Chapter 3
Agent-Based Modeling in Translational Systems Biology

Scott Christley and Gary An

The Translational Dilemma and the Need for Dynamic Knowledge Representation

As noted elsewhere in this book, the Translational Dilemma, the inability to translate the successes at obtaining basic mechanistic knowledge about biological processes into clinically effective therapeutics, is the greatest challenge facing the biomedical community [1]. The Translational Dilemma consists of two primary barriers that need to be breeched (1) the need to accelerate the scope of hypothesis testing necessary to deal with the multiplicity of possible explanations of high-resolution data (the experimental throughput problem) and (2) the ability to adequately evaluate the consequences of highly complex, multicomponent, multihierarchical integrative hypotheses (the multiscale problem). Both of these issues are directly related to this requirement: biomedical researchers must greatly increase their ability to evaluate the *plausibility* of mechanistic hypotheses and their manifestation at the systemic level. Meeting this requirement will almost certainly involve harnessing the power of advanced computational modeling and computer hardware for the dynamic knowledge representation of biological systems in such a way that hypotheses can be instantiated and evaluated in silico. The ability to execute in silico experiments offers potentially the only viable path to substantially accelerate and enhance the Scientific Cycle by providing a plausibility filter for putative hypotheses. This will substantially reduce the set of possible mechanistic explanations for a particular observation and will help direct and focus the design of traditional laboratory experiments to further refine the set of possible hypotheses. This chapter discusses the

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use of agent-based modeling (also known as individual-based modeling) for dynamic knowledge representation with an explicit translational goal in the area of acute inflammation.

Dynamic Knowledge Representation with Agent-Based Modeling

Agent-based modeling is an object-oriented, discrete-event, rule-based computational modeling method [2–6]. Agent-based models (ABMs) consist of virtual environments populated with objects (agents) that execute behaviors based on programmed rules that govern their interactions with the local environment and other agents. An ABM represents a system as populations of components ("agents") where the simulation agent level of the ABM corresponds to the primary component level of the system being studied; for instance, a cell-level ABM uses agents that primarily represent biological cells. An ABM *agent class* is defined by a specification of the properties, characteristics, and rules of an agent type that govern its identity and behavior. As an ABM is executed, it creates a population of individual computational instances (an agent) of each agent class, where each individual agent possesses the behavioral rule sets and defined properties of its agent class but once created can have diverging behavioral trajectories based on the different inputs it receives within a heterogeneous simulation environment. ABM rules are often expressed as conditional statements ("if-then" statements), making ABMs 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 [7–9]. A standard conditional agent rule for a cell agent interacting with its environment might have the following format:

if Compound A (in the environment) is present, then bind to and activate Cell-Surface Receptor B (in the cell-agent)
if Cell-Surface Receptor B is activated, then increase Signal Transduction Enzyme C (in the cell-agent) by x
if Signal Transduction Enzyme C is increased beyond threshold y, then activate Transcription Factor D
if Transcription Factor D is activated, then express Gene E
and so on…

As noted above, the rule sets for agents can be of any formal type, such as a series of logical statements or a differential equation. Regardless of the specific ABM rules, ABMs allow 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 rule structure of ABM [10, 11]. As results can be readily used for dynamic knowledge representation, particularly for

