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Chapter 7
From Artificial Life to In Silico Medicine: NetLogo as a Means of Translational Knowledge Representation in Biomedical Research

Gary An and Uri Wilensky

Biomedical research today stands at a crossroads. There is a widening gulf between the extent of knowledge regarding basic mechanistic processes and the ability to integrate that information into explanatory hypotheses of system-level behavior. Techniques from the Artificial Life community can aid in bridging this gulf by providing means for visualizing and instantiating mechanistic hypotheses. This will allow the development of in silico laboratories where conceptual models can be examined, checked, and modified. NetLogo is a "low threshold, high ceiling" software toolkit that has been used to develop agent-based models (ABMs) in a multiplicity of domains and provides a good platform for the computational instantiation of biomedical knowledge. This chapter presents a brief overview of NetLogo and describes a series of ABMs of acute inflammation at multiple levels of biological organization.

7.1 Introduction

7.1.1 A Different Type of "Artificial Life"

Artificial life, as the name suggests, consists of reproducing the processes of life in a man-made, often computational, setting. A great deal of Artificial Life research has focused on examining the core properties of life by stripping away those aspects that may be present in our world resulting from historical accidents in order to develop general theories of life [43]. Software tools that have arisen to enable this type of investigation have the capabilities to reproduce those presumptive central characteristics of biological systems. However, the development of these tools has also led to a parallel but related area of investigation, one that focuses on the use of Artificial Life-derived methods to recreate and represent existing biological systems. This capabil-

ity has enabled the creation of a new laboratory environment, an "in silico" environment that can serve as a vital adjunct to traditional in vitro (in a test tube) and in vivo (in an experimental animal) experimental methods. In this fashion, Artificial Life-derived techniques and the use of ABMs, in particular, can serve a vital integrating role to address some of the major hurdles facing biomedical research. In this chapter we present examples of the use of the NetLogo integrated agent-based modeling environment [79] as a laboratory environment for biomedical research. NetLogo is a widely used general-purpose agent-based modeling environment. It is designed with the principle of "low threshold, high ceiling" [67] – that is, easy learnability for novices yet high performance for researchers. As such, NetLogo is in widespread use in both research and educational contexts. This dual-audience flexibility makes NetLogo ideal for use in interdisciplinary research contexts where its generality and ease of use enable all the research team members to participate in the modeling activity and to communicate via the NetLogo model. As such, NetLogo is well suited to the context of biomedical research, where, in general, most biomedical researchers are not cross-trained in mathematical modeling or computer simulation and often do not have the spare intellectual capital to invest in acquiring the expertise required to master general-purpose computer programming. The "low threshold, high ceiling" property of NetLogo has the following potential benefits as a biomedical research tool:

1. The rapidity with which non-computer-programming biomedical researchers can produce a tangible in silico representation of their existing mental models provides vital early positive feedback to encourage continued pursuit of a new methodology.
2. Enabling the researchers themselves to do the actual coding and modeling provides a basic practical literacy with respect to the application of simulation and computational tools to biomedical problems and will facilitate future communications with computer scientists/applied mathematicians as these applications develop and may evolve to other platforms.
3. The actual exercise of creating a NetLogo model enables formalization of existing mental models, can stimulate beneficial introspection on the part of the biomedical researcher regarding his/her underlying assumptions, and help hone in on further directions in a particular research plan.
4. The ease of "reading" and widespread use of NetLogo enable researchers to communicate and disseminate their work clearly and broadly.

The examples of NetLogo models presented in this chapter take advantage of all these benefits, with the overall goal of demonstrating dynamic knowledge representation of a particular multi-scale biomedical system: acute inflammation.

7.1.2 Modern Medicine and Limits of Reductionism: The Translational Challenge

Over the last 50–75 years biomedical research has made huge strides. The advent of molecular biology, arising from the discovery of DNA, opened a new mechanistic frontier for the examination and analysis of biological systems. Based on the principle of reductionism, the concept that finer and finer-grained analysis of components and mechanisms would provide underlying core principles and understanding, biomedical research generated huge volumes of data and hypotheses regarding the basic processes associated with health and disease. However, starting in the 1970s, it was becoming evident that biological behavior and the health/disease dynamic were very much more than the sum of their parts. The efficacy of biomedical research to provide advances in the areas of infectious disease, public health, and surgical technique was not being reproduced in addressing "systems" diseases such as cancer, critical illness, autoimmunity, diabetes, and acquired immune deficiency syndrome (AIDS). This simmering crisis was crystallized in the United States by a publication by the United States Food and Drug Administration (USFDA) of a monograph titled *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* [27]. The central problem addressed was the steadily decreasing efficiency of the output of health-care research dollars between 1993 and 2003 in terms of release of effective medical therapeutics. This represented a widening translational gulf between the bench and the bedside.

What is the basis of the translational divide? To a great degree the translational challenge arises from a combination of the multi-scale, multi-hierarchical nature of biological systems and the existing research structures that have evolved to study them. The hierarchical structure of biological systems is well recognized: gene to protein/enzyme to cell to tissue to organ to organism. The existence of these levels (which can be thought of as representing successive levels of emergent phenomena) presents significant barriers to the inference of cause-and-effect mechanistic knowledge at one level to behavior at a higher one. This epistemological barrier between scales of biological organization is one of the hallmarks of complex systems and why these systems need to be studied in an integrated fashion [94]. Conversely, the organization of the biomedical research community that has evolved to study these different scales has been based on a reductionist paradigm. The treatment of each of these levels as a separate focus of investigation has led to a compartmentalized structure and organization of the biomedical research community. As pointed out in the USFDA Critical Path statement referenced above, the consequences of structure are seen primarily in attempts to develop effective therapies for diseases resulting from disorders of internal regulatory processes. Examples of such diseases are cancer, autoimmune disorders, and sepsis, all of which demonstrate complex, non-linear behavior and are insuf-

ficiently characterized when their components are studied in isolation. The investigation of such processes therefore presents a significant challenge that must be met by the development of translational methodologies that need to function as bridges both vertically from the bench to the bedside and link horizontally across multiple researchers focused on different diseases.

Thus, there is a growing recognition within the biomedical research community of the limits of reductionism and the need to apply a systems- level approach to attempt to reintegrate the mechanistic knowledge being generated [68, 71, 59]. In particular, it was recognized that such attempts to apply complex systems analysis to biomedical problems should not strive to supercede reductionist methods, but rather provide a synthetic adjunct to ongoing research endeavors [68, 8]. The development of in silico biomedical research is the response to this recognition.

Accomplishing this goal requires dealing with the "nine hundred pound gorilla" in the room of biomedical research: a seemingly unsolvable paradox between the volume of information and the completeness of information. On one hand, the sheer volume of biomedical knowledge that has been (and continues to be generated) is overwhelming. It is extremely challenging for a single researcher to have even semi-comprehensive knowledge of the state of even a small fraction of this information; expanding the scope of this knowledge to approach the integrative goal needed for translational interpretation is functionally impossible. However, even if it were possible for a researcher to know everything that was published regarding and connected to a particular disease process or biological function, that knowledge would still be incomplete, as the multiplicity of components and their interactions necessarily means that there likely will always be additional information yet to be identified. Therefore, the common charges against the use of computer simulation and mathematical modeling focus on these two paradoxical aspects: (1) there is too much information to include and (2) something is left out.

The solution to this paradox lies in maintaining appropriate expectations and placing the development of synthetic translational tools in the appropriate context: Mathematical modeling and computer simulation are not intended to be a panacea to the challenge of integrating biomedical knowledge, but rather as improvements on methods currently employed. The synthetic process of integrating experimental results into hypotheses and conceptual models relies, as it is currently executed, heavily upon intuition. As such, it is poorly formalized and thus difficult to probe and parse when things do not turn out as expected. What is sought, therefore, are methods of formalizing the process of knowledge representation, particularly in terms of the dynamic instantiation of knowledge as a means of hypothesis visualization and evaluation. The goal is to produce probeable synthetic constructs that can be tested by both their creator and other researchers and unambiguously communicated to the community as a whole. In this context, the use of computational models should be considered a means of "conceptual model verification" [90], in which mental or conceptual models that are generated

by researchers from their understanding of the literature and used to guide their research are brought to life such that the behavioral consequences of the underlying beliefs can be evaluated. It is in addressing the synthetic aspect of science that the lessons of Artificial Life, and agent-based modeling in particular, come to the fore.

