

Chapter 9

From Silico to Vitro: Computational Models of Complex Biological Systems Reveal Real-World Emergent Phenomena

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Abstract Computer simulations constitute a significant scientific tool for promoting scientific understanding of natural phenomena and dynamic processes. Substantial leaps in computational force and software engineering methodologies now allow the design and development of large-scale biological models, which – when combined with advanced graphics tools – may produce realistic biological scenarios, that reveal new scientific explanations and knowledge about real life phenomena. A state-of-the-art simulation system termed Reactive Animation (RA) will serve as a study case to examine the contemporary philosophical debate on the scientific value of simulations, as we demonstrate its ability to form a *scientific explanation* of natural phenomena and to generate new emergent behaviors, making possible a *prediction* or hypothesis about the equivalent real-life phenomena.

9.1 Introduction

Computer simulations constitute a significant scientific tool for promoting scientific understanding of natural phenomena and dynamic processes in diverse disciplines, including biology. The need of culling significant knowledge and insights from vast amounts of empirical data, generated in recent decades about biological molecules and the millions of interactions among them, has promoted the development of innovative sophisticated computational methods and helped form new interdisciplinary research fields.

A group of researchers have developed over the last decade a computational approach termed Reactive Animation (RA) for simulating complex biological systems (Vainas et al. 2011). The dynamic characteristics of the biological objects are described based on cellular and molecular data collected from lab experiments. These data are integrated bottom-up by computational tools and methods to create a comprehensive, dynamic, interactive simulation (with front-end animated

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visualization) of biological systems behavior and development, in which the ‘simulationist’ may intervene on-line and observe in-silico on the artificial life-like system the effects of what may be considered as thought experiments.

In particular, the RA system was reported to have revealed several unexpected emergent properties, such as: (1) Competition between Thymocyte cells (part of the adaptive immune system) for sites of stimulation during their development (Efroni et al. 2007); (2) Novel features of lymphocyte dynamics, differentiation and anatomic localization (Swerdlin et al. 2008); (3) Formation of clusters of pancreatic cells that correspond well with clusters appearing early in the developing organ in-vivo (Setty et al. 2008); (4) Clear impact of two signaling factors’ expression levels on the structure and size of the pancreas during its morphogenesis (ibid). (5) Novel negative feedback loop in the regulatory network governing VPC fate specification during *C. elegans* vulval development (Kam et al. 2008).

These behaviors (and others) were not overtly preprogrammed in the molecular and cellular data integrated during the construction of the simulation and may be considered ‘weekly emergent’ phenomena (as termed by (Bedau 2013)). These discoveries consequently alerted biologists and prompted new lab experimentations of phenomena previously unknown. This renewed investigation of the real world is a process which, according to the researchers, highlights the explanatory power and the potential aid to experimentation offered by an animated interactive simulation of complex sets of data (Efroni et al. 2005). According to the developers, these models enable in-silico experiments at run-time and produce results that are similar to in-vivo experiments and suggest new intriguing hypotheses (Setty et al. 2010).

The RA system serves here as a case study for what may be considered a ‘full simulation’, a concept defined by (Humphreys 2009), as opposed to ‘core simulation’. It is a concrete computational device that correctly represents the structure of a real system as well as a temporal presentation of the model solutions representing the behavior and dynamic development of the real system.

The simulation construction is claimed (by its developers) to be a bottom-up process. Whereas top-down approaches stem from theory down to models and data production, the RA system stems from data (gathered experimentally about molecules, cells and discrete interactions that compose complex living systems), which is then systematically integrated to synthesize an accurate and comprehensive representation, serving as a model. In addition, the data put into the model is that of micro-scale molecules, and the simulation is expected to generate macro-scale emergent phenomena and behaviors, not originally programmed into the model.

However, we claim that a top-down direction is strongly integrated into the construction process, imposing environmental constraints, as well as theoretical and computational limitations, and it is the combined bottom-up/top-down process that enables the simulation to relate to real-life observations and become a scientifically-verified tool.

