9-2005

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

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Citation Details

Wakeland, W., J. Fusion, B. Goldstein, "A Tale of Two Methods—Agent-Based Simulation and System Dynamics—Applied in a Biomedical Context: Acute Inflammatory Response," 6th European Congress of Systems Science, Paris, France, September 2005.

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

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Abstract
Three specific models of the acute inflammatory response were contrasted. The first model was a recently published and rather complex agent-based model used to simulate clinical trials *in silico*. The second model was a highly simplified system dynamics model developed during the present research. The third model was also recently published, with similar objectives to the first model, but utilized a complex set of 18 differential equations. The study found that the complexity of the first and third models is likely to adversely impact their usefulness, at least for other researchers. The second model, which is too simple to be used for predictive purposes, shows potential promise as a pedagogical tool, and possibly as the foundation for a somewhat more realistic model that would still be much less complex than the other two models. A comparison table contrasts the three models/methods in more detail. The message for practitioners is one of caution--it is likely to take a considerable period of time to fully realize the potential promise of *in silico* methods such as those published recently.

Problem statement and significance
An exciting and relatively new research area is the use of agent based simulation (ABS) models and system dynamic (SD) or differential equation (DE) models to study complex biomedical phenomena such as the systemic inflammatory response syndrome (SIRS), the acute inflammatory response (AIR), and multiple organ failure (MOF) (Neugebauer 2001).

SIRS is an important problem domain for several reasons (Buchman 1997, 2001). First, it is considered one of the most significant and prevalent clinical problems in critical care medicine. Second, the phenomenon occurs at multiple system levels (molecular, cellular, tissue, and organ). Third, the complex interactions between components preclude the attribution of the systemic response to any single factor or agent. Fourth, there is a behavioral region in the case of infection where, even though the original infection may be eradicated by the immune system response and therapy, the collateral tissue damage results in system failure. Finally, while much has been learned in recent years, SIRS remains a largely unsolved problem.

While both ABS and SD/DE methods are considered by most researchers to be complementary and appropriate for studying problems such as SIRS, very little has been published that helps to delineate their relative strengths and weaknesses. This manuscript is an initial study to critically evaluate salient differences between these two methods.

Background and brief review of the literature

It has been shown convincingly in the social sciences that ABS models are able to generate remarkably complex and unexpected macroscopic behaviors from agents that utilize very simple rules (c.f., Epstein and Axtell 1996, Gilbert and Troitzsch 1999, and Resnick 1994). Furthermore, it is generally accepted that the insights attributed to these simulations of social systems are profoundly different than the insights revealed using SD/DE and other methods.

However, it is not known whether this same distinction also holds in the biomedical domain. Are the insights revealed using ABS to model biomedical phenomena profoundly different than the insights one might obtain using SD/DE in this context? In an earlier paper (Wakeland et al 2004), both SD and ABS were used to study cellular receptor dynamics and the results from both methods were compared. This research confirmed that the two paradigms are very different and possess unique strengths and weaknesses. Guidelines were provided for assessing which of the two methods might be preferred in a given situation. However, this research did not demonstrate important insights from ABS that in the authors' estimation went beyond the insights that one might achieve with SD/DE. That study acknowledged that the author's prior knowledge of SD/DE modeling was much greater than their prior knowledge of ABS, and that the results may have been influenced by the order in which the methods were applied: first SD/DE, then ABS.

One of the first studies to report the use of ABS to model SIRS/MOF was An (2001). This paper synthesized a wide variety of basic science results into an overall model that illustrated the complex dynamics seen in the clinical environment. The underlying processes (rules) were discussed in some detail, but the actual code was not provided. In additional to parameter variation, the degree of randomness could also be varied. Many graphical results were presented, some of which showed the behavior over time for different cases, while others compared the results of multiple runs with parameters varied over a wide range, or with parameters fixed but with many different randomly generated cases. The paper was organized in a fashion similar to a more typical basic science research paper in order to illustrate how an *in silico* model could be used in the much the same fashion as a traditional laboratory model.

