THE AIR FORCE *IN SILICO* – COMPUTATIONAL BIOLOGY IN 2025

Christopher Coates, Lt Col, Canadian Forces

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Air University
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ABSTRACT

The biological sciences have recently experienced remarkable advances and there are now frequent claims that “we are on the advent of being able to model or simulate biological systems to the smallest, molecular detail.” Such a capability, the product of a science known as computational biology, could radically change the health and life sciences and may have enormous impact in many fields, including military operations.

This study addresses the questions of whether or not computational biology will be able to simulate biological systems by 2025, and what the implications are for the United States Air Force (USAF). An examination of current capabilities and limitations leads to a prediction that computational biology is unlikely to be “mature” by 2025. Nevertheless, the USAF stands to benefit, even though its application will be limited to certain well understood models. Successful computational solutions are more likely to be found to biological and health problems that exhibit certain identified characteristics. A risk analysis and recommendations for USAF involvement are provided, based on likely progress of computational biology over the next 15 -20 years.

GLOSSARY

Ab initio From the beginning; based on first principles; based on the initial state.

Chronobiology The scientific study of the effect of time on living systems.

Genotype The internal coded inheritable information. While the genotype manifests itself in the phenotype, some aspects of the genome, such as recessive genes, stay hidden and are not part of the phenotype.

In silico Experiments or science conducted in computers, using their silicon chips

In vitro experiments conducted “in glass” under laboratory conditions

In vivo Experiment conducted in a living organism or natural environment

Phenotype The outward physical manifestation of an organism. It includes the physical parts; the sum of the molecules, cells, structures, metabolism, tissues, organs, reflexes, and behaviors.

Limits of simulation: A model showing every atom in a virus demonstrates that supercomputers are already on the verge of being able to simulate living things down to the smallest physical detail.

- John Horgan, "The Final Frontier," October 2006

I. Introduction

The goal of biological sciences is to understand living systems and be able to explain and predict how they function. The last 40 years have seen an explosion of progress and knowledge in the field of biology as new technologies have made it possible to study biological systems in ever greater detail and to ever smaller scales. There has been an overwhelming accumulation of data and information about these biosystems. In fact, so much data is being produced that it is unlikely humans alone can actually assimilate all the information and develop scientific hypothesis to explain the functioning of living systems. It is only through the application of computer technology that there is hope of making sense of the data being generated.[1] The ability to model biological systems, also known as computational biology, is actually very limited, and in spite of some expectations to the contrary is likely to remain that way for some time to come. Nonetheless, this study will show that by 2025 the USAF stands to benefit from computational biology, although its application will be limited to certain well understood models.

The potential value of computational biology has led to research being funded within the Department of Defense. The Defense Advanced Research Projects Agency (DARPA) has sponsored a "Protein Design Process" which aims to develop "new mathematical and biochemical approaches to the *in silico* design of proteins with specific functions." "*In silico*" describes experiments or science conducted in computers, using their silicon chips, and is differentiated from *in vivo* experiment conducted in a living organism or natural environment, or *in vitro*, which are experiments conducted "in glass" under laboratory conditions. Other DARPA programs related to computational biology include the "Virtual Soldier" program, and the "BioComputational Systems (BioCOMP)" program.[2] The U.S. Army has studied the possible impact of computational biology and MITRE has clearly identified its beneficial potential. Of particular interest is the modeling or simulation of cellular pathways, including the creation of specific biosensor proteins and counter biowarfare technologies.[3] All of these issues raise several questions. What are the actual expectations for computational biology? How should the Air Force take advantage of this new technology? What are the associated risks?

This study will examine the status of computational biology with a view to its potential benefit to the USAF and military applications. The analysis commences with a description of computational biology and then discusses many of the limitations affecting its development. Characteristics of

problems that will favor a successful solution by computational biology are identified. Two aviation problems are considered from the perspective of these characteristics as well as possible computational approaches. An analysis of the technical risk associated with computational biology is presented and recommendations offered regarding ways that the Air Force can maximize its preparedness for advances in computational biology and maintain a position of asymmetric technological advantage.

Computational Biology

Computational biology is a complex approach to understanding nature drawing together many of the classical sciences. Finding effective computational solutions requires overcoming many difficult obstacles. This section explores the state of computational biology and examines factors that will influence its development and application within the USAF.

Why Computational Biology

While some believe that biological systems will be able to be modeled best using quantum level computing and quantum mechanics,[4] this paper will argue that these techniques are not best suited to the range of scales of biological systems. Thus, other methods are being employed to couple the power of computers to the expanding biological data in order to address the larger dimensions of biological systems. The goal is to understand and predict the functioning of biological systems through the use of mathematical models and simulation.[5] This is the realm of computational biology.

Computational biology provides the possibility of *in silico* modeling of biological systems.[6] As an experimental method, *in silico* would enable the conduct of procedures that could not be accomplished by traditional *in vitro* or *in vivo* methods.[7] Advances in computational biology should facilitate other experiments or techniques, allowing the solution of complex problems such as protein folding calculations. *In silico* design is already seen to have great potential in fields such as drug development. Computational biology may also reduce the amount of animal or human testing necessary while simultaneously increasing a drug's effectiveness and reducing its costs. Outside of drug development the power of being able to model living systems at the molecular level offers the possibility of "earlier diagnoses and more powerful treatments for diseases, rapid environmental cleanup, and more robust food production."[8] In the extreme, an *in silico* version of the human body could provide the ability to achieve medical miracles.[9]

Modeling and Computational Approaches

The modeling of biological systems involves the creation of mathematical equations that represent the characteristics of the system both qualitatively and quantitatively. Different approaches to the modeling are possible, depending on the following factors: Qualitative versus quantitative requirements, the objective of the modeling, focus on particular biological process or subprocess, the scale of the model or system, and finally, the

degree of detail required from the model

The military and presumably the USAF is most interested in the ability to model effects that arise from interactions at the molecular level. For example, it would be of considerable value to be able to computationally model *in silico* (as opposed to experimentally *in vivo*), a body's interaction with a new form of a toxin.[10] Methods that involve modeling the molecular interactions are the most complex, but yield the most accurate results. This level of modeling, commencing with molecule-molecule interactions and incorporating a systems response is especially demanding and is not achievable by current technology. Nevertheless, the expansion of both biological data and knowledge, and an increase in computing power will continue to expand capabilities in this area.[11]

At the other end of the spectrum are calculations that do not treat the molecular interactions explicitly, but are much better at modeling the actions of the greater system, such as an organ or a body.[12] The following sections will examine the factors that limit computational biology, with a view to determining an effective approach for the Air Force.

Forces and Factors

Just as scientists and engineers must understand and apply forces such as gravity, or the drag of friction in order to create aircraft simulations, so too must biologists and chemists account for the forces that affect the systems they wish to model. At the molecular level biological systems are subject to many different forces, including electrostatic forces and van der Waals' forces.[13] Of course, at even smaller levels the physical properties of matter are the result of interactions of electrons. Many different equations or methodologies exist to calculate these forces and to model physical systems; for instance, the Schrödinger equation, the Navier-Stokes equation, or Maxwell's equations.[14] Other physical properties, or factors, that may impact a model of a biological system at the molecular level include covalent bond energies, atomic velocities (thermodynamics) as well as the free energy of certain reactions or configurations, such as protein folding. It is important to appreciate that there are numerous forces that affect the actions and interactions of matter at the atomic level and they are described by certain unique mathematical equations. For the purposes of this paper, it is less critical to understand the actual nature of the forces or the details of the calculations.

