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Postgenomic futures: translations across the machine-nature border in systems biology

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ABSTRACT *This article discusses the production of new "postgenomic" knowledges that aim to be more ecological and "wholistic" than the reductionist genetics of the last forty years. It examines systems biology and, briefly, developmental systems theory, which are two approaches that attempt to model complexities in biology. System biological metaphors and languages have been in part taken from engineering models of automobiles, airplanes and robots and then applied to complex living systems. Systems biology is only the most recent example and perhaps an excellent case in which to study this movement back and forth across the machine-living organism border in Euro-American biology to track how what we know to be nature and machine is constituted. This article argues for a careful analysis of this historical production specifically around the question of what is lost in translation at these border crossings and their potential consequences.*

This article analyzes two developing approaches: systems biology and developmental systems theory. The major similarity between the two approaches, and their primary divergence from earlier genetic reductionist approaches, is their attempt to grapple with complexity in biology.[1] The Developmental Systems Theory (DST) developed in negative response to the genetic reductionism of early genomics rhetorical and theoretical approaches.[2] Systems biology developed in positive response to the vast territories of information produced by the genome sequencing projects.

A result of the genetic reductionist approach was the recognition of a complexity that could not be understood through genetic reductionism. It is this complexity that both approaches are developing tools to navigate and understand.

Neither of these two approaches is mainstream genetics. DST is still on the sidelines. Its practitioners include philosophers and biologists, and some of the philosophers previously were practicing biologists. Systems biology is too new a subfield in biology to have had an impact on the daily practices of genetics, but it is fast gaining attention. As we will see, these two approaches provide new and old perspectives on genetics, medicine, and biology more generally.

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However, systems biology differs greatly from DST in its reliance on mechanistic models and principles for modeling living organisms. Many system biological metaphors and languages are taken from engineering models of the complex systems of automobiles, airplanes, and robots and then applied to complex living systems. On further analysis, it appears that technologists have also built some of their models using biological research. Thus, systems biology represents the outcome of a series of *movements back and forth across the machine-living organism border.* This article argues for a careful analysis of this historical production of systems biology assumptions specifically around the question of *what is lost in translation* at these border crossings.

That is, each version of machine and living organism contributes to the final vision of what constitutes 'mind', 'body' and 'nature' in systems biology. As social and historical studies of science have shown, particular versions of social arrangements often become embedded in conceptions and technologies of nature and machine. Someone authors each concept and technology in particular contexts. This article argues that we need to examine this authorship and the ways in which such authorship becomes embedded in technologies as regulatory practices that in turn produce particular kinds of minds, bodies and nature. In order to do so, we have to understand which versions of machines and which versions of nature move back and forth, and when, across the machine-nature border in the production of systems biological knowledge. By examining these multiple border-crossings, we may be able to track how what we know to be nature and machine is constituted. I refer here not just to representations, but also to material natures and machines. The promises of systems biology—that is, fabricated organs, drug treatment regimes, and the 'healthy' body—are material productions and interventions.

An analysis of the production of systems biology with a brief comparative exploration of an alternative approach—in this case, developmental systems theory—may be useful for rethinking scientific research in process. That is, by examining researchers' assumptions, we open up the processes of scientific production to other assumptions and other parties who want to be involved in determining what are considered to be healthy bodies. This suggests that social studies of science, and genetics in this particular case, needs to study the production of science as well as the impacts of new technologies on society.

Complexity in biology

The end of the last millennium was a time of glee and disappointment in biology and medicine. The international human genome projects were nearing completion, but they left us with too few genes to account for the complexity of bodies, diseases, and therapeutics (e.g., Venter *et al.*, 2001). However, this news was only the final straw. Many biologists were already cognizant that genes were not going to solve all of their problems, especially biomedical problems. In 1998, NIH officials were already discussing strategies for integrating the 'tidal wave' of data produced by the human genome projects. They understood that

the style of analysis performed in benchside biology was not going to be able to make sense of the volume of data. Transforming data to knowledge and eventually to therapeutics and other products would they argued require another kind of work. A strategy that was then the 'buzz' of the community was 'bioengineering'. The idea was 'to bring together engineers, computer scientists, mathematicians, physicists and biologists to work on biological problems that are becoming increasingly multidisciplinary in nature' (Agnew, 1998, p. 1516). By 1999, interest in the multidisciplinary modeling of complexity to explore 'the systems of life' was evident in the building of multidisciplinary centers in major research universities across the country (Service, 1999). In May 2000, the National Science Foundation issued its call for research proposals on the theme of 'biocomplexity':

> Biocomplexity refers to phenomena that result from dynamic interactions among the biological, physical and social components of the Earth's diverse environmental systems. We commonly experience these phenomena as the 'whole being greater than the sum of the parts'. Biocomplexity arises from the interplay between life and its environment, i.e., from the behavioral, biological, social, chemical and physical interactions that affect, sustain, or are modified by living organisms, including humans. (National Science Foundation, 2000)

Today, we are told that the age of the genome is past, that the genome no longer provides all the answers, that we have instead Rnomics (for RNA), proteomics, systeomics, and physiomics.[3] There is even a journal called simply 'Omics'. The goal of the human systeome project, for example, is 'to complete a detailed and comprehensive simulation model of the human cell at an estimated error margin of 20% by year 2020, and to finish the identification of its system profile for all genetic variations, drug response, and environmental stimuli by year 2030' (Kitano, 2001a, p. 25). Genome researchers also asked for further funding to explore, for example, the growing importance of RNA in regulation in eukaryotes, the many complexities of protein structure (especially folds and loops) and activities, and interactions among genome, transcriptome, and proteome cross graphed with the interactions among the molecule, cell, organism, and ecosystem.

Systems biology: an attempt to solve the problem of biocomplexity

Systems biology is an emerging field of research that is part of the focus on biocomplexity. It is the new buzzword, just as bioengineering was the buzzword in 1998 and genomics was the buzzword in 1990. Systems biology promises to help make sense of the bits and bytes of information produced by the transnational genome projects. From James Watson to Francis Collins, genomics leaders have promised that genetic knowledge would help cure many of the ills of the world. Despite sincere hopes and hyperbolic rhetorics, they have been slow to produce significant clinical therapies or cures, especially for complex diseases.[4] The road from the bench to the bedside has been strewn with complexities

that reductionist genetics had not envisioned. Indeed, it has been argued that genetics is not a useful language for producing therapies for complex diseases. The difficulty is that common complex diseases like heart disease, cancer, asthma, and Type II diabetes have complex etiologies that likely involve small influences of many genes, interactions among genes, and interactions among genes, other molecules, cells, and environments.

The name 'systems biology' has been used by several different groups of researchers to refer to their approaches. For some, systems biology works as an umbrella term for projects focused on specific biological networks. For others, systems biology is defined in terms of its theoretical methods borrowed from systems theory, mathematics, statistics, computer science, artificial intelligence, physics, engineering, and robotics (which includes computer science and engineering) and applied to understand and model biological systems. This article analyzes systems biology approaches that provide theoretical frames, rules, and principles for modeling biological systems for different situations and entities and at different levels of function.[5]

In contrast to reductionist *genetics*, one could argue that systems biology is attempting to model biological complexities as organized systems in order to understand them. Systems biology seeks to explain how organisms function by using information on DNA, RNA, and proteins to develop systematic models of biological activities. It wants to connect networks, pathways, parts, and environments into functional processes and systems. The focus is on functioning organisms and less on environments, but systems biology does attempt to incorporate environments into its models.

An example of a complex problem that molecular genetics has not been able to solve is epigenesis. The molecular genetic framing of epigenesis has not succeeded in explaining the processes of development of different tissues and organs during embryonic development.[6] These processes proceed by successive gradual changes that are complex and eluded molecular genetic explanations. Early arguments that the processes are coded in the genes have not always been accepted as adequate explanations by embryologists. For example, they cannot explain the complexities of epigenetic expression where the same genes are expressed only when inherited from the mother, not from the father, and vice versa. Termed 'genomic imprinting', this mechanism is depends on the environment. Princeton biologist Shirley Tilighman (1999) called this the 'paradox of Mendelian genetics', where two individual organisms can have the same genetic sequence but show different states of heritable gene expression.