A recent issue Critical Care Medicine included two highly relevant papers on this topic (An 2004, Clermont et al 2004) as well as a short editorial article (Marshall 2004) that contrasts *in silico* modeling with *in vivo* and *in vitro* research. The editorial is both encouraging and cautionary, warning that the potential benefits of this new approach rest heavily upon the correctness of model algorithms and model data. It asserts that ABS models have yet to prove themselves by predicting effects that were not previously known.

(An 2004) extends the author's earlier work, using the ABS model of SIRS to conduct *in silico* experiments that generally replicate the [disappointing] results of several large-scale clinical trials of cytokine-directed anti-mediator agents. The author also evaluated several hypothetical clinical trials, and found that they too would be likely to not achieve statistically significant results. He also showed how ABS models could be used to help design more effective clinical trials. In addition to the graphical and tabular results, extensive model details were provided, including a website containing the actual model used to conduct the experiments.

(Clermont et al 2004) developed a DE-based model to study immunomodulatory strategies for treating cases of severe sepsis. Their focus was to assess the feasibility of using DE models to improve the design of clinical trials. The model was used to simulate 1000 patients that were subjected to various simulated treatments. The results were presented in much the same fashion as results would be presented from an actual clinical trial. This research replicates *in silico* the general findings from actual clinical trials--that it is very difficult to design a treatment strategy that is effective over a broad range of sepsis patients. The authors provide an appendix that gives the model equations and parameters.

Another recent publication of interest is Vodovotz et al (2004), which reviewed mathematical models of the acute inflammatory response. This paper emphasized the need for non-reductionist approaches, and featured results from both An (2004) and Clermont et al (2004). The paper also looked closely at the validation strategies used to assure the correctness of the model logic and model data.

Research methodology

Phase I. The research began by examining the details of the ABS model developed by An (2004) and the Netlogo (2005) implementation of the model. The model is quite complex, requiring 14 pages of procedures. There are 14 different "breeds" of agents, each of which has unique logic. Some minor differences were observed between the logic documented in the paper and the model provided on the web. For example, the Appendix to the paper provided formulae indicating that certain model variables are divided by 2, whereas this was not the case in the actual model code. Also, in some cases, the dependent variables used to compute a given independent variable were different.

A variety of experiments were run using the corrected Netlogo code, both to confirm the results and to learn as much as possible from the model. Observing the graphical display during several short model runs indicated that most of the simulated tissue was either healthy or severely "damaged," with a "sharp" boundary between the two regions. This suggested that that the model could probably be scaled down without loss of utility. The area of the modeled region was scaled down factor of 4. Also, the number of "cases" per experiment was reduced from 100 to 10, and the time per run reduced from 28 to 7 simulated days. Other minor changes were also made, including modifying the logic so that the iteration number would not be incorrectly reset to zero and to force the initial infection to be automatically invoked for the first iteration instead of requiring the user to remember to push a particular button at the start of the run.

Sufficient experiments were run to reproduce the results reported in Figure 1 of An (2004). These were run on multiple computers to reduce the total elapsed time. The total elapsed computer time was nearly 30 hours. The computers used included three laptops with processor speeds varying from .4 to 1.2 GHz. The results clearly showed the Initial Injury (IIN) values that demark the lower and upper boundaries of the "region of interest" (ROI) described by An (2004).

The next set of experiments required many more runs than the first set, so it was necessary to further optimize the model logic. The primary changes were: 1) to reduce small values of biochemical agents to zero in order to lessen the number of calculations required in the diffusion process, 2) to move the "divide OXY by 100" from inside the SUM operation to outside the SUM, and 3) to calculate the SQRT function used in the injure-sterile and injure-infection procedures one time instead of calculating this function IIN times for each iteration. These changes speeded up model execution by a more than a factor of two, dropping the computer time required to run the experiments from 70 to 30 hours.

Procedures were also added to the model to make it easier to run experiments that incrementally removed the effect of individual model components and combinations of components. These

experiments test the impact of removing T-cells and T-cells germinators from the model. First, the five initial values associated with T-cells were set to zero, one at a time. Next, selected combinations of two or three initial values were set to zero simultaneously. Finally, all five initial values were set to zero. For each parameter set, 20 cases were simulated, for each of two different values of IIN. The IIN values were chosen to reflect the lower and upper bound of the ROI where the uncertainty in outcome is the highest.