"Molecular dynamics" is the method most commonly employed to calculate the behavior of biological models. Combining the forces and factors mentioned above into potential functions or "force fields" provides molecular dynamics a means to adjust these fields in response to experimental determinants, or to address particular aspects of the system. Molecular dynamics also provides one of the only means to calculate the large number of molecules active in a biological system, although considerable limitations remain, as will be discussed later.[15]

The classical level, or the macroscopic level, is the level where

physical bodies act and the effect of the molecular or chemical changes is actually expressed. Interactions at this level are largely governed by Newton's laws and calculations or computations are generally conducted using differential equations – both ordinary and partial.[16] Chemical reactions, including enzymatic reactions of biological systems, may be seen to occur between the classical level and the molecular level and are commonly modeled by their own combination of differential equations.[17]

For military purposes, the greatest value is in achieving the ability to model an entire biological system, for which the level of computation of most interest is the lowest level possible -- that of atoms or molecules. Therefore, what is required is the ability to model an entire biosystem based on molecular level calculations. This is a daunting task as the requirement to solve all the equations simultaneously is enormously challenging. The next section will describe the difficulty inherent in modeling whole biosystems, which has implications for the USAF's development of computational biology.

Multi-scale Computations

In principle, the most accurate computations would be those that employed quantum mechanics to calculate the behaviour of matter in a biological system. However, quantum mechanics cannot deal with the time scales of biological importance (seconds or greater) or the large number of atoms or molecules involved.[18] At the other end of the spectrum is continuum, or classical mechanics, which does not address the interactions of interest, at the molecular level. As a bridge between the two, molecular dynamics does a relatively good job of dealing with microscopic systems on the order of 10^4 - 10^6 atoms for periods on the order of nanoseconds. Some reports suggest that molecular dynamics can provide acceptable data for more complex problems of up to 10^6 molecules for longer periods on the order of microseconds.[19] Nevertheless, there remain several gaps in the ability to compute the behavior of biological systems. The gaps in computational ability are indicated in Figure 1, wherein each box represents a computational method.

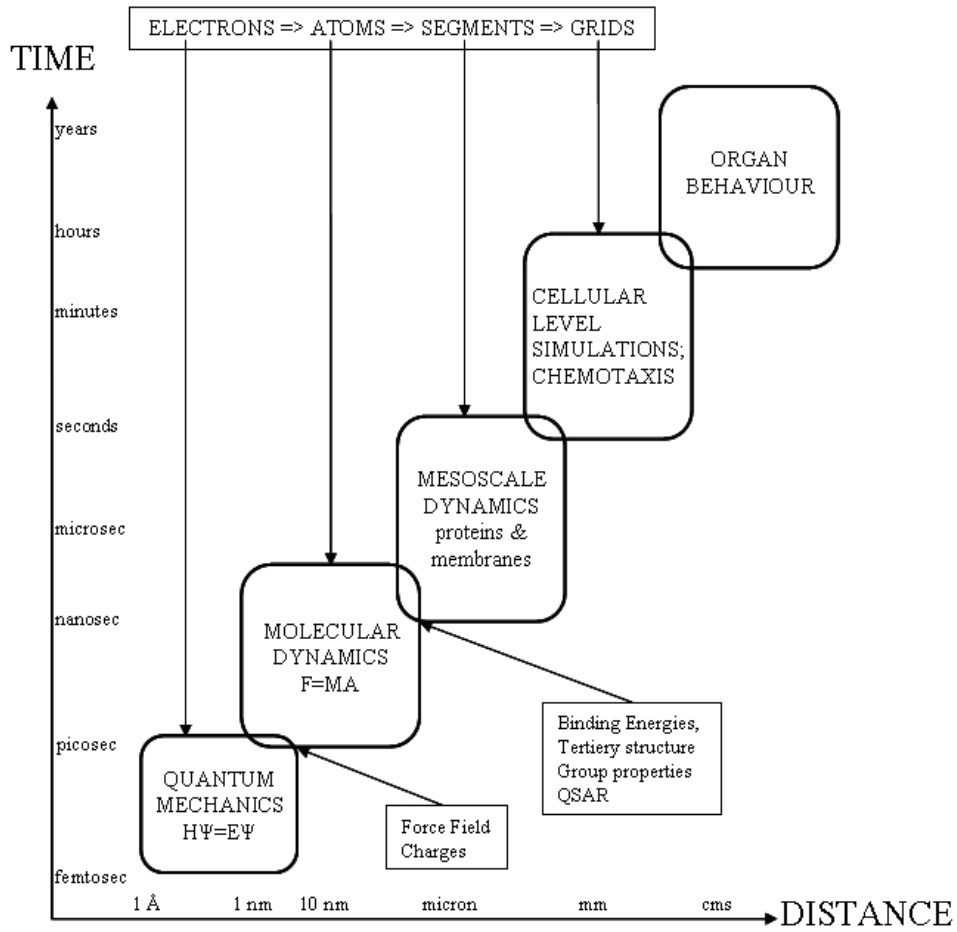

Figure 1: Hierarchy of Computations and Simulations[20]

The relative abstractness of Figure 1 does not clearly represent the actual range of interactions in a biological system. Biological functions can span the order of nanoseconds to seconds or longer. The dimensions of molecules such as DNA cover three orders of magnitude themselves. There is currently no technology or method available to effectively span the length and time scales applicable to biological systems. A "theory of everything" would be a single physical theory that alone explains the behaviour of all matter and energy in the universe. Such a theory does not exist currently, nor is one expected in the near future.[21] Thus, in order to model biological systems by 2025, the challenge will be to find a means to apply the results from each computational level to the successive (or previous) level. Science is currently at the point of knowing what has to be done (i.e. bridge the levels), but does not have a means to do it. It is not simply a matter of computational power. It involves a lack of relevant theory or method to transfer the information from one level to another.[22]

Because of these obstacles, any USAF approach to computational biology must recognize the difficulty of spanning the time and size scales, and as such limit its planning to those applications that are amenable to a single computational method. The USAF should not expect problems that span

several orders of magnitude in time or distance or that require multiple computational methods to be solved in the near term. Any attempts to build multi-scale computational biology solutions will likely need to build on a successful program of experimentation and development.[23] These notions will be revisited as the analysis provides additional insight into computational biology in 2025.

