To appear in: European Journal of Philosophy of Science, on-line July 2016 (in press 2017)

TITLE:

Interdisciplinary Problem-solving: Emerging Modes in Integrative Systems Biology

Miles MacLeod

University of Twente

Nancy J. Nersessian

Harvard University

Abstract:

Integrative systems biology is an emerging field that attempts to integrate computation, applied mathematics, engineering concepts and methods, and biological experimentation in order to model large-scale complex biochemical networks. The field is thus an important contemporary instance of an interdisciplinary approach to solving complex problems. Interdisciplinary science is a recent topic in the philosophy of science. Determining what is philosophically important and distinct about interdisciplinary practices requires detailed accounts of problem-solving practices that attempt to understand how specific practices address the challenges and constraints of interdisciplinary research in different contexts. In this paper we draw from our 5-year empirical ethnographic study of two systems biology labs and their collaborations with experimental biologists to analyze a significant problem-solving approach in ISB, which we call *adaptive problem solving*. ISB lacks much of the methodological and theoretical resources usually found in disciplines in the natural sciences, such as methodological frameworks that prescribe reliable model-building processes. Researchers in our labs compensate for the lack of these and for the complexity of their problems by using a range of heuristics and experimenting with multiple methods and concepts from the background fields available to them to search out good techniques and practices for transforming intractable problems into potentially solvable ones. The relative freedom lab directors grant their researchers to explore methodological options and find good practices that suit their problems is not only a response to the complex interdisciplinary nature of the specific problem, but also provides the field itself with an

opportunity to discover more general methodological approaches and develop theories of biological systems. Such developments in turn can help to establish the field as an identifiably distinct and successful approach to understanding biological systems.

1. Introduction

The influx of high-level computational, mathematical and engineering modeling techniques and new data collection technologies into contemporary biology is generating new approaches to complex biological problems largely unfamiliar to the traditional experimental approaches of established biological disciplines such as molecular biology. Philosophers are only just beginning to investigate and understand these practices, particularly the extent to which they transform biological practice and biological thinking. But what is also particularly interesting about these fields is their essential interdisciplinarity, which requires problem-solving based on the coordination of multiple kinds of expertise and multiple methodologies.

There is an emerging body of literature in philosophy examining interdisciplinary science which trace back to Darden and Maull's original exploration of "interfield theories" (1977); theories generated to explain phenomena that occur on the boundaries of established disciplines or fields. Interdisciplinarity is being tackled in a variety of ways. Many philosophers of science are seeking to understand and assess interdisciplinarity in science, particularly the need for multiple approaches to many problems, through the agency of traditional philosophical discussions about reductionism, pluralism and incommensurability (see for instance Holbrook 2013; Longino 2013; Mitchell 2003, as well as Darden and Maull 1977). Other philosophers are exploring the desirability of conceptual and methodological integration amongst specific fields, such as between evolutionary and developmental biology or cancer research (Plutynski 2013; Brigandt 2010; Brigandt and Love 2010; Love and Lugar 2013). The kinds of integration that can be studied on this basis are broad and include forms of integration that take place through model-exchange rather than collaboration (e.g. Ross 2005; Grüne-Yanoff 2011; the special issue in Perspectives on Science 21(2) 2013 edited by Grüne-Yanoff and Mäki). Yet others perceive that there is often a degree to which interdisciplinary interactions between fields might be contested or detrimental for at least one of the fields involved if another has imperialistic tendencies (see Mäki 2013). These tendencies need to be unearthed, and countered if unjustified.

What is lacking so far, in the philosophical literature at least, is a close examination of scientific practices in interdisciplinary contexts, and the variety of different forms of interdisciplinarity they give rise to. Recent work in this vein by philosophers of science has focused on understanding the practical social epistemological and methodological conditions interdisciplinarity requires (see Andersen 2010; Andersen and Wagenknecht 2013; O'Malley 2013; Leonelli, 2013). Our goal is to examine how interdisciplinary environments shape problem solving; that is, to identify particular problem-solving practices in interdisciplinary contexts and understand or explain why they have the form they do given the nature of the contexts (see Nersessian and Patton 2009; Nersessian and Newstetter 2014; MacLeod and Nersessian 2014).

In this paper we consider problem-solving methods and strategies in integrative systems biology (ISB), which models complex large-scale biological systems. ISB takes an explicitly interdisciplinary approach to modeling these systems, by attempting to integrate mathematical and computational knowledge of engineering, applied math, and computer science, with the experimental methods and biological knowledge of biochemical reactions and pathways that are the domain of molecular biology. Using data from a 5 year ethnographic study of two systems biology labs our aims here are to map out some of the methodological landscape of problem solving within this interdisciplinary field. We are interested in understanding the methodological choices available to researchers, how background conceptual frameworks structure their research, and the role that collaboration and integration play in their problem-solving trajectories.

We describe the interdisciplinary characteristics of ISB (section 2.1) and the problem-solving strategies researchers use in response to them (section 2.2). Problem solvers function in a highly *adaptive* manner to manage the difficult cognitive tasks that the lack of theoretical structure and shared epistemic values creates, searching out good methodological (including collaborative) strategies for transforming complex problems into tractable ones by drawing upon a wide range of background methods, concepts, and expertise. Methodological choices extend upward to different choices by lab directors for how to organize their labs, whether to collaborate externally or integrate internally the various skills required for building reliable models, and even the manner by which they choose to conceptualize the goals and aims of systems biology. *Adaptive problem solving* can be understood as a response to the complex problems and methodological uncertainty faced by researchers working in these interdisciplinary contexts. We argue that this kind of methodological exploration encouraged by lab directors also makes sense at the level of the promotion and development of the field itself, as it improves the chances of finding general methodological strategies and general theoretical results (section 2.3).