The data collection procedures provided within the model by its developer (An 2004) were not enhanced. This was a mistake, as it greatly increased the time required to analyze the data and format the results for presentation.

Phase II. In this phase, a highly simplified SD model was built that attempted to capture the essential feedback loops described in An (2001) and An (2004). The goal was to determine if a much simpler SD model could exhibit the same large-scale behavior as the more complex ABS model. Since the goal of the model was merely to exhibit qualitatively similar behaviors (such as tipping points in key state variables), no attempt was made to achieve quantitative similarity. The theory behind this type of exploration is that large-scale behavior derives more from the relations in the model than from the specific quantities.

From model components described by An (2001 and 2004), a list of the most important variables in the model was created, and the key interactions between variables were identified. This initial list contained nine items and fourteen interrelationships. A causal loop diagram (CLD) was used to graphically depict these relationships. Each relationship in the CLD was marked either "+" for positive (reinforcing) influence or "–" for a negative (balancing) influence. The CLD made it much simpler to identify positive and negative feedback loops, which are often the main drivers behind the behavior of a model. The CLD in this case contained several positive and negative feedback loops. The presence of intermingled positive and negative feedback loops indicated that one or more tipping points are likely to be found in the dynamic behavior of the system. A tipping point occurs when a dominant reinforcing effect gives way to a balancing effect or vice versa.

The CLD was used to develop an SD model, which was implemented using the Stella (2005) software program. During its implementation, the model was every further simplified. The numbers of injured epithelial cells and infectious agents were implemented as the two "stocks" (integrals, or state variables) in the model. The numbers of neutrophils and mononuclear cells were modeled as fixed initial conditions, and two of the other variables were removed because they could be derived from the other values and did not participate directly in the feedback loop structure. This model was used to explore the relationships between key variables and the initial values of the state variables and constants. This was easy to accomplish due to the simple structure of the model.

Phase III. We then studied the DE model published by Clermont et al (2004), including an attempt to independently reproduce the results by implementing the equations and parameters provided in the appendix of the paper. While this seemed a straightforward task, the complexity of the model made it somewhat daunting. We entered into Matlab (2005) the 18 differential equations, five functions and more than 80 constants as indicated. A few minor typographical

errors and omitted values were corrected as seemed most reasonable, but the researcher's were not confident that their implementation was 100% correct. We then attempted to perform experiments with the model by specifying values for the 11 floating parameters, and using Matlab to solve the resulting equations.

Phase IV. The final phase of the research compared and contrasted the results of the prior phases. This comparison was both subjective, and, to the extent possible, based on objective data. This type of research design is appropriate for exploratory research aimed at producing *suggestive* rather than definitive results.

Results

Phase I Results. Figure 1 shows the initial experimental results using the ABS model. The x-axis indicates the initial injury number IIN, from 0 to 1000. For each value of IIN two points are shown, the end infection (EIN) and the end oxygen deficit (EOD), where end refers to the end of the simulation run (considered to be one week after the initial injury/infection in our case vs. four weeks used by An). Each point represents the result from one of the 10 simulated cases. The mean values for each of these 10 cases is also shown, in a larger font, with line segments connecting these points. When IIN is small, both the mean EOD and mean EIN are also small, indicating a favorable prognosis. When IIN is very large, both EOD and EIN are large, indicating an almost certain unfavorable outcome. An [2004] describes the center region of Figure 1 as the "region of interest," where EIN is small, but EOD remains large. In this region, the autoimmune response has ameliorated the injury/infection, but tissues were damaged in the process and appear not to be able to recover.