In this paper we initially review the contemporary philosophical viewpoints about the ability of computer models to scientifically explain real-life phenomena. We then investigate aspects of explanatory simulations construction process, which allow them to produce novel emergent behaviors, demonstrated through the RA modeling system.

9.2 Can Models Explain?

Scientific models and simulations are inevitably based on idealizations and abstraction of real-world entities and complex systems. Nevertheless, many philosophers of science believe that, under certain circumstances, such models may offer genuine scientific explanation and even prediction for real-world previously-unknown phenomena. Carl Craver (2006) claimed that models' explanatory power stems from their mechanism, and he distinguished between 'how possibly models' (which 'describe how a set of parts and activities *might be* organized such that they exhibit the explanandum phenomenon') and 'how actually models' (which 'describe real components, activities and organizational features of the mechanism that *in fact* produces the phenomenon'). While 'how possibly models' may be useful in constructing a space of possible mechanisms, the 'how actually models' begin with an accurate and complete characterization of the phenomena and show how the mechanism actually works.

Earlier, Ernan McMullin proposed the 'Hypothetico-Structural' account of explanation for models, suggesting that it is the structure of the model and the way in which its entities are combined, which constitutes the explanation (McMullin 1985). McMullin described a process of 'de-idealization', in which researchers may justify the explanatory power of a model by adding-back features that were deliberately omitted or assumptions that were too over-simplified during the model construction, while formally and theoretically justifying these corrections.

Woodward (following David Lewis (1973, 1986)) interpreted the explanation process as revealing information about patterns of *counterfactual* dependencies, being able to respond to 'what-if' questions, or '*what* sort of difference it would have made for the explanandum *if* the factors cited in the explanans had been different in various possible ways' (Woodward 2003, p. 11). This account was recently expanded by Bokulich (2011), who also required that the model should adequately capture the '*relevant features*' of the real world system (based on detailed empirical data). This step, she claimed, 'plays a central role in distinguishing between those models that are merely *phenomenological*, 'saving the phenomena', from those models that are *genuinely explanatory*'.

9.2.1 Simulations Are More Than Models

In recent years there has been an awakening among philosophers of science, seeking to clarify the role played by simulations and their epistemological standing within the space defined by theories, models and scientific experiments. Some claim that simulations are simply 'models', that cannot produce any novel knowledge, which had not been implicitly included within its base theory and assumptions (Eckhart 2010).

Others (including us) regard simulations as a unique scientific activity, which has ‘*a life of its own*’ and consequently – deserves an epistemology of its own (Winsberg 2003, 2006). Winsberg claimed that simulations gain their credibility from the ‘antecedently established credentials of the model building techniques employed by the simulationists’ and the cumulative results gained by it, whereas they are close enough to the predicted results, based on real-world experiments. This view is supported by Morgan and Morrison (1999), who view simulations as ‘*autonomous agents*’, theory-independent entities and their construction as a process which involves broad and diverse types of knowledge, intuition and inspiration. Others supporting this view include Humphreys (2009), Fox-Keller (2003) and Lenhard (2007).

The latter referred to the ability of simulations to scientifically explain and to provide a ‘*pragmatic mode of understanding*’. A simulation, he claimed, ‘opens up a new mode of quantitative understanding, based on the deployments of epistemically opaque models whose behavior is made assessable by simulation’ (Lenhard 2006). This is a mode of ‘*understanding by control*’, through controlled intervention, manipulation of various components or parameters and through effective visualization of the dynamic results. As a result, simulations offer new instrumental access to phenomena, which can provide surprising predictions.

Mark Bedau (2008) referred to weakly-emergent phenomena, created through simulations, whose ‘explanation works simply by tracing through the temporal details in the complex web of micro-level causal interactions that ultimately generate the macro-events’.

