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The creative industry of integrative systems biology

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Abstract Integrative systems biology (ISB) is among the most innovative fields of contemporary science, bringing together scientists from a range of diverse backgrounds and disciplines to tackle biological complexity through computational and mathematical modeling. The result is a plethora of problem-solving techniques, theoretical perspectives, lab-structures and organizations, and identity labels that have made it difficult for commentators to pin down precisely what systems biology is, philosophically or sociologically. In this paper, through the ethnographic investigation of two ISB laboratories, we explore the particular structural features of ISB thinking and organization and its relations to other disciplines that necessitate cognitive innovation at all levels from lab PI's to individual researchers. We find that systems biologists face numerous constraints that make the production of models far from straight-forward, while at the same time they inhabit largely unstructured task environments in comparison to other fields. We refer to these environments as *adaptive problem spaces*. These environments they handle by relying substantially on the flexibility and affordances of model-based reasoning to integrate these various constraints and find novel adaptive solutions. Ultimately what is driving this innovation is a determination to construct new *cognitive niches* in the form of functional model building frameworks that integrate systems biology within the biological sciences. The result is an industry of diverse and different innovative practices and solutions to the problem of modeling complex, large-scale biological systems.

In the paper we are deliberately playing off of two senses of 'industry' one being a manufacturing activity, the other, systematic work towards a purpose.

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1 Introduction

Integrative systems biology (ISB) is an emerging transdisciplinary field that aims to revolutionize biological understanding, and thus our ability to tackle pressing bioscience problems such as cancer therapies, ecosystem protection, and biofuel production, by using computational modeling and simulation to investigate how higher-level functionality emerges from a multitude of lower-level interactions among the building blocks of biological systems. Our aim in this paper is to draw from our 4-year investigation of two pioneering research lab to show how the particular character of ISB, specifically as observed in these research labs, is unusually productive of cognitive innovation, to the point of incorporating it as a regular feature of research. As we will argue, this innovation can be tracked to the ill-structured task environments and the significant number of cognitive and non-cognitive constraints we have observed on the production of adequate informative models. Drawing from these cases we have characterized research within the field as operating within an *adaptive problem space* defined by multidimensional problem-solving tasks and emergent approaches (see Nersessian and Newstetter 2013). Research in adaptive spaces is driven by complex interdisciplinary problems, and these require that the individuals themselves achieve a measure of interdisciplinary integration in how they think and how they act. Adaptive spaces are dynamic and diachronic and span mental and material worlds. Adaptations take place through the generation of new cognitive strategies that serve to integrate these constraints with available and emergent concepts, methods, models and materials. At base however these strategies reveal the significant capacities of model-based reasoning and its flexibility for meeting multidimensional problem-solving demands that are at the center of this approach to biological systems. It is model-based reasoning that ultimately sustains the creative industry of ISB.

2 Our investigation

While we recognize there are several computational approaches to the study of biological systems, biochemical systems biology is a major area of research directed towards representing, understanding, and controlling intracellular metabolic and signaling pathways. Our study of ISB thus far comprises two biochemical systems biology laboratories. Lab C conducts both modeling and experimentation and is working on understanding cell signaling dynamics in a reduction–oxidation (redox) environment including in cases of immunosenacence and drug resistance in acute lymphoblasic anaemia. Lab G does modeling and novel algorithm development but no experimental work itself. The specific modeling problems it works on come from collaborations with experimental labs. Such problems have included work on biofuels, Parkinson's disease, atherosclerosis and heat shock in yeast.

Integrative systems biology is a new field, being approximately 15 years old (Kitano 2002), although the idea of approaching biology by means of *systems theory* itself has an older history (O'Malley and Dupré 2005). In many ways ISB is a major attempt to institutionalize systems theory. ISB aims specifically to apply large scale mathematical models through the aid of contemporary computer power and algorithmic techniques to map the structure and dynamics of complex biological systems. We should note that the emerging field of ISB has various streams. Our study participants pursue what is sometimes referred to as bottom-up systems biology, which builds models from available experimental information on particular molecular pathways and the interactions of their components (Bruggeman and Westerhoff 2007). Top-down systems biology on the other hand uses powerful mathematical techniques to "reverse engineer" system structure using rich high throughput time-series data. Hence what we give here are insights mainly relevant to practices in the bottom-up systems biology stream, and might not necessarily apply to the much more programmatic and computationally driven top-down research stream.