Figure 2 shows the results of the second set of experiments, where parameters associated with T-cell were varied significantly, essentially "turning off" their pro-inflammatory and/or anti-

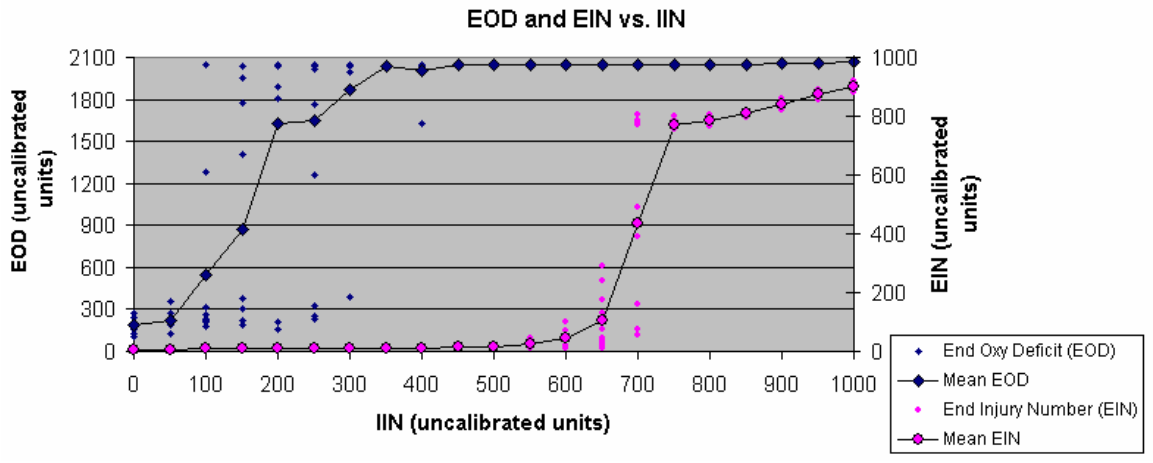

Figure 1: Reproduction of the "Zone of Interest" (An 04). The left hand curve shows the mean value of end oxygen deficit for each given value of Initial Injury (IIN). Each mean value is calculated from 10 cases (runs) for each particular value of IIN. The individual values for each case are also shown as a scatterplot. The right hand curve is similar, but shows the end injury number (EIN) for the corresponding IIN values. The region of interest is between the two curves.

inflammatory effects. Twenty cases are run for each set of parameter values. Figure 2A shows EOD when IIN = 150, near the left hand boundary of the region of interest (see Figure 1). Figure 2B shows EIN when IIN = 700, which is near the right hand boundary of the region of interest. One might expect that the pattern of outcomes in terms of EOD and EIN would be correlated to some degree with which set of parameters was used. However, as can be seen in Figure 2, the overall impact of these particular processes is essentially "lost in the noise," since the variation in the results for a given set of parameter values is much larger than the variation between different sets of parameter values. Note that when IIN = 150, EIN is near the minimum in all cases, and when IIN = 700 EOD is at the maximum in all cases; hence these graphs are not shown.

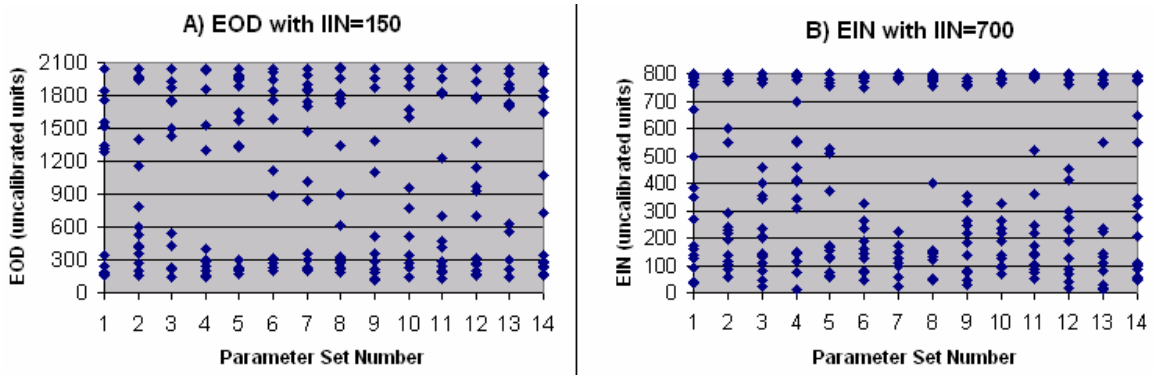

Figure 2. Graph A shows the end oxygen deficit (EOD) and graph B shows the end injury number (EIN) for each of 14 different sets of parameter values. 20 simulated cases is shown for each parameter set and for each of the two values for initial injury (IIN).