7.1.3 Agent-Based Dynamic Knowledge Representation and In Silico Laboratories

One of the major lessons from Artificial Life research is that biologically complex behaviors can be generated and substantial insights can be obtained, with relatively simple, qualitative models. The fact is that biological systems are robust, existing in a wide range of conditions while retaining a great degree of stability with respect to form and function. When Artificial Life is used to examine core biological processes (such as evolution, swarm behavior, and morphogenesis), the search for the minimal rule-set that can recognizably reproduce the desired behavior is seen as a proxy for identifying the most general and therefore most basic principles. If, however, the goal is to narrow the focus of investigation and increase the resolution of the behaviors under study, then the progressive addition of more and more details provides a mechanism for approaching a more realistic model. While one must always be careful to conflate a plausible solution with an exact solution, the correlative relationship between a set of generative mechanisms and observed recognizable behaviors has a strong tradition within both the Artificial Life and bioscience community as a basis of inference and hypothesis formation. In particular, this has been formalized as Pattern Oriented Analysis as a means of developing and interpreting ABMs, one of the primary computational techniques used in the Artificial Life community [31].

The development of ABMs is a computational modeling methodology that employs computational objects, and is rule based, discrete event and discrete time. Agent-based modeling focuses on the rules and interactions between the individual components ("agents") of a system, generating populations of those components and simulating their interactions in a virtual world to create an in silico experimental model. There are several characteristics of an ABM that sets it apart from other rule-based modeling systems:

- ABMs are *spatial*. As the field of agent-based modeling was much influenced by work in two-dimensional (2D) cellular automata many ABMs are grid based. This legacy enables spatial representation of structural relationships within a system. Non-mathematicians can model fairly complex topologies with relative ease, leading to more intuitive knowledge translation into a model. The spatial nature of an ABM also supports modeling agents with limited knowledge (i.e., input constrained by locality rules that

determine its immediate environment). The emphasis on behavior driven by local interactions also matches closely with the mechanisms of stimulus and response observed in biology.

- ABMs utilize *parallelism*. In an ABM, each agent class has multiple instances within the model, forming a population of agents that interact in (an usually emulated) parallel processing environment. Thus, heterogeneous individual agent behavior within a population of agents results in systemic dynamics that yield observable output that mirrors the behavior at the higher-hierarchical level. A classic example of this is how relatively simple interaction rules among birds can lead to sophisticated flocking patterns [58, 74].
- ABMs incorporate *stochasticity*. Many systems, particularly biological ones, include behaviors that appear to be random. "Appear to" is an important distinction, since what may appear to be random is actually deterministically chaotic. However, from a practical point of view, despite the fact that a particular system may follow deterministic rules, at the observational level it is impossible to actually define the initial conditions with enough fidelity to apply formal deterministic mathematics. Thus, capturing the sensitivity of a system to initial conditions is obscured by limitations on the resolution in characterizing the state of the system. Agent-based modeling addresses this issue via the generation of populations of agents, and a subsequent distribution of agent-behaviors. It is possible to establish probabilities of a particular behavior for an agent population as a whole (i.e., an experimentally determined response distribution of a particular cell type to a particular stimulus). This allows the generation of a probability function for the behavior of a single agent-type, which is, in turn, incorporated into the agent-type's rules. For instance, a rule may look like "In the presence of Stimulus A there is a 80% chance Receptor B will be activated." When the entire ABM consisting of a population of agents is instantiated, each individual agent follows a particular trajectory of behavior as its behavior rules' probabilities are resolved with each step of the ABM's run. The behavior of the overall system is generated by the aggregated behavioral trajectories of the individual agents, each model run producing one instance of system behavior. Performing multiple runs of the ABM thus generates a "population" of behavioral outputs to produce system behavior spaces consistent with epidemiological biological observation.
- ABMs reproduce *emergent properties*. Due to the parallelism, intrinsic stochasticity, and locally-based agent rules, a central hallmark of agent-based modeling is the fact that they generate systemic dynamics that often could not have been reasonably inferred from examination of the rules of the agents, resulting in so-called emergent behavior. To return to the example of the bird flock, superficial observation would seem to suggest the need for an overall leader to generate flock behavior, and therefore rules would seem to need to include a means of determining rules for flock-wide

command and control communication. This, however, is not nature's way: Birds function on a series of locally constrained interaction rules and the flocking behavior emerges from the aggregate of these interactions [58]. The capacity to generate emergent behavior is a vital advantage of using an ABM for conceptual model verification, as it is often the paradoxical, non-intuitive nature of emergent behavior that "breaks" a conceptual model. The structure of ABMs facilitates the development of aggregated multi-scale models [8, 100]. They have an intrinsically modular structure via the classification of agents based on similar rules of behavior. ABM rules are often expressed as conditional statements ("if–then" statements), making agent-based modeling suited to expressing the hypotheses that are generated from basic scientific research. Individual agents encapsulate mechanistic knowledge in the form of a set of rules concerning a particular component. The importance of this encapsulation in agent-based modeling (as opposed to the compressed representation of knowledge with a mathematical formula, such as a biochemical rate law) is the placement of the mechanistic knowledge within a compartmentalized object. Instantiating agents and their governing rules in a virtual world creates an in silico experimental environment, or a virtual laboratory [6, 7, 65]. In doing so, agent-based modeling goes beyond the mere instantiation of this knowledge as a single case by concurrently generating multiple instances of a particular encapsulation/object. Because of this property, an ABM is an expansion of mere rule-based and object-oriented methods. Multiple individual instances have differing initial conditions by virtue of existing in a heterogeneous environment. Because stochastic components are embedded in their rule systems (a well-recognized property of biological objects [45]), individual agents have differing behavioral trajectories as the ABM is executed. This results in population-level dynamics derived from the generation of these multiple trajectories, population dynamics that, when viewed in aggregate, form the nested, multi-scalar/hierarchical organization of biological systems [90, 91, 92].

In this environment, researchers can instantiate thought experiments in an in silico environment, to test the veracity and validity of their conceptual models by comparing the simulated experiments against more traditional in vitro and in vivo experimental results. ABMs have been used to study biomedical processes such as sepsis [6, 7, 9], cancer [100], inflammatory cell trafficking [11, 64], and wound-healing [49, 73].

One vital aspect of the use of agent-based modeling is to perform the trans-hierarchical function desired in an integrative modeling framework. This moves toward the goal of communicable dynamic knowledge representation, easing the way for biomedical researchers to translate their conceptual models into executable form. While the era of multi-disciplinarily trained researchers is dawning, it is most likely that for the foreseeable future the majority of biomedical researchers will not be extremely facile in the use of computational tools and methods. Agent-based modeling, by its object-

oriented nature, maps well to the current expression of biomedical knowledge. It is generally more intuitive for non-mathematicians/computer scientists to use. Nonetheless, it is a daunting software engineering task to provide a user-friendly ABM development environment for computer/math novices while including sufficient, comprehensive capabilities to capture the full richness of ABM utilization. Fortunately, the introduction and ongoing development of NetLogo provides just such a platform.

7.2 Facilitating Dynamic Knowledge Representation: The NetLogo Toolkit

7.2.1 Description and Origins of NetLogo

NetLogo is a general-purpose agent-based modeling environment for modeling complex systems. It includes the core NetLogo modeling language as well as an integrated modeling environment with a graphical user interface and many modeling tools. NetLogo was designed by Wilensky in the mid-1990s. Having collaborated with Resnick on StarLogo in the late 1980s and early 1990s [56, 55, 93, 57, 94], Wilensky set out to remedy limitations of StarLogo and create the next generation of the Logo-based agent-based modeling environment. Like StarLogo, NetLogo borrowed from the Logo programming language [25, 52] both core syntactic language elements and the central object of a "turtle," the default name for a mobile agent in NetLogo. Basic NetLogo also includes stationary agents called "patches" and connective agents called "links." New classes of agents can be defined using the "breeds" construct, so users can populate their models with wolves and sheep, atoms and molecules, or buyers and sellers. Constructing a NetLogo model involves choosing agents to represent aspects of the to-be-modeled system and giving them rules of behavior and interaction which they execute at every tick of a clock. One can then run the model and observe the emergent behavior of the system. Patches are typically used to model aspects of the environment, such as earth, grass, or atmosphere, that are computationally active, though stationary. So, at each time tick, grass may grow and be available for sheep agents to eat, earth may absorb percolating oil, and atmosphere patches may harbor carbon dioxide molecules [77, 76, 66]. In most natural science models, mobile agents affect each other through local interaction, thus the spatiality of the patches becomes the vehicle for agent interaction. Agents interact with their spatial neighbors. In many social science models, spatiality is not the dominant form of interaction. Agent communication can happen at a distance and is governed by social connection between (human) agents. The "links" agents typically model these social connections. In such models, agents interact with

their "link neighbors," the agents with whom they are linked regardless of their spatial locations.