Our lab participants take the distinguishing feature of their bottom-up approach to be that the models allow them to describe how elements (in our case enzymes and metabolites) operate and interact within a systemic context or environment, and thus express particular system-determined properties and behaviors. They contrast this approach with traditional molecular biology that pursues these elements "in isolation" through in vitro analyses of the properties and structure of individual biomolecules. Of particular interest, our participants are not in fact biologists, and many confess to having limited biological knowledge. Rather they come most particularly from engineering, and sometimes applied mathematics backgrounds. Many claim "general engineering" undergraduate backgrounds. Their primary skills and knowledge are in computational model building and model-based reasoning, combined with general knowledge of the properties and features of engineering systems (control theory, signal processing, etc.). Several of the Lab C researchers, including the director, also conduct experimental research targeted specifically to obtain data for their models. Lab G researchers need to rely on experimentalists outside of their lab.

2.1 Methods[1]

We have been conducting a 4-year mixed-methods investigation of these two research labs. Our analysis was developed and triangulated from several data sources. We employ the standard ethnographic data collection methods of participant observation, informant interviewing, and artifact collection. In Lab C we observed researchers as they conducted their work on the bench tops, as they

[1] Our interdisciplinary research group comprises Ph.D. level researchers with expertise in ethnography, qualitative methods, linguistics, psychology, philosophy and history of science, cognitive science, and learning sciences. Student researchers (graduate and undergraduate) have come from programs in cognitive science, intelligent systems, human-centered computing, and public policy. All members of the team received apprenticeship training in ethnography, qualitative methods, and cognitive-historical analysis.

used instruments, devices, and equipment; we attended lab meetings, which were audio-taped to compliment the field notes; we sat in on PhD proposals and the weekly journal club. We determined after preliminary field observation that it would not be possible to collect this kind of data for Lab G since researchers work only on computers and often do their work from home. They do not have regular lab meetings or journal club. In the first year of our study, the Lab G director did organize several lab meetings specifically to introduce us to their research and 2 meetings joint with Lab C. In both labs we conducted unstructured interviews with the lab members and some collaborators outside of the lab. We collected relevant artifacts including powerpoint presentations, paper drafts, published papers, grant proposals, dissertation proposals, and completed dissertations. Thus far, we have collected 56 interviews in Lab C and 39 in Lab G (all fully transcribed) and have audiotaped 15 Lab C research meetings, 7 Lab G meetings and 2 joint meetings. At present approximately eighteen percent of the transcribed interviews are fully coded.

Broadly consistent with the aims of grounded theory, we have been approaching interpretive coding analytically and inductively (Glaser and Strauss 1967; Strauss and Corbin 1998) enabling core categories (and eventually "theory") to emerge from the data and remain grounded in it, while being guided by our initial research questions. Coding began with weekly collaborative meetings by at least two research group members. A small sample of interviews was analyzed progressively line-by-line from beginning to end, with the aim of providing an initial description for most if not all passages in the interview. A description and code was recorded only when both researchers were in full agreement about its fit and relevance to the passage and, initially, there was no attempt to minimize the number of coding categories. Initial codes were presented in our full research group meetings (all had read the transcripts in advance) and codes were discussed until there was agreement. Descriptions and codes were revisited throughout the process in keeping with new discussion on the text as well as new observations in the laboratories. Axial coding aimed at continuous refinement and verification of the categories and connections between them. Codes were analyzed for conceptual similarities, overlap, and distinction and were grouped together under super-ordinate headings, and so forth, until no further reductions could be made. Altogether the team identified 127 codes organized into 16 superordinate categories.

In addition, we used cognitive-historical analysis (Nersessian 1995) on the data from traditional historical sources (publications, grant proposals, laboratory notebooks, and technological artifacts) to recover how the salient representational, methodological, and reasoning practices have been developed and used by the researchers. We sought out the daily and diachronic dimensions of the research by tracing the intersecting trajectories of the human and technological components of the laboratory, conceived as an *evolving cognitive-cultural system* (Nersessian 2008) from both historical records and ethnographic data. We used these combined data and analyses to develop an understanding both the nature of cognition and of learning in these settings. This novel combination of methods has enabled developing thick descriptions and analytical insights that capture the dynamics of inquiry characteristic of research laboratories.