Following these philosophers (and others), we identify five characteristics of simulations (specifically of complex biological systems), which are necessary for their potential explanatory power. They:

1. Are based on actual, up-to-date *scientific theories and data* from experiments and observations.
2. Can dynamically *yield emergent phenomena* (either behaviors or structures), which may be recognized visually or computationally.
3. Allow in-silico experimentations through dynamic intervention, control and manipulations.
4. Include intensive *validation & verification* loops against *real-world* observations at *various hierarchy levels*; and
5. Make *testable biological hypotheses*, which can promote new in-vivo lab experiments.

Specifically, the two latter characteristics are those that ‘make the difference’, we claim, between *Phenomena-Generating simulations* (‘how possibly’, models that merely ‘save the phenomena’) and *Phenomena-Elucidating simulations* (‘how actually’, genuinely explanatory models).

The RA-based models are presented as an example for models that can scientifically explain certain biological complex phenomena and predict others.

9.3 Constructing an Explanatory Predictive Simulation

9.3.1 *The Bottom-Up/Top-Down Conflict*

Many models of complex systems are developed based on scientific theories and include complex mathematical structures, the equations of which are not analytically solvable. Computational simulations of such models are often expected to produce data about the time-dependent behavior of these systems. The simulations' construction process is then directed from the theory (top) downwards to the concrete (computerized) implementation, relevant to a specific physical system. In different cases, a solid broad theoretical framework might not exist, and scientists rather construct simulations from the bottom upwards. Data are collected from lab experiments and observations, focusing on specific aspects of the physical (biological) system, and the simulated model is developed to gain insights about the whole system's dynamic behavior. Philosophers of science have debated over the construction process and the way it affects simulations' ability to explain real-world phenomena and to produce novel and useful knowledge.

Eric Winsberg claimed that the knowledge produces by computer simulations is the result of inferences that are downward, in the sense that they are drawn from high theory down to particular features of phenomena (Winsberg 2001, 2009). Simulations are meant, he said, to *replace* experiments and observations as sources of data about the world, where real data are sparse. Winsberg proposed a hierarchical taxonomy of model types involved in top-down construction: Mechanical models, (concrete) Dynamic models, Ad-hoc models, Computational models, and finally- a 'model of the phenomena', which is a 'manifold representation that embodies the relevant knowledge gathered from all relevant sources about the phenomena', including the visualization and interpretation of the results (Winsberg 1999).

Bottom-up construction is often referred to as 'synthesis' or Inductive Inference. Various parts of the system are initially specified in detail (under constraints of existing knowledge and implementing technology). These parts are then joined together to form bigger entities, which are then connected to others, forming complex interactivity and mutual dependencies, finally adding up to the whole desired system.

Popular computerized techniques, such as Agent-based Modeling (ABM) or Cellular Automata (CA), are operating from the bottom-upwards. Out of local interactions between low-level entities and local pre-defined state transitions, new patterns and behaviors may be revealed in higher system levels:

Situate an initial population of autonomous heterogeneous agents in a relevant spatial environment; allow them to interact according to simple local rules, and thereby generate-or grow up- the macroscopic regularity from the bottom-up. (Epstein 1999)

Bottom-up models, which are inherently nonlinear, enable synthesis and formation of complex, dynamic patterns or behaviors, and are popular in modeling behaviors of natural or social complex systems.

A major criticism against such modeling practice stems from the fact, that nearly every phenomenon may be produced in such a manner, regardless of its relevance to real-world systems. Stephan Lansing is quoted to have stated that:

One does not need to be a modeler to know that it is possible to ‘grow’ nearly anything in silico without necessarily learning anything about the real world. (Richardson 2003)

Others also claimed against the feasibility and validity of pure bottom-up construction, saying that theory is essential to provide epistemological access to scientific phenomena and to explicate the data (Schindler 2007). The same inevitable conclusion was drawn following an intensively study of designing and engineering emergent systems, to generate desired complex global behaviors from simple local actions (Fromm 2005a, b, 2006): ‘a bottom-up approach alone is not feasible... the number of combinations and configurations grows exponentially with the number of states, elements and rules’.