One primary subjective result from phase I was the sense that the ABS model may be unnecessarily complex. The fact that it takes many hours or even days to run a set of experiments limits the practical utility of such a model. The high degree of complexity also makes it difficult to assure that the logic matches the modeler's intent, much less reality. On the other hand, a major strength of the ABS model is that is shows exactly how the researcher believes that the various mechanisms actually work. This is excellent.

Phase II Results. The SD model is shown in Figure 3. Feedback loops include: a positive loop for the creation of infectious agents (IAs); a negative loop for the activation of mononuclear cells (MNCs) by injured epithelial cells (ECs); a positive loop between neutrophil (PMN) respiratory bursts and injured ECs; a negative loop between PMN bursts and IAs; another negative loop including PMN bursts, IAs and EC injuries; a positive loop around PMN bursts and EC injuries; and a positive loop from PMN bursts to EC injuries to MNC activations. The output of a sample run shows IAs falling, while also causing a rise in injured ECs. The number of injured ECs begins to fall once the infection is under control, and, eventually, all the ECs are healed.

The equations used in this model are very simple. MNC activations are the sum of injured ECs and infectious agents, limited by the number of MNCs. PMN respiratory bursts are calculated the

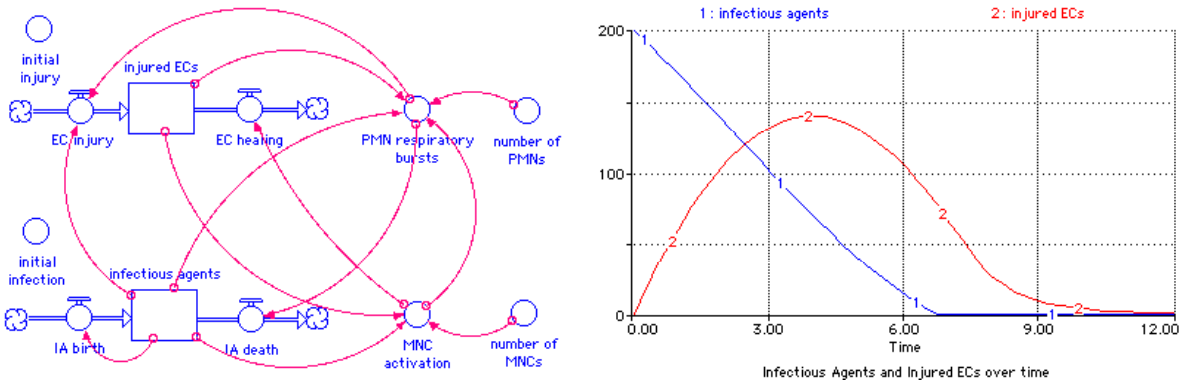

Figure 3. The SD model is shown on the left, and the result of a typical run is shown on the right.

same way, also including MNC activations in the sum, with a scaling constant applied. The inflow of EC injuries is the sum of the PMN bursts and IAs, with scaling constants to make IAs more injurious than PMN bursts. The outflow of injured ECs equals MNC activations, and the outflow of IAs equals PMN bursts. Finally, the inflow of IAs is 0.1 times the current population, as a modest growth rate. The scaling factors and initial conditions are all arbitrary and without units, chosen only to give relative weights to the relations in the model.

We ran a series of experiments with the model while varying the initial numbers of IAs. The results of these runs are shown in Figure 4. Each simulation was run the same length of time,