Degree of Complexity

In addition to the challenges of multi-scale calculations in computational biology, the shear complexity of the biological systems being modeled is a dimension of its own. This further increases the difficulty of creating acceptable models or simulations. A biological system such as a cell, let alone tissue or an organ, represents the highly interconnected and interrelated simultaneous expression of countless chemical and physical relationships. For a single cell it is necessary to model enzymatic synthesis of numerous small molecules such as lipids while simultaneously "including DNA replication, RNA processing, RNA modification, extra tRNAs to decode the whole genetic code, some additional essential translation components and chaperones." [24] It would still be necessary to represent membrane proteins with their "significant conformational changes, including signalling, transport, and regulated ion conduction."[25] Some aspects of biological systems are too complex to understand without the assistance of computers, although the application of computers and information sciences is not a guarantee of success. Along with the examples mentioned above, higher order modelling requires "understanding the interactions of tens of thousands of different proteins as they generate functionality at all levels through cells to organs and systems." [26]

Further, creating "a unified model of an organism" - is not just a matter of building a mathematical model of what is currently known.[27] What is "currently known" is insufficient. The scientific knowledge of biological systems is constantly expanding, and is doing so at an ever increasing rate.[28] As data becomes available and traditional biology is no longer able to handle the increasing amount of information, new fields of biosciences have emerged to study the many relationships. Just as "genomics" was formed to study the "genome" (a combination of the words gene and chromosome) these new fields are commonly referred to as "~omics." Proteomics, transcriptomics, metabolomics, epigenomics, physiomics, lipidomics are all neologisms that categorize some of these new areas of study.[29]

Modeling of such highly complex systems is incredibly difficult. Just as modeling economic systems or global weather can be problematic, modeling of biological systems faces the paradox of "garbage-in, garbage-out." A model of a biological cell or organism may be "a system of hundreds of coupled nonlinear differential equations with thousands of poorly known rate constants."[30] The potential for multiple errors in such a situation is enormous and the models are so complicated it might not even be possible to predict ahead of time which areas are critical or merit closer attention.

Dealing with this complexity of biological systems may seriously impede the creation of satisfactory models or simulations of the type desired by military users (e.g. Virtual Soldier). So complex are the problems that it is possible that our current means of thinking or approaching the situations are insufficient and the language used to describe biological systems will likely require entirely new means of expression to facilitate understanding and allow acceptable simulations to be completed.[31]

Stochastic and Deterministic Effects

This section builds on the previous description of the degree of complexity affecting biological systems. Not only are the systems composed of an enormous number of interrelated compounds and processes all acting simultaneously, the activities of many of the molecules within a cell do not follow predictable or regular patterns. As prediction is one important goal of a simulation, the challenge described here is one of great impact on creating a successful model.

A common method of calculating the large number of interactions involved in a biological system employs systems of differential equations. However, differential equations are not well-suited to deal with several aspects of biological activity at the cellular level. For example, differential equations do not easily describe "state changes, discontinuities, irregular geometries or discreteness (low copy numbers)" inherent in biological systems.[32] These physical properties result in biological systems exhibiting stochastic rather than deterministic behavior. Although these are microscopic-level phenomena, the stochastic fluctuations in the cell frequently occur at points close to unstable equilibria, amplifying the impact of the stochastic fluctuations even to the point of creating observable macroscopic effects.[33]

While some cellular processes can be adequately described by deterministic methods and a system of differential equations, others cannot. For example, in membrane models, such as those of cells, the stochastic nature of diffusion of ions through the membrane affects the reproducibility of results. The small number of molecules typically involved in signaling pathways renders them unsuitable to deterministic methods and stochastic models have performed more realistically. Further emphasizing the stochastic nature of biological systems is the manner in which diffusion plays a role in cells.[34]

Stochastic models and simulating diffusion may be computationally expensive to model while deterministic models may be difficult to implement in a manner that recreates experimental data. The inherent fluctuation in a stochastic model may render it unattractive to a search for a predictive simulation; however, the apparently random character of nature cannot be left out simply due to its computational undesirability. As the USAF determines uses for computational biology, it will need to acknowledge the possible random results of an accurate model and to be ready to apply other statistical methods, such as Monte Carlo simulations, in order to produce results suitable for prediction.

Computational Limitations

Computational biology is only possible due to the vast computing resources available today. Nevertheless, computational biology is in fact limited by today's computational power. While the improvements in computational power could be described in accordance with Moore's Law,[35] the challenges of computational biology are enormous, and may exceed the expected increases in computing capability.

Several years ago the computational power of "state-of-the-art parallel supercomputers" allowed highly predictive calculations treating only hundreds of atoms for time scales of picoseconds, while molecular dynamics calculations of tens of thousands of atoms for nanoseconds were becoming common, although they were somewhat less predictive. A straightforward application of Moore's Law would predict an increase of about three – four doublings in capability in the intervening five or six years. Computational biology's calculations appear to have increased, in fact, roughly in parallel with Moore's Law doubling rates, as current molecular dynamics simulations involve slightly less than hundreds of thousands of atoms for tens to hundreds of nanoseconds. These molecular dynamics simulations incorporate approximations that would introduce errors, some of which may be critical, over the period of extended, biologically interesting calculations. Wholly predictive quantum mechanical treatments remain well beyond the capabilities of current computers.[36]

In spite of advances in computing power, computational biology remains far-removed from the objective of thousands of molecules for up to seconds of simulation.[37] Using current methodologies, achieving the desired level of computation would represent an increase of greater than ~10^9 times in computing power. Even if computing capacity continues to increase in accordance with Moore's Law, with a 1000-fold increase in computational capability by 2025, the computers will still be six orders of magnitude below the level needed to begin to engage in computational biology. It must be noted that even an increase of 10^9 in computing power would only provide the ability to simulate certain cellular systems, and may not provide a means to predictively model whole cells, organs or organisms.

As the US military pursues the promise of computational biology to address problems that can not be solved by empirical *in vivo* or *in vitro* methods, it must remain cognizant that the expected increase in computing power predicted by Moore's Law will not overcome computational biology's limitations by 2025. This means that only those problems that can be addressed based on existing and expected increases in computing power should be selected for study using computational biology. Problems that require greater computing capacity are at a high risk of failure. However, the Air Force may benefit by exploration of new methods of simulation to achieve the increases in scale required for biologically relevant simulations.

Protein Folding

Protein folding is the process by which a protein's string of constituent

amino acids adopts its biologically active, complex, three-dimensional shape. Understanding this process is often seen as a critical requirement of computational biology, as in some areas the challenges of modeling protein folding may be easier to solve than the brute force computing discussed above.

Cells may be thought of as small factories, and the proteins in them are the tiny machines that produce all the requirements for life. While the sequence of amino acids that constitute a protein may be derived from the genetic code, the sequence does not reveal any knowledge *per se* about the functionality of a protein. It is the shape of each protein that is a critical element in its activity, and this is the reason that understanding protein folding is such a critical problem.

The calculation of protein folding simply based on first principles and the known molecular structure, also known as *ab initio* calculation, remains an enormous challenge.[38] However, if protein folding could be solved then it may be possible to unravel many of life's mysteries from the genetic code.[39] A cell may contain tens of thousands of different proteins with 100 to 10 million copies per cell and thus the protein folding problem is a central concern for computational biology. Compared to modeling of ligand-receptor binding and interaction, protein folding may appear to be rather straightforward. And it possibly is, by comparison. Nevertheless, even with today's massive computing capability it is still not possible to compute a solution to the problem of protein folding for biologically relevant proteins. The fastest computer currently available, the MDGRAPE-3 (specifically designed for molecular dynamics calculations and capable of one petaflop) would take approximately three years to calculate the folding of a protein involving a total of 32000 atoms in the peptide and its aqueous environment. In fact, it is currently only possible to consider the folding of a relatively small polypeptide, a fraction the size of many proteins of interest.[40]

The problem is rendered more difficult as protein folding is a dynamic process. The huge number of atoms and bonds in a protein molecule leads to enormous complexity in the folding process. Further, the energy or stability of a protein folding *in vivo* (or *in vitro*) can be affected by many outside influences. Should a calculation arrive at a particular low energy, stable configuration it will stop the folding process. Depending on the folding sequence taken by its amino acids a protein may adopt a stable configuration either *in vivo* or *in silico* that is different from the configuration obtained in the other environment. Although the *in silico* configurations are not necessarily biologically relevant, currently the only way to determine if the stable calculated configuration is the correct one is to compare it to experimental data. There are conceivably so many of these alternate stable configurations that it might be extremely difficult to calculate or model the correct one. In short, the intracellular environment and/or the protein synthesis process might affect the folding in such a way as to "direct" the protein folding in a certain manner. Detailed knowledge of these variables may assist with the resolution of the computational problem, but serves to highlight the

complexity involved.

