Chapter 15
Agent-Based Modeling Approaches to Multi-Scale Systems Biology: An Example Agent-Based Model of Acute Pulmonary Inflammation

Gary An, Michael Wandling and Scott Christley

Abstract Implicit in systems biology is the concept that the whole is greater than the sum of its parts. Agent-based modeling, an object-oriented, discrete event, population-based computational modeling method, is well suited to meeting this goal. By viewing systems as aggregates of populations of interacting components, agent-based models (ABMs) map well to biological conceptual models and present an intuitive means by which biomedical researchers can represent their knowledge in a dynamic computational form. ABMs are particularly suited for representing the behaviour of populations of cells (i.e. "cell-as-agents"), but ABMs have also been used to model molecular interactions, particularly when spatial and structural properties are involved. Presented herein are a series of ABMs of biomedical systems that cross multiple scales of biological organization, as well as a detailed description of an example ABM of acute pulmonary inflammation. Because of these characteristics agent-based modeling is a useful addition to the suite of equation-based mathematical modeling methods found in systems biology, and can serve as an integrating framework for dynamic knowledge representation of biological systems.

Keywords Inflammation · Agent-based modeling · Translational systems biology · Complex systems analysis

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Abbreviations

ABM	Agent-Based Modeling
ABMF	Agent-Based Modeling Format
AI	Artificial Intelligence
ALI	Acute Lung Injury
APIABM	Acute Pulmonary Injury Agent-Based Model
ARDS	Acute Respiratory Distress Syndrome
CMA	Computational Modeling Assistant
DAMP	Damage-Associated Molecular Products
EINISI	Enteric Immunity Simulator
I-κB	I-kappa-B
NCBO	National Center for Biomedical Ontology
NEC	Necrotizing enterocolitis
NF-κB	Nuclear Factor kappa-B
ODD	Overview, Design and Detail Protocol
ODE	Ordinary differential equation
PMN	Polymorphonuclear neutrophils
TGF-β1	Transforming growth factor-β1
TNF-α	Tumor necrosis factor-α
VILI	Ventilator Induced Lung Injury

15.1 The Translational Dilemma in Biomedical Research

The greatest challenge facing the biomedical research community is the ability to translate the successes at obtaining basic mechanistic knowledge about biological processes into clinically effective therapeutics. There is a growing gap between the capability to acquire and analyze data and the ability to effectively and efficiently evaluate the hypotheses generated from that data. This is the Translational Dilemma. Recognition of this gap was made evident in 2004 when the United States Food and Drug Administration released a white paper titled: "Innovation or Stagnation: Pathways for the Future of Biomedical Research" [1]. This report noted that while there has been steady increase in funding for basic biomedical research there has been a concurrent steady decrease in the number of new clinically effective therapeutics brought to the bedside. These divergent trends are not sustainable. A recent review analyzed the roots of the Translational Dilemma and defined it as: *the inability to efficiently translate data into viable mechanistic hypotheses across levels of biological organization, and limitations in the ability to test those hypotheses in a meaningful and efficient way* (see Fig. 15.1) [2]. Currently, biomedical research faces two fundamental limits to its goal of being able to develop new interventions that can beneficially affect human health:

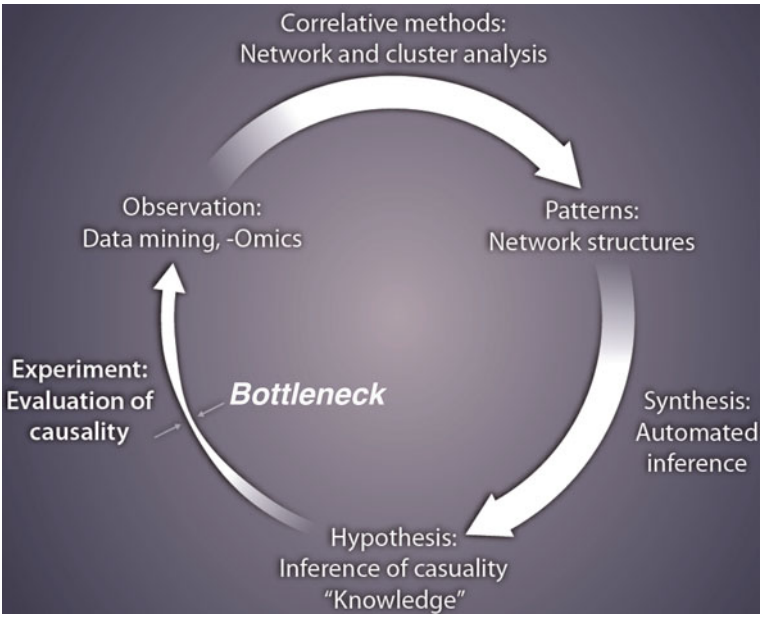

Fig. 15.1 The current imbalance in the scientific cycle. Technological advances in the past few decades have greatly increased the ability to generate, collect and correlate data, but a process bottleneck has developed at the point of being able to evaluate hypotheses via experiment. This bottleneck restricts the ability of the biomedical research community to efficiently and systematically reduce the space of possible hypotheses to those that are plausible. Augmenting this iterative cycle will identify those hypotheses that will be targeted for further investigation and refinement, and serve as potential points of therapeutic control. Reprinted with permission from Ref. [2]

(1) achieving the breadth of hypothesis testing necessary to deal with the multiplicity of possible explanations of high-resolution data (throughput problem) and (2) adequately representing the complexity of integrative hypotheses (multi-scale problem). Both of these issues are directly related to the need to greatly increase the ability to evaluate the plausibility of mechanistic hypotheses, and will almost certainly involve using computational modeling and simulation for dynamic knowledge representation and hypothesis instantiation. The ability to execute in silico experiments offers the potential to substantially accelerate and enhance the Scientific Cycle by providing a plausibility filter for putative hypotheses to help direct traditional experimental design to separate sets of plausible hypotheses and provide a wider search capability for plausible solutions. This chapter will discuss the use of agent-based modeling (also known as individual based modeling), for dynamic knowledge representation, and provide specific examples in the area of acute inflammation.

15.2 Dynamic Knowledge Representation with Agent-Based Modeling

Agent-based modeling is an object-oriented, discrete-event, rule-based computational modeling method [3–7]. An agent-based model (ABM) represents a system as populations of components where the simulation agent level of the ABM corresponds to the primary component of the system being studied. An ABM *agent class* is defined by specific properties governing its identity and behavior, and an ABM creates a population of individual computational instances of each agent-class. Each individual agent therefore possesses the behavioral rule sets and defined properties of its agent class, but once created can have diverging behavioral trajectories based on differing inputs within a heterogeneous simulation environment. ABM rules are often expressed as conditional statements ("if-then" statements), making ABM suited to expressing the hypotheses that are generated from basic science research, though it should be noted that the general conditional nature of simulation agent rules does not preclude the encapsulation of other types of mathematical or computational models (i.e. differential equation, stochastic or network) as rule systems [8–10]. Regardless of the specific ABM rules, ABMs offer the ability to achieve a close mapping between the natural language expression of hypotheses present in publications (the current means by which this knowledge is communicated within the community), and the structure of ABM [11, 12]. This property facilitates the use of agent-based modeling as a means of dynamic knowledge representation, particularly for non-mathematicians/computational scientists. ABMs are also intrinsically multi-scale, utilizing behavioral rules (Scale #1) to determine individual agent behavior (Scale #2) and then aggregating individuals into population dynamics of the global system (Scale #3). These levels can theoretically be nested, to provide a comprehensive depiction of a multi-scale biological system (see Fig. 15.2), making ABMs well suited for creating modular models [7, 8, 13–15].