NetLogo comes with an extensive library of sample models (over 300 as of release 4.0.2 of NetLogo in December 2007) from a wide variety of content domains [80], including natural sciences such as physics, chemistry, and biology, and social sciences such as sociology, psychology, and linguistics, and engineering domains such as materials science, industrial engineering, and computer science, and professional disciplines such as medicine, law, and business. NetLogo is freely available from [86] and comes with extensive documentation, code examples, and tutorials. For a good introduction to the methodology of agent-based modeling, including exploring constructing, testing and verifying models, see the textbook by Wilensky and Rand [90].

7.2.2 Design Philosophy Behind NetLogo

A core design principle of NetLogo, also originating in the early Logo community, is the principle of "low threshold, high ceiling" (sometimes rendered as "low threshold, no ceiling") [52, 67]. What this principle means, on the one hand, is that the language should be simple enough for a novice without programming background to be able to learn and productively use within minutes of starting. On the other hand, the language should be powerful and robust enough to be used by researchers in their scientific work. These twin design objectives are traditionally seen as conflicting: One either designs an educational tool for novices and students or one designs a professional tool suitable for scientists in their research. However, Wilensky started out with the hypothesis that these goals could be reconciled in one environment and, together with his colleagues at the Center for Connected Learning and Computer-Based Modeling (CCL), has been continuously developing and refining NetLogo so as to be more useful to each of these communities.

Core aspects of NetLogo design addressed to novices are natural-language-inspired syntax, graphical world present at start-up, easy-to-build drag and drop interfaces, and extensive help, documentation, sample models, and code examples. Core design features addressed to power users include an extensions application programming interface (API) through which users can write their own NetLogo libraries (in Java), support for replicability of model runs, programmatic control of agent execution order, and support for probability distributions of agent variables and for a variety of network layouts.

Although the criterion of low threshold is typically interpreted as being targeted to novices and high ceiling being targeted to researchers and advanced users, the design rationale for NetLogo hypothesized that both goals are actually important to both communities [82, 67]. On the high-ceiling side, the reasoning is that novices benefit from being able to smoothly move from elementary modeling to more advanced modeling without having to change

modeling languages or platforms. Moreover, and this is important for educational adoption, schools are much more easily persuaded to adopt software that is used in universities and in research contexts – one need not convince them that the software helps the students learn better, one can just point them to the scientific and commercial uses and they become interested in giving their students the same tool as they will use later on in life. On the low-threshold side, we have argued that low threshold is very important for researchers as well. Many researchers do not consider themselves programmers, and therefore, once they have created a conceptual model, they delegate the task of implementing the model to a programmer. This practice can lead to mismatches in understanding between the two parties and, consequently, to incorrect models [89]. Moreover, if the researcher can build the model himself/herself, then the researcher can much more rapidly and fluidly explore the design space of the model and make better progress in his/her research. Finally, the easy readability of a low-threshold language enables researchers to read and verify each others' models, leading to greater cumulativity in the scientific community. From the widespread adoption of NetLogo in both scientific research communities and in educational contexts, we conclude that the hypothesized compatibility of the two design goals has been successfully implemented. NetLogo has a large and active community numbering in the tens of thousands, with over 160,000 downloads in 2008 (and millions of web page hits). Its discussion lists are very active and include researchers, educators, students, businesspeople and policy-makers. NetLogo is in use in scientific research across a wide range of content domains and there is a rapidly increasing inclusion of NetLogo models in scientific research publications (e.g., [4, 37, 18, 42, 44, 17, 32, 38, 40, 64, 62, 29, 69]). This list is not intended to be comprehensive, as it is constantly being added to; interested parties should visit the NetLogo homepage and look in the "Community Models" section for an updated list of projects [85].

In a recent comparison of research-oriented agent-based modeling platforms [54], the authors admitted that, at first, they did not plan to include NetLogo in the comparison set, as, given its educational intent, they assumed it would be too limited for research purposes. However, after examining it more closely, they found that it was eminently suitable for research: "we found we could implement all our test models in NetLogo, with far less effort than for other platforms," that "NetLogo is by far the most professional platform in its appearance and documentation," and that it "is quite likely the most widely used platform for ABMs."

NetLogo is also in use in many thousands of educational contexts, especially in middle schools, high schools, and universities as well as museums and other informal learning contexts. Wilensky and colleagues have designed a number of effective model-based curricula for use in both precollegiate and undergraduate contexts. Topics covered include probability and statistics, kinetic molecular theory, reaction chemistry, electricity and magnetism, ecology, evolution, robotics, materials science, and microeconomics [12, 87, 2, 13, 1, 14, 88, 95, 61]. The CCL and colleagues have conducted hundreds of NetLogo workshops for teachers, researchers, students, and would-be modelers of all stripes.

7.2.3 NetLogo Features

NetLogo is a full-featured agent-based modeling environment and contains many sophisticated capabilities suitable for modeling Artificial Life. NetLogo is in continuous active development. Since version 1.0 in 1999, NetLogo has advanced considerably on both low-threshold and high-ceiling dimensions. Notable features include the HubNet [98] architecture that supports participatory simulations [57, 80, 19, 97, 41], where users can assume the role of agents alongside virtual agents, facilitating social science experimentation on a large scale [39, 30]. NetLogo also contains (1) NetLogoLab[15] that connects NetLogo to external hardware-based actuators and sensors and enables the grounding of models in local real-world data, (2) BehaviorSpace [96], a model analysis package that enables automated parameter sweeping, experimental analysis, and parameter space visualization, and (3) System Dynamics Modeler [83], a stocks and flows simulator that can be used alone or integrated with multi-agent simulations to create hybrid models that combine ABM and System Dynamics features [72]. Furthermore, NetLogo 4.0.2 was released in December of 2007 and contains many new and improved features. For instance, a major component of NetLogo is its models library, which contains hundreds of pre-built models, each with detailed explanations and extensive curricular activities, ready to be used as seed models. In the latest version of NetLogo, there are new models of biological evolution, mathematics, physics, neural networks, evolution of social cooperation, linguistics, psychology, management, and geographic information software (GIS). Some major new components that have been recently added include the integration of language primitives that facilitate the building, analysis, and examination of network models, enhancements to analysis and visualization of multiple model runs, and enhanced facilities for user-authored extensions of the core language. Users have taken advantage of the latter to build many such extensions. Of particular note to researchers and Artificial Life modelers are two new extensions: an extension that enables NetLogo to import GIS data files into a model and to generally play well with existing GIS software and a second extension that provides a library of genetic algorithm primitives for use in evolutionary computation.

The features and design philosophy of NetLogo offer several benefits to its use in the biomedical community. In keeping with its legacy as an educational tool, we note that there is great potential for use of NetLogo in medical school education, and we have made plans to integrate NetLogo into medical education here at Northwestern University. As alluded to above in Section 7.1,

its "low threshold, high ceiling" characteristics make NetLogo well suited to implementation as a computational adjunct to current biomedical research. Evidence of its utility can be demonstrated in the range of research areas where NetLogo has been applied: intracellular signaling [10], acute inflammation [6, 7, 9, 72], inflammatory cell trafficking [64, 11], wound healing [49], and morphogenesis [46]. This chapter will focus on demonstrating how NetLogo can be used to effect multi-scale knowledge integration through the use of agent-based modeling, as well as demonstrating some of the capabilities of the NetLogo toolkit, particularly with respect to three-dimensional (3D) topologies.