2. Problem-Solving in Integrative Systems Biology

Modern computational resources and new data collection technology have been the principal generators for the contemporary explosion in systems biological research. Systems biology, however, has a long history, notions of which stretch back to even before von Bertalanffy (Trewavas, 2006). The unifying idea behind systems biology is that a system as a constraint on the function, arrangement, and evolution of its parts. The modern field is about 20 years old and can trace many forms of influence including at the least von Bertalanffy's general system theory, passing through cybernetics, but also mathematical ecology, systems engineering, and physiology itself. Other streams leading to the systems approach include a history since the 1960s of mathematical models being constructed in molecular biology, at a small scale, which might be said to have been scaled up today due to the affordances of modern computation, as well as much work in mathematical biology itself on biochemical and physiological systems (Trewavas, 2006; O'Malley, 2005; Krohs, 2007).

Modern systems biology is not however one homogenous approach, but in fact a diverse collection of practices that represent different attempts to instantiate systems theory in biology (O'Malley, 2005). For instance, a small contingent of systems biologists are working in a tradition closer to cybernetics by seeking out a general theory of systems and networks, laws, and so forth. Most systems biologists, however, are looking for tools for modeling and controlling the particular systems or classes of systems they study, which leads to the diversity. As often observed, there are two main methodological streams in systems biology (Krohs, 2007; Bruggeman, 2007). The first, labeled top-down, imports and adapts concepts and techniques from systems engineering using new high-throughput data technologies to reverse engineer system structure. The branch we have studied, which identifies itself as integrative systems biology, lies in or closer to the bottom-up tradition. It tackles, in particular, biochemical systems, either metabolic or gene-regulatory. The principal goal is a systems-level understanding of large-scale systems, meaning in practice, to capture the dominant dynamical (quantitative) relationships of networks by virtue of mathematical representations.[1] ISB fundamentally requires an interdisciplinary approach to building systems models. The primary characteristic that marks the kind of interdisciplinarity we have found in our investigation of ISB is *epistemic interdependence*. Addressing phenomena at the biological systems level requires integrating experimental data and biological expertise from molecular biology with computational and mathematical expertise and methods from computer science, applied mathematics, and engineering. The interdependence arises because questions posed cannot be addressed without both benchtop data and computational modeling and simulation. Systems dynamics can only be analyzed computationally but adequate data of the right sort are required to build models and verify hypotheses stemming from simulations, when experimentally tractable. So collaboration among experimentalists and modelers is required for progress but given the disparate training of these researchers, as the situation now stands, collaboration is fraught with difficulties. Although we have interviewed both kinds of researcher in our study our focus has primarily been on the modeler. Much of the expertise and methods ISB draws upon in modeling was developed initially for non-biological systems, and there exist few methodological frameworks and experience for managing the integrative work. As we will see, these frameworks must be worked out in the context of specific problem-solving processes. We discuss below various aspects of problem-solving in ISB as evidenced in our research.

[1] As O’Malley and Dupre point out however there is not a well-developed concept of “system” that all groups and sub-groups share (O'Malley, 2005). Further many systems biologists are rather ambivalent towards pursuing a general theory of biological systems and acknowledge that a sufficient class of well-validated and robust models does not yet exist. They describe the current shared commitment of systems biologists as a commitment towards an approach that “foregrounds mathematical modeling in order to transcend piecemeal analysis.” (1273)

The findings we present and interpret here derive from a five-year ethnographic study of two laboratories in a major research university in the United States that self-identify as "integrative systems biology." They pursue quite different research strategies for building models. "Lab G," which represents the dominant practice in systems biology at this point in time, is a purely computational lab that works by collaborating with a wide range of experimental bioscientists. "Lab C," on the other hand, has a fully equipped wet-lab for its modelers to conduct their own bench-top experiments in the course of building models. They supplement their own experimentation by consultation, and in some cases collaboration, with bioscientists external to the lab. We have characterized these researchers as "bimodal" (MacLeod and Nersessian, 2013b, 2014). Researchers in both labs come from quantitative fields, mostly engineering, but also applied mathematics. In the five years we observed these labs, only one researcher had an undergraduate background in computer science, although in other labs in the field it appears to be more common. Lab G had a collaborator from a biological lab who, as a postdoctoral researcher, was transitioning to becoming a modeler and periodically visited the lab and proved to be a significant resource for the engineers' biological questions. The director of lab G also has extensive biological knowledge his researchers depended upon. The manger of lab C had an MS in biology (she became a graduate student near the end of our study) and the director of the lab was fully trained sequentially in engineering and then in experimental biology. Most researchers in both labs were PhD students, though lab G had a few postdocs. We also interviewed external experimental collaborators who worked with lab C and G members. We use ethnographic data-collection methods of participant observation (lab C), informant interviewing, and artifact collection. In both labs, we conducted unstructured ("open") interviews. We attended lab meetings and collected and analyzed relevant artifacts including Powerpoint presentations, paper drafts, published papers, grant proposals, dissertation proposals, and completed dissertations. We collected 44 interviews in lab G, 62 in lab C, and tape recorded 15 research meetings for lab C, 7 for lab G, and 2 joint meetings of the labs. Over the course of our research project[2], our researchers comprised 3 faculty, 2 postdocs, 1 graduate student and 1 undergraduate. Our expertise included philosophy of science, cognitive science, general psychology, linguistic anthropology, mathematics, and learning sciences.