15.2.1 Properties of Agent-Based Models

ABMs are related to other spatially discrete modeling methods, most notably cellular automata, though the mobile capability ABM agents and ability to represent a wider range of model topologies could lead to consideration of cellular automata as a special type of ABM. Similarly, neural nets can be considered ABMs, with the nodes representing instances of an agent class, and the network structure being the model topology. However, in practice, many ABMs have several characteristics of agent-based modeling that set it apart from other object-oriented, rule-based modeling systems (such as Petri nets, Boolean or Bayesian Networks), even though at its purest definition, they could all be potentially viewed as ABMs:

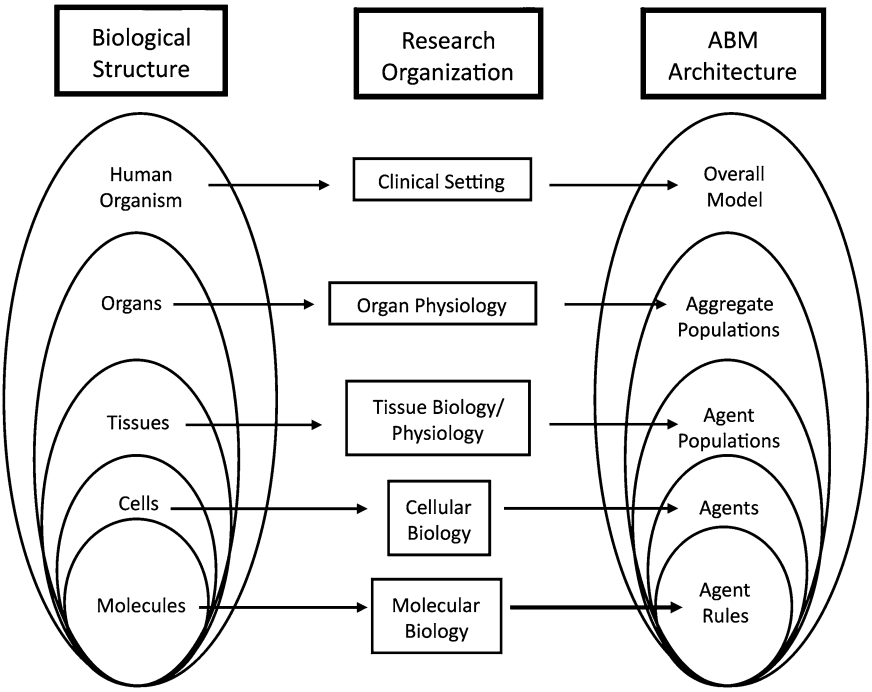

Fig. 15.2 The mapping between scales of biological organization, research community structure and agent-based models. This diagram maps the similar structure of organizational scales present in biological systems, the research communities studying them and the architecture of an ABM. Note that scales of organization are nested in the biological system and the ABM, reflecting the trans-scale coupling seen in both systems. Alternatively, the research community structure is disparate and compartmentalized, arising from both social and pragmatic logistical factors. Reprinted with permission from Ref. [12]

1. Agent-based models (ABMs) readily incorporate *space*. In an ABM agent behavior is driven by interactions determined by agent neighborhoods defining the communication and interaction network for each agent. An agent neighborhood can be represented as a two-dimensional square grid (very common), a 3-dimensional cubic space [8, 13], 2- or 3-dimensional hexagon cal space [12, 16] or as a network topology, as a neighborhood does not necessarily mean physical proximity but rather the configuration of some set of other agents with whom an agent can interact. This definition of an agent neighborhood is consistent with the bounded nature of the sense-and-respond and message passing capabilities of biological objects.
2. ABMs utilize *parallelism*. In general, each ABM agent class has multiple computational instantiations that form a population of agents, each capable of having different behavioral trajectories. These heterogeneous behaviors produce population dynamics that are the observable, system-level output of the ABM. A classic example of this phenomenon is the behavior of flocks of birds,

in which simulations utilizing relatively simple interaction rules among birds can lead to sophisticated flocking patterns without an overall controller [17].

3. ABMs incorporate *stochasticity*. Many biological systems have behaviors that appear to be random [18, 19]. Probabilities of a particular behavior can be determined for the population as a whole, and used to generate a probability function for the behavior of a single agent that is then incorporated into the agent's rules. As a population of agents executes their rules during the course of a simulation, each agent follows a particular behavioral trajectory as its behavior rules' probabilities are resolved as the simulation progresses. A set of behavioral outputs is thusly generated from a single ABM, producing system behavioral state spaces representing the set of population-level biological observations.
4. ABMs are *modular*. Agents represent a modular level into which new information can be added either through the introduction of new agent-types or by the modification of existing agent rules without having to re-engineer the entire simulation. Agent classes representing generic cell types can be subdivided and expanded to include a finer degree of detail with respect to sub-categories of cells while the remainder of the ABM remains essentially intact. New mediators can be similarly added by creating new cellular-state or environmental variables and rules. Multiple ABMs can be aggregated, providing that their points of contact and interaction are consistent across the incorporated ABMs [12, 13].
5. ABMs produce *emergent properties*. A central hallmark of ABM is that they generate system-level behaviors that could not have been reasonably inferred from, and often may be counter-intuitive to, examination of the rules of the agents alone. This is our definition of *emergent* behavior. ABMs are able to generate this type of behavior due to the locally constrained and stochastic nature of agent rules, and the population effects of their aggregated interactions. For example, in the bird flock an initial observation would suggest an overall leader, thereby requiring a means of determining rules for flock-wide command and control communication. This, however, is not the actual case; birds function on a series of locally-constrained, neighborhood-defined interaction rules, and the flocking behavior emerges from the aggregate of these interactions [17]. The capacity to generate non-intuitive behavior is a vital advantage of using ABM for conceptual model verification, as often the translation of generative mechanisms to system-level behavior produces paradoxical and un-anticipated results that break a conceptual model.
6. ABMs can be readily constructed using incomplete and abstracted knowledge. When constructing an ABM it is advantageous at the outset to keep the rules as simple and verifiable as possible, even at the expense of some detail. As such, meta-analyses of existing basic research often guide the development of an ABM [20]. ABMs constructed with admittedly incomplete and uncertain mechanisms representing statements of hypotheses can provide qualitative verification of those hypotheses [21]. As with all computational models, the greater fidelity of mapping between the ABM and its biological counterparts

enhances the correlation between simulation results and the real-world behaviors. An iterative process of refinement of an ABM will lead to increased detail, possibly a stronger correlation to real-world data and a greater confidence in the ability of the ABM to describe observable phenomena.

Agent-based modeling is an integrative modeling framework that can readily be used for communicable dynamic knowledge representation [11–13, 22] (see Fig. 15.2). Agent-based modeling, because of its emphasis on "things doing things", is generally more intuitive for non-mathematicians/computer scientists than more formal mathematical modeling methods such as ordinary differential equations, partial differential equations, and their stochastic variants. Agent-based modeling presents a lower threshold barrier for researchers to "bring to life" their conceptual models and integrate in silico methods with traditional in vitro and in vivo experiments [22].

Since ABMs are knowledge-based models, constructed by instantiating bottom-up mechanisms (as opposed to inductive models, where mechanisms are inferred with the goal of explaining data), agent-based modeling addresses different modeling questions than equation-based inductive models. For instance, ABMs are not readily developed directly from a mass of raw data; they require that the modeler have a mechanistic hypothesis that, when instantiated in an ABM, can be used to generate simulated data, which can then be compared to the real-world data set. One can envision an iterative process by which inductive models are applied to large data sets, wet lab experiments are carried out to investigate the mechanisms inferred from the inductive model, and the experimentally confirmed mechanisms are used as a basis of an ABM which would close the discovery loop by recapitulating the original data set.

Agent-based modeling was pioneered in the areas of ecology, social science and economics, but in the last decade they have been used to in the biomedical arena to study sepsis [12, 13, 23, 24] cancer [8, 16, 25–27] cellular trafficking [28–32] wound healing [33–35] and intracellular processes and signaling [9, 36–42]. Many biomedical ABMs focus on cells as the primary simulation agent level (with the notable exceptions of modeling intracellular processes from Refs. [9, 36–42] above). From a knowledge translation standpoint, cells form an easily identifiable level of "encapsulated complexity" that is both highly studied as a unit (i.e. cellular biology) and can be addressed with relatively straightforward input-output rules [7]. As noted above, while ABM agent rules are often logical or algebraic statements, rules can be a mathematical model in itself. There are multiple examples of embedding complex mathematical models within a cell-level ABM agent [7–10, 15, 35, 43]. These examples emphasize the potential unifying role of agent-based modeling as a means of "wrapping" different simulation methodologies. This suggests that the meta-structure of an ABM can be used as a template into which structured biomedical knowledge can be integrated to facilitate the instantiation of multiple mechanistic hypotheses [44].

15.2.2 Tools for Agent-Based Modeling

Agent-based modeling environments require addressing certain software issues beyond the basic capabilities of more traditional object-oriented programming tools. These issues include emulating parallel processing to represent the actions of multiple agents within populations, dealing with associated execution concurrency issues within those populations, establishing means of defining model topology (i.e. agent interaction neighborhood), and the development of task schedulers to account for the multiple iterations that constitute an ABM run. As a result of these issues, along with the case that many researchers who utilize ABMs are not trained computer scientists or programmers, many biomedical ABMs are created using existing ABM development software packages. These agent-based modeling environments attempt to strike a balance between representational capacity, computational efficiency, and user-friendliness. A non-comprehensive list of such ABM toolkits includes Swarm (http://www.swarm.org/index.php/Swarm_main_page), Mason (http://cs.gmu.edu/∼eclab/projects/mason/), RePast (http://repast.sourceforge.net/), NetLogo (http://ccl.northwestern.edu/netlogo/), StarLogo (http://education.mit.edu/starlogo/) and SPARK (Simple Platform for Agent-based Representation of Knowledge www.pitt.edu/∼cirm/spark [45]). All these platforms represent some trade-off among the triad of goals mentioned above. For an excellent review and comparison of many of these agent-based modeling toolkits, see Ref. [46].