3 Task environments and their constraints in ISB research

While there is much philosophical and sociological discussion about ISB and how it intersects with established sciences like molecular biology, physics, engineering, and computer science (see Bruggeman et al. 2010; Bruggeman and Westerhoff 2007; Calvert 2010; Calvert and Fujimura 2011; Krohs and Callebaut 2007; O'Malley et al. 2007; O'Malley and Dupré 2005), our focus here is on the actual experiences and activities of ISB researchers. The most important feature of practice in our ISB labs is that the well-structured task environments that characterize established sciences like molecular biology or bioinformatics do not exist. Almost every step in the process of model building requires problem-(re)structuring and judgment on the part of the researcher whether it is the choice of modeling method, construction of a representative molecular pathway, choice of literature, selection of programming software, assessment of reliable parameter values and so on. Little can be outsourced to routines or protocols. This does not mean that the task load is necessarily higher in systems biology, however. When two members of Lab G spent their summer at an experimental laboratory they reported that they worked flat out, managing an enormous number of experimental processes simultaneously. At the same time they noted the cognitive differences between the more step-by-step but highly thought-intensive requirements of modeling and the more procedural/routine but far more multitask- orientated activities of experimental molecular biology.

The unique cognitive demands ISB researchers have to deal with stem from constraints on the production of models that need to be resolved or addressed from high-level theoretical discussions among experts on down to the level of the day to day work of individual lab researchers. These constraints define an adaptive problem-solving space. Ultimately what is produced in the form of a biological model is itself the result of a *strategic adaptation* to these constraints. Lab members face in effect a multi-dimensional problem-solving task that goes beyond the task of simply applying a formalism or pre-established principles to produce a model that accounts accurately for a biological phenomenon. Any product is the result of numerous choices about how to model and what to model with the resources available. Some of the constraints on model production and model-based reasoning we have observed operating in these laboratories are as follows,

1. The biological problem: A model must address the constraints of the biological problem, such as how the redox environment is maintained in a healthy cell. The system involved is often of considerable complexity.
2. Information constraints: There are constraints on the accessibility and availability of experimental data and molecular and system parameters for constructing models.
3. Cost constraints: ISB is data-intensive and relies on data that often go beyond what are collected by molecular biologists in small scale experiments. However data are very costly to obtain.
4. Communication and collaboration constraints: Constraints on the ability to communicate effectively with experimental collaborators with different backgrounds or in different fields in order to obtain expert advice or new data. Often

these constraints are caused by cost constraints. Molecular biologists often do not see the cost-benefit of producing the particular data systems biologists need.
5. Time-scale constraints: Different time scales operate with respect to generating molecular experimental data versus computational model testing and construction.
6. Infrastructure constraints: There is little in the way of standardized databases of experimental information or standardized modeling software available for systems biologists to rely upon.
7. Knowledge constraints: Modelers often lack knowledge of biological systems and methods limits understanding of what is biologically plausible and what reliable extrapolations can be made from the data sets available.
8. Cognitive constraints: Constraints on the ability to process and manipulate models because of their complexity, and thus constraints on the ability to comprehend biological systems through modeling.

It is clear in both of our labs that researchers (including the few modelers who do experimentation) find it difficult obtaining the experimental information they need, or creating effective collaborative relationships with experimenters. In collaborations, there are barriers to effective communication on both sides, which stem from a lack of knowledge of each other's work and of the potential advantages of collaboration. Our interviewees report for instance that experimenters generally do not see the point of modeling or distrust its results. To them it averages over the fine-tuned mechanical detail they think is essential to understanding molecular interactions or it simply makes too many simplifying presuppositions. This reflects a basic disagreement between modelers and experimentalists over epistemic values, such as what counts as good research, i.e., how one can study and account for biological phenomena. This disagreement is difficult to overcome unless experimenters can come to understand how the simplifications systems biologists make can be productive in the context of a model and modelers can come to understand why experimental practice requires close attention to details.

