchers:
  - → Strive to reduce model complexity
  - → Continue & increase collaborative efforts to improve both model logic and model data
  - → Strive to conduct credible *prospective* scientific studies based on ABS and/or DE models of SIRS
- For practitioners, caution is advised:
  - → The idea *in silico* trials *is* intriguing and does merit considerable attention
  - → But first, much more research is needed

Discussion: Limitations & Future Research

- Limitations of this study
  - → Based on subjective impressions
  - → Utilized just one example model from the literature for each methodology
  - → The results are suggestive at best
- Future research
  - → Blend SD and DE model?
  - → Simplify ABS model to its "essence"