Molecular Embodiments and the Body-work of Modeling in Protein Crystallography

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ABSTRACT Protein molecules, those objects of increasing interest and investment in post-genomics research, are complex, three-dimensional structures made up of thousands of atoms. Protein crystallographers build atomic-resolution models of proteins using the techniques of X-ray diffraction. This ethnographic study of protein crystallography shows that becoming an expert crystallographer, and so making sense of such intricate objects, requires researchers to draw on their bodies as a resource to learn about, work with, and communicate precise molecular configurations. Contemporary crystallographic modeling relies intensively on interactive computer graphics technology, and requires active and prolonged handling and manipulation of the model onscreen throughout the often arduous process of model-building. This paper builds on both ethnographic observations of contemporary protein crystallographers and historical accounts of early molecular modeling techniques to examine the *body-work* of crystallographic modeling, in particular the corporeal practices through which modelers learn the intricate structures of protein molecules. Ethnographic observations suggest that, in the process of building and manipulating protein models, crystallographers also sculpt *embodied models* alongside the digital renderings they craft onscreen. Crystallographic modeling at the computer interface is thus not only a means of producing representations of proteins; it is also a means of training novice crystallographers' bodies and imaginations. Protein crystallographers' *molecular embodiments* thus offer a site for posing a new range of questions for studies of the visual cultures and knowledge practices in the computer-mediated life sciences.

Keywords embodied practice, expertise and training, models, protein crystallography, scientific visualization, tacit knowledge

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Natasha Myers

A new biological actor is taking center-stage in post-genomic research: the protein molecule. As journals such as *Science* and *Nature* publish new protein structures almost weekly, life scientists can be seen turning from matters of code to matters of substance – that is, from spelling out linear gene sequences to inquiring after the three-dimensional materiality, structure, and function of the protein molecules that give body to cells. In employing new digital media, augmented computer power, and innovative techniques to build atomic-resolution models of proteins, protein crystallographers and other structural biologists are transforming the very forms of data that

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populate life science laboratories and databases.[1] As these life scientists ramp up the pace of structure determination, making visible the forms and movements of a vast menagerie of proteins, the objects of molecular biology are becoming tangible and workable in new ways. With this shift from reading and writing one-dimensional genetic codes to modeling and interpreting the functions of three-dimensional and temporally dynamic protein molecules come new practical and conceptual hurdles for researchers and their students. These challenges also open up a new range of questions for social studies of scientific practice.

Protein crystallographers use interactive computer graphics technologies to build three-dimensional, atomic-resolution models of the intricate molecular structure of proteins, which are molecules made up of thousands of atoms.[2] I ask Diane, a professor of chemistry who heads a protein crystallography lab at a large East-Coast research university in the U.S.A., about the challenges her students face when learning to model proteins in three-dimensions (see Figure 1).[3] She tells me that it is hard to learn how to 'think intelligently about structure'. She points to the steep learning curve her