Developmental biology examines the elements and processes involved in the development of an organism—that is, how an organism develops differentiated parts and processes when each cell contains the same genome. Molecular genetics in its early days generally blackboxed development as a result of a complicated set of molecular instructions but in recent years has begun to analyze the processes through which complex properties 'emerge' by examining genetic and metabolic networks and pathways. That is, the detailed elements and processes are beginning to be pieced together.

In contrast to this detailed 'bottom-up'[7] approach of molecular genetics, systems biology addresses the problems of development and emergent properties by constructing principles for understanding the governance of the actions of individual elements and processes. 'The discovery of fundamental, systems-level principles that underlie complex biological systems is a prime scientific goal in systems biology' (Kitano, 2004, p. 826). Using these principles, they build mathematical models to simulate the interactions of DNA, RNA, proteins, and other elements including 'environmental' features like nutrition. They also test their models by simulating experiments to examine how these elements and interactions behave under varying conditions.

For example, one systems biology approach considered here attempts to meld ideas and methods from control engineering, mathematics, artificial intelligence and robotics to model biological systems at all levels of analysis. They use detailed molecular pathways as well as systems rules (e.g., robustness, see below) to frame an organism's functions and organism-environment interactions. The new systems biology speaks of a holistic or organismic materialism that researchers now consider achievable through new techniques and approaches and the wealth of information provided by the human genome projects.

In this fashion, systems biology's models of the functioning and development of organisms engages older discourses of wholism (e.g., von Bertalanffy, 1933, 1952; Weiss, 1955) and organicism, as demonstrated by the journal *Science's* March 1, 2002 issue's special section on 'Systems Biology'. The introduction to the section was entitled, 'Whole-istic Biology' and referenced their source of this word as Ludwig von Bertalanffy's 1967 introduction to his book, *General System Theory*, which included his writings that dated back to before 1940. Like von Bertalanffy, these approaches focus on regulation, on interactions among parts, on properties as emerging from these interactions, and on laws that govern organization of parts and processes.[8] The process of building new research programs often engages the past, whether in rhetoric or in actual ideas and technologies, thus producing traces of continuity (Fujimura, 1996, 2003).

The point I will develop is that following such traces of continuity will show that systems biology includes a host of approaches that bring different traditions of research, different epistemologies, and different ontologies to the subject of organic systems. Some approaches argue that physics is at the bottom of organic systems; others frame their studies in terms of mechanical models, others in terms of holistic approaches. Some still argue that reductionist methodology is the correct approach, while most no longer assume that reductionist genetics can answer questions of organismal functioning. (This, of course, does not include the host of molecular geneticists still working on reductionist genetics questions.)

The question I raise is whether systems biology as it is currently developing owes more to mechanistic ontologies of cybernetic systems than to von Bertalanffy's holistic ontologies. Before addressing this issue, I will describe the institutional locations of contemporary systems biology research.

Institutionalizing systems biology

In contrast to DST, systems biology appears to be gaining influence in the production of our present and future biological and medical research, even at this early stage of its intellectual and institutional development. It has been attracting attention from scientific journals, academic institutions, and private industry, as I discuss below.

Systems biology has been featured on the cover page of the journal *Science* (1 March 2002) and the journal *Nature Biotechnology* (1 October 2004). The Institution for Electrical Engineers (IEE) has begun publishing a new journal called *Systems Biology.*[9]

The laboratory that first named its research 'systems biology' began in 1999 in Tokyo in the Kitano Symbiotic Systems Project.[10] This institute was reconstituted into the Systems Biology Institute in 2004 as the Japan Science and Technology Agency's Solution Oriented Research for Science and Technology (SORST) Program because of funding changes.[11] Kitano's Systems Biology Institute's approach will be highlighted in this article, although I will present comparative information on others. Beginning in 1998, Kitano's Institute built model developmental systems of Drosophila as well as embryogenesis and neural systems of the worm C. elegans of genomics fame. Their Virtual Cell Laboratory involved modeling and analyzing aging, differentiation, and cell-cycle regulation of human cells. They have also developed models of yeast systems, cancer, and diabetes.

Kitano is a computer scientist originally trained in physics and artificial intelligence research. His systems biology has been developing in close collaboration with his robotics research. Kitano has also been working closely with John Doyle, a mathematically trained control engineer at the California Institute of Technology. Much of their work is an attempt to introduce systems theory from engineering into biology. Kitano's work integrates different methods and principles that are being used by many researchers in ways that help both to explain and promote systems biology as an approach and as a new field of research. Indeed, one could argue that he was the first to use the term 'systems biology' and to began thinking in terms of such integration.[12] Kitano summarizes systems biology in the following passage:

> To understand complex biological systems requires the integration of experimental and computational research—in other words a systems biology approach. Computational biology, through pragmatic modeling and theoretical exploration, provides a powerful foundation from which to address critical scientific questions head-on. The reviews in this special issue cover many different aspects of this energetic field, although all, in one way or another, illuminate the functioning of modular circuits, including their robustness, design and manipulation. Computational systems biology addresses questions fundamental to our understanding of life, yet progress here will lead to practical innovations in medicine, drug discovery and engineering. (Kitano, 2004, p. 826)

In 2000, Leroy Hood founded his Institute for Systems Biology (ISB) in Seattle, Washington. He had earlier founded the Molecular Biology Institute at University of Washington that has been engaged in wet lab studies of genes and genetic networks. Hood and his colleagues had been instrumental in developing technologies that have helped to produce the genetic information stored in databases and used in simulation studies. The ISB was organized in part to move his organization into the new era of systems biology. Ideker, Gaitski, and Hood (2001, p. 343) presented a formal definition of systems biology in their article, 'A new approach to decoding life: systems biology': 'systems biology studies biological systems by systematically perturbing them (biologically, genetically, or chemically); monitoring the gene, protein, and informational pathway responses; integrating these data; and ultimately, formulating mathematical models that describe the structure of the system and its response to individual perturbations'.

Harvard began a Department of Systems Biology, the first new department at Harvard in 20 years, in September 2003 and recently has publicized their program in posters that emphasize an approach based on systematic experimentation, measurement, and computation modeling. The faculty members' training includes organismal development (e.g., of cytoskeletons), biochemical pathways that regulate normal mammalian cell growth and diversions from those pathways (e.g., signal transduction pathways). Their PhD program encourages applications from students with backgrounds in biology, engineering, computer science, chemistry, physics, and mathematics.[13] While Harvard's is the first formal university department in the field, other universities have been hiring 'systems biologists' in the last two years.

Although they did not specifically use the term 'systems biology', many major research universities began to invest in multidisciplinary approaches to analyzing genomic data at the turn of this century. Many of these multidisciplinary centers focused on the interactions among genomic data including genes and proteins, but there was little mention of environments. Nevertheless, this focus on interactions could lead to systems approaches. The centers included Harvard, Princeton, California Institute of Technology, University of Chicago, University of Pennsylvania, Johns Hopkins, Stanford, University of California, Berkeley. [In the 2 April issue of *Science*, Service (1999, p. 81) published a list of institutions committed to the 'Building Boom in Multidisciplinary Centers'.]

The Institute for Advanced Study (IAS) at Princeton also established a new Center for Systems Biology. Originally begun as IAS's 'theoretical biology' group, the Center achieved its new name 'to reflect the biology initiative's new focus on research at the interface of molecular biology and the physical science' under the leadership of Arnold Levine. Their focus is on mining databases of genomic information to examine questions of evolution and development with interests in disease causation. 'Research interests of the CSB group include genetics and genomics, polymorphisms and molecular aspects of evolution, signal transduction pathways and networks, stress responses and pharmacogenomics in cancer biology' (IAS Newsletter, 2004, p. 4).

Although the above programs are oriented towards basic research, other institutions have practical applications as their research targets. The Department of Energy has begun a program called Genomes to Life, which uses systems biology to study problems of environmental cleanup and new energy sources. Francis Collins of the National Human Genome Research Institute (NHGRI) has generated a new project to connect genes to the environment.

Industry has also begun to invest in the systems biology approach with drug discovery and reverse engineering as their primary goals.[14] Chemical and Engineering News announced in 19 May 2003, that many companies are specializing in systems biology are building computational models that will connect the molecular with the physiological which is the basis for their drug discovery process. The companies include Gene Network Sciences that develops simulation of cells.