There are also structural barriers such as the time-scale differences. As the Lab G director expressed, "…the other people in the group [the experimentalists] are just not producing data quickly enough. And so he [the modeler] is sitting there…and sort of trying to develop methods for something he doesn't really know what the methods are supposed to be for… because the data are just not there. And that's a big issue, because the speed of those things, of those developments is different… I still maintain, I've said it for 20 years, you need 10 experimentalists for every modeler." Experimental work takes in general much longer than the running of a computer simulation. Although building a good model can take years of careful work, the model-building process often stalls when data from experimenters are required. The rate at which adjustments to a model can be made with new data is much quicker than the rate at which data can be assembled. Often modelers are left in temporal limbo waiting for the data they need build their models as well as to confirm the models are on the right track. The experimental-labor requirements for effective modeling are difficult to satisfy. As a result, modelers are forced to forage in the available experimental literature for useful data and are constrained by the

limitations and incompleteness of those data and the lack of comprehensive or complete existing databases for most biological systems. At the same time most modelers, especially in Lab G, do not have in-depth biological knowledge. Courses will not necessarily fix this because they need in-depth knowledge for each new system they model, which could be cancer today and biofuels tomorrow. This lack of knowledge complicates their ability to assess the relevance of data they find recorded, for instance, under experimental conditions different from what they need or with different cell lines.

Further systems biology lacks any generic software platforms that could assist the modeling process. There are no "industry-wide tools" according to one Lab G researcher, nor would it be clear what they should look like, given the diversity of modeling techniques systems biologists pursue. Most end up writing new software themselves using programs like Matlab and developing their own personal software systems. In dealing with complex biological systems cognitive constraints are also central considerations. The fact that researchers in our laboratories study chemical elements within a systemic environment means a whole host of reactions and chemicals need to be studied simultaneously in the context of a model. But there are constraints on what can be handled and controlled by a modeler. For individual researchers it is important for them to model systems that are not so large that they are cognitively intractable, even with the aid of computers, and of no use for understanding the biological system at hand. At the same making the model too specific and comprehensive at a small scale requires refined interaction data that is not likely to be available.

In established disciplines like molecular biology constraints like these have been addressed over time through particular methodologies, protocols and routines, lab organizations and educational programs that generate well-structured task environments. In our ISB labs, however, these constraints and problems are requiring innovative strategies on behalf of researchers extending from the way they construct models to the identities by which they choose to define themselves. The constraints and problems operate at multiple levels. The lab directors grapple with them at the level of laboratory organization and individual researchers at the level of their individual biological problems. In general we have found that because there is such fluidity in the field, lab directors reach different solutions in terms of how they structure their laboratories while individual researchers address the problems in their own individual way. In neither lab however is there a strong top-down patterning that tries to predetermine the problem-solving strategy their lab individuals choose.

4 Innovative cognitive strategies

Our labs reveal innovative ways in which model building is being adapted and expanded to meet the constraints (enumerated above) and produce informative biological models. Here we outline the most significant ways emerging from our investigation.

First, an understanding of the complexity of the biological phenomenon is built up initially through working out details of biological pathway diagrams from

literature searches and adopting modeling frameworks, and then applying a recursive process of building the model. Chandrasekharan and Nersessian (2011) have documented the various cognitive roles model-building play in creating enhanced cognitive powers of integration, simulation, and abstraction and intuitions about the behavior of the phenomena. They note in particular the importance of creating a synthesis of a range of experimental data, enabling dynamical tracking of variables, and running unlimited scenarios. As these simulation models gain complexity they come to *enact* the pathway for researchers, as they learn to think about the biological system through the model. Arriving at a "feel for the model" in this way gives them the cognitive ability to make the judgments that better fit the model to the biological system. Specifically, models are used to create a counterfactual space that provides researchers with a way of narrowing down on a good representation by working with certain possibilities, and excluding others. This space provides the modeler with flexibility to think about biological phenomena in more general terms than the experimenter who operates only with particular experimental results. For instance, in one striking case in Lab G, a modeler discerned the existence of a new functional metabolite in a system that experimenters, without this large-scale perspective, had failed to. The researcher was able to do this because a discrepancy between the dynamics of his model and the biological system indicated to him a missing element. These modeling practices are no doubt shared with other fields. ISB, however, lacks fundamental principles or background theory of the nature say of physics, so model-building is essentially a recursive process of learning the biological system by bootstrapping. Model-building is an essential discovery process.