2.1 The Interdisciplinary Characteristics of ISB

There are many varieties of interdisciplinarity in the sciences and studying problem-solving practices provides a way to develop more nuanced accounts (see, Nersessian & Newstetter 2014). The main characteristic of systems biology is that its researchers draw largely on the knowledge, concepts, and methods of a discipline (e.g., engineering or biology), but formulate problems that cannot be addressed without resources of one or more other disciplines. Thus there is an inherent *epistemic interdependence* among the collaborating fields, which is likely to remain given the complexity and sophistication of the research required from each participating field. This interdependence was

[2] This research was funded by the US National Science Foundation.

expressed perceptively by a senior bioscientist who was just establishing a collaboration with lab G and coming to understand the affordances of modeling for his research for the first time:

> *…team science is the only way it's gonna work these days. It's really gonna get hard to write a single investigator RO1 these days and expect to get funded because everyone is now realizing the interconnectedness of everything. And for me to be able to sit here and think that I can have all the expertise in my tiny little brain to do everything with all these approaches that I don't understand at all is ridiculous. So we really are trying hard to build a research team, and G4 [lab g director] has been part of this since day one. Absolute day one. So you know, we gather data, we talk with G4 about how those data need to be put together, and what kind of inferences can he help us generate out of them. But I'm never gonna be able to replace G4. It's not like I can hire a post-doc and just do it, right? You really need to have the interaction with people… you're gonna be much more on one side than the other. So you need the other half of your brain to be in another person, G4.*

But, it is important to keep in mind that such interdependence is also likely to affect mutual changes in understanding, methods, and other practices in regions of the participating disciplines. ISB is integrative in that it incorporates and adapts mathematical concepts, especially from systems engineering and control theory, as well as engineering modeling techniques, computational algorithms and methods from computer science, and experimental techniques, knowledge, concepts, and data from molecular biology.

Problem solving in ISB requires building, simulating, and verifying a computational model of the phenomena under examination. Research in the labs we investigated depends on both high-level disciplinary skills and expertise – an essential division of labor – but that the same time necessitates that researchers, whether biologists, engineers, or mathematicians, step outside of their backgrounds and engage with new or transformed methods and concepts, while integrating information from a variety of familiar and unfamiliar sources. Moreover, the particular nature and affordances of the problem-solving task, rather than a fixed methodological program or theoretical framework, dominate model-building. There is little yet in the way of standardized approaches that can handle the variety of data circumstances and most problems require tailored methodological solutions where parameter-fixing is concerned. Standardized approaches might not in fact be possible, which puts a premium on innovation and creativity in modeling processes. Problem solving is further characterized by numerous constraints inherent in the nature of the research space that pose a considerable cognitive load. These include constraints on: data availability and accessibility, computational processing and time-scale (different time-scales for conducting experiments and running simulations), experimental possibilities, and collaboration.

We have collected and analyzed the perspectives of researchers entering ISB from engineering, applied math, and biosciences and have gained first-hand insight into those skills and values they develop to manage this complex problem space – what we label an a*daptive problem space* (Nersessian and Newstetter 2014). It is notable that researchers in our labs, while claiming to do "systems biology," do not identify as *systems biologists* but rather identity functionally as *modeler or experimentalist* (sometimes, *biologist*). In this section we lay out some of the specific challenges for participants in this interdisciplinary space. In section 2.2 we develop an analysis of *adaptive problem solving* as a means through which ISB researchers manage the complexity of the problems they address.

2.1.1 Lack of shared methods, practices and epistemic values

The *modeler*, coming usually from an engineering background, faces three principal challenges for which they are usually unprepared:

1) Given *the nature of the research space*, engineers entering the labs are often:

1. uncertain of the role their background will play in systems biology modeling
2. unsure of what the methodology of systems biology is and how to operate without structured problem solving routines
3. unsure of the appropriate epistemic values of systems biological research
4. unsure of how to identify their own lab practices among the variety of methodological approaches that characterize ISB.

It is important to keep in mind that modelers are not trained as systems biologists, but as a kind of engineer (e.g. electrical or telecommunications) and thus prior knowledge often will not help them deal with these uncertainties. The importance of their background is not their knowledge of specific engineering systems, but rather their particular approach to problem solving, which they reference as the ability to "think systematically" and "debug problems." This enables them to cope with the lack of routines and unstructured task environments. Epistemic values that favor precision and exactness that come with handling engineered systems have to be transformed when dealing with "messy" biological systems.

2) Given the need for *biological knowledge and collaboration*, engineers entering the labs need to:

1. respond to and manage their lack of biological knowledge, which can be overwhelming
2. develop collaborative interactions with biologists as a source of data and knowledge usually without having any understanding or experience of experimental practices and possibilities in the biosciences.

Again, modelers face not only the hurdle of having to acquire biological knowledge and extract data from a literature in which they have no background, but also have to decide what is sufficient for the problem they are addressing. They need to develop relations with biologists (usually the PI of the biological lab, when they are graduate students in the modeling lab) without having understanding or experience of experimental practices and what is feasible in experimental biology.

3) Given the *complex non-task-orientated nature of problem solving of ISB*, engineers entering the labs need to:

1. identify the constraints on solving a largely unstructured, wide open problem
2. learn cognitive techniques for managing the complexity of biological systems.

Systems biology models complex non-linear problems that unlike the engineered systems they were trained to work on are "messy," "noisy," and often highly interconnected. Modelers need to learn how to make inferences about network data and structure based primarily on mathematical knowledge. Most importantly they need to learn how to rely on the affordances of the model-building process itself (Chandrasekharen and Nersessian 2015), iteratively using a partially built model to provide insight into the biological network to improve the model step-by-step.