> 'Our mandate has been to exploit genomics, proteomics, and molecular biology data to create the world's most complete, sophisticated, and accurate computer simulations of human cells and bacterial cells...' The company, which has specialized in oncology and infectious diseases, currently has models of a colon cancer cell and *Escherichia coli* bacteria. (Henry, 2003, p. 51)

Entelos is a company that creates 'top-down' models. 'We start with the high level system phenomenon and work down.... The end point that we care about is not a protein-protein interaction' (Henry, 2003, p. 51). Instead, they aim at the behaviors of 'the integrated human system' to investigate the progression of diseases. Their aim is to find the gaps in the knowledge of the system in a process similar to that of reverse engineering. Another company, Genomatica, is modeling metabolism:

> Genomatica has concentrated on microbes such as E. coli and yeast. The models can be used to predict the performance of an optimally designed microbial strain. Genomatica researchers have found they can use selective pressure to force the organisms to evolve to reach the optimal state, which could have uses in designing microbial strains for bioprocessing and in finding ways to overcome antibiotic resistance. (Henry, 2003, p. 55)

What is systems biology?

Much of the buzz about systems biology may be hyperbole akinto that of the first excitement around biotechnology. Biotechnology too was going to produce bacteria that would gobble up oil spills in Alaskan waters. Biotech was going to produce drugs that would cure devastating diseases. Biotech was going to produce information that would allow scientists to genetically engineer bodies. In earlier eras, similar hyperbole was associated with artificial intelligence research and many other scientific projects that required substantial funding. Ten years from now, science journals will probably write about a new buzzword, a new hype. While the buzz associated with biotechnology has faded, the institutional

changes that it wrought—most notably, the alliances among academic biology, industry, and venture capitalism—continue to influence the conduct of biology today. Could systems biology produce a similar transformation?

A related set of discussions has circled around whether or not systems biology is really new.

I contend that systems biology is new and that it is worth our while to understand because it introduces new technologies for implementing high level principles in the modeling and simulation of the relationship between parts and processes that promises to represent biological functioning in a more complex fashion.

A major emphasis in systems biology is the modeling and simulation of biological systems according to particular principles or rules. There are differences in terms of which rules are dominant in any system, which system is in focus, which elements are included in a particular system, and whether and how these simulations are integrated with wet lab biological experiments. 'Wet lab' biology refers to research on living biological materials in contrast to 'dry lab' research that examines and manipulates biological information using computational tools. Computational experimentation is a major emphasis of systems biology. Experiments include introducing perturbations into simulated systems to see what happens under different conditions. The information used in the simulations is taken from databases.

Researchers also ideally like to confirm the results from simulated experiments in wet lab experiments. Some systems biologists conduct their own wet lab experiments (e.g., with viruses) and some work collaboratively with molecular biologists.[15]

> The goal of this research program is to establish a new paradigm of biological research.... We propose that computer simulation which models mechanisms of biological processes should be used together with actual biological experiments, instead of using abstract mathematics describing average behaviors of the system, so that results of simulation (which are virtual experiments) can be verified by tangible experiments.... (Kitano *et al.* 1997, p. 275)

As a pragmatic matter, the study of systems using computer simulation saves on high costs in time and money. Systems biology attempts to understand biological activities and events by considering many of the elements and activities involved in producing any one activity or element. The volume of information that needs to be considered and observed during manipulation is too much for wet lab experimentation. Simulation allows researchers to assess which values of the parameters that describe the system are likely to produce useful outcomes, before investing in actual molecular manipulations.

To return to our example of epigenesis, Tilghman (1999) states that 'the expression of individual genes is not being regulated by one, two, or five proteins but by dozens'. Some regulate specific genes; others work more broadly. Some sit on DNA all the time, while others bind temporarily. 'The complexity is becoming

mind numbing' (Service, 1999, p. 81). Thus according to systems biologists problems of epigenesis, development, and emergent properties benefit from the use of guiding principles to build mathematical models that simulate the interactions of DNA, RNA, proteins, and other elements.

In developmental biology, Gilbert (developmental biologist) and Sarkar (philosopher of science) (Gilbert & Sarkar, 2000, pp. 7–8) argue: 'emergent properties can now be approached experimentally as well as conceptually, and the time is right to re-assess Bertalanffy and Weiss' work in light of our new computational and biological prowess. Reductionist methodology[16] was required because one could not vary more than one component at a time and keep track of the results. Computers can do this.... The combination of microarray and computer technology may finally allow us to have a multivariable developmental biology of the kind that Bertalanffy and Weiss would have appreciated'. Gilbert and Sarkar present examples of some work already done and provide some examples of top-level concepts that are useful, even necessary, for thinking about developmental systems.[17]

A cancer geneticist I interviewed notes that Kitano's approach to systems biology allowed for the location of 'a key element in the analysis of the logical makeup of a system' that allows wet lab biologists to 'develop precise experimental ways to perturb the system and report on the response to perturbation...Kitano...gives ways by which to detect feedback loops and paths of causation'. The cancer geneticist further states that: 'I have read over Kitano's Nature Review Genetics article with some astonishment. He nicely packages a number of considerations, each of which has a long intellectual history: feedback—positive and negative; buffering (capacitors); evolvability; canalization; and good old phage lambda—on which I was teethed in moving from chemistry to biology... [This is useful for thinking about] how to link that emergent "systems analysis" with our emergent understanding of human biology'. This researcher regards Kitano's systems approach as useful in generating mouse strains—that is, in vivo systems—by which to analyze complex biological processes.[18] Nevertheless, the back and forth between simulation and wet lab experimentation is still rare.[19]

Some researchers involved in systems biology say that it is not a new field—that the analysis of networks and regulatory systems has always been around. Others say that it is basically what biologists have always studied—the physiology of cells. At the first International Conference on Systems Biology organized by Kitano in Tokyo in 1999, Nobel laureate biologist Sydney Brenner's comment to me was: 'What's new about this? This is what early physiologists were doing'.

However, the new systems biology is different from early physiology in several ways. First, researchers note that the data required to analyze complex physiological systems is now large and diverse enough to allow the kinds of analysis that were not previously possible. Indeed, the data sets are too large to be analyzed without a systems approach. According to Christophe Schilling, vice president and chief technology officer at Genomatica in San Diego:

> The difference is that it hasn't been until recently that we've had the experimental tools available to begin to look at biological systems.

> Those experimental tools... have forced people to take a systems approach. If you're faced with looking at a microarray with thousands of genes on it, it's [difficult] to understand that those are a thousand components that are all working together inside a cell. (quoted in Henry, 2003, p. 46)

Second, the focus of systems biology is different from the biology of physiological systems, according to Hans Westerhoff, a professor of microbial physiology at the Free University in Amsterdam. Systems biology focuses on the region between the individual components and the system. "It's different from physiology of holism, which studies the entire system. It's different from reductionist things like molecular biology, which only studies the molecules. It's the in-between" (Westerhoff, quoted in Henry, 2003, p. 47).

Similarly, according to Kitano (2002a, p. 1663):

> ...a system-level understanding requires a shift in our notion of 'what to look for' in biology. While an understanding of genes and proteins continues to be important, the focus is on understanding a system's structure and dynamics. Because a system is not just an assembly of genes and proteins, its properties cannot be fully understood merely by drawing diagrams of their interconnections. Although such a diagram represents an important first step, it is analogous to a static roadmap, whereas what we really seek to know are the traffic patterns, why such traffic patterns emerge, and how we can control them.

The difficulties of studying the interactions among the many variables in the system and those between different systems within a system are exacerbated by the enormous quantities and qualities of data. 'You have to be looking at multiple variables simultaneously and how they interact with one another, rather than any specific single variable in isolation', said Douglas A. Lauffenburger, professor of biological engineering and a member of the Computational & Systems Biology Initiative at MIT (quoted in Henry, 2003, p. 4).