On the other side, a pure top-down (Macro-to-Micro direction) approach is definitely not enough, since it would be impossible to predict the opposite, micro-to-macro direction.

Consequently, combining both theoretical-methodological analysis and experimental-based synthesis seems to be necessary for creating a full explanation for the dynamics of a complex system (Weber 2002). Theory and experiments should be merged methodologically, in an ‘*explorative cooperation*’, which enables simulations to reproduce realistic dynamics of known phenomena (Lenhard 2007). Constraints, limitations and assumptions should be imposed (from ‘above’) on the (bottom-up) evolving dynamic simulated self-organizing entities, in an ongoing loop, recursive and adaptive process.

Most biological entities are ‘complex’ in the sense that they interact with and are influenced by entities of different (‘higher’ and ‘lower’) scales. In order to fully describe (and hopefully understand) a specific biological entity (e.g. cell), an integration of numerous sources of data is essential (from disciplines such as molecular biology, biochemistry, genetics – from the ‘bottom’, as well as cell biology, structural biology, developmental biology, evolution, physiology, anatomy and others – from the ‘top’).

Consequently, following Fromm (and others) we strongly support the claim that constructing an explanatory simulation of a complex (biological) system requires an *iterative two-way approach*, combining bottom-up synthesis processes, guided by top-down constraining feedbacks. Scientific low-level data about specific components of the system should be collected and integrated from the bottom upwards. These parts can then be joined together to form bigger entities, which are then connected to others, forming complex interactivity and mutual dependencies, finally adding up to a whole complex system. Concurrently, environmental and structural constraints, as well as high-level theoretical limitations, should be imposed from the top-downwards. It is the combined bottom-up/top-down process, which enables the simulation to relate to real-life observations and become a scientifically-verified tool.

9.3.2 Validation and Verification Against Real-World Data

The transition from a huge set of data into dynamic interactive computer models requires primarily the construction of an idealized conceptual model, based on the building block entities selected for modeling and on the desired scale of modeling (e.g. molecular, cellular etc.).

During this stage, missing elements – such as unknown values, transitions between untested scenarios, initial conditions – should be interpreted and creatively completed, based on the developers’ instincts, intuition, inspiration or any other non-empirical reason.

Following classical model engineering methodologies, initially proposed in the 1970s and then extended (Sargent 2009), we propose a diagrammatic scheme for the construction of valid simulations, which tightly relate to the real-life simulated system and which can scientifically explain observed behaviors in that system. Such simulations may test in-silico new hypotheses and subsequently predict novel, previously unknown behaviors, which emerge computationally and may be subsequently tested in laboratories.

The simulation process is an ongoing iterative process, which involves validation and verification of the simulated results, by comparing them to data and scientific predictions based on experimental data. This iterative *trial-and-error* procedure includes feedback loops from the bottom upwards and from the top downwards. At each step, the simulated system’s components, its parameters and inner architecture may vary and get re-designed repeatedly, until sufficient correlation is achieved with the simulated system, based on criteria determined by the designers.

Once specific architecture is set and parameters are fixed for a ‘*trial*’, the simulation is executed in what may be considered an ‘in-silico experiment’. A bottom-up synthesis is taking place, where simulated components perform step-by-step execution as defined, interact with one another, values and states are modified, inputs are considered for calculations and etc. Out of the dynamics of the cumulative concurrent interactions and causal effects, ‘finally’ (at a specific time stamp defined by the observers) some new feature evolves, which is recognizable at a higher hierarchical level or scale. Simulated (numerical or visual) data are collected, analyzed and compared (computationally or visually) to the expected, lab-based results.

The gap detected in this comparison includes the ‘*error*’ and decisions need to be made. As long as the gap does not satisfy the researchers, they need to join forces, expertise, creativity and skills to make the most efficient and practical modifications (of parameters, feedback loops, interactions, hierarchical levels, environmental conditions, entities definitions, algorithms and more). These modifications yield a new simulation – basis for a new ‘*trial*’ scenario, and so on.