The *experimentalist* entering into collaborations with modelers faces their own specific problems:

1) Given *the nature of the research space*, experimentalists entering into collaborations with systems modelers need to:
    1. modify epistemic values that devalue abstraction
    2. understand the affordance of models as a value in their own research.

One of the main issues we have observed to hamper collaboration is that biologists are deeply skeptical that a model can both abstract away information and still provide an effective representation. This attitude stems partly from their own lack of understanding of the nature and affordances of mathematical models and the power of mathematical methods to approximate complex relations in a simple manner. It is also not obvious to the biologist how a model might assist them in their own research, viz., how a simulation model can serve to direct experimentation more fruitfully and act itself as an experimental system.

2) Given the need for *collaboration on models,* experimentalists need to:
    1. understand the constraints and data needs of model-building
    2. be willing to adapt their experimentation to the demands of modeling.

In the current circumstances a collaboration usually starts with a biologist approaching a modeling lab and asking "I have some data can you model it," without any real understanding of the data demands for dynamic models. These demands are often not within the customary experimental practices of molecular biology, which does not usually need for its purposes the time series data needed by modelers. Experimental collaborators are often reluctant to give modelers access to the excel spread sheets of unused and unpublished data. Most modelers in our study were working with limited, incomplete parameter data, scavenged from the literature, and with data that were not clearly appropriate for their modeling tasks, such as *in vitro* data, steady-state data, or data for a related (homologous) system or the same system in another species of cell. This lack of data ramps up the significance and complexity of the parameter solving task for the modeler.

Challenges such as those listed prevent experimentalists and modelers from coordinating effectively on model building, and put constraints on what assistance in problem solving modelers can get out of a collaborative relationship. Difficulties in collaborative relationships magnify data problems, preventing modelers from obtaining the data they need to fill holes in the literature. This can be an even more difficult problem when there are uncertainties over pathway structure as there often are, leaving modelers to have to deal with these extra degrees of freedom in their solution spaces by having to model and compare several pathway alternatives. Often modelers have to compensate for lack of data through skilled mathematical, algorithmic and computational work such as inferring network structure mathematically, using bootstrapping algorithms such as Monte Carlo techniques to sample complex parameter spaces and applying simplification strategies based on mathematical argumentation about the structure of these parameter spaces.

We note, based on our research in lab C, collaboration is itself a methodological choice that individual researchers or lab directors can make, but it is not a necessary one. The lab C director, for instance, has provided wet-lab facilities and encourages modelers to learn to do their own experimentation, which relieves the need for significant collaborative interaction, although it does not alleviate the need for modelers to figure out how to integrate their models with existing molecular biological literature or seek expertise from molecular biologists. The lab C director, trained as both a modeler and a molecular biologist tries to fulfill this latter need in part and has also employed an MS-level molecular biologist to run the wet lab. However several of our researchers expressed the view that although there will be some bimodal researchers, systems biology is unlikely to make this the dominant strategy because of the difficulties inherent in obtaining the necessary training to do both modeling and experimentation well. Even the sequentially trained bimodal postdoctoral collaborator with lab G saw inherent difficulties in making this the dominant strategy of the field:

> *What I get from my personal experience is that I lose a lot of time going from one side to the other. … it would probably be more efficient to have a student doing lab work and another student dealing with the problems of modeling…. Both fields have their own problems, you*

know. Doing experiments is not a straightforward thing, a student needs to have his brain focused on that and the issues that will come from performing experiments. And performing experiments sometimes is an art. Just like modeling. (G7)

2.1.2 Lack of Background Theory and Task Structure

In attempting to take novel skills and resources from non-biological disciplines and apply them to complex biological phenomena, the field operates presently without established theoretical or methodological frameworks for modeling biological systems that apply generally (MacLeod and Nersessian 2013a). Unlike physics-based modeling, which dominates the philosophical literature on modeling, there are no theories of the biological systems phenomena to provide theoretical approaches that, if followed, reliably produce good models. Canonical modeling frameworks do exist, such as Biochemical Systems Theory (BST), that have been designed mathematically to be able to capture a range of nonlinear behaviors biological networks usually exhibit, within the degrees of freedom of their parameters (Voit, 2000; Voit, 2013). However such approaches do not cover the wide variety of data situations in which modelers find themselves. Modelers can have only steady state/equilibrium data; they can have incomplete time series data; they can only have *in vitro* data. Almost always, modelers need to tailor their approach to fit their specific data situation of the problem. Modelers often frame this as saying that they look at their data and see what they can get out of it. As G16, a graduate researcher who came to lab G from telecommunications engineering told us, contrary to her expectation, working on one project does not necessarily prepare you for the next:

… when I talk to G10, his project, like his kind of data are different. Like he has it for… different gene knockouts and then, more of steady state data. And then like G5's data are different. His are [not time series]…and then you could [get] creative with it, like you could say, I've tried different things and then it took me a while to realize that's not the way…that's not what I can use. Like G10 could use it for his project because of this and that. For me, it's not going to work because I have this dynamic data, which is different.

These differences require, for instance, choosing a modeling framework that best seems to fit what is possible with the kind of data, finding ways to extrapolate data, making simplifying assumptions about network structure or parameter values to fit what is possible with the data, and modifying the modeling framework mathematically. Something similar can be said about algorithmic strategies for parameter estimation.