15.2.3 Agent-Based Modeling of Inflammation

The use of agent-based modeling has dramatically increased since the year 2000, and is now a generally accepted means of performing computational biology. As is the case when discussing any specific modeling method, it should be reemphasized that agent-based modeling is only one of an array of methods that can be used to represent and investigate biological systems (such as those covered in other chapters in this book). Each of these modeling techniques has its strengths and weaknesses, and potential modelers need to recognize that the modeling method chosen should be tailored to the question(s) being asked of the model [47]. One of the most effective ways of communicating the capabilities (and limitations) of a particular modeling method is through the use of examples. Towards this end, the following sections list a series of ABMs of different aspects of inflammation, followed by a more detailed description of the development and use of an ABM directed at a specific issue, that of acute pulmonary inflammation.

We focus on ABMs of the inflammatory response because inflammation is one of the most basic and ubiquitous processes in biology: in addition to growth, metabolism and replication, the response to injury leading into repair is a core function of all organisms. It is highly evolutionarily conserved, and in multi-

cellular organisms is a well-coordinated network consisting of specialized cell types and molecular mediators [47, 48]. The inflammatory response can be described simply as: (1) Sensing of damage or threat, (2) Containment and clearance of the threat, and (3) Repair of the damaged tissue. Intrinsic to all of these steps are counter-regulatory controls intended to limit and modulate the response. Evolution has operated on the components of the inflammatory response to produce systems that are robust over a wide range of heterogeneous insults, with trade offs on the efficacy of the pro-inflammatory response versus the negative consequences of an overly sensitive and exuberant response. While this balance generally operates well it is subject to disordered behaviour with significant consequences on the development of disease. Diseases such as sepsis, trauma, inflammatory bowel diseases, chronic wounds, autoimmune diseases and asthma are the direct result of disordered and inappropriate inflammation, while many other diseases, such as cancer, diabetes, atherosclerosis, Alzheimer's, and obesity are associated with inflammatory processes as either a generative mechanism or a means of perpetuating the disease. This is because inflammation can damage normal healthy tissues, which in turn leads to the production of molecules that re-stimulate inflammation. Acceleration of this forward feedback loop can lead to disordered inflammation that promotes organ dysfunction and death [47–51], Inflammation may also manifest in slower degenerative processes that share many common mediators with acute pro-inflammatory insults [52]. However, experience has shown that caution must be exercised in targeting inflammation with pharmacological agents. Because of its ubiquitous role in homeostasis, modulation of inflammation is fraught with unintended systemic consequences, such as gastrointestinal toxicity of cyclooxygenase-2 inhibitors [53, 54] or increased susceptibility to infection in persons taking TNF-α inhibitors [55, 56] or the general failure of anti-cytokine therapies for sepsis [24]. The difficulty in engineering safe and effective therapeutic agents directed at inflammation is a primary example of the Translational Dilemma in biomedical research. Because of these characteristics inflammation represents perhaps the ideal target for systems biology and computational modelling with agent-based modelling, and the following sections list a series of ABMs of different aspects of inflammation across a range of organizational scales. This brief survey of inflammation-related ABMs is followed by an example describing in more detail the development and use of an ABM directed at a specific issue, namely that of acute pulmonary inflammation.

15.2.3.1 ABMs of Inflammation-Related Intracellular Processes

The characterization of intracellular pathways is the traditional focus of systems biology, with a long history of work and achievement in the development of mathematical models of cellular signaling and metabolic control. These models are generally biochemical kinetic models, utilizing differential equations and stochastic methods based on the Gillespie Algorithm. However, the use of discrete-event, particle based modeling, exemplified by agent-based modeling, is growing

in this arena. With increasing awareness of the influence of the complex, compartmentalized environment of the intracellular milieu on intracellular dynamics, there is a need to account for issues of molecular crowding and spatial heterogeneity of the reaction milieu and how they affect enzymatic reactions within the intracellular environment. Additionally, the presence of sub-cellular structures, cytoskeletal elements, organelles, and compartments call for the increasing incorporation of spatial properties and detail. Ridgway et al. [40] used an ABM of intracellular signaling to demonstrate that the reaction dimension determining biochemical kinetics within a prokaryotic cytoplasm was reduced from the expected three dimensions to nearly two, with significant consequences for the dynamic modeling of control loops in which subtle changes in feedback determine the direction of a molecular switch. Pogson et al. [39] developed an ABM of control pathways affecting the transcription factor Nuclear Factor kappa B (NF-kB). These studies demonstrating the importance of the spatial distribution in terms of nuclear translocation of the constitutive inhibitor of NF-kB, I-kappa-B (IkB), and the binding of IkB to actin, a cytoskeletal protein, a mechanism subsequently identified in their laboratory [38]. We developed an agent-based architecture called Spatially Configured Stochastic Reaction Chambers to demonstrate that even an abstract representation of enzyme kinetics could, if sufficient pathway component detail was included, reproduce canonical behavior at the cellular level, as in the effect of preconditioning on the behavior of the Toll-like Receptor 4 (TLR-4) signaling pathway [36]. Similarly, an ABM of NF-kB response to endotoxin utilized molecular level agents nested within "mega-agents" representing different inflammatory cell types to reproduce recognizable dynamics of endotoxin response, including priming and tolerance at both the transcription factor and cellular activation level [42].

15.2.3.2 Cell-Level ABMs of Systemic Inflammation and Simulated Trials for Sepsis

The cell-as-agent level of component representation provides perhaps the most intuitive link between the laboratory-derived basic mechanistic knowledge and the structure of an ABM. Some of the earliest examples of biomedical ABMs were focused at this level [23, 24, 26], leading to the realization that even abstract agent-rules could produce very recognizable dynamics that could provide deep insights into the essential characterization of a disease process. For example, an early ABM of systemic inflammation and sepsis viewed the inflammatory process as being governed by interactions at the endothelial blood interface [23]. This ABM generated four clusters of distinct trajectories of model-system behavior purely by altering the degree of initial perturbation, trajectories that matched the four primary clinical scenarios associated with systemic inflammatory response. This ABM also demonstrated that the mechanistic basis of inflammation was the same whether the initiating insult was infectious, as in classical sepsis, or tissue damage, as in severe trauma.

The endothelial-surface systemic inflammation ABM was further extended to perform in silico clinical trials based on published and hypothetical inflammatory-mediator-based interventions [24]. Published pharmacologic properties of a series of mediator-targeting compounds were inputted into the ABM simulating a sepsis population. The efficacies of the interventions were then evaluated against a simulated control population. None of the mediator-directed interventions led to a statistically significant improvement in simulated patient outcome, including a set of immune augmenting interventions (e.g. addition of Granulocyte Colony Stimulating Factor) and combination anti-cytokine therapy (intended to overcome possible pathway redundancy). While these results were not totally unexpected, the exercise demonstrated that the ABM could be used as a means of assessing the veracity of the proposed intervention: i.e. what are the global consequences of intervening in a particular pathway, and is it actually a good idea to intervene at this point? The confirmation that what appeared to be intuitively plausible points of mechanistic intervention did *not* in fact behave as expected when placed in a systemic context demonstrated the potential usefulness of agent-based modeling and dynamic knowledge representation for hypothesis verification. We suggest that one of the primary roles of dynamic knowledge representation is exactly this type of hypothesis evaluation and verification, intended to reduce the set of plausible hypotheses and thereby help direct future investigation by eliminating therapeutic dead-ends.