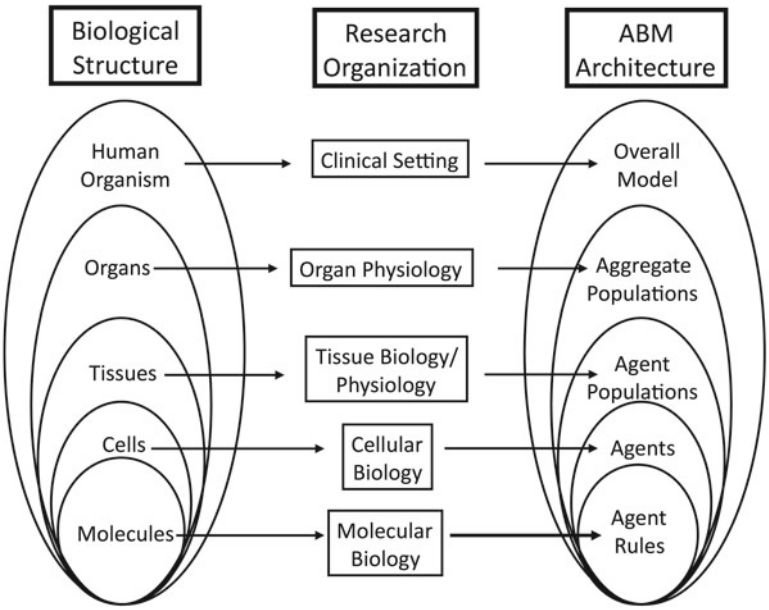

Fig. 3.1 The mapping between scales of biological organization, research community structure, and agent-based models. This diagram maps the similar structure of organizational scales present in biological systems, the research communities studying them, and the architecture of an ABM. Note that scales 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 [11]

researchers not expressly trained in either computational or mathematical modeling by allowing them to more easily translate their biological knowledge into a computational form.

ABMs also intrinsically cross multiple scales of biological organization by necessarily involving at least three levels of system organization. Scale #1 is the lowest level of system process represented, and this is accomplished by the agent's behavioral rules. Scale #2 is the "middle" level corresponding to the primary component level chosen, and processes at this level are represented by the behavior of an individual agent. Scale #3 is the "system" level consisting of the global phenotype under investigation and is generated by the aggregate behavior of populations of agents. To use an example of a cell-as-agent ABM, Scale #1 then represents molecular events associated with signaling and protein synthesis, Scale #2 represents the behavior of an individual cell as it changes state, secretes something or moves, and Scale #3 represents tissue behavior arising from the interactions between populations of cellular agents. Furthermore, these levels can theoretically be nested, to provide a comprehensive depiction of a multiscale biological system (see Fig. 3.1), making ABMs well suited for creating modular models [6, 7, 12–14].

Related Modeling Methods

Given the description above, it is clear that agent-based modeling is actually a very general means of system representation and as such is viewed as quite similar to many other modeling methods. In fact, many of these types of modeling methods can be considered as subtypes of ABMs, leading to a great deal of variability in the use of the term "ABM." As such, it is useful to clarify the distinctions between certain other commonly used modeling methods and agent-based modeling as the term is used in Translational Systems Biology. One of the most closely related modeling methods is cellular automata (CA), particularly two-dimensional CAs. Cellular automata involve a discretely divided space into a series of "cells," such that the state of each particular cell is defined by a set of rules dependent upon the states of some defined neighborhood of cells. Classical examples of two-dimensional CAs are Conway's Game of Life [15] and Kaufman's N-K System [16]. These systems can be seen as ABMs where there is a single agent class (the basic unit "cell"), which does not move, and a set of agent rules that govern an agent's state transitions. Another closely related modeling method is the Cellular Potts Model (CPM), developed by Glazier and Graner, where the states of points on a lattice are determined using probabilistic rules, and membership in a particular group of points is used to define superstructures representing cells or aspects of tissue [17]. Each of these methods has its own benefits and uses, most often governed by a combination of the resulting model's use and the data available to construct the model. For instance, while "movement" can be simulated using a CA, it is often less intuitive for a biologist to think of a cell's movement as a progression of cellular variables across a grid as opposed to a specific computational object that changes its position. As another example, while a CPM can allow cells to change their size and shape (where a "cell" is defined by a group of lattice points), the means by which a lattice point's membership in a particular cell, often expressed as a Hamiltonian representing an effective energy function, does not readily map to a biologist's knowledge set (as evidenced by the relative incomprehensibility of the prior terms!). At one level (i.e., in terms of the actual execution of the binary code), the distinction between these methods and agent-based modeling may be a distinction without a difference; however, in terms of facilitating knowledge representation, the component-centric emphasis of agent-based modeling is more consistent with how most biological systems are conceptualized (i.e., "things doing things").