7.3 NetLogo Models of Acute Inflammation

This chapter presents a series of NetLogo ABMs representing multiple scales of organization and integration. These models all involve aspects of the acute inflammatory response (AIR). The inflammatory response represents the body's initial reaction to injury and infection and is a ubiquitous process found in all tissues. In addition to dramatic expression in the face of severe infection or injury (as seen in sepsis and massive trauma), inflammation also provides a key link between damage and repair, as the healing process relies upon signals initiated during the AIR. Furthermore, it is increasingly recognized that inflammatory processes are essential to the maintenance of normal homeostasis, as the body exists in an ever-changing environment and is involved in such ubiquitous conditions as atherosclerosis, obesity, and aging. Therefore, acute inflammation is a prototypical example of a multi-scale biocomplex system and thus suited to examination and characterization using agent-based modeling.

The series of NetLogo ABMs have been developed at multiple levels of resolution, extending from intracellular signaling leading up to simulated organ function and organ–organ interactions. The specific model reference system for these ABMs is the clinical manifestation of multi-scale disordered acute inflammation, termed systemic inflammatory response syndrome (SIRS), multiple organ failure (MOF), and/or sepsis. These clinical entities form a continuum of disseminated disordered inflammation in response to severe levels of injury and/or infection and represent one of the greatest clinical challenges in the current health-care environment.

7.3.1 NetLogo ABM of Intracellular Processes: The Response to Inflammatory Signals

Perhaps the greatest translational challenge for biomedical research exists in the step between intracellular mechanism and the behavior of cellular populations. The extensive characterization of intracellular processes forms the bulk of ongoing biomedical research, and the ability to integrate this information is the subject to the burgeoning field of Systems Biology. While there are notable exceptions (see [16, 53] for examples of ABMs used to characterize intracellular processes), in general, the systems biology community has used more traditional methods of mathematical modeling based on differential equations and stochastic algorithms. This method has been successful in modeling kinetic processes in well-mixed systems, classically manifested as biochemical reactions. However, at a basic level, biochemical processes involve discrete events between molecules and particles. If the goal is to characterize these processes in the context of their influence on cellular behavior, it is possible to accept a level of abstraction that eliminates the details of the molecule–molecule interaction by labeling them generically as interaction events. The emphasis is shifted to representing the interaction–event. Accomplishing this requires two realizations (1) Molecules do not have volition to direct their movement to find their reaction partner and (2) cells are not bags of molecules (i.e., cells are not well mixed systems), and because molecules have no volition, spatial and environmental conditions within the cell must somehow direct signaling pathways by increasing the likelihood that participants in steps of a signal cascade will actually contact each other. Incorporating a spatial component to the characterization of signaling pathways, such as relating enzymes to the internal cytoskeletal architecture or simulating the effects of molecular crowding (that suggest that biochemical rate constants are dependent on an intracellular context [59]), can accommodate this. A modeling system can utilize abstraction at the level of the signaling event, without details as to what happens at a molecular structural level during the event. Interaction rates can be qualitatively scaled, as similar classes of interactions act within the same general time frame, and the emphasis on physical proximity renders fine parsing of these rates unnecessary. Rather, the focus is on characterizing conditions that lead to interaction events: molecular movement across space, likelihood of interaction events occurring, and the ordering of signaling enzymes. This leads to a particle view of signal transduction, where interactions within a reaction cascade follow a spatial architecture that is defined by the sequence of the signaling pathway. "Particles" are used to represent signaling events, and viewing the trajectory of the particle through the various reaction spaces can simulate transduction through a signal cascade. This modeling architecture is termed Spatially Configured Stochastic Reaction Chambers (SCSRC) [10]. Of note, the SCSRC utilizes and expands upon one particular type of basic NetLogo model, the GasLab models in the Models Library representing gas behavior via particle dynamics [78, 80, 81]. The transition from discrete particle behavior to the global system behavior expressible via the Ideal Gas Law equations provides an analogy for the underlying precept of the SCSRC: modeling biochemical reactions, which are usually expressed as rate equations, from a discrete, particle-based standpoint. This is an example of how

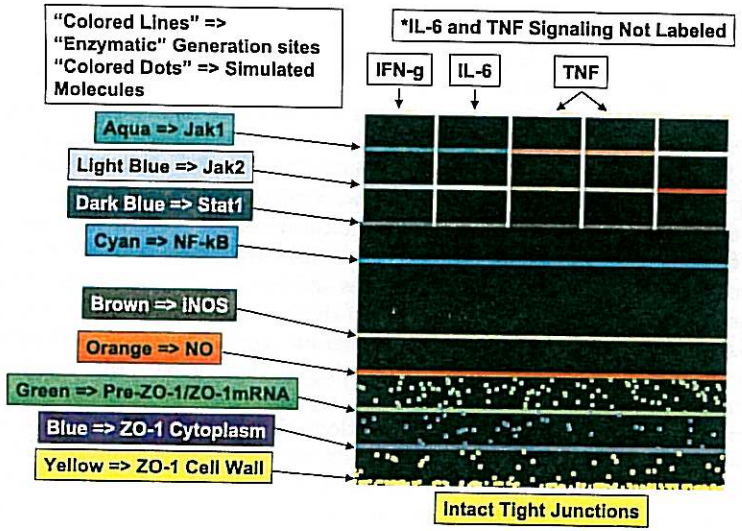

Fig. 7.1 Architecture of NetLogo ABM of intracellular signaling and metabolism: A SCSRC model of a gut epithelial cell.

NetLogo's extensive model library can serve as a source of seed models to aid in the development of specific biomedical models.

In the SCSRC each simulation space represents a single cell. The space is a grid of 2D squares. The agent level is at the particle level, where each agent represents an abstracted molecule within the signal transduction cascade. The space is subdivided into a series of smaller rectangular compartments. The particular example presented here represents the pro-inflammatory signaling events in a gut epithelial cell and the effect those events have on tight-junction protein metabolism, an important component of epithelial barrier function (Fig. 7.1). The design features of the SCSRC are derived from the two central premises listed above: (1) Molecules do not behave volitionally and (2) spatial and structural factors influence the sequence of molecular interactions and signal transduction. The movement rules for agent-molecules in the SCSRC follow a semi–Brownian random-walk while they are simulating the molecular events of signal transduction. The subdivided compartments are reaction spaces that represent the close proximity of spatially located signaling enzymes. This proximity simulates either the arrangement of enzymes along cytoskeletal elements or the effects of molecular crowding in the cytoplasm. The apposed borders of the reaction spaces represent sequential enzymes of the signal cascade. The entry of a molecule-agent into the reaction space through one of these "enzyme" borders represents the chemical reaction event catalyzed by the enzyme, producing the signal molecule and introducing it into the reaction space. The molecule-agent moves in a random fashion eventually

encountering the opposite border representing the next enzyme in the signaling pathway, and is transformed as it passes through that border into the next reaction chamber. As mentioned above, the specifics of the chemical reactions are abstracted into a state transition for the molecule-agent. Primarily, the state transition is merely a change in the labeling of that molecule-agent (to keep track of the signal as it propagates), but occasionally it results in altering the way it interacts with subsequent enzyme-borders. For instance, inhibitory activity is simulated by agent–border interactions that lead to the affected areas of the enzyme border being unable to execute the signaling state transition for subsequent encounters with up stream molecule-agents. The number of molecule-agents of a particular type represents the strength of a signal. The spatial configuration of the chambers of the SCSRC is defined by the sequence of a signaling/synthetic pathway. Each enzymatic step is represented by the horizontal "bars" abutting a reaction chamber. Specific qualitative types of enzymatic reactions, such as signal amplification, inhibition, or activation, can be specified in the encounter rules between the agent-molecules and the enzyme-borders. The reference model for the molecular processes in this SCSRC model is a well-described human cultured enterocyte model (Caco–2) and its responses to inflammatory mediators, including nitric oxide (NO) and a pro-inflammatory cytokine mix ("cytomix") that includes tumor necrosis factor (TNF), interleukin–1 (IL–1), and interferon-gamma (IFN–gamma) [33, 36, 35, 60]. Figure 7.1 demonstrates the structural architecture of these signaling pathways. This is a screenshot of the SCSRC model of a single gut epithelial cell, representing the pro–inflammatory signaling and tight-junction protein components. The inflammatory signaling complexes are at the top of the model and tight-junction protein pathway chambers are at the bottom. "Dots" present in each chamber represent molecules being synthesized and transported by the various enzyme complexes. In this figure, the only "Dots" present are in the tight-junction proteins present in the baseline cellular state.The response of the model to inflammatory stimuli can be seen in the screenshots displayed in Fig. 7.2.