15.2.3.3 Cell-Level ABMs of Wound Healing of Skin and Soft Tissue

As a system of response and repair, inflammation is intimately tied to healing. Many cellular and molecular mediators are shared between acute inflammation and healing; for instance the anti-inflammatory mediators that limit and contain the propagation of the pro-inflammatory response, such as Interleukin-10 and transforming growth factor-β1(TGF-β1) are themselves growth factors. Wound healing is also an intrinsically spatial process, as damaged tissue is removed and replaced by surrounding "normal" tissue. Therefore, ABMs of wound healing represented a natural direction of development arising from the early inflammatory ABMs. Wound healing ABMs have been used to shed basic insights on the spatial nature of skin wounds and their healing [34, 57], to represent the mechanistic pathophysiology of diabetic wounds and to posit potential mechanistic targets for therapeutics development [33], and offer the potential for personalized medicine by modeling individual responses to injury and therapy in vocal chord trauma [58, 59]. The diabetic wound ABM [33] was used to determine the phenotypic effects of under-activation of latent TGF-β1 and over-production of tumor necrosis factor-α (TNF-α), both associated with diabetes, and generated a host of emergent features characteristic of diabetic ulcers. Moreover, this ABM was used to test in silico the effects of both current therapies for diabetic ulcers (namely wound debridement and treatment with platelet-derived growth factor) as well as novel

interventions (e.g. inhibition of TNF-α or addition of TGF-β1) [33]. The ABM of vocal fold inflammation and healing attempted to create personalized sets of models by calibrating parameters using data on cytokine levels in laryngeal secretions of individual human volunteers subjected to experimental phonotrauma. Patient-specific computational simulations were created based on baseline levels of cytokines as well as at 1 and 4 h after phonotrauma. These simulations generally predicted the levels of cytokines at much later time points (24 h), and were used as the basis for simulated therapy [58, 59].

15.2.3.4 ABMs of Organ-Level Inflammation

A critical point of the translational dilemma is the transfer of cellular and molecular mechanisms, which are measured and characterized in the laboratory environment, to the level of organ level physiology and phenotype, which is the primary means by which disease is defined and diagnosed. It is here that the population-oriented capabilities of agent-based modeling can serve an important translational role. As a result there has been a great deal of interest in producing ABMs that represent organ-level manifestations of inflammation.

Intestinal Inflammation

The intestinal tract is subject to a variety of inflammatory conditions, both acute, such as in systemic shock, gut-derived sepsis and necrotizing enterocolitis, as well as in more chronic diseases, such as inflammatory bowel disease. The nature of the inflammatory processes in the gut is particularly notable due the persistent presence of huge numbers of microbes that can initiate and propagate inflammation. While the study of the gut ecology has been traditionally divided into those who study the host (epithelial biology and immunology) and those who study the microbes (microbiology), there is an increasing recognition that these two fields need to be merged into a comprehensive characterization of the host-microbe environment [60]. The integrative capabilities of agent-based modeling may play a particularly important role in this arena, and there has already been some preliminary work in this direction. A group at the Virginia Bioinformatics Institute has developed the Enteric Immunity Simulator (EINISI), an ABM environment to investigate the pathogenesis of enteric diseases related to the immune response to pathogen and reproduced the dynamics of bacterial dysentery [61]. Our group at the University of Chicago has developed an ABM of gut host-pathogen interactions specifically related to virulence activation of *Pseudomonas aeruginosa*, an important nosocomial pathogen, and the development of gut-derived sepsis [62]. This ABM contains a detailed representation of *P. aeruginosa* virulence activation pathways integrated with an abstracted gut epithelial surface. The ABM's output is mapped to in vitro and in vivo experimental platforms of gut-derived sepsis, used to simulated a more clinically relevant manifestation of intestinal ischemia

resulting from systemic shock than currently possible using in vivo techniques (i.e. non-lethal systemic shock), and has been used to identify gaps in the low-phosphate-sensing model of *P. aeruginosa* virulence activation in circumstances of major abdominal surgical stress. Additional laboratory experiments are in the process of being performed to more comprehensively characterize the factors involved in low-phosphate-related *P. aeruginosa* virulence activation. Finally, we have also developed an ABM that represents a unifying hypothesis underlying the pathogenesis of necrotizing enterocolitis (NEC), the leading cause of gastrointestinal morbidity and mortality in the premature infant population [63]. NEC is a complex, multi-factorial disease that involves prematurity, enteral feeding and a bacterial component resulting in bowel inflammation and necrosis. The research community has found it extremely challenging to create laboratory models that can comprehensively reproduce the range of pathogenic components associated with NEC, mainly related to the extreme degree of experimental perturbations required to generate the NEC phenotype in vivo. We have formulated a minimally sufficient unifying hypothesis of NEC that posits that the fundamental deficit in infants susceptible to NEC is immaturity of the ability of the neonatal gut epithelial cells to manage reactive oxygen species, including those produced as a byproduct of cellular respiration. When this basic feature was instantiated in the NEC ABM, and then overlaid with the other recognized contributing factors, a recognizable pattern of cascading systems failure was demonstrated to be necessary for the generation of the NEC phenotype. Specifically, immature neonatal gut epithelial cells had increased fragility to inflammation propagating challenges, such as metabolic stress (from feeding), decreased mucus barrier integrity and bacterial contacts. It is hoped that this ABM can be used to integrate the multiple theories and mechanisms currently studied concerning the pathogenesis of NEC.

Pulmonary Inflammation

The lung is an organ that is commonly subjected to inflammatory insults and responses, either through direct infection, inhalation of particulate matter, or in a "bystander" role associated with systemic inflammation. One type of pulmonary infection that has been the subject of extensive agent-based modeling is tuberculosis. ABMs have been used to study inflammatory cell control mechanisms associated with the generation of pulmonary granulomas [64], and the pathogenesis of pulmonary tuberculosis has been modeled using a multi-scale architecture where ODEs representing the molecular dynamics of TNF-α signaling were embedded within inflammatory cell agents [10]. Another ABM examined the pulmonary inflammatory response to inhaled particulate matter and the subsequent transition from acute inflammation to fibrosis [65]. While relatively simple in terms of cellular agent rules and types of mediators represented, this ABM was able to reproduce histological patterns of pulmonary inflammation and fibrosis seen in a clinically relevant murine model of particulate inhalation. Finally, in Sect. 15.2.4 we present a detailed description of an ABM of acute pulmonary

inflammation designed to examine the dynamics of acute lung injury from trauma, pneumonia, and systemic sepsis.

15.2.3.5 Multi-Organ Inflammation and Failure

The structural/anatomic approach to multi-scale modeling can be taken one step further by using the modular property of agent-based modeling to link individual organ ABMs in a multi-scale architecture. The approach was introduced in an ABM of the gut-lung axis of systemic acute inflammation and multiple organ failure [13]. This ABM incorporates multiple structural and anatomic spaces, e.g. endothelial and epithelial surfaces as aggregated by cell-type into organ-specific tissues and finally to organ-to-organ interconnections and cross-talk. This architecture also *translates* knowledge across domain specialties (molecular biology to clinical critical care), representing molecular and cellular mechanisms and behaviors derived from in vitro studies, extrapolated to ex vivo tissue experiments and observations, leading to patterns of organ-specific physiology, and finally simulating clinically relevant, interconnected, multi-organ physiology including the response to ventilator support of acute respiratory failure. This ABM also posited certain characteristics of the gut-derived pro-inflammatory compound that is circulated in the mesenteric lymph and induces pulmonary inflammation. Examining the time course of pulmonary inflammation and comparing that to generated factors following intestinal ischemia suggested that the mesenteric lymph inflammatory compound was not an initial inflammatory cytokine, nor a translocating luminal compound manifesting decreased intestinal permeability, but rather a substance reflecting cellular damage of gut tissue with properties consistent with damage-associated molecular patterns (DAMPs). This last hypotheses remains to be completely confirmed by the sepsis research community, but at this time appears to be consistent with ongoing research in this area [66].

15.2.4 An Example ABM of Acute Pulmonary Injury

Herein we present a description of the development of an ABM focused on representing existent knowledge concerning acute pulmonary inflammation and the dynamics of various types of acute lung injury. We term this ABM the Acute Pulmonary Injury ABM (APIABM). The primary goal of this example is to demonstrate some of the steps and modeling issues related to the development and use of an ABM. While the APIABM is a relatively simple model and its output is qualitative in nature, these characteristics actually emphasize one of the greatest advantages of agent-based modeling, namely the ability to relatively quickly and with limited computational overhead instantiate mechanistic biological knowledge into a computational model that can produce recognizable behaviors. There is a significant role for qualitative modeling within the greater context of the discovery

phase of science [2, 36] and in particular the ease with which agent-based modeling maps to biological knowledge and can be performed with a "low threshold, high ceiling" strategy [22] that allows for future modular expansion of the ABMs. As all modeling can be considered as selective abstraction, we have abstracted out a fair amount of molecular detail in the APIABM as to not distract from the cellular functions of interest. Additionally, rather than presenting detailed simulation experiments we instead emphasize the calibration/validation steps, and then discuss future directions that can be taken with this model. For interested readers, the entire APIABM can be downloaded from http://bionetgen.org/SCAI-wiki.