Agent-Based Models Versus Multiagent Systems

In addition to closely related modeling methods, there is also ambiguity in the use of the term "agent." The distinction between an "agent-based model" and a "multiagent system" is just such a situation. Both terms are widely used in the computer science and the modeling and simulation community and are often used to mean the

same thing: a computer program that utilizes multiple computational agents. However, in terms of the types of systems they usually describe these two methods actually represent very different types of computational tools. Therefore, for purposes of comparison, we define a distinct difference between these two entities (noting that the following distinction is not intended to be a definitive description of the distinction but rather is intended to clarify the differential usage of the term "agent" in the context of Translational Systems Biology).

We consider "agent-based modeling" as a simulation method, where the model constructed is intended to mimic or represent some other reference system, which is the subject of investigation. The computational agents making up the ABM are intended to represent specific types of components in the real world where selected characteristics of the real-world object are reflected in the nature of the rules incorporated into the simulation agent. Since a main benefit of agent-based modeling is the ability to represent populations of real-world objects at the individual level with simulation agents, in many circumstances ABMs consist of a large number of individual instances of simulation agents derived from a single agent class.

Alternatively, an "agent-directed" or "multiagent system" is generally used to describe a computer system design solution, where computational agents perform tasks related to the implementation of a particular computing goal. These computational agents generally have some decision-making capacity, which may be augmented using artificial intelligence approaches, that allows them to manage the information flow within a particular software implementation. In multiagent computer systems, the computational agents generally do not have a specific real-world reference object for a computational agent, rather there is a set of recognized tasks in information flow management that can be expressed as a set of algorithms and packaged for execution by a computational agent.

Properties of Agent-Based Models

As noted above, 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. 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.

Representation of Spatial Relationships

Agent-based models (ABMs) readily incorporate *spatial relationships*, be they manifest in an actual spatial topology or a topological interaction neighborhood linking

individual agents. 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 three-dimensional cubic space [7, 12], two- or three-dimensional hexagonical space [18, 19] 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. This may also be used to represent physical interactions and forces between agents that affect their subsequent behavior.

Representation of Parallelism and Concurrency

ABMs simulate *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 [20]. This property is well suited to the tendency in biology towards classification: the grouping of similar biological entities that share some set of properties and behaviors. Biological systems are then readily characterized as being composed of some types and numbers of these entities. This type of conceptual representation exactly suits the architecture of an ABM.

Incorporation of Stochasticity and Randomness

ABMs readily incorporate *stochasticity*. Many biological systems have behaviors that appear to be random [21, 22]. Whether these behaviors are truly random, or just merely appear to be due to a lack of finer grained knowledge is, from an operational standpoint, often irrelevant as long as the probabilities of a particular behavior can be determined for the population as a whole experimentally. These probabilities are then 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.

Modular Architecture

ABMs are *modular*. Agents represent a distinct and circumscribed 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 reengineer the entire simulation. Agent classes representing generic cell types can be subdivided and expanded to include a finer degree of detail with respect to subcategories 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, 19].

Generation of Non-Intuitive System-Level Phenomenon

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 [20]. The capacity to generate nonintuitive 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 unanticipated results that break a conceptual model.

Facilitation of Useful and Detailed Abstraction

ABMs provide for high-fidelity component abstraction of system structure. ABMs can be readily constructed using incomplete and abstracted knowledge, yet produce surprisingly highly "realistic" system level behavior. Because of this property it is advantageous in the initial steps of developing an ABM 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 [23]. ABMs constructed with admittedly incomplete and uncertain mechanisms representing statements of hypotheses can provide qualitative verification of those hypotheses [24]. 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 [10–12, 25] (see Fig. 3.1). Agent-based modeling, because of its emphasis on "things doing things,"

is generally more intuitive for nonmathematicians/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 [2].