In systems biology, new computational tools facilitate this multivariate analysis. For example, data mining is generally a bottom-up, brute force approach to analyzing vast quantities of data. However, data mining does not benefit from the kind of top-down, hypothesis driven analysis that early physiologists performed, in part because it is more difficult to formulate useful hypotheses when the amount of data to be considered is so large. This is because hypothesis driven-science of early physiology required that scientists have substantial knowledge of the biological organism or system in order to efficiently make useful hypotheses. Thus, in contrast and in addition to Leroy Hood's definition of systems biology where 'the integration of... two approaches, discovery and hypothesis-driven science, is one of the mandates of systems biology' (Ideker, Galitski & Hood, 2001, p. 344), I argue that there is yet another layer of top-down principles, which guide hypothesis driven science in systems biology.[20]

A fourth difference related to the third is the potential to simulate the impacts of different environments on organismal systems. Some researchers argue 'human systems biology could ultimately turn out to be more like an ecological problem than one of molecular biology' (Nicholson & Wilson, 2003, p. 669). Thus, for example, complex systems models could take into consideration the roles of diet, nutrition, and microbial factors in the development of complex diseases and in the efficacy, metabolism and toxicity of drugs in human populations. Nutrition has been considered to be a set of significant factors in disease susceptibility, progression, and recovery, but often was not taken seriously because direct causal links were difficult to model or experiment. Systems biology proposes to accomplish such modeling in mammalian—e.g., human—physiological systems.

Still, many researchers argue that biological models have a long way to go before proving themselves. In 1999, Marc Kirschner, a cell biologist at Harvard Medical School who became the Chair of Harvard's new Systems Biology Department in 2003, expressed this skepticism: 'Models haven't had a lot of respect among biologists. They don't have enough of the biological character built in', and thus often don't reflect the true complexities of real biological system' (quoted in Service, 1999, p. 82). Based on my recent interviews, this situation has changed and modeling and simulation have more respect now, but there are still reservations and questions.

Systems biology modeling: analogies to machines, cybernetic systems, and artificial intelligence

Perhaps because it attempts to encompass and explain organismal systems or perhaps because it builds on many traditions of biology, systems biology can be read as a history of modern biology, where organisms have been conceptualized through analogies with physical systems, mechanical systems, cybernetic systems (which were based on mechanistic systems), functional systems, and—as we have seen—holistic systems. The fascinating aspect of systems biology is that its narrative descriptions incorporate all these analogies. However, I suggest here that systems biology as it is currently developing owes more to mechanistic analogies than to von Bertalanffy holistic ontologies.[21]

Mechanical analogies and cybernetic systems dominate the principles guiding systems biology modeling and simulation. For example, the language of circuitry is ever-present in systems biology:

> Consider a hypothetical example where variations of gene A induce a certain disease. Susceptibility relationships may not be apparent if circuits exist to compensate for the effects of the variability. Polymorphisms in gene A will be linked to disease susceptibility only if these compensatory circuits break down for some reason. A more mechanistic, systems-based analysis will be necessary to elucidate more complex relationships involving multiple genes that may create new opportunities for drug discovery and treatment optimization. (Kitano 2002b, p. 208)

Gene regulatory networks, metabolic networks, and signal transduction networks are also part of systems biology discourse and work with mechanical systems analogies.

This mechanistic analogy is further combined with control theory in systems biology. Control theory is 'the mathematical study of how to manipulate the parameters affecting the behavior of a system to produce the desired or optimal outcome'.[22] Control theorists in engineering work on problems such as traffic flow and traffic control: recall Kitano's language in the last quote of the previous section where he describes the knowledge objects of systems biology as 'what we really seek to know are the traffic patterns, why such traffic patterns emerge, and how we can control them' (Kitano, 2002a, p. 1662).

Similarly, Leroy Hood likens his systems biology to solving problems in mechanical systems with control as a key ingredient.

> Let me use the example of a systems approach towards analyzing how a car functions. First, one would use discovery science to identify all the different types of elements in a car—mechanical, electrical, and control. Second, one would formulate a preliminary model of how the car functions from prior knowledge. Third, one would drive, accelerate, brake, etc., the car and use global technologies to measure how all of the elements behaved with respect to one another under these various conditions. The behaviors of the different kinds of elements—mechanical, electrical, and control—would be integrated and compared to the model predictions. Hypothesis would be generated to explain the discrepancies between model predictions and experimental data and a second round of hypothesis-driven, global analyses carried out and the results would be used to reformulate the model. This process would be repeated until the experimental data and the model were in agreement with one another. (Hood, 2002, pp. 25–6.)

Nicholson and Wilson (2003, p. 672), organic chemists, present a more dynamic, probabilistic, but still mechanical model of metabolism in the form of a Pachinko model diagram. A Pachinko machine is a pinball machine, many of which sit in rows on rows in Pachinko parlors in sites across Japan.

Finally, Kitano (2004, p. 829) explains robustness using a Boeing 747 as his model:

> The concept of robustness is best described using the example of modern aeroplanes. Many commercial passenger aeroplanes have an automatic flight control system (AFCS) that maintains a flight path (direction, altitude and velocity of flight) against perturbations in atmospheric conditions. This can be accomplished by a feedback control in which deviations from the defined flight path are automatically corrected. AFCS is the crucial component that allows the robust maintenance of the flight path by controlling the aeroplane's flight-control surfaces (rudder, elevator, flaps, aileron, etc.) and the propulsion

> system (engines). AFCS is generally composed of three modules with the same functions, thereby creating redundancy, although each is designed differently (heterogeneity) to avoid a common mode failure. Three computers are made that are modular, so that failure in one module does not affect the functions of other parts of the system. This type of mechanism is implemented using digital technologies that decouple low-level voltages from digital signal (ON/OFF of pulses), thereby preventing noise from influencing its functions. Although this is a simplified explanation of the actual system, the concept applies to details of the basic system as much as it does to the more complex systems. Although there are differences between man-made systems and biological systems, the similarities are overwhelming. Fundamentally, robustness is the basic organizational principle of evolving dynamic systems, be it through evolution, competition, a market niche or society.

Cybernetic theory and biological systems. Control theory is a close relative of cybernetic theory.[23] As I suggested earlier, control theory and cybernetic theory's views of the human-machine relationship are more dominant in some versions of systems biology than is von Bertalanffy's version of systems theory. Developed by scientists (e.g., Norbert Wiener, John von Neumann, Claude Shannon) working during World War II in operations research to develop war related technologies, cybernetics was framed as a command and control communication system. It incorporates information theory and systems analysis. In information theory, 'communication and control were two faces of the same coin', and 'control is nothing but the sending of messages which effectively change [control] the behavior of the recipient'. Biologists who also worked in operations research used some of this language to rethink problems in biology. Indeed, some of them used cybernetic theoretical and technological framework to rework biological representations of life itself.

According to historians of biology Donna Haraway (1981–1982), Lily Kay (2000), Evelyn Fox Keller (2000, 2002), and literary analyst N. Katherine Hayles (1999), the application of cybernetic theory to biological problems led to the formulation of molecular biology's view of the bodies of humans and other animals as information systems, as networks of communication and control. They further argue that cybernetic technologies alone were not capable of transforming biology; that language, metaphors, and analogies were critical for this reshaping of biology.

Most significant in this reshaping was cybernetic science's framing of problems of complexity. It was and is a way to think about how to control complex systems, to develop an order in a system that allows one to control complexity. For example, Keller argues that molecular biology began to seriously engage cybernetic theory when it had to deal with problems of development. She argues that the development of whole complex organisms could not be explained by

traditional embryology. In order to investigate this complexity, molecular genetics were incorporated. However, the molecular genetics of that era could not explain the complexities of development in part because of the limitations of Crick's dogma (DNA makes RNA makes protein). It was this meeting of developmental biology and complexity that led to the use of cybernetic theory to produce a view of the organism as a machine or a set of regulatory networks and simultaneously produced the field of developmental biology. As molecular developmental biology was born, so were feedback loops, cycles, and more.

Control and design. In this era of biocomplexity, cybernetic theory reappears as control and design. Kitano's Institute's approach aims at what they call the control and design method, a version of cybernetic theory's command and control. Control and design methods are especially aimed at producing designed biotechnologies, including promises of more effective cancer treatments and reverse engineered organs. For example, by modeling biological systems as mechanical systems, Kitano (2002a, p. 1662) hopes to delineate how the 'mechanisms that systematically control the state of the cell can be modulated to minimize malfunctions and provide potential therapeutic targets for treatment of disease'.

Kitano also argues that biological systems models will be used to simulate potential effects and inefficiencies of drug therapies.