To further complicate the situation, there are many modeling frameworks and other choices that modelers need to make, such as choices about what parts of pathways to represent and interactions to model; how to represent the interactions mathematically; which computer programs to model in; which data sets to rely on and so forth. As G16 explained the problem, *when you say "modeling" it's very broad,…like there's signaling pathways and there are metabolic pathways and they have their own specific things about them. And…no there are not routines. In each case, you see what kind of data you have and what you could do actually with them.*

In fact the need for pragmatism and flexibility is built into the fabric of our labs. A successful result can be simply obtaining a robust representation in accordance with the data that makes successful predictions. Solving the problem is prized, irrespective of the method used to solve it. Again, in G16's words:

It's just….solving the problem – doesn't matter how. Like figuring out – getting information from the data…and the other thing is changing the system so that you get the effects you want to have….And then whatever method you want to use that's fine with him… G4 thinks that if you get certain results with that – that's enough for a PhD. 'Cause that means you understood the systems.

This pragmatic stance in the face of the complexity of the problem-solving tasks is well-established in ISB, and pragmatic attitudes about the role and value of models were frequently expressed by our interviewees.

As such bringing quantitative and biological knowledge, methods, and researchers together to tackle unfamiliar and highly complex biological problems generates distinct characteristics for ISB. Despite the epistemic interdependence, the background disciplines are not set-up to be integrated smoothly. Researchers from these disciplines differ widely in their knowledge, methods, and epistemic values. Further modelers, themselves, lack a theoretical framework for model-building; they especially lack task routines. Background disciplines like engineering provide few methodological constraints that must be followed in ISB modeling. As a result, in our investigation, problem solving never proceeded by following and relatively smoothly integrating canonical problem-solving strategies. Problem solving works *adaptively* in this interdisciplinary context.

2.2 Adaptive Problem Solving

To handle their complex problems given the lack of disciplinary affordances of standardized methods and routines, and the difficulties of collaboration, modelers engage in what we call "adaptive problem solving." We introduced the notion of an *adaptive problem space to* capture the kind of problem-solving context in which managing the complexity and uncertainty of biological systems requires iterative and incremental methodological adaptation and problem transformation that we have hinted at above. All problem solving is, of course, adaptive to some degree, but what is remarkable about ISB is the extent to which routine problem solving depends upon its researchers being able to think innovatively and adaptively under a heavy cognitive load.

In our study of ISB we find that the problem-solving processes often require transforming a problem from one that is too complex to solve in the current context into one that can be solved through iterative processes that search through and adapt strategies for representing the problem and spaces of solutions given the governing constraints. Within adaptive spaces there is no ready-made path or reliable theory-guided routines for finding acceptable solutions. Instead researchers must rely heavily on adaptive strategies, often improvised ad hoc, to explore and understand their specific problem and try out whatever tools they can find that work to explicate it and solve it. This includes making mathematical inferences about new components that modelers calculate need to be in a network to get it to function properly, but are not yet accounted for in the biological literature.

Adaptive problem solving employs strategies of problem transformation that incorporate and integrate experimental, computational, mathematical, and engineering approaches into systems biology. In this interdisciplinary context many of these methods have themselves to be adapted for the new subject matter and research environment. We witness two main kinds of transformations in the labs we studied. The first are *problem transformations* and the second, *conceptual/methodological transformations.* Problem transformations generally happen at the level of the individual problem to simplify or get better traction on it. These are imported engineering strategies and heuristics that help transform the dimensions of a problem. For instance, modelers, sometimes with advice from bioscientists, might situate a network under study within a broader network, on the basis that the broader network reveals connection between parameters in a sub-network ways that have an important effect on the behavior of the sub-network and helps elucidate otherwise confusing dynamics. Another quite common strategy is to use an engineering method called sensitivity analysis to isolate the elements of a network that play the most significant role in the dynamics of the network. This can be used to simplify the network representation or to identify parameters that do not have too great an effect on the dynamics within reasonable biological values. These parameters can be just assigned values to reduce the parameter-fixing problem. Additionally, modelers often black-box component systems or component interactions to reduce the complexity of their problems and, conversely, un-black box them if it appears that a subsystem is having a nonlinear effect on the network. And, if building a good model does not seem resolvable for a given network, an alternative that exhibits the same or similar phenomena which is simpler or for which better data are available is worked on instead. Researchers we studied often switched systems in this way or switched cell types for the sake of better data, with the hope of being able to modify the model in the direction of the original problem.

The second kind of problem transformation can take place both with individual problems but also at a higher theoretical level. This form of adaptation is built around importing and transforming concepts and methods from other fields, particularly engineering and mathematics, to abstract biological phenomena into a form appropriate for mathematical and engineering-type analysis. ISB modelers import and adapt concepts and methods from engineering and mathematics at all levels, from the individual problem to designing methods for classes of problems. As stated, the conceptual resources of systems biology derive to a significant extent from engineering, particularly control theory, which has developed techniques for measuring and deciphering electronic signaling networks. Systems biologists have borrowed concepts such as system control, modularity, redundancy, noise and sensitivity and adapted them to biological contexts over many years preceding modern computational systems biology. Metabolic Control Analysis, developed from the 1960s is based on engineering analysis of network control which derives from sensitivity analysis in engineering (Westerhoff, 2009). We have found that individual modelers in our labs often experiment with their own adaptations from their different engineering backgrounds. For instance, one researcher we tracked who had a background in telecommunications engineering was trying to apply wave-smooth techniques from signal processing to smooth noisy biological data. In fact almost all the methods ISB modelers use are adapted from, or bear a close relation to, those used in systems engineering and other engineering fields. These include, but are not limited to, simulated annealing methods of parameter-fixing, Monte Carlo tools of parameter estimation, and nonlinear network analysis.