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 since 2000 they have increasingly been used to in the biomedical arena to study sepsis [11, 12, 26, 27], cancer [7, 18, 28–30], cellular trafficking [31–35], wound healing [36–38], and intracellular processes and signaling [8, 25, 39–44]. The majority of biomedical ABMs utilize cells as the primary simulation agent level, though there are several exceptions of modeling intracellular processes from [8, 25, 39–44], and we consider the use of agent-based modeling in epidemiology, with its extremely rich background [45], as a separate discipline. From the standpoint of addressing the Translational Dilemma, cells form a ready 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 [6]. 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 [6–9, 14, 38, 46]. These examples emphasize the potential unifying role of agent-based modeling as a means of "wrapping" different simulation methodologies. This suggests that the metastructure 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 [47].

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

Table 3.1 Freeware agent-based modeling toolkits

Toolkit name	Language/ Platform	Degree of programming expertise?	Degree of flexibility?	Website
Swarm	Objective C, Java	High	High	http://www.swarm.org
Netlogo	Windows, Macintosh, Linux	Low	Low	http://www.ccl.northwestern.edu/netlogo/
Starlogo	Windows, Macintosh, Linux	Low	Low	http://education.mit.edu/starlogo/
Repast	Java	Moderate/high	Moderate	http://repast.sourceforge.net/
MASON	Java	Moderate/high	High	http://cs.gmu.edu/~eclab/projects/mason/
SPARK	Java	Moderate/high	Moderate/high	http://www.pitt.edu/~cirm/spark/

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 noncomprehensive list of such ABM toolkits can be seen in Table 3.1. 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 [48].

Agent-Based Modeling of Inflammation

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 modeling with agent-based modeling. 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 [49]. One of the most effective ways of communicating the capabilities (and limitations) of a particular modeling method is through the use of examples. Since the rest of this book includes detailed descriptions of several ABMs involved in Translational Systems Biology, this chapter presents a few examples of types of ABMs not explicitly covered elsewhere in this book.

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 deterministic and stochastic differential equations. However, the use of discrete-event, particle-based modeling, exemplified by agent-based modeling, has certain applications 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 subcellular structures, cytoskeletal elements, organelles, and compartments call for the increasing incorporation of spatial properties and detail. Ridgway et al. [42] used an ABM of intracellular signaling to demonstrate that the biochemical reaction kinetics in the prokaryotic cytoplasm was reduced from three dimensions to nearly two dimensions, 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. [41] 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 [40]. 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 [25]. A screenshot of the SCSRC for TLR-4 can be seen in Fig. 3.2. 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 [44].