Verification and Validation steps should be integrated into the simulation at any possible link, specifically:

- Between the conceptual model and real-life data: Iteratively determine the computerized entities, interactions, modules, layers and parameters that faithfully represent the real-life system at hand.
- Between the computerized the conceptual models: making sure that the simulation implementation faithfully represents the conceptual model;
- Between the computerized model and real-life data, at two important paths:
 - Make sure that *all* known experimental data integrated into the simulation (at every hierarchical level relevant to the simulation), can be faithfully *reproduced* by it.
 - Test and verify newly identified (in-silico) emerging behaviors or phenomena (which may be considered *testable biological hypotheses*) against (newly suggested) lab experiments or real-life observations.

Simulations which inherently include such validation and verification loops within their two-way (bottom-up and top-down) paths are, we claim, *Phenomena-Elucidating simulations*, which may provide an actual scientific explanation for real-world complex behaviors and even predict new emerging behaviors (Fig. 9.1).

9.4 The Reactive Animation Simulation Environment

9.4.1 General

Over a decade has passed since David Harel, a leading computer scientist, presented an exciting vision:

Our long-term aim is to model a full multi-cellular animal as a reactive system. Specifically, the *C. elegans* nematode worm, which is complex, but very well defined in terms of anatomy and genetics. The challenge is to construct a full, true-to-all-known-facts, 4-dimensional, fully animated model of the development and behavior of this worm (or of a comparable multi-cellular animal), which is easily extendable as new biological facts are discovered. (Harel 2003)

Such a model should be ‘fully executable, flexible, interactive... which would help uncover gaps, correct errors, suggest new experiments and help predict unobserved phenomena’. In addition, it ‘would be set up in such a way that biologists would be able to enter new data themselves as it is discovered, and even plug in varying theses about aspects of behavior that are not yet known, in order to see their effects.’ (Harel 2005)

It has been a main goal of the research group to design simulations that can produce emergent phenomena, unknown behaviors that would raise speculations, which would be further tested through lab experiments.

An extensive computer simulation environment, termed ‘Reactive Animation’ (RA), was developed, based on the assumption that biological systems are ‘large-scale complex systems that maintain an ongoing interaction with their environment and can thus be specified as reactive systems’ (Harel and Setty 2008). Reactive