The ability of computational biology to address the fundamental problem of protein folding is essential to achieving the desired result, that is, simulating the response of a cell or biological system to a novel stimulus. Without such a capability, simulations might remain entirely empirical and have relatively restricted predictive value, limited strictly to those relationships that have been previously determined *in vivo* or *in vitro*. There would be no "intentional biology" or "*in silico* drug design" as previously described. It seems possible, however, that by 2025 advances in computational power, accompanied by possible increased knowledge of the physics, biochemistry and biology involved, may permit *ab initio* computations of protein folding.[41] The problem of protein folding provides a benchmark of sorts for the challenges facing computational biology by 2025, and may provide an indicator of the ability to achieve the objective of a predicative biological science. The potential of computational biology will depend on the ability to draw together many scientific disciplines to solve the complicated challenges.

II. Visualization

This section will address an aspect of computational biology that is not a limitation *per se*, but does affect the science and will continue to do so out to 2025. It will examine the role of visualization in facilitating multidisciplinary participation in computational biology. The impact of visualization may contribute to recommendations regarding the manner in which the Air Force might approach the technology.

Multidisciplinary Involvement

Its very name indicates that computational biology is a composite science, related to both biology and computer science. In fact, it is recognized that progress in computational biology will require a true "partnership between scientists in both disciplines, and the capacity to communicate in both directions."[42] A complete understanding of the science and the optimization of its full potential will likely also require the participation or the expertise of computational chemistry and computational physics.[43] The informational component must also be satisfied and will probably require experts in networks and information technology, "computing, computation, modeling and simulation, computer science, computer engineering, informatics, information technology, scientific computing, and computational science."[44]

Of the sciences mentioned there is a conceptual line that can be drawn between the qualitative science of, for example, biology and the quantitative sciences of chemistry, or physics. Quantitatively biased, computer scientists work with abstractions while biologists tend have much less experience with mathematically-based models, such as those favored by computational theorists. Due to the high degree of complexity of biological systems, biologists traditionally observe higher-level phenomena that are the result of levels of order well above those responsible for atomic and molecular level behavior. This may affect both their perception as well as their experience. Thus, on the one hand, biologists tend to believe that there are practical limits to reductionism and that "[h]igher-order understanding" will always be necessary, while on the other hand, the quest continues for more detailed, "reductive explanations" within the bio-sciences.[45] Nevertheless, mathematically-based models and reductionist explanations have been very limited in biology compared to the physical and computer sciences. Furthermore, there is often physical as well as intellectual separation between researchers in these different fields, and the most successful approaches to computational biology will need to bridge the gaps.[46]

Crossing the domains of chemistry, biology and physics , with strong links to computer science, computational biology presents challenges to traditional scientific methods, skills and cultures. [47] The next section will discuss one aspect of the crucial need to find a common language.

Requirement for Visualization

As explained in the previous section, biologists tend to think qualitatively and to share ideas and concepts in a descriptive, interpretive manner. Their partners in computational biology -- chemists, physicists and computer scientists -- are more apt to approach problems quantitatively and express theories mathematically.[48] Visualization is both a powerful and successful means for these two communities to connect their concepts and share hypotheses.

Virtual Cell is a computational biology program that specifically uses graphical representations "designed for cell biologists" to allow biologists to communicate and share ideas with the mathematical modelers of their virtual cell. As biologists are often not trained in computational sciences, the development of specifically-designed programs, software and models is a key enabler to facilitating and integrating their participation and expertise in computational biology. Their collaboration is critical to the long-term goals of computational biology and the ability to generate "unified" models and simulations.[49]

The enormous amount of data and information being generated in the life sciences is giving rise to a phenomenon where computers are no longer only adjuncts to the categorization or recording of data, but the associations and interactions are themselves only revealed through the power of computers. That is to say, the development of knowledge from the data is intrinsically tied to the use of computers and computation. The biological questions associated with such methods "could not readily be posed without visualization."[50] Given the complexity of the data, biological modeling and simulation are essential to further research and powerful computing capabilities are fundamental to the science.[51]

The trends describing computational biology mentioned above: multi-disciplinary, visually enabled, and computationally dependent, will continue for the foreseeable future. Leading up to 2025 the USAF should facilitate the advantages offered by computational biology by establishing conditions that optimize those characteristics. Biological problems selected for computational analysis ought to be amenable to, or already part of a visually enabled system. The use of multidisciplinary teams is more likely to yield successful computational solutions, and facilitate the design and prediction of biological systems.

III. Approaches to *In Silico*

Two approaches have dominated efforts to develop effective models, or simulations, of biological systems. The two approaches could be described as bottom-up and top-down. They are also appropriately titled as the reductionist approach and the systems approach, or alternatively the quantitative approach versus the qualitative approach. The name of each approach describes many of its characteristics as well as the difference from the other one.

The bottom-up approach tends to start at the sub-nanometer level, using quantitative information, often employing molecular dynamics style calculations to build a model that is predictive.[52] These models or simulations may be readily subjected to testing with experimental data in order to refine the model or they may be used themselves to trial experiments for the first time. The quantitative, reductionist models can "guide experiments" and may "rapidly spur increased understanding" of biological systems,[53] although they are inherently complex and subject to the challenges of computational biology previously described.

The top-down approaches provide an "idealized picture" or model that allows an integrated "understanding to emerge".[54] The Sun Center of Excellence for Visual Genomics at the University of Calgary supports a top-down, holistic approach to simulation by continually integrating and adding new knowledge as it is gained from experimentation. Their simulations will grow in a more empirical manner than those following a reductionist approach. As such insights will more likely result by identifying associations rather than from actual computational predictions.[55]

There are advantages to both approaches: a systems approach may provide an important framework within which new information and knowledge can be integrated; the bottom-up approach offers the promise of being at the level where "emerging science" is actually taking place. However, the greatest potential for success appears to lie in a combination, or integration of both approaches. It is likely that "21st century biology will be based on a synergistic mix of reductionist and systems biologies,"[56] and it is in this mix of the two approaches that the true power of computational biology will yield great results. The Air Force should favor an approach to computational biology that facilitates or promotes the integration of the reductionist and integrationist approaches.

Based on the analysis, the future of computational biology will be multidisciplinary and empowered by visualization; should benefit from an integration of reductionist and systems approaches; and is unlikely to attain its full potential due to increases in computing power alone. Looking out to 2025, what other considerations regarding this powerful science could influence Air Force actions and decisions now and in the future?