Second, the importance of finding solutions for cognitive constraints is not just a concern for individual researchers. In fact modeling is being adaptively shaped at all levels. At the higher theoretical level a modeling scheme such as Biochemical Systems Theory (BST) can be understood as a response to informational and cognitive constraints (Sorribas and Savageau 1989; Voit et al. 2012; Voit 2000). BST uses power laws which allow a modeler to black-box or average over processes for which knowledge is limited or the mechanisms complex, while providing detailed ways of fitting unknown system parameters algorithmically with limited data. It promises informative models for middle-level scale systems. But there is also a cognitive dimension. BST facilitates a program of model-building that enables researchers in the process of building and fitting the model to develop an intuition or understanding of elements of the system through their cognitive interaction with the model. It works by building knowledge of a system through the process of correcting and expanding the model from a schematic starting point. Hence the model-building process provides methods and tools for overcoming the cognitive constraints of dealing with complexity. BST can be understood as a methodological innovation. It does not aim primarily to define what a biological system is or what a complete model of a system should be. It rather aims at an accommodation between cognitive and informational constraints and the complexity of biological systems in the form of a process for developing mid-sized models.

Third, as important skills for dealing with informational and collaborative constraints, researchers learn strategies for devising models that fit the information

that is available or accessible. As one Lab C participant expressed "the good modeler knows how much to restrict the system so that he has most of the things that are known and very few things that are unknown". A Lab G participant referred to this kind of process as the "art of modeling". Engineering ideas such as sensitivity analysis are also applied to try to fathom which interactions in a system are the central ones in order to get a good approximate understanding of a network. If the model is accurate enough then increasingly powerful algorithmic techniques, the development of which takes up a significant proportion of Lab G's time, can be used to fix down unknown parameters.

Fourth, the ideal process of interaction with experiment for a modeler would be a recursive one. Modelers get information on parameters they need from experiment to build better models which can then be used to guide further experimentation and so on. As we have noted this kind of interaction is often out of reach due to collaborative constraints. As such lab directors make different choices about how best to manage the problem of parameterization and lack of adequate experimental data generally. Lab C runs a strategy of bringing experimentation into the lab and producing *bi-modal* researchers who can both model and experiment. This bi-modal strategy has the benefit that these modelers can design and run the experiments they need to fit and validate their models, and possibly be available to obtain data for the pure modelers in the laboratory. The bi-modal researcher also has better knowledge of how experiment works and can direct their modeling decisions on the basis of what is potentially accessible information, both in terms of what they can do experimentally and what might be available and reliable in the literature. As one bi-modal researcher put it "I like the idea that I'm building my model things are popping up in my head oh wow this would be a good experiment I plan out the experiment myself and then I go into the lab and I and I do it." She also noted how difficult it would be to explain what she needed to a pure experimenter. The bi-modal strategy, however, should not necessarily be seen as a universally better solution to the problems ISB faces. In the words of the Lab G director, "If you do the experiment yourself, you know what the data are like; you know how reliable they are. You know the kind of assumptions you made in order to produce the data…. So you get better idea about the whole context. On the other hand, life is complicated, and to do good modeling is a full time job; to do experiment is a full time job. And if you don't want to do two full time job, then something will suffer from it." You can end up with "modeling lite and experimenting lite".

Lab G in fact pursues only *uni-modal* research. Researchers are full-time modelers. We have observed the trade-offs here quite closely. Lab C participants tend to work closer to the biology, and have richer biological knowledge (although they are rarely trained biologists) and give richer mechanistic accounts of systems. At the same time they do not have the mathematical skills to abstract on the larger scale, and hence their models tend to be of a smaller scale than in Lab G. Much of the work in Lab G is producing and improving algorithmic tools that can deal with lack of biological knowledge and lack of detailed mechanistic understanding. As such, they are developing different cognitive strategies in terms of different skill sets for tackling the constraints. However, they a highly dependent on collaborators for the experimental data they need to validate their models.