7.3.2 NetLogo ABM of In Vitro Gut Epithelial Barrier Experiments

This subsection describes the translation of the mechanisms and behaviors of the SCSRC into a cell-as-agent-level ABM as seen in an in vitro experimental model of gut epithelial barrier function (epithelial barrier agent-based model = EBABM) [9]. As opposed to the agents being molecules and signaling enzymes in the SCSRC, each agent in the EBABM represents a single cell. The output of the SCSRC has been translated into a series of algebraic relationships for agent state variables corresponding to the molecular agent classes in the SCSRC. The EBABM utilizes a model architecture derived from another

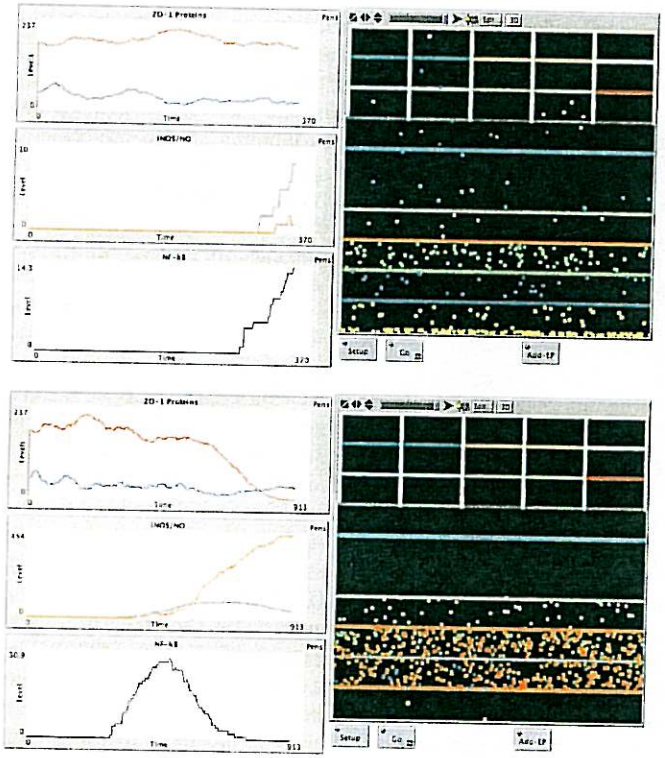

Fig. 7.2 Screenshots of gut epithelial cell SCSRC in response to inflammatory stimuli. The top panel is a screenshot of the SCSRC just after the addition of the inflammatory signal. "Dots" representing signaling molecules can be seen in each chamber. The graphs demonstrate the rise in levels of "NF-kB," and the activation of "iNOS" and "NO." The bottom panel is a screenshot of the SCSRC near the end of a run. The signaling molecules have disappeared, "iNOS" is starting to decrease while residual "NO" is still present.

paradigmatic type of NetLogo model, the "patch-centric" cellular automata–like 2D grid models [75, 76, 66].

The topology of the EBABM is a 2D square grid. The grid has 21 × 21 cells, in each of which there is an epithelial cell agent ("epi-cell"). The size of this grid was chosen as a representative portion of a total cell culture surface for reasons of computational efficiency; the processes being modeled by the EBABM are proportional to the cell surface area and the model could be, if desired, scaled up to any size. There are also two additional simulation "spaces" – one layer representing the apical extracellular space (from which the diffusate originates) and another layer representing the basal extracellular space (into which the diffusate flows if there is permeability failure). A screenshot of the EBABM during an experimental run can be seen in Fig. 7.3.

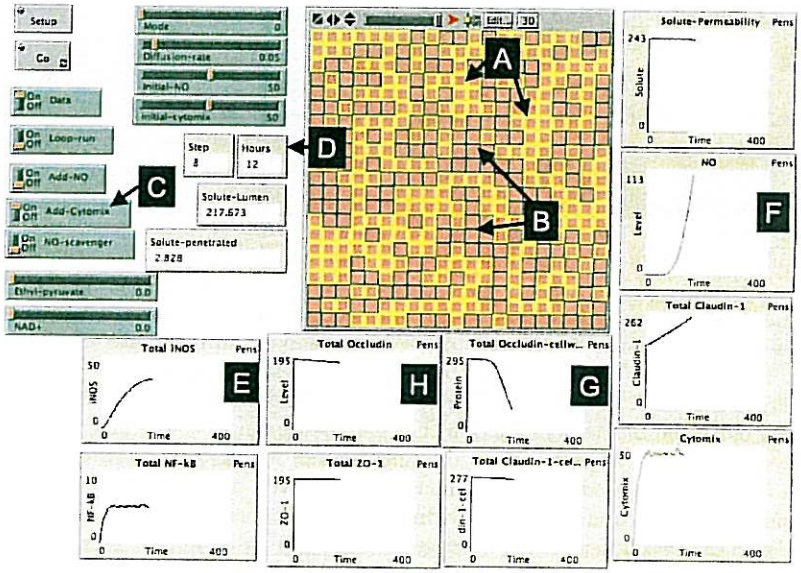

Fig. 7.3 Screenshot of the graphical user interface of the EBABM. Control buttons are on the left; Graphical Output of the simulation is in the center. In the Graphical Output, Caco–2 agents are seen as squares, those with intact tight junctions with light borders (letter A), those with failed tight junctions are bordered in black (letter B). This particular run is with the addition of cytomix (letter C) seen after 12 hours of incubation (letter D). The heterogeneous pattern of tight-junction failure can be seen in the Graphical Output. Graphs of variables corresponding to levels of mediators (letters E and F) and tight-junction proteins (letters G and H) are at the bottom and right. This figure is reprinted under the terms of the Creative Commons license from [9].

Each epi-cell has eight immediate neighbors, and at each contact point there is a simulated tight junction (TJ). The integrity of the TJ requires both apposed epi-cells to have adequate production and localization of TJ proteins.

The importance of the EBABM lies in the translational function it plays as a transitioning step between the intracellular behavior represented and modeled using the SCSRC, and the aggregated cell-type models that are described in the following subsections. The EBABM is thus a critical validation step in the modular construction of a multi-scale ABM architecture.

7.3.3 NetLogo ABM of Organ Function: Gut Ischemia and Inflammation

The next level of ABM development is intended to simulate organs as a synthesis of two distinct hypotheses of disseminated inflammation and organ failure: viewing disordered systemic inflammation as either a disease of the endothelium [5] or a disease of epithelial barrier function [26]. The endothelial surface is the primary communication and interaction surface between the body's tissues and the blood, which carries inflammatory cells and mediators. Endothelial activation is a necessary aspect of the initiation and propagation of inflammation, particularly in the expansion of local inflammation to systemic inflammation [5]. On the other hand, end-organ dysfunction related to inflammation can be seen as primarily manifest in a failure of epithelial barrier function. Pulmonary, enteric, hepatic, and renal organ systems all display epithelial barrier dysfunction that has consequences at the macro-organ level (impaired gas exchange in the lung, loss of immunological competence in the gut, decreased synthetic function in the liver, and impaired clearance and resorptive capacity in the kidney) [26]. The organ-level ABM reconciles these two hypotheses by integrating the epithelial barrier component, used to represent the consequence of individual organ failure, and the endothelial/inflammatory cell component that provides the binding interaction space that generates, communicates, and propagates the inflammatory response [9]. The primary cell classes in this architecture are endothelial cells, blood-borne inflammatory cells (with their attendant subtypes), and epithelial cells. Therefore the structure of the organ ABM involves the 3D linkage of the cellular surface ABMs already developed representing these two systems, the EBABM representing epithelial function and a previously published endothelial/inflammatory cell ABM [6, 7]. The result is a bilayer organ model (see Fig. 7.4).