IV. Computational Biology Solutions By 2025

Models

In a previous section it was mentioned that an increase in the computational capacity of molecular dynamics has occurred, and observations support the conclusion that the growth is expected to continue.[57] In contrast to the pure bottom-up or top-down approach already described, various simulation models have been employed with more or less success. This section will discuss some of the models and attempts to increase the effectiveness of computational biology.

Early efforts at simulation or modeling of biological of systems include recent attempts to model cellular functions. Examples of these include: DARPA's BioSPICE, a cellular model based on the modeling of electronic circuits;[58] a dynamic cellular automata (DCA) cell "simulator used to simulate cellular and biochemical processes", called SimCell;[59] Virtual Cell, a "fully modular computational framework that provides a general approach to modeling the spatially organized and interdependent chemical events that underlie dynamic cellular processes";[60] or the "E-Cell Project" which aims "to model and reconstruct biological phenomena in silico."[61]

The BioSPICE simulation approaches the process of simulation from a direction not familiar to biologists, but proven in the field of electrical engineering. The SPICE-style model also provides a framework for the possible incorporation of spatial variations in cells, which is generally recognized as necessary but is essentially not reflected in other simulations. Given the structural and topological differences between cell types, there is the possibility of additional layers of complexity if each cell requires a unique SPICE-like framework to model its behavior.[62] The problem becomes even more difficult if the framework changes throughout the life of a cell.

Another model is the DCA cell simulator. It uses a novel approach also, but one does not require an in-depth knowledge of ordinary or partial differential equations to model cell activity.[63] Although DCA is also a recent addition to the modeling options it may provide an alternative in the event that previously known methods cannot deal with a particular problem.

In general, all the models listed above are basic and less accurate or precise than will be necessary for accurate predictions. Nevertheless, they do represent current attempts to model biological systems. In most cases these cellular models have had more value as tools to research modeling, than as biologically predictive simulations or models. To be more accurate, models will have to incorporate finer scale molecular information, although doing so will accentuate many of the challenges previously discussed. These models are described in order to demonstrate that *in silico* modeling is not new; that the challenges to be confronted are not a result of an Air Force or military requirement; and that in spite of present efforts there is no clear path to success for computational models.

For the foreseeable future there is likely to remain a "mismatch between scales at which we can be reasonably confident of the fundamental interactions (here atoms and electrons, at scales of angstroms and femtoseconds) and scales at which we want to understand biomolecular structure and function (tens to hundreds of nanometers, milliseconds and longer)."[64] It would appear that realistic near-term (5 – 10 years) goals for computational biology might involve modeling sub-cellular entities such as a "digital ribosome"[65] or perhaps the *ab initio* modeling of membrane proteins, as their various states may reveal functional significance.[66]

One proposal to overcome the challenge of multi-scale calculations is the use of a layered hardware array. Several methods have been considered to implement this idea. In one option, a "hierarchical model" employs a series of computers at each level of the multi-scale simulation. For instance, "molecular-scale model simulations (say of virtual cells) … communicate or receive parameters from simulations on other CPUs which take cellular or whole organ structure into account."[67] In this way, computations are conducted by sets of CPUs, or computers, for each computational level, while alternate sets operating at other levels feedback into levels both above and below. Current information technology does not support this computational methodology and will require close integration between biologists and information scientists to produce the desired results. The hierarchical model is most similar to the reductionist approach, and would have predictive capacity.

Another scheme, similar to the hierarchical model is an "integrated" model consisting of computer chips that are built to act like biological components. The computer links the "biological chips" to each other to create a model of an organism.[68] Unlike the hierarchical model which would permit reprogramming of the CPUs at each level, the integrated model is contingent upon the ability to rapidly design, produce and redesign chips in order to allow tuning of the simulation. Depending upon the chip-design process, the integrated model follows much more of an empirical, or systems approach and consequently may be less predictive.

A third possibility for a successful solution to computational biology by the 2025 timeframe is the advent of functional quantum computing. It has been speculated that quantum computing may permit algorithms that facilitate "simulation of molecular and quantum phenomena."[69] On the other hand, a recent evaluation of the potential of High Performance Computing indicates that "capability is presently not a key limiting factor" to the challenges of computational biology.[70] Given the current predictions concerning the development of quantum computing,[71] a detailed examination of the relationship between computational biology and quantum computing is beyond the scope of this paper. Should quantum super-computing capabilities become available before 2025, then this may require the reevaluation of some of the conclusions in this paper. The Air Force should continue to monitor quantum-computing developments and reevaluate the approach to computational biology as quantum computers begin to be fielded.

Another possible solution may be derived from the study of materials, where simulation "methods, tools and engines" may be generated in order to "seamlessly and autonomously traverse, in a bidirectional manner, multiple length and time scales."[72] However, building on the two models proposed above, there is the potential that combining chips that accurately model their associated bio-component with CPUs to model less proven aspects would link the best features of the hierarchical and integrated models. In terms of potential for the Air Force in 2025, the proposed models may be feasible; however, they are very complex and would require the expertise of possibly more different technologies and scientific fields than previously described.

Experimentation

One important aspect of modeling in general and the modeling of complex systems in particular, such as biological ones, is that a model or a simulation is simply an extrapolation or an inference based on data that has been observed. Depending on the accuracy of the observations, and their degree of comprehensiveness, there is a realistic likelihood that the simulation could be incorrect.[73] In terms of computational biology experimentation serves several key functions.

In the first place, experimentation provides the basic data from which the models are validated. As previously explained, first principle, *ab initio* calculations of an entire cell are not yet possible. Experiments are therefore required in order to create accurate models. The experiments determine "biochemical reaction rates, electrophysiological data on membrane transport dynamics, diffusion of cellular species within cellular compartments, and the mechanical properties of cellular structures"[74] and others from amongst an almost endless list of additional phenomena. Experiments also serve to validate the simulation methods, once the models have been derived.[75] Proper use of experimentation will lead to opportunities to improve and refine the models, which will in turn reveal more of the biological system's underlying structures and associations.

In the case of first principle or *ab initio* calculations such as molecular dynamics, the use of experimental data may reduce the number of variables that need to be calculated, facilitating larger scale or longer time calculations. In addition, the accuracy of molecular dynamic force fields may be refined through experiment, resulting in more precise or exact simulations.[76] At larger scales computational biology will benefit from direct observations, as microscopy and pathology provide data that refines the modeling of organs and other tissues.[77] Bioinformatics, the science that deals with the vast amounts of biological data or information, is still in the early stages of creating the databases necessary to manipulate and understand these data. Nevertheless, the complexity of biological systems is such that accurate simulations and models will ultimately depend on the assimilation of large amounts of experimental data, regardless of the scale from which they are derived.

Conflicting Theories and Information

Although the options and predictions presented above do not clearly specify the future of computational biology they do leave the impression that progress will occur and that success may be possible one day. On the other hand, conflicting theories and information do exist. In fact, the expectations for computational biology may be tempered somewhat by the factors presented in this section.