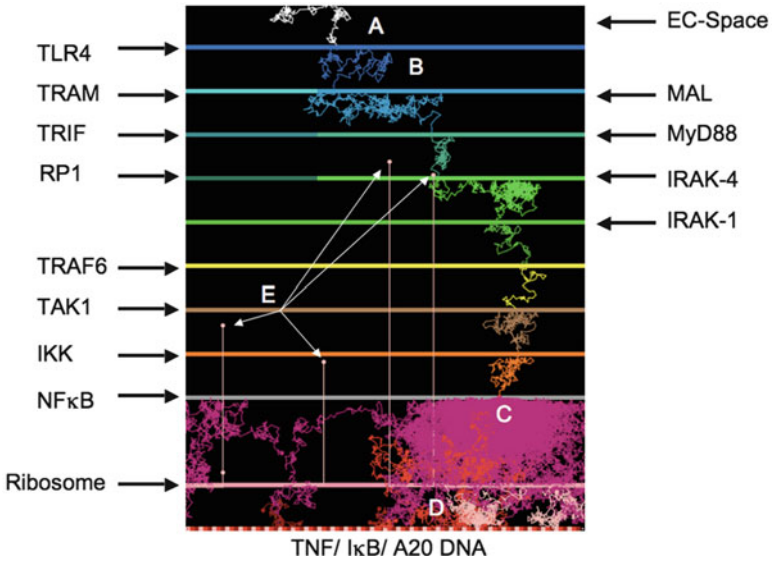

Fig. 3.2 Screenshot of spatially configured stochastic reaction chamber (SCSRC) model of TLR-4 signaling. This figure demonstrates the underlying architecture of the SCSRC as well as the signal trajectory of a single LPS signal agent. Reaction chambers are oriented vertically, and TLR-4 signaling propagates from the "top" of the model (representing extracellular space) towards the "bottom" (DNAs). The various signal transduction proteins are represented as *horizontal bars* across the model. The trajectory of a single LPS signaling agent as it passed through the various layers of signaling. Note the irregular path of the agent, reflecting the random movement rules that reflect the stochasticity in molecular dynamics. Letter "A" denotes the initial extracellular space where the LPS agent is introduced. Letter "B" denotes the first intracellular reaction space immediately under the TLR-4 border. Letter "C" demonstrates the signal amplification at the NF-κB activation site, as the single signal agent results in multiple NF-κB agents. Letter "D" denotes the DNA reaction space, as additional amplification can be seen in simulated transcription. Letter "E" labels synthesized TNF molecules in the process of transport to the extracellular space, seen as the straight trajectories. This figure is reprinted with permission from [25]

Cell-Level ABMs of Systemic Inflammation and Simulated Clinical 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 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 [26, 29]. For example, an early ABM of systemic inflammation and sepsis viewed the inflammatory process as being governed by interactions at the endothelial blood interface [26]. 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 [27]. 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 anticytokine 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.

ABMs of Multiorgan Inflammation and Failure

The structural/anatomic approach to multiscale modeling can be taken one step further by using the modular property of agent-based modeling to link individual organ ABMs in a multiscale architecture. The approach was introduced in an ABM of the gut–lung axis of systemic acute inflammation and multiple organ failure [12]. 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 crosstalk (see Fig. 3.3). 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, multiorgan physiology including the response to ventilator support of acute respiratory failure. This ABM also posited certain characteristics of the gut-derived proinflammatory 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 neither an initial inflammatory cytokine nor a translocating luminal compound

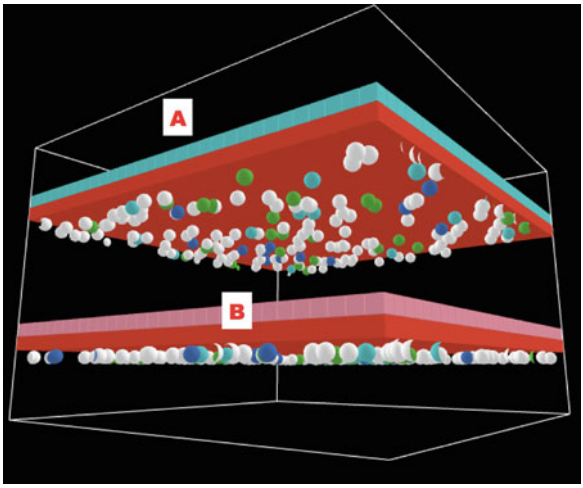

Fig. 3.3 Screenshot of multibilayer gut–lung ABM of systemic inflammation. The multiple bilayer topology of the gut–lung ABM is seen with the upper bilayer (letter A) representing the pulmonary bilayer, with *aqua cubes* representing pulmonary epithelial cell agents, *red cubes* representing pulmonary endothelial cell agents, and below are spherical inflammatory cell agents. The lower bilayer (letter B) represents the gut bilayer, with a similar configuration, the only difference being that gut epithelial cell agents are *pink*. Circulating inflammatory cell agents move between these two bilayers on a time schedule calibrated to the rate of systemic circulation and gut lymph flow. This ABM represents an aggregate of several submodels including endothelial-based inflammation and epithelial tight-junction protein metabolism. This ABM was able to reproduce the effects of gut ischemia in propagating the development of acute respiratory failure, the salvaging effects of mechanical ventilation, and posited the nature of the gut ischemic product driving respiratory failure as being tied to endothelial cell/tissue damage. Figure reproduced with permission from [12] under the creative commons license

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 [50].