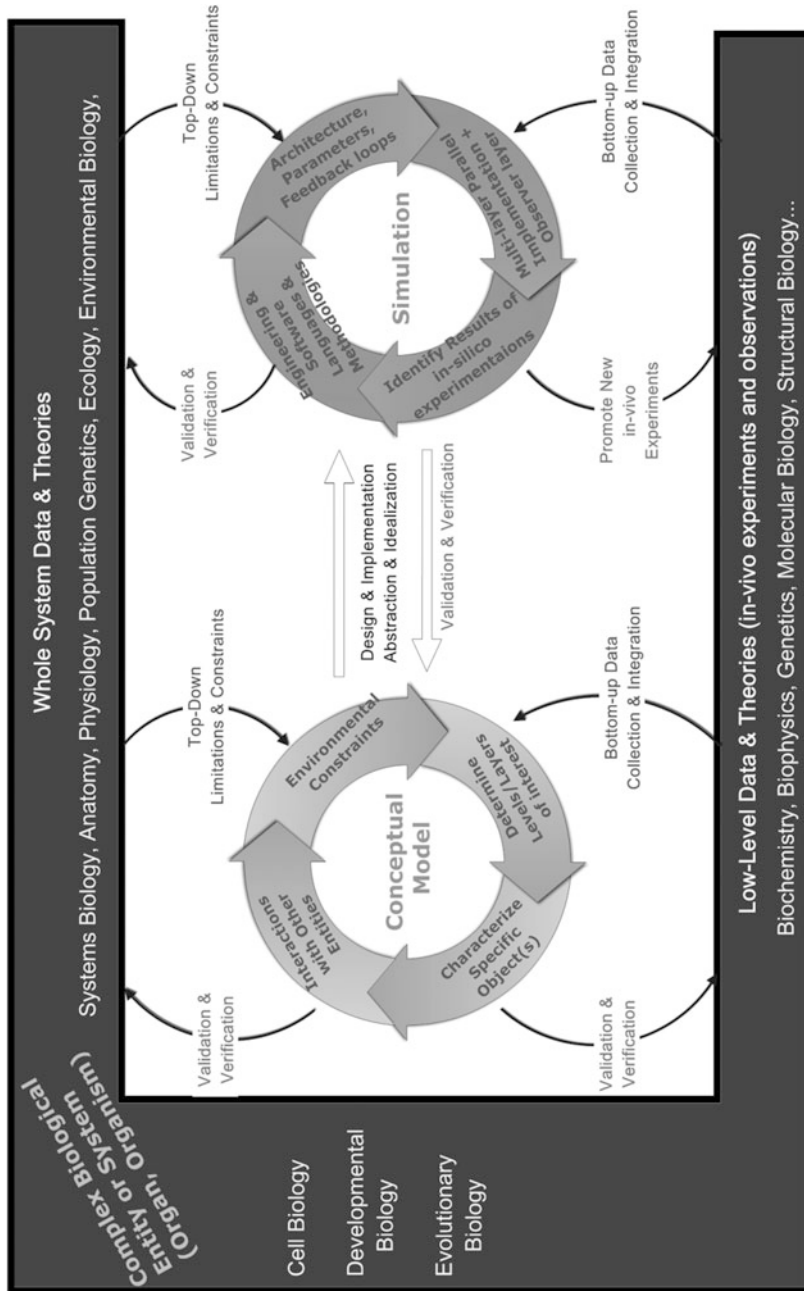


Fig. 9.1 Schematic relationship between a real-world complex system, the conceptual model and the simulation. The validation and verification loops are inherently combined into the simulation at all scales and levels

systems are designed by exact and full specification of all possible reactions of the system (or parts within) to potential inputs or stimulations.

The methodology, initially based on ‘state-charts’ (Harel 1987), was chosen for its ability to describe a complex system’s dynamic behavior, which is multi-scale, hierarchical and concurrent. The methodology was enhanced into a ‘scenario-based’ model, where ‘scenarios’ are statements based on ‘if-then’ logic, that document the *results* (usually phenotypic) of (in-vivo) experiments conducted under specific *conditions*. These data are based on extensive research and information resources, gathered from different aspects and disciplines relevant to the modeled system (e.g. anatomic, physiologic, genetic, molecular, cellular, etc.). Each statement is described by a ‘Live Sequence Chart’ (LSC), which represents specific conditions, known to result in some observed behavior for a specific system component. These modular and hierarchical mechanisms are interconnected by ‘events’ (that may be deterministic or random) and by ‘objects’ that may be referred to by multiple charts.

Information about the environmental conditions, physical constraints or boundary terms are imposed upon the modeled system, based on theory or whole-system prior knowledge.

RA system allows experimenters to intervene in the simulation and observe in-silico (through an integrated dynamic animation front-end) the results of ‘thought experiments’ (‘what-if?’ questions). The following section presents just a few of the emergent phenomena detected by the modelers.

9.4.2 Examples of Emerging Behaviors in RA Simulations

9.4.2.1 Model #1: Thymocyte Development

Data about Thymocyte development was used to generate an integrated dynamic simulation of the biological process termed ‘T-Cell Education’, through which stem cells reach mammalian thymus, undergo various modification and selection, until a small amount of candidate cells survives and becomes an essential part of the adaptive immune system (Efroni et al. 2005, 2007).