The Human Genome Project has gone a long way toward increasing the understanding of the genome. However, much remains to be determined about the manner that genes affect the control of practically all cellular activities.[78] Without understanding of the "rules" of genomics the application of computational biology may miss essential relationships. On the other hand, the rules themselves may prove so complex that current approaches to modeling will be insufficient.

What may be the most important theory in biology, natural selection, may also conflict with the essence of simulating biological systems. It is generally assumed that biological systems are the product of natural selection, and to some degree the understanding of underlying mechanisms is derived from a deduction of or "reverse engineering" of the pressures of natural selection.[79] The conditions that led to a particular cellular trait or behavior no longer exist and this either renders the reverse engineering very difficult, or may lead to erroneous conclusions if incorrect conditions or assumptions are applied.

Finally, it has been proposed that the theories relating to cellular functional and molecular biology are simply too vast and too complicated for a single human mind to grasp.[80] If this is so then computational biology would not be an adjunct to the progress of bioscience, it would be an absolute necessity for continued exploration of biology. Whole aspects of biosciences would cease to exist outside of the computer-rendered understanding of the relationships of cells and other systems. Experimental data could not be validated or even assimilated outside of the "*in silico*" world that contains all the understanding of bioscience. While the computer program "Bluejay" appears to be a browser for biological sequences it is designed as a knowledge integration tool.[81] It is seen as the type of program that will constitute one element of the response to biology's "grand challenge" that involves the combining of vast amounts of experimental data into a coherent model of an organism. Bluejay is intended to be part of a change in the way that biologists treat their data, promoting the creation of distributed networks of bioinformatics tools and data, together constituting the known universe of biodata.

The future of computational biology may be affected by as-of-yet undiscovered advances or unexpected scientific changes. By 2025 new physical theories for such properties as electrostatic interactions could have a large impact on computational biology and modeling of biological systems.[82] The "correct treatment of hydrogen-bonded systems and of proton-transfer" may require the development of new theories or new calculation methods that

account for these variables.[83] Computational biological models will need to be adjusted as we learn more about intercellular and larger scale biological processes.

The possible conflicting theories and other considerations presented above highlight the challenges faced in predicting the development of computational biology. For those serious about applying the benefits of computational biology they should ensure that the risks identified above are mitigated through the use of multidisciplinary, networked teams and collaborative approaches.

V. Air Force Problems and Computational Biology

Computational biology presents the promise of creating an "intentional biology" in which substances and processes are the planned result of the directed, calculated actions – of "biological design and manufacturing."[84] This would offer great potential in many fields of human activity, several of which are or could be of interest to the Air Force, including materials science and medicine. This section will identify possible Air Force projects or problems to which computational biology could be applied and will examine the Air Force' risk vis-à-vis the development of computational biology from now to 2025. The following sections will identify the potential for computational biology to impact the Air Force's programs in those fields.

Bioweapons vs. Biomedicine

Computational biology could address biological areas of interest to the Air Force, both from a medical protection perspective and a bioweapon perspective. Before addressing possible medical areas of Air Force benefit, it is important to briefly discuss the Air Force's interest in computational biology and biowarfare activities.

The United States is a signatory to the Biological Weapons Convention and it is unlikely that the US will decide to pursue a bioweapons program. Computational biology will therefore not be used in relation to bioweapons. There is potential, on the other hand, for computational biology to enhance biodefence capabilities. This area is primarily the responsibility of the Defense Threat Reduction Agency (DTRA)[85] and is being addressed through their research efforts. Computational biology would not provide an apparent or additional reason for the Air Force (*per se)* to invest in this area beyond the plan already identified.[86] The Air Force should participate actively with the projects, if an air nexus develops. Due to the responsibilities assigned to DTRA, the Air Force should benefit from the results of the studies and there is no reason for the Air Force to lead or otherwise invest in computational biology-related biodefence projects.

As mentioned above, biofuels is another organic, biologically related area of potential interest to the Air Force. Computational biology could potentially assist with the development of the biofactories necessary to produce biofuels. There is significant commonality between the requirements of the Air Force and society at large regarding this and other beneficial products of computational biology. In areas such as fuels and biomaterials, it is unlikely that by 2025 the Air Force could achieve significant breakthroughs beyond those that may result from civilian led research and development, and there are insufficient Air Force-only reasons to wish to seek the lead. Although the Air Force does have a large vested interest in developing alternate fuel sources, within the timeframe under consideration computational biology is not likely to provide a solution. If there was not a

unique area of Air Force interest in computational biology, such as those presented below, then perhaps it would make sense to pursue computational biology and new fuel sources, but that is not the case. It should be sufficient for the Air Force to mine the results of other's efforts in this area, given the numerous challenges to be solved before computational biology can provide ready-solutions to bioengineering problems.

Health care is an area in which computational biology is commonly purported to offer benefits.[87] It is not surprising therefore that the ongoing computational biology projects associated with the Department of Defense are oriented around health care priorities.[88] The likelihood that healthcare and computational biology would offer significant opportunity should not be any different for the Air Force. Scientific and organizational leadership is already established in both the military and civilian aspects of computational biology and the health and biosciences, and the Air Force should attempt to take advantage of that existing expertise.

The Air Force should therefore apply its computational biology efforts in the area of health and medicine. If the previously identified significant challenges in computational biology could be overcome, then there is considerable potential for this new technology to make significant differences in bioscience and healthcare practices. Outside the reasons that the Air Force might avoid seeking leadership in health aspects of computational biology, there are reasons to believe that the Air Force should seek familiarity, or a certain level of competency, in the field of computational biology. The Air Force would accept considerable risk by not achieving the capacity to exploit computational biology rapidly, if and when the science is able to provide practicable results. What areas of health or medicine could the Air Force pursue to attain and maintain a competency in computational biology?

Air Force, Computational Biology, and Health Science Models

In many respects the Air Force's medical requirements are similar to those of the other services and the population at large. There is no particular reason for the Air Force to pursue a computational biology solution for the problems in "general" medicine, as it is expected that the other leaders in the field will pursue possible solutions. The Air Force should pursue solutions to problems which are related to aviation's distinctive requirements and operating environment. Two examples will be examined and their suitability for computational biology will be compared and contrasted.

Although computationally very difficult, one area of potential long-term interest is to determine the predisposition of different people to various Air Force operating environments, or Air Force tasks.[89] The Air Force could benefit from being able to accurately predict a person's susceptibility to environmental factors such as G-forces, or exposure to hazardous fuels. Combined with other biologically determined criteria, these factors could identify someone's suitability for employment as either a pilot, or an aircraft refueller, for example. Resistance or reaction to these stresses may result from a combination of physiological factors, not simply the presence or

absence of a particular gene. To be successful, the computational solution would provide a "computational model" of a specific human that could be subjected to any particular stress and the systemic response of that person could be determined. The idea is predicated on the linkage between a person's genotype and their phenotype, or their expressed characteristics. In addition, while a particular genotype would lead to certain characteristics, or phenotype, it might be the combination of many phenotypes that would determine how the person would react to external and internal stresses. The benefits of this capability to the Air Force would be considerable.