Fifth, one set of skills that are universally important for ISB researchers to cultivate are the requirements of *cognitive flexibility* and *epistemic pragmatism*. Cognitive flexibility is the ability think outside one's established framework, and to be able to take a different perspective on a problem. Epistemic pragmatism refers to a willingness to be pragmatic about what can be achieved with a model, what techniques can be properly used to build it, and the standards for success applied to it. These are basic to adaptability. In one respect this means the modeler and the experimenter each being able to comprehend the perspective of the other in order to facilitate interaction by becoming aware of the constraints the other might be under. This can help each better anticipate what might be gotten from the relationship, and to develop a more systematic bipartisan interaction (see also Shrager (2007) on the importance of creating a platform for developing interactive expertise). In the context of the labs we study, pragmatism and flexibility reflect an ability to perceive there are no readily available solutions to the problem-solving task at hand that manage all their constraints and to accept that they must move beyond the model templates, stock examples, and taught procedures for building models and develop their own strategies and take on new perspectives. Being pragmatic means accepting these limitations and looking for practical outcomes without presumptions or presuppositions about the nature of the systems they are dealing with or the "correct" ways of analyzing them. Pragmatism and flexibility mean adapting skills and concepts from their disciplinary background, particularly engineering, to fit the new problems in biology. Biological systems are not mechanical or electrical circuit systems, and it requires flexibility of thinking and a measure of pragmatism to be able to take from those understandings what works in the biological case and apply it, while at the same time drawing on the constraints of the biological problem. This particular adaptation of past knowledge to new problems is a principal source of conceptual innovation in our laboratories. Systems biologists routinely think about biological systems as circuits and use loosely at least circuit analogies when explaining the notion of a system, which for them is a structure that can be built and disassembled part by part or component by component, or can be reverse engineered into its functional modules. They use engineering vocabulary to expresses system-level dynamics and properties like robustness, noise, and modularity. At the same time they have to manage the language of molecular biology; a language of reactants and products, enzymes and metabolites. Most researchers in our labs do not have general biological knowledge, but they have to build up extensive knowledge of the system they are investigating.

Our participants learn how to interlock engineering and biological concepts and language through model-based reasoning. A principal technique is to translate biological interactions into networks of arrows and boxes. As one participant put it: "We take a map that a biologist has drawn and in some sense translate it into a map that we can deduce the math from." Arrows and boxes are classical circuit-like visualizations from engineering. They are mathematical structures to which engineering concepts and actions can be applied, like sensitivity analysis. They have noise, they exhibit design principles. They are structures which can be "tweaked" like a car engine to get them to work the way the biology does. The procedure is "to put meaning into the arrows", by tracking down functional

dependencies (the input/output relations) from the literature and employing parameter fixing algorithms to tweak parameters to fit the data. Many have learned to do this not by focusing on the raw data of experimentalists, but rather by looking for trends in the data that demonstrate particular dynamic relationships between variables which can be graphed, thus engaging a more visual representation which better-suits their modeling strategies. Learning to translate between engineering and biological concepts is a central cognitive and conceptual innovation of the field. Researchers understand perfectly well at the same time that this process means giving-up biological information for the sake of having a model. It is a conceptual accommodation of both biology and engineering.

But cognitive flexibility and epistemic pragmatism also help overcome previous disciplinary biases. One bi-modal researcher, for instance, described herself as an "open canvas" in terms of her ability to overcome typical experimentalist distrust of modeling, and incorporate it as a tool in her "toolbox." She stressed at the same time an important element of pragmatism, which is being pragmatic about the understanding of systems it is possible to achieve: "you don't necessarily need to understand every single interaction of every single molecule in every single second to sort of understand the overall dynamics…" The best we can aim for in her words are "approximations." This attitude conditioned in fact the way she learned to deal with the expanding complexity of her case. This researcher proved particularly pragmatic and cognitively flexible, which may well be a necessary condition of successful bi-modal research. She developed her own largely innovative approaches to modeling, being able to do classic model-building work, but also to incorporate model building into sustained experimental work, building models as she progressed in order explicitly to direct her experimental work. In this context she described her model building as creating a mathematical framework that could help her understand what she was seeing experimentally not a "full-blown model."

Pragmatism, indeed, is appreciated as an epistemic virtue across both laboratories. A Lab G researcher described the best lessons he brought from his experience in industry where he had been employed as an engineer to the ISB lab as "being very adaptable to different situations, different demands, and keeping a very flexible perspective in problem-solving." This pragmatism expresses itself commonly throughout both labs as a general regard of the fallibility and limited nature of their biological models. Many of our researchers are critically aware of the role assumptions and simplifications play in getting anywhere but also in compromising an outcome. They have learned to cognitively track assumptions strenuously in the first place to prevent them from becoming entrenched and taken for granted, but also because tracking them helps to communicate with biologists who are suspicious in general of such simplifying assumptions. Learning cognitive flexibility in this respect also helps them track the biologist's point of view.