Both the original endothelial/inflammatory cell ABM and the EBABM were developed as 2D models. In order to create the bilayer topology of the organ ABM, it was necessary to convert both of these models to the 3D version of NetLogo [84], with each model represented as a layer of agents projected in the XY plane. The two layers were then juxtaposed: the endothelial layer below and the epithelial layer above along the Z axis. The simulated blood vessel luminal space occupied another XY plane one place inferior to the endothelial surface along the Z axis. Inflammatory cells move only in this plane. The organ luminal space occupied the XY plane at one place superior to the epithelial axis along the Z axis. This space contains the "diffusate" that leaks into the gut in cases of epithelial tight-junction failure.

In vivo models that examine the inflammatory behavior of the gut either look at a local effect from direct occlusion of gut arterial flow [70, 63] or as a result of some systemic insult, be it hemorrhagic shock, endotoxin administration [50], or burn injury [47, 24]. These studies suggest that the primary

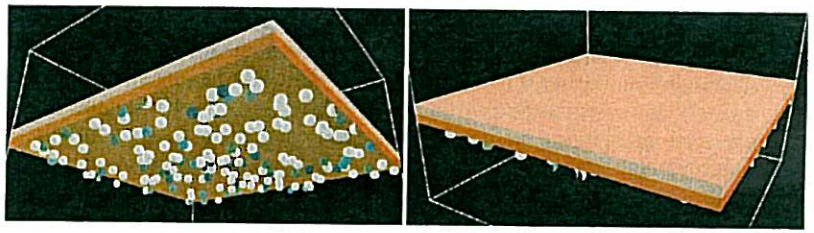

Fig. 7.4 Screenshots of bilayer configuration of the gut ABM, following the structure for hollow organs described in the text. The left panel is the view of bilayer from endothelial surface. The lower surface consists endothelial cell agents, with spherical inflammatory cell agents seen just below. Inflammatory cell agents move in the plane immediately below the endothelial surface. The right panel is the view of bilayer from epithelial surface. Each cube represents an epithelial cell agent, governed by rules transferred from the EBABM. Impairment of TJ protein metabolism is shown by darkening of the shade of the epithelial cell agent, with the epithelial cell agents eventually turning black and changing their shape to a "cone" when TJs have failed. This figure is reprinted under the terms of the Creative Commons license from [9].

process that initiates inflammation in the gut is ischemia and reperfusion and the subsequent effects on the endothelial surfaces within the gut. The measurable outputs of the reference models exist at different scales. At the cellular level, tight-junction integrity and epithelial barrier function is one measured endpoint [99, 35], however, the organ as a whole also has an output: the nature of the mesenteric lymph. Multiple studies suggest that ischemia to the gut (and subsequent inflammation) leads to the excretion of an as-of-yet unidentified substance in the mesenteric lymph that has pro-inflammatory qualities. Some characteristics of the substance can be identified from the literature: It is an acellular, aqueous substance [21], is greater than 100 kDa in size [3], does not correspond to any currently recognized cytokine, and is bound or inactivated by albumin [51]. The time course of the production of the substance is identified to some degree [22, 20] but it is unclear if it arises from a late production of inflamed cells or is a product of cellular degeneration or apoptosis (programmed cellular death) or is a transudated bacterial product from the intestinal lumen. The uncertainty with respect to an identified mediator provides a good example of how the ABM architecture deals with incomplete knowledge. Based on the characteristics defined above, we make an ***hypothesis*** regarding this substance with respect to its origin, but we acknowledge that this is, to a great degree, a "best guess." Doing so establishes a knowledge bifurcation point, allowing the development of potential experiments and/or data that would nullify the particular hypotheses. A specific example will be demonstrated next.

The nature of the initial perturbation was altered to match that seen in the reference experiments (i.e., tissue ischemia). With the premise that the inflammatory response was generated at the endothelial surface, the initial

perturbation was modeled focusing at the endothelial layer, with the response of the epithelial component being subsequently driven by the output of the endothelial–inflammatory cell interactions. Rather than having a localized insult with either infectious agents (simulating infection) or sterile endothelial damage (simulating tissue trauma), as was the case in the base endothelial–inflammatory cell ABM, gut ischemia was modeled as a percentage of the total endothelial surface rendered ischemic. The degree (or percentage affected) of the initial ischemia was controlled with a slider in the NetLogo interface. Therefore, "Percentage Gut Ischemia" (= %Isch) represents the independent variable as initial perturbation for this model. To address the issue of modeling the production of the post-ischemic, pro-inflammatory lymph, attention is focused on linking the knowledge that has been acquired regarding the characteristics of the substance and relating this information to the components of the organ ABM. The known characteristics listed above are used to exclude potential candidate substances/actors from consideration. Specifically, this group comprises any of the cellular agents and any of the included cytokines. Therefore, the search is limited to the following:

1. An as-of-yet unidentified compound linked to cellular damage. An example of such a compound would be high-mobility box protein 1 (HMGB–1), which to date has not been looked for in the post-ischemic mesenteric lymph. In the organ ABM, this variable is termed "cell-damage-byproduct," and it is calculated as a function of total endothelial damage with a set decay rate consistent with that of other bio-active compounds associated with inflammation.
2. A luminal compound that diffuses in response to TJ barrier failure. This would correspond to potential byproducts of gut bacterial metabolism, or bacterial toxins, or other soluble aspects of the gut luminal environment that would leak into the gut tissue by virtue of the loss of barrier function. This variable is represented by "gut-leak," which is equal to the "solute" (from the EBABM) that penetrates the failed barrier.
3. A downstream metabolite of compounds generated by the inflammatory process. These would most likely be compounds generated by superoxide and nitric oxide (NO) reactions. For purposes of these simulations, levels of NO will be used as a proxy for this possible candidate.

Therefore, the goal of the organ ABM simulation runs will be to examine the time course levels of these three values and identify which one (if any) matches the reported time course effects of the post-ischemic mesenteric lymph. The first step was to determine the greatest non-lethal level for "Percentage Ischemia" (%Isch). It should be noted again that the name of this variable is descriptive for how it is implemented in the ABM, and not intended to match quantitatively, per se, with measured ischemia in vivo. Rather, %Isch is representative of the initial conditions for the simulation that will produce a pattern of simulation behavior that matches that of the in vivo system [31]. A parameter sweep of this value was performed, using a

previously described method [6] with the goal of identifying the greatest non-lethal level of %Isch, which was %Isch = 35. The output from the organ ABM with %Isch = 35 evaluated the time courses for three global output variables: "cell-damage-byproduct," "gut-leak" and NO. The pro-inflammatory properties of the post-ischemic mesenteric lymph were noted to increase the most at 3 hours and 6 hours and remain out to 24 hours [22, 20]. Examining the time courses of these three global output variables the candidate compound that most closely approximates the pattern identified in the literature was the "cell-damage-byproduct."

As discussed above, this possible source of the unknown compound in the post-ischemic mesenteric lymph is based on the recognition of certain late pro-inflammatory mediators produced by activated and damaged cells, HMGB–1 being the most studied as a possible key mediator in the pathogenesis of sepsis [48]. To date, there have been no studies examining the production or presence of HMGB–1 in the post-ischemic mesenteric lymph. However, based on the information generated by the organ ABM, and placed in the context of the knowledge framework concerning the characteristics of pro–inflammatory mesenteric lymph, we will make a hypothesis that some later byproduct of damaged gut tissue, rather than a diffused material or direct metabolite of first-pass inflammatory mediators, is the responsible compound in the post-ischemic mesenteric lymph. It is recognized that this is "guided speculation;" however, it also demonstrates how the construction and use of models in the ABM architecture is an evolving process that parallels the development and refinement of conceptual models. As will be seen in the next subsection, the next scale of biological organization to be addressed in the ABM architecture involves the extension and integration of this hypothesis.