As stated above, the problem of using computational biology to determine the suitability of a person for particular Air Force employment is difficult and contradicts many of the characteristics already identified as desirable for a computational problem. First, this problem does not focus on a particular molecular level interaction, but rather attempts to model the effect of a large number of interactions at levels from the molecular to the cellular to the whole body. Second, this problem has many dimensions. These include the possibility that one's development and environment influence a person's reaction to stress, in addition to genetics and direct phenotypic factors. These additional dimensions combine to magnify the complexity of the problem making it highly complex. Third, it is difficult to visually represent the solution to the problem, which may reduce the capacity for multidisciplinary teams to work on it. Fourth, experimental data, critical for the development of an effective model, may be hard to obtain to support computational efforts. The difficulty with the experiments arises from the complex nature of the problem itself. It is certain that many experiments will be conducted over the next decade that will assist in understanding the relationship between genotype and phenotype. However, the complexity of the human system is such that the results will not be directly useful for computational solutions and would require many series of experiments to clarify the underlying relationships. Thus, experimental design would be complicated and may not effectively support the development of a computational solution. Lastly, this problem is effectively a systems problem, likely requiring a systems approach to provide a solution. A described above, a problem suitable to a combination of both systems and reductionist approaches is favored. In this case there are too many potential critical pathways, or "starting points" to allow a reasonable, efficient reductionist approach.

Although a computational model of human suitability for Air Force employment is unlikely by 2025, there is a more restricted problem of AF interest. It has been recognized that aviation warfighters are particularly susceptible to sleep disruption and that the rapid deployment across numerous time zones can cause risk to "safety, health, well-being, and mission completion."[90] The study of chronobiology is of relevance to the Air Force both for aircrew who deploy cross time zones as well as for shift workers who are required to maintain operations around the clock. There may be potential for increased problems with a growing emphasis on global expeditionary operations combined with the preference for reach-back operations from

continental United States to support the forward deployed locations. [91] Several methods have been studied to mitigate the impact of desynchronization, or "jet lag" on reduced cognitive performance. While stimulants such as caffeine may be appropriate in some circumstances, side-effects lead to the possibility of restricted use. A more fruitful approach might involve altering a person's circadian rhythm prior to the "time shift", in order to "preclude the jetlag."[92] Computational biology may provide the means to generate an effective model of human chronobiology. It meets many of the criteria for a problem amenable to a computational approach. For example, it deals with several molecular level elements, including the source of the circadian rhythm itself as well as the means to alter the cycle. There is the potential to seek molecular level understanding of the effects of melatonin or other compounds with similar effect.[93] In addition, the chronobiology problem is relatively bounded. On the surface it does not appear overly complex (albeit in the end it may be determined to be so) and should permit the science to focus on development of the model, rather than exclusively on the underlying science. Third, the question should permit integration of both reductionist and systemic approaches. In fact, a systemic model is already being utilized to both study and predict the effects of sleep deprivation.[94] The existence and utilization of a systemic model should assist the development of multi-level models of human chronobiology and may increase acceptance, by those who may otherwise resist, of other approaches, such as reductionist or molecular level models. Fourth, although the method of visually representing a chronobiology model is not readily apparent, visualizations are an element of the output of the systemic model. Similar to other dynamic cellular processes, it is likely that it will be possible to visually represent molecular and cellular aspects of the chronobiology model, once they are determined. Finally, given the relatively limited scope of the problem it should be possible to conduct experiments at many different levels aimed at further understanding the processes and rules affecting chronobiology. Experiments at the systemic level are already conducted and the use of a multidisciplinary team would allow experiments to be conducted through cellular and molecular level research.

The problem of chronobiology may present an ideal opportunity for the Air Force to pursue computational biology, developing the networks and expertise that will allow the evolution of a computational biology capability within the service. As previously mentioned, the Air Force should seek to leverage computational biology developments within DOD and commercial industry, to orient and assist its efforts. Addressing a problem important to aviation medicine, such as chronobiology and desynchronization, should permit the Air Force to maintain technological superiority over likely adversaries; the enduring hallmark of its success.

Risk Analysis

This section addresses the risks to the USAF associated with possible advances in computational biology. It will also provide additional insight into recommendations for the AF regarding development of computational biology skills and technology.

A fundamental aspect of the risk analysis will depend upon the likelihood of the dispersion of computational biology. The greater the dispersion then the greater the potential, presumably, that the technology would become available to an adversary of the United States. Many aspects of biology and biotechnology are expected to be widespread by 2025, but these are generally focused or specialized sciences and technologies that are already well developed at the undergraduate level.[95] On the other hand, computational biology is very complex, requires a high degree of integration of diverse sciences and technologies, and for the foreseeable future is likely to remain the purview of advanced multidisciplinary teams capable of intricate, demanding analysis and synthesis. The degree of sophistication to create effective simulations of a biological system is extreme.[96] It seems unlikely that the required skills will become available outside of highly networked, conventional, state sponsored laboratories and institutions. Given this expectation, what are the risks facing the USAF?

In the case of the development of computational biology by 2025, potential events that could present a risk[97] to the USAF are: 1) That another state or state-sponsored group develops computational biological capabilities ahead of the U.S. [98] 2) A failure of the USAF to adequately anticipate or prepare for advances in computational biology. 3) An inability to create computational biological solutions despite investment in the technology. 4) If the assumption that computational biology will not disperse is wrong, a leakage of this technology beyond state control would also pose a risk.

Unfortunately, the likelihood of the first of these occurrences is actually quite high. By some measures the U.S. lead in knowledge development is threatened, with the other countries generating an increasing proportion of advanced science and engineering graduates.[99] The conditions are thus favorable for others to take the lead in computational biology. Fortunately, if it occurs the consequences may not be too serious. Provided the technology is developed by a state sponsored organization or organizations, it is likely that that such a country or group of countries is relatively advanced and thus would be either friendly or at least non-hostile to the U.S. As a result, there is reduced likelihood that computational biology will be used for sinister purposes. Further, it is possible that one of these friendly, or at least non-hostile, states develops computational biology for beneficial purposes, and that the benefits will be shared. It is worth noting that this analysis presumes that probable adversaries to the U.S. would be unlikely to foster the advanced, sophisticated, multidisciplinary highly networked research teams necessary to develop computational biology to an effective level.

To mitigate the risk of another group developing computational

biology ahead of the U.S., a USAF-sponsored team would need to develop global relationships with computational biologists allowing the U.S. to remain abreast of developments around the world. This may prove difficult as some members of the U.S government oppose "increasing … scientific exchanges with China,"[100] which could work against these risk mitigation efforts. In the case of computational biology, reductions in scientific communication with technologically advanced or developing countries such as China would increase the risk that U.S. scientists were not involved in or aware of important advances. Due to its dependence on networks, computational biology is unlikely to progress as a well guarded secret. However, political obstacles to scientific communication could set the stage for technological surprise and should be avoided.

Another risk is that the USAF fails to prepare for advances in computational biology. As a multidisciplinary field, computational biology does not have an obvious "champion" within the scientific community,[101] and as such there is the potential that no one will advocate for pursuit of the funding and programs required to establish computational biology within the USAF. The USAF could easily assume that DARPA's computational biology program is sufficient for the military and that there is no specific requirement to become involved. Computational biology only offers a long-term potential and therefore AFRL and the USAF may find it more beneficial to invest in other technologies with more immediate promise. All of these factors combine to reduce the likelihood that the AF would eagerly pursue computational biology as a beneficial science. Yet, by not pursuing the science the USAF increases the probability of the risks associated with the failure to prepare for development of this technology.