Applying these engineering methods of network analysis to biological systems requires conceptual transformation of the underlying biology into a form that can be subjected to this kind of analysis, which can be quite foreign to the largely non-quantitative approach of molecular biology. As researcher G2 expressed it, what she and her fellow modelers do with biological systems, *"we take a map that a biologist has drawn and in some sense translate it into a map we can deduce math from."* The pathway diagram, which is familiar to biologists and can be used in collaboration, plays the key role in this transformation. While for molecular biologists the pathway diagram represents a set of qualitative causal relationships amongst molecular elements, for modelers the arrows can be represented as rates and the nodes as concentrations of molecules. In G2's words modelers put *"[mathematical] meaning into the arrows*," by giving them precise quantitative values. This process necessarily involves much simplification and abstraction of what they refer to as "messy," "dirty" and "noisy" biological systems and adaptation of engineering methods to such systems so that they can be modeled quantitatively. Resolving the data into a meaningful and useful form for models is a significant challenge that often requires ingenuity in methodological adaptation, such as the data-smoothing technique from signal processing we mentioned above.

In general, situations that call for adaptive problem solving include following features:

1. complex uncertain problems: problems lacking data and accessible information

2. unstructured task environments: no widely effective problem-solving routines, need for methodological flexibility and innovation

3. many possible solutions: different models produced by different methods may be equally adequate representations of a system

4. dependence on constraints: modeling strategy dependent on available and accessible data or other constraints. Constraints cannot be satisfied independently.

Specific adaptive responses apply to the particular dimensions of the problem being addressed. Common ones mostly learned from engineering include:

1. situating the network under study within a broader network: the broader network may connect in important ways to the original and help elucidate otherwise confusing dynamics

2. isolating dominant network elements in order to create a simplified network

3. black-boxing component systems or component interactions or alternatively de-black-boxing them

4. network replacements, such as finding a simpler network that exhibits the same or similar phenomena for which better data are available.

Implementing these responses often relies upon not just bringing in engineering methods, and computational and mathematical techniques that can facilitate them, but also biological knowledge that helps discriminate good moves from bad ones. In general researchers frequently work across these disciplinary boundaries by experimenting with and using combinations of different methodological approaches, heuristics and conceptual resources from these background fields, and applying them to help transform or re-represent their original problem in more solvable ways. Failures provide invaluable insights into their problems, and information on what to try next. As a result researchers acquire new skills and new knowledge in fields they have no formal training in. In our study the degree to which lab directors allowed graduate students and postdoctoral modelers the flexibility to choose how to solve their problems and what background methods and concepts to rely on was quite remarkable.

Adaptive problem solving can be rationalized as both a response to complexity and a response to the lack of disciplinary constraints. It provides a cognitively manageable strategy for handling complexity where disciplinary guidance is lacking. As in the case of any interdisciplinary field, the relationships among background methods and theories and problem-solving choices and strategies are more complex than in the disciplinary case. For philosophers seeking to understand problem solving in interdisciplinary contexts, it is necessary to understand how the background methods and theories of the different disciplines mesh in problem-solving processes so as to delimit the possibilities for and scope of interdisciplinary interactions and integration within the field. This kind of investigation can help us zoom in on the novel and particular features of organization that interdisciplinary fields might exhibit.

2.3 Adaptive Problem Solving and the Development of Integrative Systems Biology

Adaptive problem solving can be rationalized as a response to both complexity and a lack of disciplinary constraints faced by individual researchers operating in these complex interdisciplinary contexts. The result is a high degree of methodological diversity and localized problem-solving that make it hard for this new field to identify a canonical sets of methods and theories which would unify the field or solidify ISB in substantial way, beyond its broad philosophical claims about the need for "systems thinking" and for the use of mathematics and computation. This makes it difficult for many of its participants to construct meaningful identities as "systems biologists", insofar as there is nothing yet substantial to identify with (see Osbeck and Nersessian, in press). Further insofar as methodological unity and a body of theory is important to the status and legitimacy of a field, it might seem counter-productive to allow and support adaptive problem-solving as a principal mode of working. However, we suggest here that the strategy of adaptive problem solving is a reasonable response for achieving such goals in the complex interdisciplinary contexts systems biologists face.

As we have noted the researchers we interviewed have a hard time identifying themselves as systems biologists due to lack of a body of theory or common methodology with which to identify the field. Some systems biologists are relaxed about this, defining systems biology rather loosely as just the application of mathematics and computation to biological systems (see O'Malley and Dupre 2005). At the other end of the spectrum however some systems biologists perceive the justification for mathematical approaches to lie in their ability to produce general results and insights. They identify success on these terms as a mark of scientific maturity and source of validation for systems biology (see for example Westerhoff and Kell 2007). Theoretical progress in the application of mathematics contributes to methodological development. Theories like Biochemical Systems Theory are attempts to create general methodological platforms that can be applied across a large class of biological systems and studied to produce general knowledge about such systems (Voit, 2000).

The labs we investigated do take different stances on the theoretical goals of systems biology. As such even the basic understanding of what the field is supposed to achieve remains open to discussion and evaluation (MacLeod and Nersessian 2014). The lab G director promotes general theoretical goals for systems biology as a field, including the discovery of design and operating principles. The lab C director is however more pragmatic and sees the role of the field more as an adjunct for molecular biology, assisting it to advance its own theoretical agenda through models, but not aspiring to any kind of general mathematical theory of biological systems. Both labs are however deeply concerned with methodological development and developing better more general problem-solving strategies as a measure of progress and success in the field. Likely any scientific field is invested in such goals. Methodological development does not just help vindicate the field, it creates a core of techniques its practitioners can teach to its students as identifiable systems biology methodology, it reduces the stress on graduate researchers and improves the efficiency of problem solving. These are all desiderata for establishing the field as a distinct, productive and ongoing enterprise.