5 Conclusion: creative industry through model based reasoning!

All these features amount to cognitive innovations that have emerged in response to the unstructured task environments and constraints that confront systems biology

and its attempt to apply mathematical models to biological complexity. It is remarkable the extent to which ISB in our labs has elevated creativity and cognitive innovation to an almost industrial level, as a central component in the production process of models. This level of creative industry contrasts with those epistemic values of scientific disciplines that esteem the skilled performance of researchers with ready-made tools or the ability to apply a theoretical perspective. Rather in our labs something like raw model-building takes its place. In the absence of theoretical background, analogies are incorporated from other disciplines to provide representation-building materials and constraints. Every project a researcher undertakes is often fresh as far as their knowledge of the biology is concerned, and often requires new analogies, new data, new software, new interactions and new modeling techniques. In fact researchers skip among biological systems which a molecular biologist would spend a life on.

We can identify two broad cognitive features governing and promoting this innovation. Firstly, the essential flexibility and cognitive power of model-based reasoning is the material resource that our researchers are relying upon for developing new cognitive adaptations to multi-dimensional problem spaces. As Nersessian (2008) has described it, model-based reasoning is a process of generating novel representations through the abstraction and integration of constraints from many different contexts (literature, target, analogical source, modeling platforms and so forth). Here our researchers use their knowledge of the affordances and constraints of simulation models and engineering analogies for generating representations to construct functional model-building systems. They leverage on the fact that there are different ways to put such systems together using different analogies, new software, alternative mathematical or computational techniques, new lab organizations, collaborative relationships and so on. Their skill with model-based reasoning allows them to integrate a wide-variety of constraints with new cognitive strategies that can produce models under the circumstances.

A particular instance of the capacity of model-based reasoning that researchers in our labs rely upon is to use their knowledge of the mechanics or logic of their models to shape problems to fit available modeling techniques. When researchers approach their problems, characterized as they often are by limited data and complexity, they make calculations and assessments given their knowledge of what is possible with the models they can build. This helps them find a way to efficiently represent their problems. Specifically, how our researchers think through the mechanics of modeling to put together a modeling framework in the circumstances evokes an analogy with the way engineers build material systems. When building a bridge an engineer adjusts his or her construction according to what is functionally possible given the environmental landscape and construction materials available. Likewise systems biologists filter the data to find the elements that can be used to build a functional model, while taking into account what they do not have and cannot get, and what a model could possibly do without. This compatibility of method is one reason that engineering ideas derived from control theory or sensitivity analysis are so useful here: They are methods of finding manageable grounds for model building. BST, for instance, can be understood in these terms. The framework attempts to integrate cognitive and informational constraints into a

model-building formula that approximates and idealizes biological interactions and systems (through power laws for instance) in a way that can be fit to a system of ODEs. Adapting a problem to one that can be solved from one that cannot is the central function of an adaptive problem solving environment. Not only are methods and data transformed but also how the problem is understood and represented, until a coherent solution can be reached.

Secondly the drive to innovate new model-based cognitive strategies we observe in ISB can be understood as an instance of cognitive niche construction (Clark 2008; Wilson and Clark 2009).The search to replace these unstructured constraint-ridden task environments with their own functional model-based cognitive systems that operate within the established research landscape is promoting this innovation, both collectively and individually. While at the highest levels the founders of systems biology including our lab directors work to create a niche for the importation of engineering ideas into biology and develop new modeling frameworks like BST to support such research, individual ISB researchers rely on specific models and what they know about them to generate environments in the context of biology in which they can function. ISB researchers are relying on model-based reasoning in order to generate new model-based workspaces or task environments in response to the constraints. These environments serve to build in new functional collaborative relationships. Ultimately then systems biologists are using model-building and its affordances to carve out an adaptive problem-solving space in between biology, computing, and engineering in which they can operate.

Whether this process will result in ISB remaining a field or is a process on the way to constructing a new (inter)discipline remains to be seen. It is possible of course that ISB might just be an instance of a discipline in transition and much of the flexibility and pragmatism we observe might dissolve once settled protocols and standardized software are in place. This may well be true, in which case ISB provides a developmental case study of a how a new field matures. Yet we think we have highlighted enough of the cognitive features of the work of ISB to suggest that there are structurally different things about the way it operates at least in our two otherwise quite different labs including the collaborative relationships and mixed skill sets the field depends on and the complex problem solving tasks it confronts, that we are witnessing the formation and institutionalization of a rather different kind of scientific methodology.

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