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Reproducing Published Results from *In Silico* Computer Models of the Acute Inflammatory Response to Severe Sepsis

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Reproducing Published Results from *In Silico* Computer Models of the Acute Inflammatory Response to Severe Sepsis

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Background

Recent studies[1,2] describe computer simulation models of the acute or systemic inflammatory response (AIR or SIR) to severe sepsis, a condition that can lead to multiple organ failure and death. One study used an agent-based model, while the other used differential equations (DEs) to simulate a randomized clinical trial. Both studies obtained results similar to the actual results from a successful clinical drug trial of severe sepsis[3,], suggesting that *in silico* (simulated) randomized clinical trials may be used to design more effective *in vivo* clinical trials.

Objective

• Reproduce published results of two *in silico* models of severe sepsis

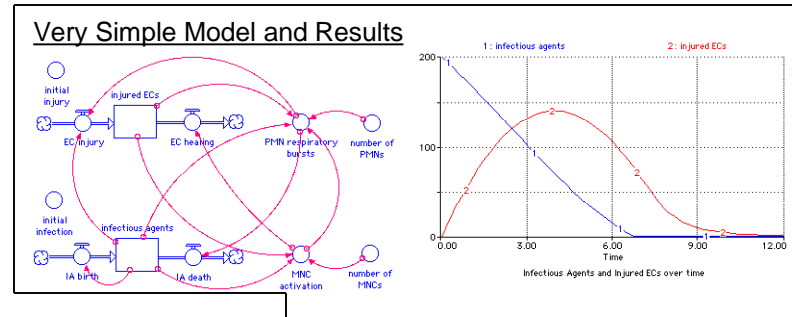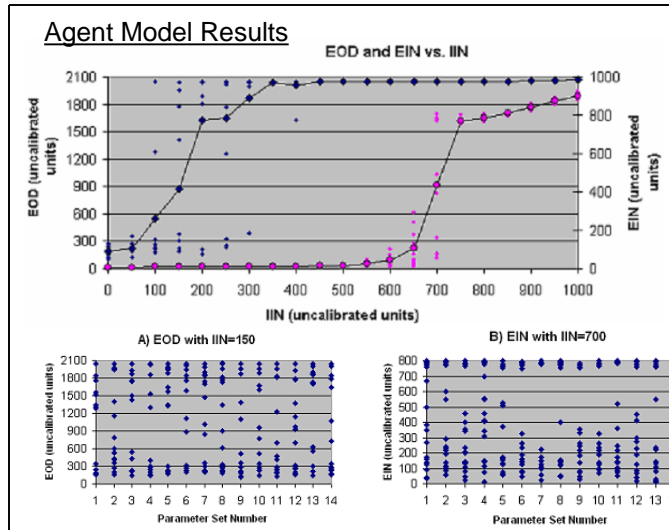• Study relationship between model complexity and experimental outcomes

Methods

(1) Used original investigator's agent-based model to re-run experiments; then ran same experiments with key model logic missing

(2) Implemented equations & parameters in original paper; later, obtained equations and #'s from the investigators and used them to run simulations

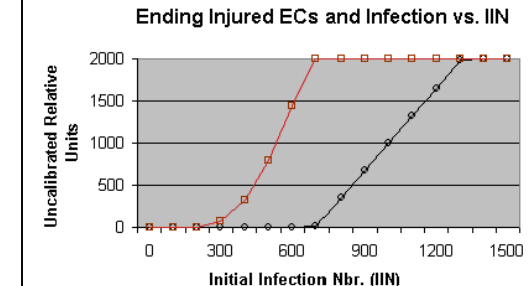(3) Created very simple model; ran similar experiments

Results

(1) Agent-based model results successfully replicated. But nearly identical results were obtained with key portions of the model logic missing

(2) Unable to replicate the published DE model results due to numerous discrepancies in the equations and parameter values: simulated tissues always failed to recover

(3) Very simple model demonstrated outcomes ranging from full recovery to partial recovery (eradication of the initial infection, but oxygen deficit remains high) to failure to recover from the initial infection

Agent Model Results

EOD and EIN vs. IIN

A) EOD with IIN=150

B) EIN with IIN=700

No support for hypothesis that results differ by parameter set number ($\alpha<.01$)

Very Simple Model and Results

Infectious Agents and Injured ECs over time

Ending Injured ECs and Infection vs. IIN

Discussion/Conclusion

• Replicating outcomes from model-based research is important

• Researchers must determine the simplest model that can generate the phenomenon of interest

• More research needed before *in silico* experiments can be used to improve clinical trial design.

[1] An, G (2004) "*In silico* experiments of existing and hypothetical Cytokine-directed clinical trials using agent based modeling" *Crit Care Med* **32**(10):2050-2060.
[2] 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.
[3] Bernard G, J Vincent, P Laterre, et al (2001) "Efficacy and safety of recombinant human activated protein C for severe sepsis" *N Engl J Med* **344**:699–709.