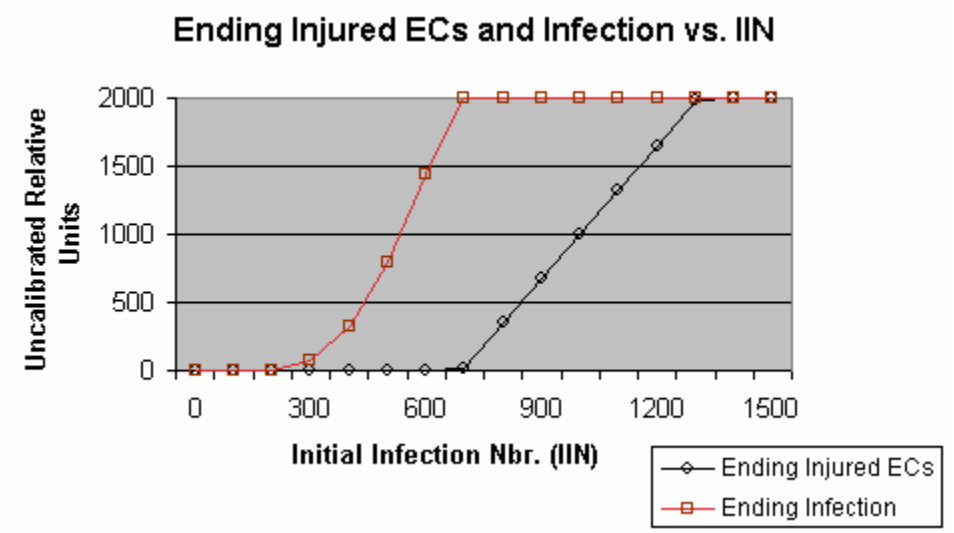

Figure 4: The region of interest as portrayed by the SD model. The model was run for a set length of time while varying the initial infection. The "zone of interest" is in the middle where the system may fail even though the infection is cured.

the amount of initial EC injury was set to zero, and the numbers of IAs and injured ECs were capped at an arbitrary maximum representing system failure or total infection. The graph shows small infections that are easily healed on the left, large infections that overwhelm the system on the right, and the region of interest (ROI) in the middle, where system failure can occur even if the infection is cured. In this region, the injury to ECs from infection and PMN bursts is too great for the MNC to heal, even after the infection has been controlled.

The process of creating this SD model demonstrated that the important, large-scale behavior of a system could be captured in a very simple model. While the current SD model may not represent physiological reality, and would be of little use in a clinical setting, it would definitely seem to have potential use as a tool for understanding and exploration. The model is visually informative, and could be relatively easily understood by non-modelers. It could also serve as a starting point for further refinements, such as converting the variables to use realistic units or adding additional relations in order to represent physiological reality. However, such efforts to extend the model would be likely to come at the expense of usability and understanding.

Phase III Results. We sought to replicate the results of the DE model in order to explore and understand it, and also to gather results that could be compared with the other two models. We made some progress in the former goal, but not the latter. The sheer complexity of the model, coupled with our lack of knowledge on the reasoning behind it, made it very difficult to fully understand it. The model definitely seems very rational and well structured, and clearly much effort had gone into making it physiologically realistic.

When we tried to run experiments with the DE model, we found that we were unable to get useful results. Part of the problem was technical, as we had difficulty solving the equations in Matlab. We did not know what solver best fit the problem. Nor did we know the appropriate time step or error tolerance, and so on. When we did find a solver that appeared to work, we were not sure how to interpret the results, or even if we could trust them, given the assumptions we made while implementing the model. So, even in a case where the researchers had done an exemplary job of documenting a very complex model, we were still unable to replicate their results. We did not contact the researchers for help, and our comments are not intended to in any way impugn their work.

Summary of the Results. Table I summarizes the results from each phase of the research by contrasting each of the models in terms of relevant characteristics such as the number of variables utilized, computational requirements, etc.

Table I. Summary comparison of the three models

Characteristic	**The ABS model**	**The SD model**	**The DE model**
Size of model	14 agent types ~500 lines of code 53 state variables 3 varied parameters ~60 implicit constants	2 state variables 2 varied parameters 5 constants	18 state variables 11 varied parameters 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 physiological realism	Medium	Low	High
Potential clarity for clinicians	High	High	Low
Ability to replicate results	Medium	High	Low

Discussion

This study indicates that the differences in the three models evaluated—an agent based simulation model, a system dynamics model, and a differential equation-based model—are quite significant. Despite these differences, the methods do seem to be complementary, as had been suggested by others. For example, the descriptions of the interactions between agents in the ABS model suggested the feedback loops used to formulate the SD model. Further, there is a strong correspondence between the different classes of agents in the ABS model and the state variables used in the DE model.