A systematic integration of cellular and molecular data was performed bottom-up into an accurate and comprehensive representation of the system. A specific goal of the researchers was to ‘reveal multi-scalar unexpected emergent properties and to guide experimentation in thymocyte development’. Several such properties were observed and reported:

- The experimental micro-scale molecular database (e.g. gene expression profiles, markers gradients etc.) integrated into the model was shown to suffice for generating (and thus validating) *realistic whole-organ, macro-scale thymocyte dynamic migration between functional anatomical locations*. Thymic fine anatomical structure was characterized according to 12 distinct developmental stages (<http://www.wisdom.weizmann.ac.il/~dharel/ReactiveAnimation/demo.htm>). The animation shows that immature cells proliferate at specific zones, while mature cells proliferate at anatomically different locations.

- Visualization of cell dynamics provided a view of emergent physiology, including the existence of *competition* between individual thymocytes for sites of stimulation, in order to engage in productive interactions with epithelial cells. This feature was unknown before (it cannot be seen in static histologic sections) and was therefore *not explicitly programmed into the simulation*. Rather, it was a behavioral derivative that emerged from the lower-level data that constituted the model.

In-silico manipulation of various parameters suggested that such competition could comprise an important factor in three different emergent properties of the T-cell maturation process, and these suggestions promoted lab experimental validation efforts.

- RA's interactive nature makes it possible to *knock out molecules or cells* (in-silico) and observe the effects. Each knockout influenced the resulting thymus morphology in a different way, a phenomenon that RA made visible quite effectively. As the researchers reported (2005), 'Others have already experimentally validated in-vivo two of the three predictions we made after these simulations'.

9.4.2.2 Model #2: Pancreas Organogenesis

A fully executable, interactive, visual 4D simulation of the organogenesis¹ developmental stage of a mouse pancreas was developed, using the RA modeling system. Execution of the model provided a dynamic description of pancreas development, culminating in a structure that remarkably recapitulates morphologic features, seen in the embryonic pancreas (Setty et al. 2008, 2010).²

The model was designed in the cellular level, where pancreas cells were modeled as autonomous agents, sensing their environment and acting accordingly. The behaviors were determined based on bottom-up data, gathered from numerous lab experiments. In addition, top-down constraints were imposed, related to environmental entities (e.g. Extra-Cellular Matrix³), responsible for inter-cellular processes.

Several emergent properties revealed by the simulation were reported:

- The emerging 3D structure was compared against 2D histological sections of the pancreas at different stages, which revealed a close visual resemblance, indicating that the simulation captured quite well the pancreatic morphogenesis in mice.

¹The term Organogenesis refers to the development of a functioning, anatomically specialized organ from a relatively small number of relatively undifferentiated precursor cells, and is critically influenced by factors involving multiple scales, dynamics, and 3D anatomic relationships (Setty et al. 2008).

²Animation: <http://www.wisdom.weizmann.ac.il/~yaki/wisDay/index.html>. Demonstrating movie: <http://www.pnas.org/content/suppl/2008/12/17/0808725105.DCSupplemental/SM1.mov>

³Extracellular Matrix (ECM) is a collection of extracellular molecules secreted by cells that provides structural and biochemical support to the surrounding cells.

- Dynamic interaction enabled to test the influence of modifying expression levels of specific regulating factors (as well as other environmental conditions, e.g. layout of blood vessels) on the pancreas morphology (the emerging 3D structure). The results were reported to become the subject of a collaborative testing, for an experimental (lab) validation.
- The simulated formation of clusters was observed, of pancreatic cells not expressing a specific gene (Pdx1), which ‘corresponds well with the primary transition clusters appearing early in the developing organ in vivo’. The researchers emphasize that they ‘did not have anything like this in mind when we started out, and the model was not explicitly programmed to do so’. Being able to trace the evolutionary origin of each cell within the simulation enabled the researchers to predict the nature of processes leading to such cluster formation, predictions which triggered new lab experiments (Setty et al. 2010).