As there are very few immediate consequences for the USAF as a result of failing to prepare for advances in computational biology, adequate risk mitigation is of low cost. Failure to mitigate this risk may have the consequence of surrendering America's traditional asymmetric technology advantage. To avoid this, the USAF should eventually get involved in computational biology, but could delay the decision until the technology was more advanced. Risk mitigation here should involve periodic reassessments of computational biology advancements to reassess the decision to invest or not.

The third risk is the possibility that the USAF invests in computational biology, but that the investment would fail to produce results. Because the probability of major computational biology breakthroughs before 2025 is low, the most serious risk here is that even if computational biology cannot be demonstrated, the efforts would likely produce advances in the many fields that contribute to computational biology. These advances are likely to have value, and failing to be on the leading edge of this research risks opportunity costs in other areas of interest for the Air Force. Looking ahead, this argument strengthens the recommendation that the Air Force support the pursuit of an aviation related problem by a computational biology team.

The final risk is that of proliferation of computational biology

technology beyond the realm of large state-sanctioned organizations. While unlikely, if it were to occur, the potential consequences for the U.S. are potentially serious, even if the risks to airpower are rather small. Quite possibly the greatest threat would involve the development of a novel biological weapon by a non-state actor. In contrast, the direct aviation-related risk of a non-state actor developing the capacity to effectively model or simulate biological systems would likely be low. Nonetheless, the impact of a novel biological weapon on the U.S. and her allies could be significant. .

To mitigate this risk, the Air Force should therefore support the requirements of the other agencies who exercise primary responsibility to mitigate the risks associated with bioweapons, such as DTRA, or other threats that would increase with advances in computational biology. Even though the direct threat to airpower is likely to be low, the broader threat to the entire joint force is such that risk mitigation is warranted.

The analysis indicates that there is generally low risk for the USAF associated with development of computational biology. The most dangerous aviation related threat is that a potential adversary country develops the technology ahead of the U.S. and the USAF loses an asymmetric technological advantage in a potentially beneficial emerging science, while the most likely possibility is that the USAF fails to invest or anticipate the advances of computational biology. The measures to mitigate these risks are related. Addressing the first risk practically eliminates the second one. In order to mitigate the aviation risk of a potential adversary developing the technology ahead of the U.S., the USAF should encourage its own growth and participation in the science. Particular attention should be paid to ensure that scientific exchange and involvement occurs with countries that have technological sophistication and growing national power. In the event that the USAF does not pursue a computational biology program of some sort, there remains the potential to mitigate the situation by implementing a plan to eventually become involved, as the technology becomes more advanced. Overall, the greatest risk is realized by failing to pursue computational biology at all, in which case the most dangerous risk may also become the most likely.

VI. Recommendations and Conclusion

Recommendations for the AF

Over the next 20 years, computational biology will offer great potential to increase understanding of some biological systems, and may provide new, powerful means for the Air Force to address specific problems of concern. The following measures are recommended and will permit the Air Force to maximize its preparedness for advances in computational biology; minimize the risks presented by the advent of this new technology; and situate the Air Force to maintain a position of asymmetric technological advantage:

1. Support Air Force involvement in an advanced multidisciplinary team or teams that will pursue a computational biology approach to solve a problem of interest to the Air Force;
2. Select an Air Force problem that arises from a molecular level interaction; that is relatively simple; that provides an opportunity to model both reductionist and systemic aspects of the system; that lends itself to a visualization of the system's simulation; and, that can be supported by experimental science;
3. Encourage development of U.S. science and engineering networks, especially communication and exchanges with teams studying computational biology in technologically developing and militarily capable countries; and
4. Identify a problem in aviation medicine, such as that of jet lag, "desyncronization", as a vehicle for the Air Force to develop and apply the techniques of computational biology.

Conclusion

This study examined the military potential of computational biology out to the year 2025, and identified possible considerations, risks, and actions for the Air Force. Advances in biotechnology and computer science have opened the door to a revolutionary understanding and manipulation of biological systems. A key aspect is the potential of computational biology, which could provide the ability "to simulate living things down to the smallest physical detail."[102] If effective "*in silico*" simulations of biological systems were possible, then it might open the door to intentional or designer biology, altering the manner in which health and disease are managed and providing opportunities to create novel materials with precisely bioengineered properties. Numerous projects directly relating to computational biology, such as those sponsored by DARPA, are ongoing with a view to exploiting the science's potential.

Computational biology is an exceedingly complex science that draws on the expertise of a wide range of scientific disciplines. Although based on many well developed sciences, the techniques that would allow the simulation

of biological systems are only starting to be understood. Numerous significant challenges, such as the lack of a satisfactory method of solving the multi-scale problems of biological systems, the stochastic nature of the intracellular molecular environment and the unparalleled complexity of biological systems reduce the likelihood that effective simulations of biological systems will be available by 2025. Even the significant advances in computing power expected over the next 20 years will not permit models to be created unless pending, fundamental scientific questions are resolved.

While there is potential that visualized simulations of complete biological systems will remain unlikely, computational biology should allow certain "*in silico*" solutions to be developed. Those problems that are most likely to lend themselves to a computational solution share certain characteristics that were identified and are reflected in the recommendations. Due to the enormous potential of computational biology the Air Force should develop a capability in the science from which it could expand if desired, or when the science is more mature. Resolving the problem of jet lag, "desynchronization," was suggested as an example of an aviation-centered challenge that the Air Force might successfully pursue.

The Air Force's risk associated with the development of computational biology was examined and is assessed as relatively low, regardless of the approach selected. Although the aviation related risks are low, there is greater risk associated with bioweapons as a result of computational biology's significant potential in the fields of medicine and materials. The risk is such that the Air Force should consider the requirements to support other defense and governmental agencies using computational biology to study this area. To mitigate any residual risk the Air Force should implement a plan to develop expertise in computational biology and should encourage international scientific and engineering exchanges.

Computational biology and the ability to visually simulate biological systems is not simply a fantasy. In the not too distant future it is likely that "*in silico*" simulations and models will form the foundation of a new approach to health care, warfighter management, and materiel engineering. There is an opportunity today for the Air Force to prepare itself to take advantage of this powerful new technology. As computational biology is not a sure thing or a guarantee of success in the next five or ten years there will be a temptation to not invest time, energy or resources in this new science. On the other hand, computational biology is sure to provide a winning advantage to those willing to master its challenges. As Dr. Dennis Waitley has said, "Life is inherently risky. There is only one big risk you should avoid at all costs, and that is the risk of doing nothing." And so it is with computational biology.

Notes

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[98] This risk assumes that a non-state actor or organization would not develop computational biology related technology ahead of the United States. The assumption is founded on the knowledge of the enormous multidisciplinary challenges faced by computational biology. While it is acknowledged that a non-state actor may be able to marshal significant scientific capability, in the timeframe under consideration it is seen as overwhelmingly unlikely that the many different disciplines necessary could be harnessed without the involvement of a state or at least state sponsorship. Nevertheless, the last risk will address the possibility that this assumption is incorrect and a non-state actor manages to develop and employ computational biology outside of state control.
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Maxwell Air Force Base, Alabama 36112
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