> [Biological systems] models may help to identify feedback mechanisms that offset the effects of drugs and predict systemic side effects. It may even be possible to use a multiple drug system to guide the state of mal-functioning cells to the desired state with minimal side effects. Such a systemic response cannot be rationally predicted without a model of intracellular biochemical and genetic interactions. It is not inconceivable that the U.S. Food and Drug Administration may one day mandate simulation-based screening of therapeutic agents, just as plans for all high-rise building are required to undergo structural dynamics analysis to confirm earthquake resistance (Kitano, 2002a, p.1664).

Some systems biologists use design and control methods to develop 'strategies to modify and construct biological systems having desired properties' (Kitano, 2002a, p. 1662). In his article 'Reverse Engineering of Biological Complexity', California Institute of Technology control engineer John Doyle presents his plan to represent the biological complexity of the architecture of an organism and then reverse engineer it to potentially produce organs for transplantation and other applications (Csete & Doyle, 2002; see also Noble, 2002).

Doyle begins his reverse engineering by analogizing complex technologies, like the Boeing 747, to biological organisms. His argument is that they are alike in systems-level organization.

Control engineers and chemical engineers use complexity models in mathematics to model complex systems like airplanes, organisms, and now organs. They borrow key principles from mechanical systems and apply them to biological systems. Terms like 'robustness' and 'optimality' are examples.

Robustness

In engineering language robust systems allow organisms to adapt to and cope with environmental changes for optimal functioning. In order to promote robustness, control engineers try to build systems using four key parameters: feedback systems; redundancy—having multiple backup components and functions is key to keeping an engineered system robust; structural stability—where intrinsic mechanisms are built to promote stability; and modularity—where subsystems are physically or functionally insulated so that failure in one module does not spread to other parts and lead to system-wide catastrophe.

> Convergent evolution in both domains produces modular architectures that are composed of elaborate hierarchies of robustness to uncertain environments, and use often imprecise components... These puzzling and paradoxical features are neither accidental nor artificial, but derive from a deep and necessary interplay between complexity and robustness, modularity, feedback, and fragility. This review describes insights from engineering theory and practice that can shed some light on biological complexity. (Csete & Doyle, 2002, p. 1664)

Kitano relatedly has proposed a model of cancer as a robust system that resists traditional drug therapy. 'At the cellular level, feedback control enhances robustness against possible therapeutic efforts' (Kitano, 2003, p. 125). This control protects normal cells, but cancer cells—once they have been transformed from normal cells—may also have a similar robustness. Note the control engineering language in this next statement: 'Computer simulations have shown that a cell cycle that is robust against certain perturbations can be made extremely fragile when specific feedback loops are removed or attenuated, meaning that the cell cycle can be arrested with minimum perturbation'. Kitano (2003, p. 125) argues for a 'systems drug-discovery' approach that aims to control the cell's dynamics, rather than its components...'. Many researchers within academic and pharmaceutical laboratories are using a similar approach to develop more effective therapeutics.

> Given the importance of robustness for the understanding of the principles of life and its medical implications, it is an intriguing challenge to formulate a mathematically solid, and possibly unified theory of biological robustness that might serve as a basic organizational principle of biological systems (early attempts date back to the middle of the last century). Such a unified theory could be a bridge between the fundamental principles of life, medical practice, engineering, physics and chemistry. This is a difficult challenge in which a number of issues have to be solved, particularly to establish mathematically well-founded theories. However, the impact would be enormous. (Kitano, 2004, p. 834)

Limitations on analogies to biological systems

The control engineering approach appears to be a top down, engineered systems approach to biological organisms that begins with particular design requirements and principles. In contrast, biological organisms are ostensibly the results of evolution, which means that the organism and the species as well as the evolving environments are historically contingent products. Is the engineered systems approach too mechanistic and naïve, given the historical and contingent production of biological organisms?

Kitano has an answer for evolution. He encompasses evolution into his model of complex, robust biological systems:

> It is now increasingly recognized that robustness is ubiquitous. So, what are the principles and mechanisms that lead to the emergence of robustness in biological systems? My theory is that robustness is an inherent property of evolving, complex dynamic systems — various mechanisms incurring robustness of organisms actually facilitate evolution, and evolution favours robust traits. Therefore, requirements for robustness and evolvability are similar. This implies that there are architectural requirements for complex systems to be evolvable, which essentially requires the system to be robust against environmental and genetic perturbations. (Kitano, 2004, p. 829)

However, Kitano recognizes that biological regulatory systems cannot be fully analogized to mechanical systems. There are clear indications that he (and other systems biologists) recognizes that organic systems are more complex than current engineered systems. For example, when discussing the development of anti-cancer drugs, Kitano theorizes the robustness in of cancer disease states where cancer cells can alter themselves and their surroundings to promote their survival. The system he theorizes is a very complex one, more related to Developmental Systems Theory than to car mechanics:

> Although the general principles of robust systems are well established, there remain a number of unresolved issues concerning their evolution and execution in specific biological systems, and how they can be manipulated or designed. Control theory has been used to provide a theoretical underpinning of some robust systems, such as adaptation through negative feedback. However, this approach has limitations. For example, current control theory assumes that target values or statuses are provided initially for the systems designer, whereas in biology such targets are created and revised continuously by the system itself. (Kitano, 2002b, p. 208)

Representations of the complex human brain: from machines to biological systems to machines. Kitano was originally trained in physics and computer science. At one point in his career, he helped to develop a robot with human-like neuronal

control systems that would enable the robot to learn and develop. This was SONY's AIBO, a robotic pet dog whose name functioned as a Japanese word that means pal or friend and as an English acronym for Artificially Intelligent Robot. In his Symbiotic Systems laboratory (1999–2004), robotics engineers developed—among others—PINO, a pint sized walking humanoid robot and an artificial voice recognition system. For Kitano, robots were laboratories for his efforts to improve artificial intelligence software. For him, 'a symbiotic system' was the best way to format the development of artificial intelligence. 'Current research is aimed at the development of novel methods for building intelligent robotics systems, inspired by the results of molecular developmental biology and molecular neuroscience research'.

For Kitano, 'symbiotic intelligence' was a complex biological system analogized as a cybernetic system:

> The underlying idea is that the richness of inputs and outputs to the system, along with co-evolving complexity of the environment, is the key to the emergence of intelligence. As many sensory inputs as possible as well as many actuators are being combined to allow smooth motion, and then integrated into a functional system. The brain is an immense system with heterogeneous elements that interact specifically with other elements. It is surprising how such a system can create coherent and simple behaviors which can be building blocks for complex behavior sequences, and actually assemble such behaviors to exhibit complex but consistent behavior. (Kitano, 2001b, http://www.symbio.jst.go.jp)

Similarly, Rodney Brooks, MIT computer scientist and the director of MIT's Artificial Intelligence Laboratory, is credited with convincing the computer science world of the benefits of studying biological systems such as the human brain for developing robots and other intelligent machines. Brooks said that an understanding of the complex organization of biological systems could be used as the groundwork for establishing complex robotic systems:

> How it is that biological systems are able to self organize and self adapt at all levels of their organization—from the molecular, through the genomic, through the proteomic, through the metabolic, through the neural, through the developmental through the physiological, through the behavioral level. What are the keys to such robustness and adaptability at each of these levels, and is it the same self-similar set of principles at all levels? If we could understand these systems in this way it would no doubt shed fantastic new light on better ways to organize computational and post-computational systems across almost all subdisciplines of computer science and computer engineering. Thus our grand challenge is to find a new 'calculus' for computational systems that let us begin to control the complexities of these large systems that we are today building on an ad-hoc basis, and holding together with

> string and baling wire, instead of with genuine understanding. (Brooks, 2004)

In contrast to Brooks, Kitano became steadily less interested in robots and more interested in using computational systems to do systems biology. Kitano is now using control engineering and robotics to model living systems. He has moved from producing robotics that emulate biological systems to simulating biological systems using robotic systems.

Beyond the seamless border between humans and machines

The fascinating conclusion to the human-machine analogy is that systems biology appears to be one where the representation of *biological systems and engineered systems are converging in a kind of symbiotic interaction.* This representation makes sense when we remind ourselves that human scientists have been building what we know of both biological systems and engineered systems, and the analogies between the two, since at least the 17th century (e.g., Hammond, 1997; Otis, 2002; Morus, 2002; Westfall, 1978). John von Neumann used a formulation of how the human brain worked as his model for the first digital computer. It appears that systems biology, the most recent biological approach to understanding biocomplexity, represents the outcome of *movements back and forth across the machine-living organism border.*[24] One question I ask is *what is lost in translation?*

The writings of artificial intelligence ethnographer Lucy Suchman and feminist theorists of science Karen Barad and Donna Haraway are most relevant to my discussion of this question.