The process of ABM construction and use is described in the general context of the Overview, Design Concepts and Details (ODD protocol), an attempt to help standardize the description of ABMs and their uses [67]. The ODD protocol was originally developed for ABMs studying ecological and social systems, and though it does not present an exact fit with the use of agent-based modeling as a means of biomedical dynamic knowledge representation (notable discrepancies include: format-driven redundancies; potential disruption of explanatory flow, particularly in terms of describing the mapping between the biology and the ABM; non-applicability of certain categories, such as learning and adaptation; the inherent imprecision of the term "emergence"; and lack of section concerning calibration) it does provide a useful framework in which the rationale and process behind the design of an ABM can be communicated. We utilize a modified version of the ODD protocol as the organizational framework for the description of the APIABM.

15.2.4.1 Purpose

The modelling purpose of this ABM is to dynamically represent the molecular, cellular and organ-level dynamics of acute pulmonary inflammation and provide a unifying basis for the response to multiple types of acute lung injury, namely direct trauma (pulmonary contusion), bacterial infection (primary pneumonia), and systemic inflammation (acute lung injury/acute respiratory distress syndrome or ALI/ARDS). These disease processes represent a major source of morbidity and mortality in the acutely and critically ill patient, and present significant diagnostic and therapeutic challenges to medical practitioners. The complexity of the inflammatory response means that effective modulating therapies need to be the "right drug for the right condition at the right time," a criteria that requires disease characterization at a level of resolution not currently achieved (and this includes –omic characterization, which just provides for a series of high-dimensional snapshots). By integrating existing mechanistic knowledge, down to the scale of putative molecularly targeted interventions, to produce a recognizable organ-level phenotype in the form of edema patterns, the APIABM can serve as a dynamic bridge to fill in the gaps in existing knowledge and data.

15.2.4.2 Entities, State Variables, and Scales

The Entities in the ODD refer to the objects from the reference system represented in the ABM. Entities can refer to the active components of the system (i.e. the agents/individuals), subcomponents sensed/used/manipulated by the agents (i.e. variables in the agent or the environment) or aggregated collections of agents or sections of space that make up the ABM's environment. Each entity has a set of state variables that defines its current state. For agents these state variables would correspond to molecular components such as receptors, enzymes and genes, for the spatial environment, these state variables would represent levels of secreted mediators or extracellular structures. The set of state variables is consistent for a particular entity type, but individual values of the state variables distinguish one entity from other entity of the same type and are used to track how a particular entity changes over time [67]. In the APIABM entities range from cellular mediators to alveolar space, and are discussed in more detail in the sections below. In order to distinguish computational components in the APIABM from their biological referents, we will use a different font to denote `APIABM components`.

We have elected to abstract the large number of specific molecular species into functional groups, which are then assigned to aggregated descriptive variables. For instance, the plethora of pro-inflammatory cytokines involved in pulmonary inflammation is represented by a single variable called `pro-inflammatory cytokine`. We justify this modelling decision based on the fact that we are not interested in high-resolution examination of molecular interactions, but rather what the overall consequences of these types of interactions have on the behaviour of cellular populations. This is one example of how the "encapsulated complexity" offered by agents allows investigation of higher-level system properties even given incomplete knowledge, as is often the case, of lower-level detail.

Agents/Individuals

In developing an ABM one of the first modelling decisions to be made involves selection of the agent level. As noted above, the agent-level should represent a level of "encapsulated complexity" that exists in sufficient numbers such that a population of agents can be modelled, but not too many numbers such that the population size abuts computational limitations. The cell types represented include alveolar epithelial cells, monocytes, macrophages, neutrophils, and bacteria. The behaviours exhibited by each cell type reproduce those that are known to exist in situ and vary in response to changes in the inflammatory milieu of the tissue in which they are located. A description of the agent classes and their state variables with their process flow can be seen in Table 15.1. A more detailed explanation of the rules for each agent class is found in the Process Overview and Scheduling Sect. 15.2.4.3.

Table 15.1 Agent types and their state variables

Cell type/agent class	State variables
`Monocytes`: Circulating precursors to macrophages	• `Age` • `Chemotaxis-Threshold`: Threshold value of `damage-signal` and `pro-inflammatory-cytokine` to stop movement and transform into a `macrophage`
`Monocyte-makers`: Simulate bone marrow generation of monocytes	• `Generation-Rate`
`Macrophages`: Inflammatory cells with controller functions, primary source of pro- and anti-inflammatory mediators	• `Age` • `MP-activation`: Activation state of the `macrophage` • `Pro-inflam-receptor`: Activated by the presence of `pro-inflammatory-cytokine` • `Pro-inflam-signal-kinase`: Activated by the activation of `pro-inflam-receptor`, activates `pro-inflam-gene` • `Pro-inflam-gene`: Produces `intracellular-pro-inflam-stimulus` • `Intracellular-pro-inflam-stimulus`: Produced by `pro-inflam-gene`, produces and secretes `pro-inflammatory-cytokine` • `Anti-inflam-receptor`: Activated by the presence of `anti-inflammatory-cytokine` • `Anti-inflam-signal-kinase-p`: Activated by activation of `anti-inflam-receptor`, activates `anti-inflam-gene-p` • `Anti-inflam-signal-kinase-a`: Activated by activation of `anti-inflam-receptor`, activates `anti-inflam-gene-a` • `Anti-inflam-gene-p`: Produces `intracellular-anti-inflam-stimulus-p` • `Anti-inflam-gene-a`: Produces `intracellular-anti-inflam-stimulus-p` • `Intracellular-anti-inflam-stimulus-p`: Produced by `anti-inflam-gene-p`, inhibits amount of `pro-inflammatory-cytokine` produced and secreted • `Intracellular-anti-inflam-stimulus-a` produced by `anti-inflam-gene-a`, produces and secretes `anti-inflammatory-cytokine`

(continued)

Table 15.1 (continued)

Cell type/agent class	State variables
`Neutrophils (PMNs)`: Inflammatory cells that are the initial responders to inflammatory insult and primary actors on the lung tissue	• `Age` • `PMN-apoptosis` • `Pro-inflam-receptor`: Activated by the presence of `pro-inflammatory-cytokine` • `Pro-inflam-signal-kinase`: Activated by the activation of `pro-inflam-receptor`, activates `pro-inflam-gene` • `Pro-inflam-gene`: Produces `intracellular-pro-inflam-stimulus` • `Intracellular-pro-inflam-stimulus`: Produced by `pro-inflam-gene`, produces and secretes `pro-inflammatory-cytokine` • `Anti-inflam-receptor`: Activated by the presence of `anti-inflammatory-cytokine` • `Anti-inflam-signal-kinase-p`: Activated by activation of `anti-inflam-receptor`, activates `anti-inflam-gene-p` • `Anti-inflam-signal-kinase-a`: Activated by activation of `anti-inflam-receptor`, activates `anti-inflam-gene-a` • `Anti-inflam-gene-p`: Produces `intracellular-anti-inflam-stimulus-p` • `Anti-inflam-gene-a`: Produces `intracellular-anti-inflam-stimulus-p` • `Intracellular-anti-inflam-stimulus-p`: Produced by `anti-inflam-gene-p`, inhibits amount of `pro-inflammatory-cytokine` produced and secreted • `Intracellular-anti-inflam-stimulus-a` produced by `anti-inflam-gene-a`, produces and secretes `anti-inflammatory-cytokine`
`PMN-makers`: Simulate bone marrow generation of Neutrophils (PMNs)	• `Generation-Rate`
`Alveolar epithelial cells`: Epithelial cells lining the alveolar airspace, they provide barrier function between the airspace and the lung interstitium. In the APIABM these agents also represent the barrier between the circulation and the interstitial tissue	• `Damage`
`Bacteria`: Generic infectious agents that are introduced to simulation pneumonia	• `Bacteria-Age` • `Bacteria-Energy`

Spatial Units and Environment

The topology of the APIABM is a 2-dimensional square grid with edges that wrap forming a torus. This world structure was selected in great part due to the constraints placed by the software system, NetLogo [68], in which the APIABM was implemented. We were willing to accept these limitations given the ease with which models of biomedical systems can be rapidly implemented and prototyped in NetLogo [22]. The two-dimensional grid spaces ("patches" in NetLogo terminology) are the fundamental spatial units of the APIABM, each possessing state variables representing extracellular mediators and structures that make up the microenvironment experienced by the cellular agents occupying them. A screenshot of the APIABM can be seen in Fig. 15.3. The patches represent an abstract cross-sectional depiction of the lung parenchyma, with specific focus on representing the alveolar air spaces and their interposing interstitial tissue. Patches at x- and y-coordinates that are multiples of 5 are given the state variable "alveolar interstitium", while the rest are given the state variable "alveolar space". For a complete list of the state variables of the spatial units see Table 15.2. A detailed explanation of these can be found below in the Process Overview and Scheduling section.