9.4.3 Bottom-Up Data Integration with Top-Down Environmental Constraints

In the models presented above, dynamic characteristics of the biological system were specified based on facts and data gathered from numerous lab experiments reported in formal research biological papers. These data were translated and integrated bottom-up into modular and hierarchical ‘statecharts’ (which may generally be referred to as agents). The dynamic user interface enabled interactive intervention and manipulating of the biological simulated objects by the user, while visually observing the online consequences and effects. Thus, researchers could observe in-silico emerging behaviors (which were not specified or coded into the simulation) and predict the results of comparable future in-vivo experiments.

Computer models of living systems reflect their distributed, parallel and interactive nature. Simple agent-like autonomous entities interact locally, producing global emergent behaviors that evolved dynamically at higher system levels. As noted before, allowing the simulation to freely evolve bottom-up may result in behaviors not relevant to the actual living systems. Therefore, models must be constrained and limited according to existing scientific knowledge, imposed from the top downwards, so that emergent features would be restricted to the relevant solution space.

Accordingly, despite the RA developers’ strong claim that the simulation is constructed bottom-up, we claim that a significant element of rational engineering design was included, based on a whole-system view of the biological objects, which inevitably posed top-down constraints. The entities selected by the researchers (as equal to specific biological entities) and the interactions between them, as well as the environmental representation, are all derived from system-level knowledge, from knowing the entire simulated organism (or organ) and decomposing it into distinct, isolated entities, under adequate abstractions and simplifications. The animated

visualization system highly relates to the holistic systematic output, desired by the researchers. For example, detection of spatial physical separation between developing T-cells at different stages requires a detailed anatomic knowledge of the Thymus, which is the basis for the gentle design of the computerized simulated Thymus. Moreover, the computerized entities called ‘T-cells’ need to be allowed (by the simulationists) to move within the computerized space in pre-defined manner which relates to a-priori scientific findings. The visual output system should be designed to present such spatial movement in a way that has a meaning to biological observers. These considerations enforce constraints upon the simulation, which limit the space of potential emergent behaviors and make them verifiable.

9.5 Summary – Why are These Simulations Explanatory?

Simulations of biological processes often produce impressively visualized life-like behaviors, which may resemble certain aspects of the biological systems. For the most part, these simulated phenomena represent ‘Life as it could be’, hypothetical scenarios which are not testable in real life. The RA Simulation, we claim, represents ‘life as we know it’ (surely, under numerous limitations, such as the scale of modeling, which obviously does not currently go down to the sub-molecular chemical level; in addition, a high level of abstraction and simplification is inherently applied, due to computational and implicational constraints). Its credibility, capability to predict and explanatory power stem from its ability to accurately represent real biological phenomena, which are successfully validated against numerous sources of real-life data.

The RA developers state that:

Tradition says, first understand, and then make a model to explain what you understand. RA (Reactive Animation), at least for complex living systems, turns the process around: first make a dynamic model, that integrates the data, then you will understand. A model that represents faithfully the dynamic crossing of scales and layers is itself an explanation of the living system’s emergent properties. (Cohen and Harel 2007).

The simulations were developed based on thorough, comprehensive knowledge of the biological systems, and entities were carefully defined based on real-world mechanisms, enabling the models to discover dynamic systematic features. This corresponds to Craver’s explanatory ‘how actually’ models category.

The RA models seem to grasp the actual structure (entities, interactions, environmental) and the characteristics which are causally responsible for the traits of the complex (needs to be explained) entity, and thus construes an explanation and a direction for further research, according to McMullin’s Hypothetico-Structural explanation account.

These simulations enable researchers to examine and observe dynamically the results of ‘what-if’ scenarios, in-silico experiments related to real-life system. This relates to Lenhard’s pragmatic account: The observed behavior is quantitative

understood through the ability to produce the phenomena, to dynamically intervene and control its nature through the simulation, as well as predict novel, emergent unknown phenomena, which can be later confirmed (verified) through newly designed lab experiments.

The excessive validation steps integrated into the simulation environment provides a high level of confidence in the simulation by establishing a solid link between the (conceptual and computational) models developed and the real biological complex system.

This renewed investigation of the real world is a process which strongly supports and highlights the explanatory power and the potential aid of such simulations to biological research.

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