Suchman argues that the versions of human intelligence in artificial intelligence programs are representations of their designers' ideas of how human minds work.[25] AI and robotics researchers endow their designs with specific characteristics and definitions *they* define as 'human'. These include ideas about emotionality, embodiment, sociability, the body, subjectivity, and personhood. Although there is no one way that a human mind works, the field of artificial intelligence projects 'a kind of generalized humanism onto machines in a way that requires the denial of difference for its 'success' as a project (the basis for the famous Turing test)…. The subject in this imaginary is, at its core, the disembodied Cartesian brain/mind, connected to (in the sense of input/output) and propelled through a pre-existing 'world' via an ingeniously designed and instrumentally effective, but subservient, body' (Suchman, 2001, p. 2). Suchman's project is to make explicit the authorship of the version of the human that then becomes embodied in machine intelligence and to 'keep our eye on the ways in which autonomous machine agency might be consistent with regulatory practices aimed at producing certain kinds of humans and excluding others' (Suchman, 2001, p. 7).

> My concern is that far from recognizing the deep interrelations of persons and artifacts, contemporary discourses of the intelligent machine simply shift the site of agency from the human to his machine progeny. This does not mean that human power is lost.

> Rather, as in claims for the independent voice of nature in the practice of positivist science, the assertion of autonomy for technology depends upon the obscuring of authorship. And just as claims for nature's autonomy ensure the power of the scientist, it is precisely in the obscuring of authorship that the power of the technologist is renewed. (Suchman, 2001, p. 7)

Similarly, my purpose here is to make explicit the authorship of 'minds', 'bodies' and 'nature' as they are being created through systems biology and to argue that we need to examine the ways in which such authorship becomes regulation such that particular kinds of minds, bodies and nature are produced. In order to do so, we have to understand which versions of machines and which versions of nature move back and forth, and when, across the machine-nature border in the production of systems biological knowledge. By examining these multiple border-crossings, we will be able to track how what we know to be nature and machine is constituted.[26] I refer here not just to representations, but also to material natures and material machines. Robots, fabricated organs, drug treatment regimes, and the 'healthy' body are material productions and interventions.[27]

Karen Barad proposes the concept of 'intra-action' which is useful for thinking about this movement of concepts. Following physicist Niels Bohr's view that 'theoretical concepts are defined by the circumstances required for their measurement' (Barad, 1998, p. 94), Barad argues that concepts and theories are the products, not the foundations, of our interventions. More importantly, Barad argues that 'phenomena' formed through the process of 'intra-action' is the basic ontological unit in place of some idea of an 'object' (as in objectivity) that exists independent of all human interventions and a 'representation' that exists in the minds of humans. For Barad, phenomena are the results of the 'intra-actions' among the observers, the object observed, the tools with which we measure the object, and the circumstances of the measurement. Thus, the material observed is also active in its own production.[28]

Donna Haraway's notion of the body as a material-semiotic node is also an inspiration for Barad and for my analysis.

> The notion of a 'material-semiotic actor' is intended to highlight the object of knowledge as an active part of the apparatus of bodily production, without ever implying immediate presence of such objects or. . .their final or unique determination of what can count as objective knowledge of a biomedical body at a particular historical junction. Bodies as objects are material-semiotic generative nodes. Their boundaries materialize in social interaction; 'objects' like bodies do not pre-exist as such. (Haraway, 1981–1982, p. 208)

Machine intelligence then is the outcome of a particular kind of intra-action or material-semiotic node. In the case of cybernetic and information theoretic models and productions of nature, Haraway argues that cybernetics had at its base a structure meant to control and dominate, to achieve and affect power.

She argues that cybernetics is fundamentally a discourse based on domination and hierarchy. These 'command-control systems' were 'ordered by the probabilistic rules of efficient language, work, information and energy' (Haraway, 1981–1982, p. 246). In addition, argues Haraway, this view of the exchange and use of information for a particular end is an example of capitalist mentalities and theories of male dominance. Before capitalism, understandings of how nature (human, plant or animal) worked differed from a view of means and ends, of goal attainment. Cybernetics contributed to this capitalist view of animal behavior the idea that information was the key commodity of exchange.

Haraway maintains that cybernetics theory is not a reduction of social organization and human/animal behavior to biology. Instead, animal behavior too is read in terms of engineering, labor sociology (the organization of labor of Frederick Winslow Taylor), linguistics (semiotics, to understand how systems of signs affected behavior patterns), philosophy, and operations research. That is, the complex constituents in cybernetic engineering have shaped both the human sciences and Nature since WW II (Haraway 1981–1982, p. 251). Just as cybernetics produced models of nature then, so too are models of machine function being used to produce models of nature now.

However, Haraway's analysis is not without hope and optimism. Because bodies or theories are material-semiotic nodes, she argues that we can find or create other ways, other languages, for thinking about the body, about nature, about life that will be productive of 'faithful accounts of a 'real' world, one that can be partially shared and that is friendly to earth-wide projects of finite freedom, adequate material abundance, modest meaning in suffering, and limited happiness' (Haraway, 1993, p. 579). Her point is that once we understand that our ways of viewing and interacting with biological projects are material-semiotic productions, then we can seek alternative projects, alternative bodies and behaviors. Instead of command and control, perhaps we could consider co-existence or symbiosis?

These other possibilities will not happen without a lot of work. They cannot be wished into existence. 'It is possible to know something else, but only on the basis of equally concrete material practice and social relations nurturing other productions of scientific discourses and technologies' (Haraway, 1981–1982, p. 247).

Are there alternative discourses, alternative materialities? I argue next that developmental systems theory is a discourse that challenges and could develop systems biology in directions that are not based on a command-control framework.

Developmental Systems Theory (DST)

Developmental systems theory incorporates what appear to be more complex models of biology using development and ecology as their primary examples.

A diverse group of philosophers of biology, anthropologists, and biologists have over the last 25 years developed a perspective on development and evolution that

generally has been termed developmental systems theory. Susan Oyama has been one of DST's primary advocates, and her work was heavily influenced by population geneticist Richard Lewontin. Oyama and her colleagues have published several books on the topic.[29] There are differences and debates among these participants, as exemplified in their writings and conferences. This way of thinking has been regarded by some as unimplementable, undoable, unfeasible, except as a way of thinking, a philosopher's enterprise. Yet, it is more compatible with systems biology as presently conceived than is reductionist genetics, and it also serves as a comparative model for examining systems biological models. As I have argued in the last sections, biological models always incorporate theoretical assumptions and principles, including researchers' assumptions of minds, bodies, and nature. DST theorizing may help to expose these kinds of assumptions in systems biological models and wet lab experiments. Further, given the newly available genomic information, new informatic systems software for mapping regulatory networks, and the combined efforts of mathematics, statistics, and computer modeling, parts of DST models may now be implementable in the fashion of systems simulations.

DSTers also bring their own assumptions to the table. My point here is not to argue that DST assumptions are necessarily more correct than systems biology assumptions, but instead that each brings different assumptions with their approaches to understanding and intervening in nature. Thus, DST gives us a comparative framework for understanding systems biological assumptions.

DST writers provide an alternative conception of biology that manages to provide ways of talking about the material body without reducing it to the product of genes or any other static understanding of provenance. Their approach melds processes of an organism's development with ideas from evolution. For example, Oyama discusses the development of the organism's body with its behaviors within its various environments in what she calls a constructivist interactionist framework. The organism's body develops in conjunction with its behaviors within various environments through its lifetime.[30] That is, what an organism does, how it behaves, also affects the ways in which it develops in the future, all of which in turn affect its environment. DSTers do not deny the actions of genes, but neither do they put them front and center as blueprint. This was, in its time, an alternative to conceptions of gene action in molecular biology and a radical alternative to sociobiological discourses.

Oyama's approach to development and evolution allows her to bring the two processes together... 'by means of the concept of a developmental system: a heterogeneous and causally complex mix of interacting entities and influences that produces the life cycle of an organism. The system includes the changing organism itself, because an organism contributes to its own future, but it encompasses much else as well' (Oyama, 2000b, p. 1).