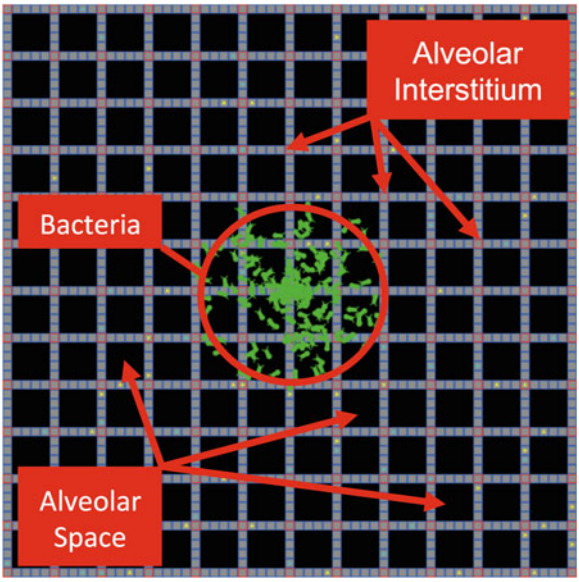

Fig. 15.3 Screenshot of acute pulmonary injury agent-based model (*APIABM*). This screenshot displays the overall architecture of the APIABM, which includes a regular lattice of alveolar interstitium, on which move the inflammatory cells, with interposed areas corresponding to alveolar space. This screenshot also displays an initial localized inoculum of bacteria prior to the execution of the model. Pulmonary edema is seen as *bluish-white patches* within the alveolar spaces (see Figs. 15.4, 15.5, and 15.6), with brighter areas corresponding to higher levels of edema fluid

Scale

Since ABMs iteratively execute a set of rules and commands, the time scale of the ABM is often tied to the length of time it takes for the reference system to perform the actions reflected in the ABM rules. For the ALIABM, each iteration of the program (or "tick") represents ~7 min in reference system time. The disease processes being simulated have general time courses of ~72 h for development, with recovery (should it happen) taking ~14 days. Based on these timeframes the simulations were run for 14 days of simulated time.

15.2.4.3 Process Overview and Scheduling

The dynamics of the pulmonary inflammation arise from the actions and interactions of the cellular agents in response to the conditions of the patch on which they are located. Cellular agents are also able to sense certain variables on the patches immediately adjacent to them (such as for allowing the simulation of chemotaxis). As noted above the cells of interest are alveolar epithelial cells, monocytes, macrophages, neutrophils and generic bacteria; the rule sets for each of these agent-classes constitute a submodel of the APIABM. An overview of these cell submodels is presented in this section. For a comprehensive list of the state variables for each type of agent class, refer to Table 15.2.

Monocytes

Under baseline conditions, monocytes move/circulate throughout the alveolar interstitium and represent a potential source of additional pulmonary tissue macrophages with a differentiation rate corresponding to the lifespan of the macrophages (see Macrophages). After an insult is applied, `pro-inflammatory cytokines` and damage signals are released secondary to inflammation and when they are present above a set chemotaxis threshold, the transformation rate is accelerated as `monocytes` migrate to the focus of inflammation and subsequently differentiate into `macrophages`. `Monocytes` are repleted by an "off-screen" `monocyte-maker` that represents the hematopoietic activity of the bone marrow.

Macrophages

Under baseline conditions, `macrophages` move randomly through the alveolar interstitium. When they encounter pro-inflammatory stimuli they migrate towards the focus of inflammation. Additionally, in response to inflammatory mediators, `macrophages` release pro-inflammatory, anti-inflammatory, and tissue repair cytokines.

Table 15.2 Spatial units and patch variables

Spatial unit	State variables
`Alveolar space`: Represents air-fill spaces of the lung parenchyma. Volume and surface area represent the gas-exchange surface of the lung	• `Capillary-Leak`: Represents the rate at which edema fluid is produced and transferred into the `alveolar space`. Determined by the presence of damaged `alveolar epithelial cells`
`Alveolar interstitium`: Represents the tissue of the lung, forms the walls of the alveolar space	• `Fluid`: Represents edema fluid that has leaked from the interstitium into the airspace
General patch variables: These are extracellular variables, generally representing secreted/produced mediators that are sensed by and responded to by the different cell types	• `Pro-inflammatory-cytokine`: Produced and sensed by `macrophages`, `monocytes` and `neutrophils` • `Anti-inflammatory-cytokine`: Produced and sensed by `macrophages` and `neutrophils` • `Damage-signal`: Produced by `alveolar-epithelial-cells` and sensed by `macrophages`, `monocytes` and `neutrophils` • `Cytotoxic-compound`: Produced by `neutrophils` and results in `damage` to `alveolar-epithelial-cells` and kills `bacteria` • `Nutrients`: Produced by `bacteria` damaging `alveolar-epithelial-cells` and consumed by `bacteria` to increase their `energy`

As seen in Table 15.1, the `macrophages` in the APIABM have numerous state variables. `Macrophages` have an `age`, which is initially set at 3,000 ticks, which corresponds approximately to a 14 days lifespan [69]. This value decreases by 1 with every tick until it reaches 0, at which time the `macrophage` dies and is removed from the simulation. We note that given the time frame of the current set of simulations (14 days) we could have excluded `age` as a `macrophage` state variable; however, our goal is to not produce "one-off" models, but rather incorporate selected aspects from the reference system with an eye towards additional simulation experiments in the future. For instance, a natural next set of simulation experiments using the APIABM would examine the immunocompromised phase of sepsis, which extends the simulated time frame out to 28 days or beyond. Additionally, the inclusion of the `age` variable eases the possible inclusion of mechanisms that may either speed or attenuate programmed cell death (apoptosis).

`Macrophages` include representation of both pro-inflammatory and anti-inflammatory state signalling pathways. The state variables that make up these pathways represent the various components of the molecular signalling cascades that drive the response to and the release of cytokines during the inflammatory response. These include representations of receptors, signalling kinases, genes and

transcription/translational events. Patch variables representing pro-inflammatory stimuli are sensed by macrophages, which respond by activating pro-inflammatory receptor variables, which in turn leads to activation of pro-inflammatory-kinases, activation of pro-inflammatory-genes, with subsequent production and release pro-inflammatory cytokines. Similarly, a macrophage's anti-inflammatory receptors can be activated, leading to activation of anti-inflammatory-kinases of two types leading to two sets of genes; those associated with inhibiting pro-inflammatory cytokine production, and those associated with the production of anti-inflammatory cytokines. These two pathways represent positive and negative feedback control systems, respectively, on macrophage function.

Neutrophils

Under baseline conditions, neutrophils move randomly throughout the alveolar interstitium. Neutrophils respond to pro-inflammatory stimuli by turning on their activation state variable. Activated neutrophils migrate towards the pro-inflammatory signals, which triggers the activation of signal cascades, pro-inflammatory-kinases, that result in the release of further pro-inflammatory cytokines as well as cytotoxic-compounds representing reactive oxygen species (ROS). Neutrophils also have an age, which is set to 1,000 ticks, approximating a life span of 5 days, and are repleted by an "off-screen" neutrophil-maker representing the hematopoietic activity of the bone marrow.

(Generic) Bacteria

Bacteria represent the introduced pathogens that cause primary pneumonia. Bacteria induce tissue damage, leading to the release of tissue damage compounds that stimulate the activation of the host inflammatory response. The primary bacteria state variable is energy. Bacteria acquire energy through their tissue damage induction, and when they reach a set energy threshold they will replicate. If they are prevented from inducing tissue damage, their energy degrades at a rate of 1 per tick until it reaches 0, at which time the bacteria die. Bacteria are also killed by activated neutrophils and the presence of cytotoxic-compound.

Alveolar Epithelial Cells

Alveolar epithelial cells are stationary cells representing the cellular components of the alveolar interstitium comprising the lung parenchymal tissue. Alveolar epithelial cells sense and respond to inflammatory stimuli in

their local microenvironment, and also form the barrier between the fluid in the interstitial space and the gas-exchange spaces of the alveoli.

The primary state variable determining the function of the `alveolar epithelial cells` is `damage`. When high levels of `pro-inflammatory cytokines` or `cytotoxic-compounds` are present, the `alveolar epithelial cells` become damaged, releasing their own pro-inflammatory damage signal molecules, which in turn leads to further propagation of inflammation. Also, damaged `alveolar epithelial cells` release fluid into the surrounding alveolar space, simulating the formation of alveolar edema. It is the spatial distribution of the alveolar edema pattern that forms the qualitative metric used for validation of the APIABM.