Challenges in the present study included the high degree of complexity in both the ABS and the DE models. This complexity made it very difficult to achieve a high degree of confidence that the model logic/equations/parameters were correctly implemented. The ABS and DE models provided by the original researchers both contained errors or other types of discrepancies, from missing parentheses to equations with entirely different terms. Correcting these inconsistencies took time away from the primary research activities. The high degree of complexity also dramatically increased the time required to run experiments with the ABS model and the DE model. The complexity of the DE model necessitated considerable experimentation with different integration algorithms before credible results were achieved.

The system dynamics model on the other hand, is probably too simple to be taken seriously by researchers, despite the fact that it too demonstrates the fundamental behavior modes observed clinically. Thus, its simplicity is at once its greatest weakness and its greatest strength. Because the logic is simple, it is possible to show exactly why each of the behavior modes occurs and what is required to move the system from one behavior model to the other.

The primary conclusion is that each of these different types of models is very promising and warrants further study. However, every effort should be made to find ways to reduce the complexity of the models. The present research suggests that both the ABS model and the DE model are likely to contain non-essential components. The problem with this is not simply that the models contain logic or variable that are superfluous and can be ignored. Rather, these additional components are a liability because they obscure important relationships and make it much more difficult for other researchers to confirm and/or extend the research.

The implications for clinical practice are cautionary. The parameter changes tested using the ABS model could have easily represented the potential impact of a pharmacological intervention. The research demonstrated that the impact of other variations appear to almost entirely mask the potential impact of this type of targeted intervention. While the idea of *in silico* clinical trials is very intriguing, much more research is called for.

The present study was exploratory in nature, and focused on just one example ABS model, one SD model, and one example DE model. Consequently, these findings are only suggestive in nature; further examination of multiple examples from multiple modeling disciplines is warranted.

Two specific opportunities for further research are suggested by the present research. First, the fact that the ultra-simplified SD model was able to produce the three key behavior modes indicates that perhaps a somewhat more complex SD model could be developed by borrowing key equations and interactions from the much more complex DE model. Second, the fact that significant parts of the ABS model could be neutralized with only minimal impact on its behavior indicates that it might be possible to create a simplified version of this model without an appreciable loss in behavioral fidelity.

References

An, Gary (2001) "Agent-based computer simulation and SIRS: building a bridge between basic science and clinical trials" *Shock* ***16***(4):266-273.

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.

Buchman TG (1997) Awash in data: the problem of predicting physiology in severe sepsis. *Shock* ***8***(3):232.

Buchman TG, Cobb JP, Lapedes AS, Kepler TB (2001) Complex systems analysis: a tool for shock research. *Shock* ***16***(4):248-51.

Clermont, Gilles, John Bartels, Kukmini Kumar, Greg Constantine, Yoram Vodovotz, Carson Chow (2004) "*In silico* design of clinical trials: A method coming of age" *Crit Care Med* ***32***(10):2061-2070.

Epstein, Joshua M. and Robert L. Axtell (1996) *Growing Artificial Societies: Social Science from the Bottom Up*, MIT Press.

Gilbert, Nigel G. and Klaus G. Troitzsch (1999) *Simulation for the Social Scientist*, Open University Press.

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

Matlab (2005) see The Mathworks **http://www.mathworks.com/** (software verion 7).

Netlogo (2005) see Northwestern University **http://ccl.northwestern.edu/netlogo/** (software version 2.1).

Neugebauer EA, Willy C, Sauerland S (2001) Complexity and non-linearity in shock research: reductionism or synthesis? *Shock* ***16***(4):252-8.

Resnick, Mitchel (1994) *Turtles, Termites, and Traffic Jams : Explorations in Massively Parallel Microworlds*, MIT Press.

STELLA (2005) see ISEE Systems **http://www.hps-inc.com/** (software version 8.0).

Vodovotz, Yoram, Gilles Clermont, Carson Chow, Gary An (2004) "Mathematical models of the acute inflammatory response," *Current Opinion in Critical Care* ***10***:383-390.

Wakeland, Wayne, Louis Macovsky, Edward Gallaher, Athena Aktipis (2004) "A Comparison of System Dynamics and Agent-based Simulation Applied to the Study of Cellular Receptor Dynamics," Hawaii Int'l Conference on the System Sciences.