This sense of developmental and evolutionary interdependence of organism and environment over time attempts to avoid the traditional cleavages between nature and culture, body and mind, and permits different and fruitful ways of conceiving biology, psychology, and society, as well as different relations among the

disciplines. Instead of thinking of only genes and environment, this view allows for a multiplicity of entities, relationships, and environments. According to DST proponents it allows one to think in terms of multiple systems, interconnected and measurable on more than one scale of time and magnitude. 'The stunningly oversimplified distinction between genes and environment resolves into a heterogeneous and equally stunning array of processes, entities, and environments...' (Oyama, 2000b, p. 3). Instead of one-way causal arrows, they have two-headed arrows going in many different directions towards and away from multiple entities in and through many different levels. That is, DST also allows for a shift from single to multiple scales and many kinds of relations among scales (e.g., Johnston & Edwards, 2002).

The most intriguing formulation to me in DST is that it produces a different understanding and model of heredity. 'I have taken two kinds of critiques, of innateness in individuals and of the relations between evolving populations and their niches, and connected them by means of a broader notion of heredity than has been countenanced in contemporary science' (Oyama, 2000b, p. 4). That is, DST connects ontogeny (individual development) with phylogeny (the development over time of a species, genus, or group). DST also allows for a shift from central control to interactive, distributed regulation. So it is not the gene that controls development (of an individual or species), but in a developmental system, 'control' is instead multiple and mobile, distributed and systemic (Oyama, 2000b, p. 5).

> To claim that the genes contain already formed programs, representations, 'information', or other prime movers is not only mistaken, it is to miss the contextualized richness of these processes. To capture these processes, we need...[to] shift from transmission to continuous construction and transformation. We move, then, from hereditary transmission of traits, or coded representations of traits, to the continuous developmental construction and transformation of organisms and their worlds in repeating life cycles... A changed understanding of development alters our understanding of evolution. (Oyama, 2000b, p. 6)

Their genome is not the blueprint. It is complexity, system, interaction, and contingency that rule in developmental systems theory. Oyama and colleagues were arguing and pursuing this approach during the height of molecular biology's rise to power in establishment science and well before the Human Genome Project officially began. DST may play a role now that the genome projects have happened and produced the volume of information of which researchers need models and frameworks to begin to make sense of it all.

However, a major disadvantage that DST has faced is the very complexity of its ideas. The ideas in DST are so complex that they at times appear vague and difficult to sketch. For example, Oyama's books have a dearth of diagrams, models, illustrations. Many approaches have succeeded in dominating biological enterprises with the help of visual aids that have been critical to explaining the approach to others, to gaining allies. Recall Crick's Central Dogma with its

neat diagram. Oyama herself says that, after hearing her talk about her approach or after reading her work, some people still ask, 'So where's the beef? 'I have presented an alternative conceptual perspective on development, evolution, and the relations between them. This alternative yields new ways of interpreting and elaborating on observations, and suggests other lines of research. Along the way I have cited a great deal of relevant empirical work from a wide variety of fields, yet I regularly encounter the "Where's the beef?" question' (Oyama, 2000a, p. 203). She tried at the end of her revised book on the *Ontogeny of Information* to show the difference this alteration of perspective can make by discussing the levels at which a research program can be affected and produces some investigative possibilities using a developmental systems perspective. DST seems not yet to have convinced a majority of biologists that it provides the kinds of problems or detail necessary to make this approach workable.

However, there are a number of biologists who do work within DST or with a similar ontology.[31] These biologists raise the possibility of another way of conceptualizing complexity. That is, DST may be regarded as complex within one ontology but not within another. Within the frame of reductionist genetics or rule directed biology, DST appears as too complex to produce workable experiments. DST then represents a radical reframing for these researchers, a change in one's view of of parts and of relationships among parts. However, if one adopts a different ontology, DST may appear workable. As I have been reading the DST literature, I realize that I only have a limited understanding of their 'whole', their larger project. The same could be said for other readers who read only one article or a piece of the larger project. DST is calling for an ontological change that requires a major shift in thinking and practice.

Would it be possible to create a working collaboration between DSTers and systems biologists? Are their ontologies different enough to make a collaboration impossible? Why would collaboration be desirable? First, DST and systems biology already hold some common assumptions in high regard. Each, for example, focuses on interactions and emergent features. The commonalities could be the grounds for collaborating on particular problems that could produce interesting models and alternative interventions along the lines argued for in feminist theories of science. These alternative models and interventions are the answer to the second question. DSTers have over time developed a different ontology, and a wealth of detailed biological examples, of interactions in development and evolution. They have developed their ideas through explicit discussions of how social assumptions about humans, bodies, minds, and collectivities have been incorporated into ideas of nature as well as how particular views of evolution and development have become part of the canon of evolutionary theory. Their work demonstrates that we need to carefully study how our ideas of nature have come to be what they are before we use them to produce the next set of models and interventions. DST's discussions and analyses of assumptions could therefore be useful to the development of systems biology. In turn, systems biology's computational and simulation work can help to make DST more visible, can help to map parts and interactions. Through this mapping,

DSTers may refine their arguments and models. Such collaborations and interactions between the two approaches could then produce the alternative concepts, models, and interventions.

Conclusion

This article examines systems biology and, briefly, developmental systems theory which are two approaches that attempt to model complexities in biology.

Systems biology aims to represent gene networks, cells, organs, and organisms as systems interacting with each other and with their environments. It employs complex sets of biological networks to abstractly model these interactions. Molecular networks include protein-protein interactions, enzymatic pathways, signaling pathways, and gene regulatory pathways. Cells are now envisioned as elements in a cell-signaling pathway and in a cellular computing system. Epigenetic explanations are framed as networks of genetic signals that get turned on and off depending on elements in the organism's environments. Development is often discussed in terms of reverse engineering. Biological systems then are viewed as *engineered systems*, which have traditionally been described by networks such as flow charts and blueprints. According to Alon (2003), 'remarkably, when such a comparison is made, biological networks are seen to share structural principles with engineered networks. . .' For example, three of the most important principles shared between biological networks and engineered networks are 'modularity, robustness to component tolerances, and use of recurring circuit elements' (Alon, 2003, p.1866).

In place of Alon's amazement, I argue that it is not at all remarkable that biological networks and engineered systems share these principles. Mechanical systems have been analogized to model biological systems and vice versa since at least the 17th century in Euro-American biology. Most recently, molecular biology—which itself owes much to the cybernetic model—has produced the information in genomic databases that systems biology uses as the material it molds and simulates. More significantly, the border between organism and machine has been crossed multiple times in both directions, and systems biology is only the latest new field or 'discipline' that authorizes and promotes such border crossing. In place of amazement, we need to examine the production of these similarities.

Biology is an historical subject and object. It has been constructed of bits of things piling up, the accumulation of information, the sedimentation of ideas and objects. The human genome projects of the end of the 20th century enabled the collection of masses of information through mechanization, lots of labor, private and public funds, and competition. However, making knowledge of the information is requiring other tools, a change in methodology and ontology. Systems biology is attempting to provide rules and principles to organize these bits of information into systems that help to explain the function and dysfunction of organisms. Some of these rules, concepts, and principles are borrowed from artificial intelligence, robotics, computer science, mathematics, control theory, and

chemical engineering. The borrowed principles and methods provide the means to organize and explore information, to create models that can be used to test different values of parameters. They can also be used to manipulate systems to produce different natures, new biologies. These new biologies are and will be humanly produced. Human organs and pharmaceutical therapeutics will only be the beginning.

However, the rules, concepts, and principles that systems biology borrows from artificial intelligence, robotics, computer science, mathematics, control theory, and chemical engineering are not simply mechanical terms. Systems biology again is just the latest in a history of machine-organism border crossings. As just one example, Donna Haraway, Evelyn Fox Keller, and Lily Kay remind us that genetic networks and human behavioral models like sociobiology were the products of borrowings from information theory and cybernetics. However, Haraway also reminds us that there is perhaps no originary or final nature; that humans have been and are cyborgs incorporating human, animal, and machine identities. She further argues that humans have been engineering nature for a long time for our human benefit, economic or social, but that not everyone on the globe benefits equally, that some humans have more access to the means of scientific production than do others.