Pulmonary Compartment Spatial Units

The APIABM abstractly depicts the gas-exchange structure of the lung, and is divided into patches that are either `alveolar interstitium` or `alveolar space`. Under normal conditions, mobile cellular agents have their movement confined to the patches possessing the `alveolar interstitium` state variable and therefore do not enter patches possessing the `alveolar space` state variable. The patches comprising the `alveolar interstitium` further possess a `capillary leak` state variable. In response to a set level of pro-inflammatory mediators at a given patch, the `capillary leak` state variable activates, allowing inflammatory mediators to leave the interstitium and enter the alveolar space, as occurs in situ. Additionally, the `alveolar space` patches have a `fluid level` state variable, which represents the degree of fluid leaking from the `alveolar interstitium` into the `alveolar space` through the damaged `alveolar epithelial cells`. The distribution and degree of alveolar edema represents the qualitative metric used for validation of the APIABM. The spatial unit categories and their respective state variables can be seen in Table 15.2.

15.2.4.4 Design Concepts and Initialization

In initiating a modeling project, it is of the utmost importance to define the experimental frame, thereby establishing what can and cannot be examined by the particular model. The experimental frame is defined by the scientific questions at hand, and provides direction as to the degree of abstraction used in the development of the model [70]. The APIABM is a highly abstracted representation of acute inflammation of the pulmonary parenchyma. The parenchymal focus of the APIABM is directed by the scientific goal of understanding and mechanistically unifying diseases such as pulmonary contusion (i.e. direct lung trauma), bacterial pneumonia and acute lung injury/acute respiratory distress syndrome (ALI/ARDS). There are many details of the real lung that are left out. The APIABM

does not incorporate the mechanical forces associated with ventilation, spontaneous or mechanical, and therefore cannot be used to examine the effects of ventilator associated lung injury (VILI). Our modeling focus does not require addressing the bronchial airways, and therefore specifically excludes the consequences of inflammation in the airways as is seen in asthma. The focus on acute inflammation also excludes the ability of the APIABM to represent more chronic processes such as pulmonary fibrosis, or the development of chronic obstructive pulmonary disease. While some may consider such restrictions as highly limiting the potential utility of the APIABM, the fact is that one should strive to develop the simplest model that can address a defined scientific focus and provide a recognized use for the researcher. In this case, our interest is in the acute processes that might affect the lung in a acutely ill patient, and given the role of the inflammatory response in this setting, we make the modeling decision to focus on the consequences of inflammation on the gas-exchanging parenchymal aspect of the lung, specifically manifest in the patterns of production of alveolar edema.

15.2.4.5 Initialization

One critical point to remember when using ABMs for biomedical processes is that the baseline state is one of dynamic equilibrium, i.e. health. This means that the state of the system prior to any perturbation that would lead to disease is dynamically stable. The corollary to this fact is that biomedical ABMs are not models of disease, but rather models of health that can be subsequently perturbed to generate system trajectories that correspond to disease. As such, part of the initialization process involves making sure that the APIABM produces stable behaviour absent an invoked perturbation, including stability of those cellular populations that have their life-cycle represented (namely `monocytes`, `macrophages` and `neutrophils`).

15.2.4.6 Simulations

The simulations carried out here using APIABM are geared towards demonstrating calibration and validation. Calibration involves the adjustment of parameters of the ABM to attempt to fit some set of defined descriptors of the reference system, be they a quantitative data set or some more qualitative pattern/phenotype. This latter approach, called Pattern Oriented Modeling [21], is very commonly used as a means of calibrating and validating ABMs. Initial validation of an ABM is accomplished when calibration results in satisfactory matching between the ABM and its referent with parameter values that are not clearly implausible, a level of validation is termed *face validity* [71]. Despite being the lowest level of validation possible for a simulation, establishing face validity is of extreme importance in the use of computational models for dynamic knowledge representation of biomedical systems. This is because biomedical research is primarily a discovery-oriented

endeavour, where the primary procedural challenge is being able to separate plausible hypotheses from those that are not [2, 44]. Conversely, the inability to identify a set of parameters that can achieve plausible behaviour represents a failure of face validity; in these cases the underlying rules of the ABM need to be re-evaluated. Unfortunately, there are not clear guidelines about how to identify the transition point between inadequate sampling of parameter space and determination of model insufficiency, and the fact remains that this is a heuristic process that is enhanced by modelling experience.

We utilize pattern oriented analysis in the evaluation of the APIABM, focusing on two primary system patterns: (1) matching between the time courses of the modelled processes and the known disease pathophysiology, and (2) matching between the spatial patterns of alveolar edema generated by the APIABM and those recognized in the clinical setting. Each of the simulated disease processes below will include a brief description of the nature of the perturbation, confirmation of the expected time course and APIABM screenshots demonstrating the resulting patterns of pulmonary edema. Of note, other than the code changes to implement the specific type of perturbation, there were no differences or alteration in the code of the APIABM between the different disease state simulations.

Simulation of Pulmonary Contusion

A pulmonary contusion arises from direct trauma to the chest wall with force transmitted to the pulmonary parenchyma. It is, literally, a bruising of the lung. The traumatic force leads to locally distributed tissue damage, with subsequent activation of inflammation. Pulmonary contusion was simulated in the APIABM by applying a roughly circular injury pattern centered on the Cartesian coordinates of the APIABM with increasing radius of the applied injury pattern representing progressively increasing trauma. The dynamics of the inflammatory response followed the expected trajectory, peaking at approximately 3 days for those runs able to recover. A sequence of APIABM pulmonary contusion screenshots can be seen in Fig. 15.4.

Simulation of Pneumonia

Pneumonia arises from the introduction of pathogenic bacteria into the lung, with subsequent bacterial growth, tissue damage and inflammatory response. Pneumonia was simulated in the APIABM by applying a roughly circular distribution of `bacteria` agents, where increasing number of `bacteria` and corresponding size of the inoculated area represent progressively increasing inoculum. The dynamics of the inflammatory response followed the expected trajectory, with development of a significant “infiltrate” by 3 days in those levels of initial inoculum not spontaneously cleared. A sequence of APIABM pneumonia screenshots can be seen in Fig. 15.5.

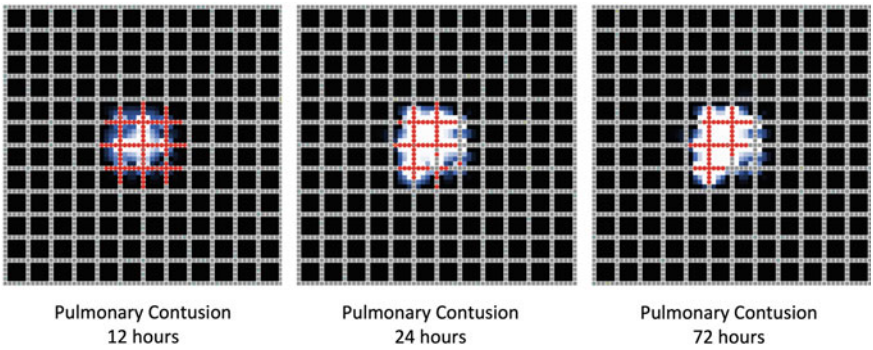

Fig. 15.4 Screenshots of 3-day course of pulmonary contusion simulated in the APIABM. This series of screenshots demonstrate the progression of alveolar edema resulting from a localized injury (sterile) corresponding to blunt pulmonary trauma. This is consistent with the time course seen both clinically and radiographically

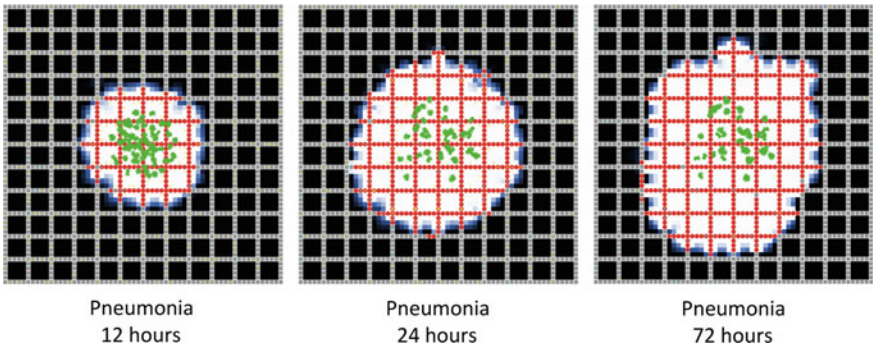

Fig. 15.5 Screenshots of 3-day course of bacterial pneumonia simulated in the APIABM. This series of screenshots demonstrate the progression of pneumonia resulting from a localized inoculation of bacteria. The pattern of alveolar edema corresponds to the evolution of a pneumonia-induced infiltrate seen radiographically