7.3.4 NetLogo ABM of Multi-organ Interactions: The Gut–Pulmonary Axis of Inflammation

The ultimate goal of all of these modeling endeavors is to create some facsimile of clinical conditions, with the hope of developing a platform that represents the complexity seen clinically. In patients, organs do not exist in isolation; their mutually complementary functions interact to sustain the organism as a whole. Disease states can lead to a breakdown of these interactions, causing a cascade effect, as single-organ dysfunction can lead to multi-system failure. Sepsis and MOF are characterized by a progressive breakdown in these interactions, leading to recognizable patterns of linked organ failure [28]. Therefore the next scale of biological organization represented in the multi-scale ABM architecture is that of organ–organ interaction [9]. The gut–pulmonary axis of MOF [47, 22, 23] is used as the initial example of organ-to-organ crosstalk. This relationship is relatively well defined pathophysiologically (although not completely, as indicated by the uncertainty of the identity of

the pro-inflammatory compound in the post-ischemic mesenteric lymph) and represents an example of multi–organ effects of disseminated disordered inflammation. Disordered acute inflammation of the lung is termed Acute Respiratory Distress Syndrome (ARDS) and is manifested primarily by impaired endothelial and epithelial barrier function, leading to pulmonary edema. This leads to impaired oxygenation of arterial blood, requiring support of the patient with mechanical ventilation. While the comprehensive pathogenesis of ARDS involves additional subsequent issues related, to a great degree, to the consequences of mechanical ventilation (specifically the effects of barotrauma and shear forces on the airways, and the persistent propagation of inflammation that results), for purposes of this initial demonstration only the initiating events associated with the development of ARDS will be modeled. Those events concern the production and release into the mesenteric lymph by ischemic gut (resulting from shock) of various pro-inflammatory mediators and their effects both on circulating inflammatory cells and the pulmonary endothelium as they circulate back to the lung via the mesenteric lymph (as discussed above). At this point, the hypothesis regarding the nature of the pro-inflammatory mediator in the mesenteric lymph is extended to the assumption that, for modeling purposes, the levels of "cell-damage-byproduct" will be the proxy for the unidentified compound that is produced in the ischemic gut and circulated to the lung, leading to inflammation of the pulmonary endothelium.

Drawing upon the endothelial–epithelial bilayer configuration for a hollow organ, a pulmonary ABM was developed utilizing the same endothelial–inflammatory cell component as the gut ABM and using rules for pulmonary epithelial cells with respect to tight-junction metabolism and epithelial barrier function [34]. The functional consequence of the intact pulmonary epithelial barrier is effective oxygenation of arterial blood (expressed at the endothelial lumen) via diffusion from the alveolar epithelial surface. Pulmonary barrier failure manifests as increased egress of fluid from the endothelial lumen into the alveolar space, affecting the transfer of alveolar oxygen to the endothelial surface. Thus, systemic oxygenation may be altered with the consequence that progressive pulmonary dysfunction would feed back to the system as whole. This leads to impaired oxygenation into the endothelial lumen, which is summed across the surface of the model to produce a measure of systemic arterial oxygen content.

The topology of the linked gut and pulmonary ABMs consists of two parallel bilayer planes, each bilayer representing one of the organ ABMs (Fig. 7.5).

The Z-axis orientation of both bilayers is the same: to allow conservation of the agent rules for equivalent agent classes (i.e., endothelial–epithelial–lumen relationships are consistent). The simulated blood flow continues to be modeled by movement in the XY plane immediately inferior to the endothelial surface. Blood flow between organs is simulated by adding a "perfusion" variable. For purposes of the model, large-caliber blood vessels and the heart are treated as biologically inert with respect to inflammation. Similarly, the

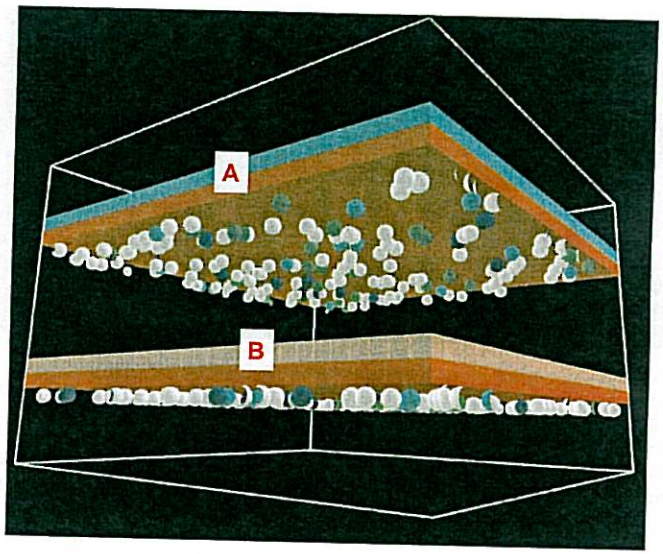

Fig. 7.5 Screenshot of multi-bilayer gut–lung axis ABM. The letter A labels the pulmonary bilayer, with cubes in the upper portion of the bilayer representing pulmonary epithelial cell agents, while the lower surface represents pulmonary endothelial cell agents, and below are spherical inflammatory cell agents. The letter B labels the gut bilayer, with a similar configuration, epithelial cell agents above and endothelial cell agents below. Circulating inflammatory cell agents move between these two bilayers in the fasion described in the text. This figure is reprinted under the terms of the Creative Commons license from [9].

flow of the mesenteric lymph is transferred from the gut ABM endothelial space to the lung ABM endothelial space.

The effects of mesenteric ischemia on pulmonary barrier dysfunction were then evaluated using a parameter sweep of %Isch to identify the inflection point between lethal and sub-lethal perturbation levels. Screenshots of both these outcomes can be seen in Fig. 7.6.

This parameter sweep demonstrated that the corresponding lethality of mesenteric ischemia in the gut–lung ABM is significantly increased as compared to the gut ABM alone, dropping the sub-lethal %Isch from 35 for the gut ABM to 11 for the gut–lung ABM. This results from the addition of the lung ABM and its effect of decreasing the maximally available "oxy" to non-perturbed endothelial agents via the consequence of pulmonary epithelial barrier function ("pulm–edema"). With increasing pulmonary edema and worsening oxygen delivery, gut epithelial agents "die" owing to a decrease in the available maximal "oxy" level to below the threshold for generalized endothelial agent activation. The impaired systemic oxygenation due to a pulmonary leak arises from pulmonary epithelial barrier failure. At the sublethal

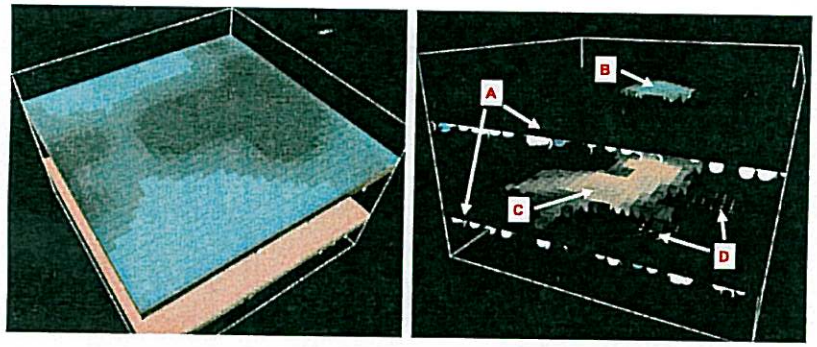

Fig. 7.6 Effect of gut ischemia on pulmonary barrier dysfunction and pulmonary edema: sublethal and lethal outcomes. The left panel is a screenshot of a representative run with a sub-lethal initial %Isch = 11 over a 72-hour run. Pulmonary epithelial cells show gradual recovery as inflammation subsides up to the screenshot time of 72 hours. The right panel demonstrates a "lethal" initial level of %Isch = 13, where impaired oxygen delivery from the lung leads to greater ischemia and cellular death in the gut. This run is terminated at 24 hours because endothelial damage is nearly complete. The letter A points to black cubes representing "dead" endothelial cell agents. The letter B points to the only remaining intact pulmonary epithelial cell agents. The letter C points to the only remaining intact gut epithelial cell agents. The letter D points to the only remaining patches of surviving endothelial agents (seen through the cones of "dead" epithelial cell agents). This figure is reprinted under the terms of the Creative Commons license from [9].