Systems biology increases both the quantity and kinds of exchanges among expertises to further obscure the border between human bodies and machines. For example, robotic-engineered systems have taken much of their form from understandings of biological systems and now robotic engineering concepts are being used to model living organisms. This further supports the conclusion that the historical production of knowledge and technologies of living organisms and engineered systems, and the rules used to analyze and manipulate them, have crossed the human-machine border too many times to maintain a clear distinction.

These multiple border crossings make it difficult to tease out the translations and transformations. Yet, tracking the slippages is necessary to the study of systems biology. This is where we who do the social study of biology can contribute to the analysis of the process as well as to the production of biological knowledge.

The reason for disentangling the materialities of engineered and biological systems is to delineate the various border-crossings in order to *understand what is lost in the translation.* By 'lost', I mean more than 'loss'. *Translations can distort, transform, delete, and add.* For example, although Kitano, Doyle, and Hood understand that the Boeing 747 and the automobile are too simple to emulate biological systems, they nevertheless use principles from these systems to model biological systems. In the process, their models still may excise whatever cannot be translated into the instrumental and technical terms of control engineering as they calibrate between biological organisms and virtual, artificially created advanced technologies. This excision does not make their productions any less material or real. Instead, one of my purposes for studying systems biology is to ask whether there are other productions that could have been made in their place.[32]

In order to answer this question, we need other models for making biological knowledge. I have suggested here that systems biology as it is currently being framed owes more to cybernetic theory than to von Bertalanffy's systems theory, to holism, or to DST's interactionism. One possible direction contemporary systems biology research could take is to seriously employ von Bertalanffy's systems theory or Developmental Systems Theory.

Developmental systems theoretical discussions of the organism's development and evolution (ontogeny and phylogeny) together with the kinds of systems biology that are being constructed by computer scientists and mathematically-inclined control engineers may together move the core of biology research away from gene-centric models and toward understandings of the body, the organism, species, and evolution in different terms to provide alternative biologies.

Each model of biology incorporates what researchers hope to accomplish, where they choose to intervene, how they choose to represent, etc. Each of the attempts above, systems biology and developmental systems theory, is one set of approaches, one kind of woven fabric. The final product, knowledge or organs, is *nature* with all its real consequences, biological and social. Those consequences may turn out to be quite different, depending on the models used to develop them. If engineering and command-control principles continue to dominate systems biology's modeling of living organisms, what will be its products and their social consequences? Does DST offer alternative models?

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Notes

1. Other ways of dealing with complexity include Kauffman's complexity theory.
2. By 'negative response', I do not mean that DST does not have a positive program. Both DST and systems biology have positive programs.
3. On systeomics, see articles by Kitano (2002a), Csete and Doyle (2002), Davidson *et al.* (2002), and Noble (2002) in Chong and Ray (2002). See also Kanehisa (2000) on 'Postgenome Informatics' and Fujimura (2003) on postgenomics and systems biology.
4. See Harris (2005) for the latest statement of this disappointment.
5. A colleague has argued that a majority of researchers use the term systems biology to refer to specific biological networks and that those who focus on theoretical frames, rules, and principles for modeling biological systems are in the minority. However, minority practice does not necessarily mean minority influence.
6. Philosopher James Griesemer (2002), what is 'epi' in 'epigenesis' depends on how one frames the 'genetic' in development and embryogenesis.

7. Note, however, that this detailed, 'bottom up' approach has been steeped in a theoretical perspective that is itself 'top down'. For example, Francis Crick's dogma that DNA makes RNA makes protein has governed molecular genetics research in the last forty years, until recent research has begun to look at feedback loops that show that this unidirectional model is far too simplistic. See, e.g., *Science*'s (2001, pp. 1063–1105) special issue on epigenetics. In contrast, DST questioned this dogma when molecular geneticists still believed in it. See, e.g., articles by Lewontin, Oyama, Griesemer, and Wimsatt in volume edited by Oyama, Griffiths and Gray (2001).
8. See Hammond (1997) for an excellent history of general systems theory.
9. *http://www.iee/org/Publish/Journals/ProfJourn/Sb/Index.cfm*
10. http://www.symbio.jst.go.jp/symbio2/index.html
11. http://www.systems-biology.org/
12. This in part is exemplified by the resistance to his initial simulation efforts around biological problems (see Fujimura, 2003).
13. See their website for more information: http://sysbio.med.harvard.edu/phd
14. Reverse engineering, for example, means working backward from a piece of completed computer hardware or software to figure out how this object has been constructed and then reproduce it. In organismal development, reverse engineering means working backward from the complete organism to figure out how development occurs and then reproducing that development.
15. See Fujimura (2003) for examples of joint wet and dry lab experiments and conflicts that prevent such collaborative projects.
16. I would argue that they mean reductionst genetics methods here. There are many forms which reductionism can take.
17. However, Gilbert and Sarkar lament the lack of bioinformatics work in developmental biology and appealed to developmental biologists to avail themselves of technologies to analyze computationally the mass of available data perhaps by retraining themselves into information scientists (Gilbert & Sarkar, 2000, p. 8).
18. Interview with author, 1 February 2005. This researcher also referred to a proposed project that would benefit and fit with Kitano's framing. This 'knockout mouse' project includes reporter inserts in every gene knockout as a key element in the resource.
19. I addressed the reasons for this lack of collaboration elsewhere (Fujimura, 2003).
20. Discovery science is, for Hood, basically the human genome project. It is the collection of 'genetic parts list of human and many model organisms; by strengthening the view the biology is an informational science; by providing us with powerful new high-throughput tools for systematically perturbing and monitoring biological systems; and by stimulating the creation of new computational methods' (Ideker, Galitski & Hood, 2001, p. 343).
21. A possible explanation is that systems biology relies on information in genomic databases as the material it uses to simulate. As Haraway (1981–1982), Kay (2000), Keller (2000, 2002), and Hayles (1999) argue, although with some differences, molecular biology was built on the cybernetic model. However, this question requires further research.
22. See Weisstein, E. W. 'Control Theory', from Math World, a Wolfram web resource. http://mathworld.wolfram.com/ControlTheory.html
23. See Mindell, Segal and Gerovitch (2003) for an excellent discussion of the relationship between cybernetics and control theory.
24. Similarly, social theories and biological theories have been analogized in previous centuries. Symbolic interactionism learned much from animal and plant ecology. Functionalism took as its model the biological functioning of organisms.
25. Philosophers Phil Agre (2000) and Hubert Dreyfus (1992) and sociologist Harry Collins (1990) have related critiques of AI.
26. See Traweek (1992) for border crossings in physics.
27. To acknowledge the agency of the material or biophysical does not mean that one accepts the readings of biologists, for example, as perfect understandings of those materialities. As the

literature in science and technology studies has shown, the practices that produce biological knowledge are formulated and performed by humans acting within cultures, social institutions, professions, career strategies, technical styles of practice, and established as well as novel protocols. Beyond the poststructuralist assumption that biology frames nature through particular lenses, science studies has demonstrated empirically how those frames and the particular readings have been produced in many different cases.

28. Bohr rejected the notion of representationalism, the belief that knowledge is a picture of an independently existing reality produced by an external observer who stands outside of the arena of investigation. Instead, Barad argues that Bohr's challenge to traditional epistemologies rejects the realism vs. constructivism debates.
29. See Oyama (2000a, 2000b). Oyama, Paul Griffiths, and Russell Gray (2001) edited a volume of articles entitled, *Cycles of Contingency: Developmental Systems and Evolution.* Population geneticists Richard Lewontin, theoretical ecologist Yrjo Haila, and philosophers William Wimsatt and James Griesemer are some of the authors included in this volume.
30. This framing of the development owes much to Richard Lewontin's and Richard Levins' critique of sociobiology in the 1970s. They aimed to break down the primacy of the gene by introducing a dialectical developmental explanation of individual organisms and species—especially in their *Dialectical Biologist* which was in turn based on much earlier articles published under the name of Isidor Nabi. Lewontin and Levins were both Marxists whose main targets were genic monism and 'reductionism'.
31. See, e.g., Johnston and Edwards (2002) and Johnston and Gottlieb (1990).
32. Like Barad (1998, p. 116), I argue that responsible science can take the form of 'refiguring material-discursive apparatuses of bodily production, including the boundary articulations and exclusions that are marked by those practices'.

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