Simulation of Acute Lung Injury/Acute Respiratory Distress Syndrome

Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) arises from activation of pulmonary inflammation by circulating inflammatory products generated by non-pulmonary systemic inflammation, such as sepsis. The multi-scale gut-lung ABM mentioned in Sect. 15.2.3.5 [13] examines the role of the mesenteric lymph in activating pulmonary inflammation, and we use the putative mechanism described by that ABM to simulate the effects of remote systemic inflammation on the lung. Systemic inflammation and subsequent production of inflammatory mesenteric lymph were abstractly represented by introducing a probability of spontaneous activation of neutrophils; this reflects both the priming of neutrophils and activation of pulmonary endothelium by inflammatory

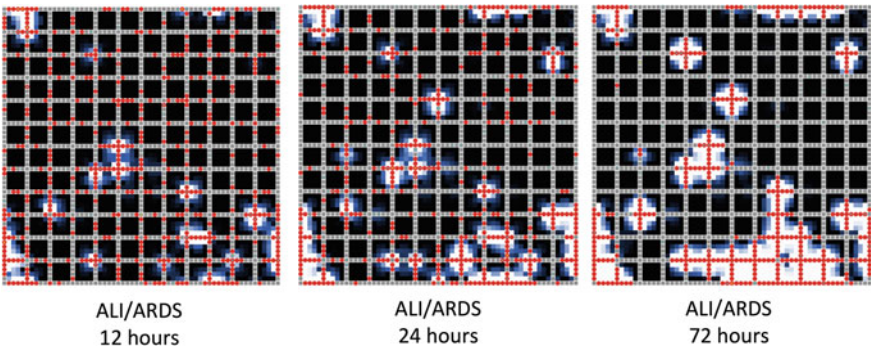

Fig. 15.6 Screenshots of 3-day course of acute lung injury/acute respiratory distress syndrome (*ALI/ARDS*) simulated in the APIABM. This series of screenshots demonstrate the progression of diffusely heterogeneously distributed alveolar edema arising for diffuse pro-inflammatory activation of the alveolar epithelium. This perturbation is consistent with the pulmonary effects of acute systemic inflammation as would be seen in sepsis or severe trauma. The time course and qualitative pattern of edema formation are consistent with the development of ARDS in the clinical setting

mesenteric lymph. The dynamics of the inflammatory response followed the expected trajectory, with the development of extensive patchy infiltrates by Day 3. A sequence of APIABM ALI/ARDS screenshots can be seen in Fig. 15.6.

15.2.4.7 Possible Extensions of the APIABM

The APIABM is a very abstract model, but due to the modular nature of ABMs it is readily extensible along a series of future development paths. Certainly more molecular detail can be included into the representation of the pro- and anti-inflammatory pathways; this could be driven by a researcher's particular interest area and desire to examine/confirm higher order behaviour related to that particular pathway. While the APIABM currently represented the alveolar airspaces involved in gas exchange, there is no functional consequence of the alveolar edema; it would be relatively straightforward to tie the edema state of each represented airspace to a gas exchange function, thereby being able to tie the inflammatory biology to a functional output of the lung. Pharmacological interventions can also be simulated: standard therapies such as antibiotics could be represented by a culling function applied to the bacterial populations, while anti-mediator interventions could be simulated as has been previously shown in in silico clinical trials [24]. More detail concerning the functions and characteristics of bacteria can be added where the specific virulence properties can be embedded into the bacterial agents to more closely approximate the complex of host-pathogen interactions in the face of inflammation [62]. Finally, the APIABM can be linked to other organ-level ABMs in a modular fashion [13], in order to capture the broader, systemically oriented genesis and consequences of pulmonary

inflammation. Interested readers are encouraged to download the APIABM from http://bionetgen.org/SCAI-wiki and explore the possibilities available from agent-based modelling.

15.3 Discussion

15.3.1 Challenges to the use of Agent-Based Modeling

As with all modeling methods, agent-based modeling is not without its limitations. One common issue shared with all computational and mathematical modeling methods is that the quality and reliability of the models are directly related to the reliability of the underlying assumptions of the model and the quality of their implementation during construction of the model. This issue can be addressed by emphasizing transparency of both underlying assumptions and implementation details with respect to the construction of an ABM. The ODD protocol, while not developed specifically with biomedical ABMs in mind, provides a useful reference point with respect to documenting the structure and goals associated with an agent-based modeling project [67].

One shortcoming of agent-based modeling is the difficulty in applying formal analysis to the relationship between the agent-rules and the behavior of the system. Due to the combined stochastic behaviour of agents and the difficulty in assigning scalar metrics to account for the spatial aspects of an ABM's output it can be very challenging to evaluate the effect of parameter values and model structure on an ABM's behaviour. Alternatively, equation-based models have well-established procedures for analytical tasks such as parameter sensitivity analysis, bifurcation analysis, and behaviour-state-space determination. Work on developing mathematical descriptions of ABMs offer the prospect that formal analysis may be available in the future [72]. In the meantime, ABM researchers use a variety of strategies, such as heuristics [6, 24], literature-based constraints [28, 31] and Latin Hypercubes [10, 64] for parameter estimation and sensitivity analysis.

Some of the apprehension associated with the analysis of ABMs can be addressed by viewing ABMs as objects more akin to wet lab experimental platforms rather than more traditional, equation-based mathematical models. Pattern-oriented analysis, in which corresponding patterns of dynamic behaviour are used to relate the computational ABM to its real-world referent, allows ABMs to be evaluated much in the same way as wet lab systems or model organisms [21]. From this regard, the stochastic and emergent properties of ABMs reinforce their ability to capture the robustness of dynamic behaviour seen in complex systems, thereby allowing more insight into their core organizational structure.

ABMs are, in general, more computationally intensive than equation based models. The increased computational requirements place constraints on both the size of ABMs in terms of number of agents as well as the complexity of their

internal rule systems. The natural solution to this bottleneck is to implement very large scale ABMs on current high performance computing platforms. However, there are intrinsic properties of ABMs, primarily related to the high degree of dynamics in the agent-to-agent interaction and communication network, that challenge the ability to implement ABM on highly distributed memory systems. Certain types of model architectures, mostly incorporating limited or relatively static interaction neighbourhoods with a high ratio of intra-agent computation (i.e. very complex mathematical rules) to inter-agent communication, are more suited to implementation on these massively parallel computer architectures. These types of models are also suited to implementation using Graphical Processing Units (GPUs), which offers the possibility of "supercomputer on a desk" computational power for selected types of ABMs [73–75]. It should be noted that there are also nontrivial modeling issues associated with parallel implementation of ABMs, aside from the computer science challenges just noted above. The selection of the scale of process to be distributed across multiple processors may have consequences with respect to concurrency and event scheduling and to the mapping of the simulation behaviour back to the biological referent; for instance attempting to distribute a single agent's rules over a series of processors. Thus far parallel ABM implementations have not explored the distribution of a single agent's execution across multiple processors, and have opted for a more organizationally defined distribution strategy that expands the overall size of the ABM (i.e. more agents) and keeps the implementation of agent-scale behaviour at the processor and sub-processor level.

15.3.2 Conclusion

The Translational Dilemma is the greatest challenge facing the biomedical research community today. Future operational procedures for biomedical science should involve technological augmentation of all the steps of the scientific cycle and allow the knowledge generated from such research to manifest in multiple areas. These include the development of highly predictive, personalized simulations to streamline the development and design of therapies, simulating the clinical application of these therapies in population studies (in silico clinical trials), and predicting the effects of drugs on individuals. We suggest that the agent-based paradigm, incorporating knowledge encapsulation, modularity and parallelism, can play an important role in the development of this meta-engineering process. Agent-based modeling can provide an integrative architecture for the computational representation of biological systems. Expanding the tools for AI-augmentation of computational dynamic knowledge representation and ties to biomedical ontologies [44, 76] can significantly reduce the threshold for the general researcher to utilize computational modelling and allow investigators to "see" the consequences of a particular hypothesis-structure/conceptual model, such that the mechanistic consequences of each component of the hypothesis can be probed and

evaluated. Dynamic knowledge representation enables the instantiation of "thought experiments:" the exploration of possible alternative solutions and identifying those that are plausible, i.e. consistent with the observed data. These models can aid in the scientific process by providing a transparent framework for this type of speculation, which can then be used as jumping off points for the planning and design of further laboratory experiments and measurements. 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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