Moving Forward: Scaling Dynamic Knowledge Representation, the Agent-Based Modeling Format

As noted in the Introduction, the Translational Dilemma arises not only difficulties in multiscale representation and instantiation but is also a throughput problem. While computational modeling (including agent-based modeling) can potentially address the former, generating these models, even with a relatively intuitive method as agent-based modeling, is currently a highly specialized, laborious, and

time-consuming task. Therefore, developing a scalable global strategy to overcome the Translational Dilemma will require substantially lowering the threshold for the general researcher to engage in computational modeling. We suggest that the process of constructing dynamic computational models can be augmented by leveraging ongoing work in bioinformatics and knowledge representation, primarily related to ontologies [10, 47, 51].

Ontologies are knowledge classification systems that provide a structured vocabulary and taxonomy for a particular scientific domain [52]. Ontologies utilize taxonomic class structures, their properties, and the relationships between the constitutive concepts to organize information within the domain. The use of ontologies is well established in bioinformatics, and many bio-ontologies are currently found in an online repository called BioPortal [53], which is managed by the National Center for Biomedical Ontologies (NCBO) [54].

However, despite their usefulness, ontologies/bio-ontologies remain primarily classification systems that define identity relationships between concepts but have difficulty expressing dynamic and functional relationships than can be used to represent mechanistic rules; this gap is the transition from a descriptive model to a simulation. There has been work converting ontology-based knowledge representations into dynamic mathematical models of molecular signaling pathways [36, 55–59]. However, while useful for representing the behavior of specific pathways, these approaches focus on working within a single ontology (namely the Gene Ontology) and do not deal with the multiscale aspects of biology, i.e., the transition of molecules to cells to tissues to the whole organism. Alternatively, ABMs are well suited to be an integrating modeling paradigm since they capture the multiscale organization of biological systems (see Fig. 3.1). We suggest that an ABM-based framework can be used to integrate the knowledge from multiple ontologies describing different aspects of a biological system (components, functions, space, etc.) in order to construct a dynamic multiscale, translational model.

We propose the agent-based modeling format (ABMF) as a framework that leverages and integrates ontological descriptions of biology to facilitate the construction of dynamic, executable knowledge representations with multiscale representational capacity [47]. The ABMF integrates terms and metadata from BioPortal ontologies into three-level modules formatted around the information and data needed to construct an ABM. These levels are centered on the level of the simulation agent in a "middle-out" configuration [6]. A schematic of an ABMF module can be seen in Fig. 3.4 and is organized in a series of orthogonal descriptive class structures that can be populated with terms extracted from BioPortal ontologies. The modular structure of the ABMF allows for nesting of modules and a recursive description of biological systems; this multiscale organizational recursion has been noted as a property of biological systems [60].

We emphasize that the ABMF is *not* "the" format for an executable ontology layer; we hope that there will be development of similar types of tools, using different modeling paradigms. However, we believe that an agent-based modeling paradigm demonstrates a robust, evolvable approach that can be spur future development.