As noted however the adaptive problem-solving practices we have described within the field seem on their face inconsistent with these goals. Researchers are not generally required to follow particular methodological norms but are instead encouraged to pursue whatever strategy works for the problem they have. The lab G director has preferences, but is reluctant to require them. This relative freedom and flexibility makes sense as a general field-wide strategy for discovering effective general methods and theories.

One way to see this is to draw from the frameworks developed in formal analysis of divisions of cognitive labor. Weisberg and Muldoon (2009), using agent-based models, model scientific discovery as a step-by-step search by agents through an "epistemic landscape" for productive or epistemically significant methods based on hill-climbing heuristics that guide how researchers explore that space. Hills in these landscapes represent the value of any particular methodological approach for solving a particular problem or sets of problems. The tallest peaks on the landscape represent the best choices. One can produce search algorithms representing different types of scientific personalities – mavericks versus followers – and analyze what combination of each might be best in a given situation. Mavericks prefer to move away from already crowded methods, followers towards them. Weisberg and Muldoon reason from their model that in "normal science" contexts a small ratio of mavericks to followers is the most cost-efficient ratio for scientific discovery. In March's (1991) words systems that "engage in exploration to the exclusion of exploitation are likely to find that they suffer the costs of experimentation without getting many of its benefits" (71).

In the ISB case epistemic landscapes are rendered complex by the many untested methodological choices and possible combinations from different disciplinary backgrounds for particular classes of problems. These choices extend over almost all levels of scientific activity from mathematical methods up to lab organization. Given the complexity of the problems involved it is very hard to evaluate how they well any will work until put into practice. Together this implies rather bumpy epistemic landscapes in ISB. These landscapes must be highly multidimensional in order to capture choices over which background methods to adapt and background fields to rely upon, and also whether or not to divide cognitive labor amongst different specialists or create bimodal researchers, and choices over problem-solving environment, such as whether labs should include both experimenters and modelers. In this context a rational field-level strategy would be one that allows or even prefers individuals to explore methodologically diverse options in order to develop as much knowledge about the value of different methodologies as possible. This approach provides a greater chance of understanding just how problem-specific methodology needs to be and spotting the more productive methods without getting stuck following less productive options.

Researchers in ISB clearly see benefits of methodological diversity at this stage of development of the field. The lab G director, for instance, while committed to certain methodologies and the theoretical development of the field, encourages his researchers to do whatever works best and to work out the mathematical details for their approach themselves. He allows his researchers to traverse a relatively wide space of potential engineering, computational, and mathematical possibilities. Methodological diversity extends to the organization and operation of research within the field, which experiments with lab organization as part of the exploration of the best and most efficient methodologies for combining resources. The lab C director, for instance, relies on bimodal researchers who do their experiments and modeling. Lab G has only modelers who collaborate. Other labs include experimentalists and modelers within them, in differing proportions depending on the focus of the research. What the "best practices" are in the field has not yet been established and is still being explored, often in the context of the choices individual researchers make in order to get a handle on the problems they want to address.

Given the complex interdisciplinary landscapes systems biologists face it makes some sense for the purposes of methodological development to encourage adaptive problem solving as a principal means of operating. The willingness of the field to encourage these practices can be understood on this basis. In general where several disciplines come together as in this case, the epistemic landscape that confronts researchers is likely to be complex and involve all kinds of considerations and constraints that make the task of finding a good method for a given problem – let alone general methods – fraught with difficulties. Building a new interdisciplinary field requires exploration and innovative behavior (Andersen 2013). This might sound like a truism but general theories such as that of Weisberg and Muldoon provide a way conceptualizing such claims and understanding more deeply why a field might pursue or encourage such practices. The result is that adaptive problem solving makes sense as a strategy not only to the individuals faced with such complex interdisciplinary problem-solving contexts but also to the architects and managers of the field who desire in the end more unified field methodologies and theories.

3. Conclusion

In the current state of play, philosophy of science is in need of detailed characterizations of interdisciplinary research practices in order to begin to map what might be philosophically relevant and distinct about them, and to consider on what basis they might or might not be rationalized as effective for both solving problems and promoting the interests new interdisciplinary fields have in methodological and theoretical development. Based on our long-term ethnographic studies we have tried to characterize the ways in which researchers in a major stream of ISB use an adaptive problem-solving strategy to explore methodological possibilities and practices traversing a terrain that incorporates methods, concepts, and practices from three background disciplines and experiment with different forms of collaborative and non-collaborative interaction. Promoting an adaptive strategy in these contexts provides a means for the field to discover more general methodological techniques and theories, which in turn serve to establish the credibility of the field. Although our analysis here applies specifically to ISB, we think our approach can provide a model for examining and comparing practices in other kinds of interdisciplinary fields. Further, whenever disparate fields come together to collaborate on complex problem-solving tasks, there is likely be methodological uncertainty, which an adaptive problem-solving strategy along the lines of what we have described above might be well-suited to address.

Acknowledgements

We appreciate the support of the US National Science Foundation in conducting this research (DRL097394084). Miles MacLeod's participation was also supported by a postdoctoral fellowship at the Academy of Finland Centre of Excellence in the Philosophy of the Social Sciences, University of Helsinki. Member of the Centre contributed much advice in earlier developments of this paper. We thank the directors of Lab C and Lab G for welcoming us into the lab and the lab-members of those labs for granting us numerous interviews. We thank the members of our research group for contributing valuable insights, especially Vrishali Subramanhian, Lisa Osbeck, Sanjay Chandrasekharan, and Wendy Newstetter. We also thank the three anonymous reviewers whose comments substantially improved the paper.