%Isch level of 11 the system is able to correct itself, with attenuation of gut ischemic damage and recovery of the pulmonary epithelisl cells, mostly occuring by 72 hours. This pattern is consistent with that seen clinically in the recovery of pulmonary edema secondary to inflammatory causes. However, the transition to lethal outcome is accomplished by only a slight increase of %Isch to 13, where the oxygen delivery consequences of pulmonary epithelial failure leads to a forward feedback loop with progressive gut bilayer ischemia. Thus, the survival space of the system would appear to be greatly limited, and it may initially suggest that this model would be unsuited to examining the range of dynamics of interest in the study of sepsis. However, it should be noted that the high lethality of mesenteric ischemia, which implies the presence of hemodynamic shock, is historically correct. Shock states, prior to the development of fluid resuscitation and respiratory support, were nearly universally fatal. This is the circumstance that is being represented with the gut–lung ABM at this point. If the goal is to simulate the clinical conditions associated with sepsis and MOF, then it is necessary to simulate the effects of organ support, to shift the survival space to the right. Doing so reproduces the fact that sepsis and MOF are diseases of the intensive care unit (ICU), arising only after the advances of resuscitative, surgical, antimicrobial, and organ-supportive care allowed the maintenance of patients in situations where they previously would have died. Therefore, sepsis and MOF can be thought

of as a previously unexplored behavior space of systemic inflammation, one where the inflammatory system is functioning beyond its evolutionarily defined design parameters [6, 7].

Therefore, a very abstract means of organ support is modeled in the form of "supplementary oxygen." This function increases the amount of "oxy" that is able to be diffused through the pulmonary epithelial barrier and is the qualitative equivalent of increasing the fraction of inspired oxygen, and therefore alveolar oxygen, to increase the partial pressure of oxygen diffused in the blood. It is qualitative insomuch as there is no attempt to reproduce the dynamics of gas exchange, or the binding of hemoglobin to oxygen in the blood, or the effects of redistributed ventilation–perfusion matching in the lung as a result of hypoxia. This degree of detail is beyond the scope of this initial demonstration model; however, the qualitative behavioral effects do show that this type of support, even abstractly modeled, increases the richness of the behavior of the model as a whole and can extend the examinable behavior space of the model to situations that can approximate the effects of organ support in the ICU. The corresponding changes in outcome with this type of simulated organ support can be seen in Fig. 7.7.

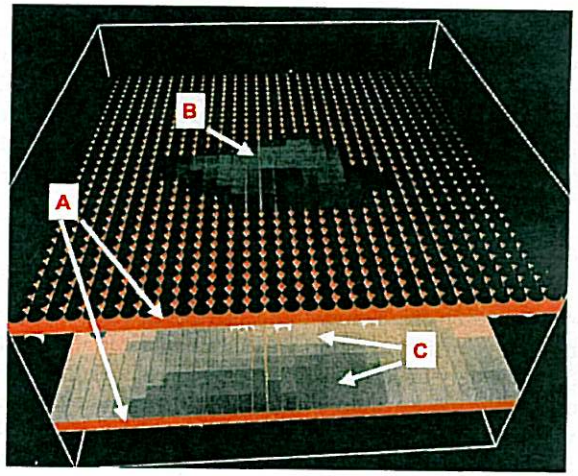

Fig. 7.7 Effect of simulated supplementary oxygen on previously lethal gut ischemia. This is a screenshot of a representative run with an initial %Isch = 15 and the addition of simulated organ support in the form of "Supplementary Oxygen" at 50%. The stabilization and initiation of recovery of pulmonary epithelial TJs at 72 hours is consistent with the clinical time course of ARDS due to an episode of shock. The letter A demonstrates the intact endothelial agent layer due to "Supplementary Oxygen" support (compare with Fig. 7.6, the panel on the right). The letter B demonstrates the recovering pulmonary epithelial cell agents. The letter C demonstrates intact and recovering gut epithelial cell agents. This figure is reprinted under the terms of the Creative Commons license from [9].

In Fig. 7.7, the initial %Isch = 15, greater than the lethal level seen in Fig. 7.6; however, the survival of the overall system is enhanced by blunting the negative consequences of impaired pulmonary function on the gut. The effect of "Supplementary Oxygen" is additive to the level of "oxy" generated by the lung ABM and distributed to the endothelial surface, effectively blunting the effect of the resulting pulmonary edema and keeping the "oxy" level above the threshold ischemic level for activation of the generalized endothelial cell agent population. As a result, the endothelial surface is maintained through the period of most intense inflammation and this allows the epithelial cells to begin recovery of their TJs. This dynamic is consistent with current managment of these types of patients and thus needs to be effectively modeled if the appropriate disease state is to be examined.

This sequence illustrates an important point in creating translational models of disease states. The tendency may be to attempt to model the pathological state being studied (i.e., creating a model of sepsis). However, it needs to be remembered that pathological states result from transitions from normal physiological behavior, and if the intent of a model is to facilitate the eventual transition from disease back to health, then the normal mechanism must be the basis of a translational model. The need to capture transitions from one state to another takes on further importance when the pathological state results, as with sepsis, from medical/clinical interventions. Therefore, the architecture of a modeling structure needs to be flexible enough to accommodate the addition and integration of these factors, and it is hoped that the presented modular structure of the ABM architecture demonstrates this capability.

7.4 Conclusion

The biomedical research community today faces a challenge that has paradoxically arisen from its own success: As greater amounts of information become available at increasingly finer levels of biological mechanism, it becomes progressively more difficult for individual researchers to survey and integrate information effectively, even within their own area of expertise. It still falls upon the individual researcher to create mental models to guide the direction of his/her individual research and, in aggregate, form the components of the evolving structure of community knowledge. However, the formal expression of mental models remains poorly defined, leading to limitations in the ability to share, critique, and evolve the knowledge represented in these conceptual models, particularly across disciplines.

These limitations can be overcome by developing methods of formal dynamic knowledge representation to enable researchers to express and communicate their mental models more effectively. By being able to "see" the consequences of a particular hypothesis–structure/mental model, the mechanistic consequences of each hypothesis can be observed and evaluated. In addition, this type of dynamic knowledge representation enables the instantiation of thought experiments, of trying out possible alternative solutions, so long as these hypotheses and assumptions are made explicit. Again, this draws upon the experience in the Artificial Life community by creating alternative worlds driven by these proposed rules. These models can aid in the scientific process by providing a transparent framework for this type of speculation, which can then be used as departure points for the planning and design of further wet lab experiments and measurements.

In short, the agent-based paradigm, with its defining characteristics of encapsulation, modularity, and parallelism, can provide an over-arching design architecture for the computational representation of biological systems. However, for this to be effective, there needs to be participation on the part of the biomedical community and its participants. Modeling and simulation toolkits such as NetLogo serve a vital role in giving novices to computer modeling an opportunity to represent and visualize their conceptual models. In particular, NetLogo provides a highly effective mixture of ease-of-use and modeling capability to make the initial foray into this arena most rewarding. It is hoped that the increasing use of this type of knowledge representation and communication will foster the further development of virtual laboratories and in silico investigations.

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Chapter 8
Discrete Dynamics Lab: Tools for Investigating Cellular Automata and Discrete Dynamical Networks

Andrew Wuensche

DDLab is interactive graphics software for creating, visualizing, and analyzing many aspects of Cellular Automata, Random Boolean Networks, and Discrete Dynamical Networks in general and studying their behavior, both from the time-series perspective – space-time patterns, and from the state-space perspective – attractor basins. DDLab is relevant to research, applications, and education in the fields of complexity, self-organization, emergent phenomena, chaos, collision-based computing, neural networks, content addressable memory, genetic regulatory networks, dynamical encryption, generative art and music, and the study of the abstract mathematical/physical/dynamical phenomena in their own right.

8.1 Introduction

Networks of sparsely interconnected elements with discrete values and updating in parallel are central to our understanding of a wide range of natural and artificial phenomena drawn from many areas of science: from physics to biology to cognition; to social and economic organization; to parallel computation and artificial life; to complex systems of all kinds.

Abstract, idealized networks – Cellular Automata (CA), Random Boolean Networks (RBN), and Discrete Dynamical Networks in general (DDN) – provide insights into complexity in nature by providing the simplest models of self-organization and bottom-up emergence. They are also fascinating in themselves as mathematical, physical, dynamical, and computational systems with a large body of literature devoted to their study [1, 5, 6, 8, 9, 14, 15, 16].

The dynamics that play out on these signaling – "decision-making" – discrete networks are difficult if not impossible to investigate by classical mathematics; numerical methods are therefore essential.