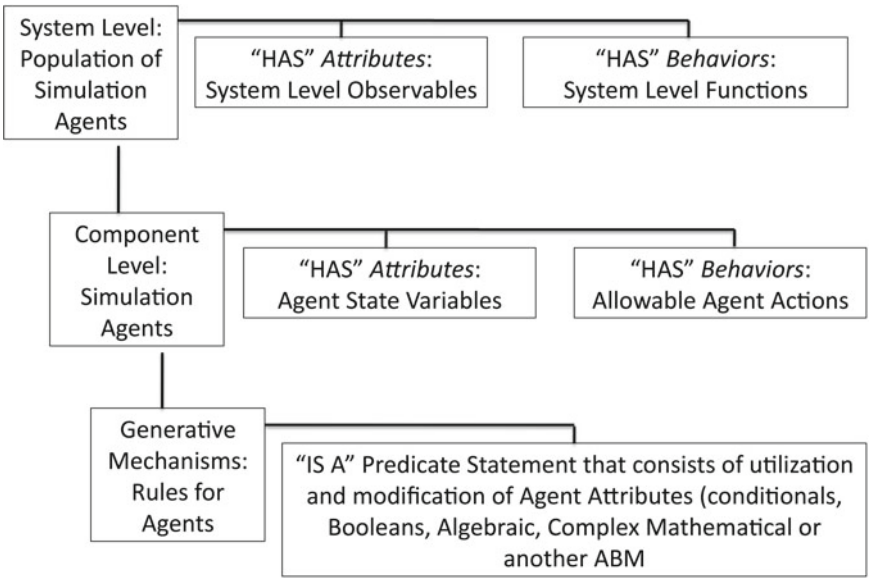

Fig. 3.4 A schematic description of an agent-based modeling format (ABMF) module. The ABMF module incorporates three levels of system representation centered on the simulation agent level, which corresponds to the classical agent level in an ABM. The system level corresponds to agent population behavior (including so-called emergent phenomenon), and the lowest level of organization, generative mechanisms, corresponds to agent rules. Inputted generative mechanisms can be in the form of any formal model system including another ABM. This gives the ABMF a recursive structure that allows nesting of ABMF modules and makes it a potential pathway to hybrid computational models that concurrently employ multiple modeling and simulation methods. Reprinted with permission from [47]

We further note that the ABMF is not a modeling platform, but rather a metastructure that helps collect and organize the components needed to construct an ABM from a biological hypothesis. There is still a significant gulf between the formatting of a biological hypothesis and the ability to construct a computer simulation of that hypothesis. The ABMF provides a pathway towards automation by leveraging the structured vocabulary and inference capabilities of ontologies. Additional text analysis and information extraction technologies can be integrated with an ABMF constructor and provide a semiautomated way to collect potential parameter values with which to populate a simulation program.

The expression of a conceptual biological model in the ABMF places that biological model into computable form, perhaps facilitating conversion into an executable simulation through the use of a semi-intelligent computational agent. There has been recognition of the importance of ontologies in the development of intelligent system-aided model and simulation generation, with several proposed schema for the development and use of ontology-driven processes [61–63]. The repetitive nature of certain steps of model construction suggests that these steps in the creation and programming of a simulation model can be expressed as task-based algorithms

embedded into an intelligent computational agent, which then treats simulation construction as a planning task using formal logical inference. Computational agents have been used in this fashion in bioinformatics for data integration and information flow management [64–68]. We have proposed that the task of converting biological conceptual models into executable simulations, including those associated with the population of the ABMF and subsequent conversion into ABMs, could be carried out by an intelligent computational agent, which we term a "computational modeling assistant (CMA)" [51]. We envision that this type of agent-directed process can semiautomate the specification-mapping work of model construction through the use of ontology-based/traditional predicate logic inference structures to generate simulation code. This will move towards achieving the translational research goal of high-throughput instantiation of conceptual models. Treating the steps of the composition process as a planning task can improve the modularity, robustness, and scalability of knowledge integration by creating a "middle-ware" discipline, i.e., *modeling*, and thereby focusing future development on the algorithmic expression of the mapping rules used in model development that form the CMA's inference instruction set. This allows expansion of the CMA's capabilities and expressiveness while maintaining interoperability with established but ongoing development in the areas of formal semantics/knowledge representation and modeling and simulation methods. We believe that this type process automation advances offered by the CMA will lead towards the development of cyberenvironments providing scalable high-throughput hypothesis instantiation and evaluation.

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 [69].

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 behavior 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 behavior. Alternatively, equation-based models have well-established procedures for analytical tasks such as parameter sensitivity analysis, bifurcation analysis, and behavior-state-space determination. Work on developing mathematical descriptions of ABMs offer the prospect that formal analysis may be available in the

future [70]. In the meantime, ABM researchers use a variety of strategies, such as heuristics [5, 27], literature-based constraints [31, 34] and Latin Hypercubes [9, 71], 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 behavior 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 [24]. From this regard, the stochastic and emergent properties of ABMs reinforce their ability to capture the robustness of dynamic behavior 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 neighborhoods with a high ratio of intra-agent computation (i.e., very complex mathematical rules) to interagent 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 [72–74]. 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 behavior 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 behavior at the processor and subprocessor level.

Conclusions

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 metaengineering 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 (such as the ABMF and the CMA) can significantly reduce the threshold for the general researcher to utilize computational modeling 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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