Andersen, H. (2013). The second essential tension: On tradition and innovation in interdisciplinary research. Topoi, 32(1), 3-8.

Andersen, H. (2010). "Joint Acceptance and Scientific Change: A Case Study." Episteme 7:248-265.

Andersen, H., & Wagenknecht, S. (2013). "Epistemic dependence in interdisciplinary groups." Synthese 190 (11):1881-1898.

Brigandt, I. (2010). Beyond reduction and pluralism: Toward an epistemology of explanatory integration in biology. Erkenntnis, 73(3), 295-311.

Brigandt, I. & Love, A. C. (2012). Conceptualizing evolutionary novelty: moving beyond definitional debates. Journal of Experimental Zoology (Mol. Dev. Evol.) 318B:417–427.

Bruggeman, F. J., & Westerhoff, H. V. (2007). The Nature of Systems Biology. *TRENDS in Microbiology, 15*(1), 45-50.

Chandrasekharan, S., & Nersessian, N. J. (2015). Building Cognition: The Construction of External Representations for Discovery. *Cognitive Science 39: 1727-1763*.

Darden, L., & Maull, N. (1977). Interfield theories. Philosophy of Science, 43-64.

Grüne-Yanoff, T. (2011) Models as products of interdisciplinary exchange: Evidence from evolutionary game theory. *Studies in History and Philosophy of Science* 42:386-397.

Krohs, U., & Callebaut, W. (2007). Data without models merging with models without data. *Systems Biology: Philosophical Foundations (Boogerd FC, Bruggeman FJ, Hofmeyer J-HS, Westerhoff HV, eds)*, 181-213.

Leonelli, S. (2013). Integrating data to acquire new knowledge: Three modes of integration in plant science. Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences, 44(4), 503-514.

Love, A. C. & Lugar, G. L. (2013). Dimensions of integration in interdisciplinary explanations of the origin of evolutionary novelty. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* 44(4, Part A):537–550.

MacLeod, M., & Nersessian, N. J. (2013a). Building Simulations from the Ground-Up: Modeling and Theory in Systems Biology. *Philosophy of Science, 80*(4), 533–556.

MacLeod, M., & Nersessian, N. J. (2013b). Coupling Simulation and Experiment: The Bimodal Strategy in Integrative Systems Biology. *Studies in History and Philosophy of Biological and Biomedical Sciences, 44*, 572-584.
MacLeod, M., & Nersessian, N. J. (2014). Strategies for Coordinating Experimentation and Modeling in Integrative Systems Biology. *J. Exp. Zool. (Mol. Dev. Evol.), 9999*, 1-10.
Mäki, U. (2013). Scientific imperialism: Difficulties in definition, identification, and assessment. *International Studies in the Philosophy of Science*, 27(3), 325-339.
March, J. G. (1991). Exploration and exploitation in organizational learning. *Organization science, 2*(1), 71-87.
Mitchell, S. D. (2003). Biological complexity and integrative pluralism. Cambridge University Press.
Nersessian, N. J., & Newstetter, W. C. (2014). Interdisciplinarity in Engineering. In J. Aditya & B. Olds (Eds.), *Cambridge Handbook of Engineering Education Research* . Cambridge: Cambridge University Press.
Nersessian, N.J. & Patton, C. (2009). Model-based reasoning in interdisciplinary engineering, *The Handbook of the Philosophy of Technology & Engineering Sciences*, A. W. M. Meijers, ed., Springer, pp. 678-718
O'Malley, M. A., & Dupré, J. (2005). Fundamental issues in systems biology. *BioEssays, 27*(12), 1270-1276.
O'Malley, M. A. (2013). When integration fails: Prokaryote phylogeny and the tree of life. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* 44(4):551-562.
Osbeck, L. & Nersessian, N.J. (2017). Epistemic identities in interdisciplinary science. *Perspectives on Science 25, in press.*
Plutynski, Anya. 2013. "Cancer and the goals of integration." *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* 44 (4):466-476.
Trewavas, A. (2006). A Brief History of Systems Biology "Every object that biology studies is a system of systems." Francois Jacob (1974). *The Plant Cell Online, 18*(10), 2420-2430.
Turner, S. (2000). What are disciplines? And how is interdisciplinarity different. Stehr, N., & Weingart, P. (Eds.), *Practising interdisciplinarity*. Toronto:University of Toronto Press. 46-65.
Voit, E. O. (2000). *Computational analysis of biochemical systems: a practical guide for biochemists and molecular biologists* Cambridge: Cambridge Univ Press.
Voit, E. O. (2013). *A first course in systems biology*: Garland Science.
Weisberg, M., & Muldoon, R. (2009). Epistemic Landscapes and the Division of Cognitive Labor*. *Philosophy of Science, 76*(2), 225-252.
Westerhoff, Hans. V., Kolodkin, A., Conradie, R., Wilkinson, S. J., Bruggeman, F. J., Krab, K., . . . Moné, M. J. (2009). Systems biology towards life in silico: mathematics of the control of living cells. *Journal of mathematical biology, 58*(1), 7-34.
Westerhoff, Hans V., and Kell., D.B. (2007), The Methodologies of Systems Biology. In Systems Biology: Philosophical Foundations, Fred C. Boogerd, Frank J. Bruggeman, Jan-Hendrik S. Hofmeyr, and Hans V. Westerhoff (Eds.), Amsterdam: Elsevier. 23-70