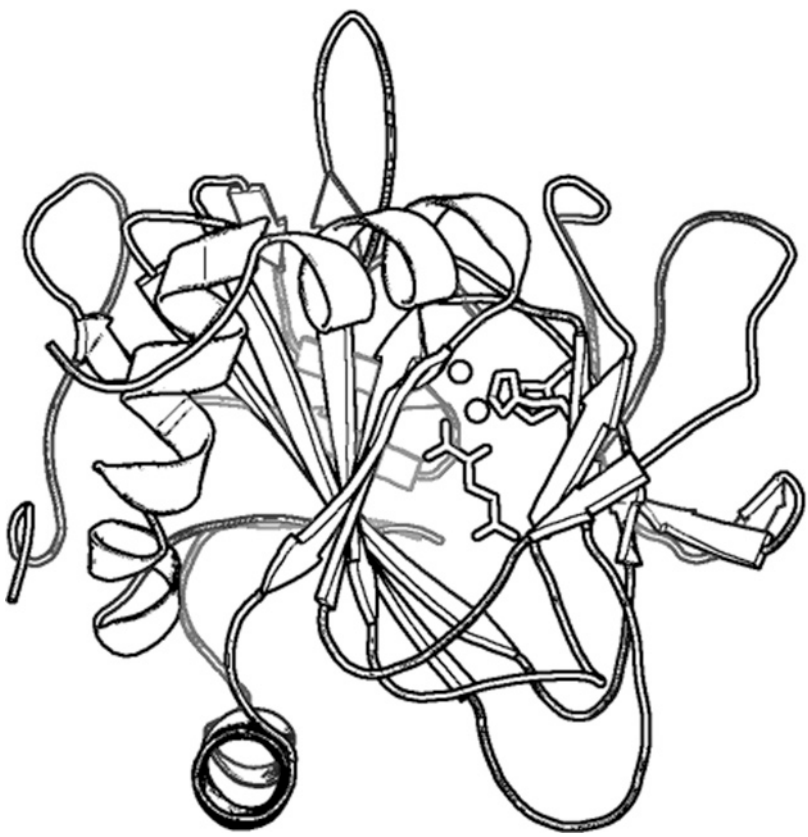


FIGURE 1
A ribbon diagram of a protein molecule. Note atomic resolution detail displaying the active site of the protein. Used with permission from an anonymous ethnographic informant.

students face when trying to master X-ray crystallographic techniques, and enumerates the challenges of building molecular models and interpreting the functions of proteins from molecular forms. Acquiring the skills to 'see what the structure is saying' is 'hard to do, and it takes time', she tells me, but eventually 'you do get better at it'. She describes what often happens when her graduate students show her computer graphic renditions of their molecules in the early stages of the building process. 'Look I connected it!' they proudly declare, presenting her their model. Yet, when she examines their models in detail, looking closely at the bond angles between the amino acids and the direction of the polypeptide chain that winds through the protein, her response is often anguished: 'What did you do to that side-chain? No! No! Let me move it back!'

As she tells the story, she contorts her entire body into the shape of the misfolded protein. With one arm bent over above her head, another wrapping around the front of her body, her neck crooked to the side, and her body twisting, she expresses the strain felt by the misshapen protein model. 'And I'll just get this pained expression', she tells me. 'I get stressed just looking at it. … It's like I feel the pain that the molecule is in, because it just can't go like that!' She feels compelled to fix the model. She mimes a frantic adjustment of the side-chain by using one arm to pull the other back into alignment with her body, tucking her arms in towards her chest and curving her torso over toward the core of her body, demonstrating the correct fold. With a sigh of relief, she eases back into a comfortable position in her chair. The comically anguished look on her face relaxes back into a warm smile.

Apparently, the students in her story had not yet acquired a *feeling for* proper molecular configuration. In a mode evocative of what Evelyn Fox Keller (1983) has described as Barbara McClintock's 'feeling for the organism', Diane expresses her feeling for the molecule. As her gestures and affects convey, corporeal knowledge appears to play a key role in her ability to 'think intelligently' about protein structure. What she has demonstrated is that structural biology is a craft practice that demands embodied knowledge.

This paper examines how practices of protein modeling rework conventional understandings of the relationships between model and modeler, and mind and body. Ian Hacking makes a distinction between 'models you hold in your hand' – material models made with 'pulleys, springs, string and sealing wax' – and 'models you hold in your head', conceptual models and mental images which function through analogy and imagination (Hacking, 1983: 216). Yet, if we take seriously Diane's experience of the pain of the misshapen molecule, such a distinction between 'models-in-the-hand' and 'models-in-the-head' does not hold. While Hacking draws these two kinds of models apart, I would argue for a deeper entwining of material and conceptual models in the *embodied imagination* of the modeler. Diane carries more than a 'mental image' of what a molecule should look like in her head[4]: seeing, feeling, and moving with the chemical constraints of the molecule, she has *embodied* molecular forms. Merleau-Ponty's (1962) phenomenology of perception argues that sensation and movement are intimately tied to

visual understandings of form. Diane demonstrates well how seeing and feeling is entangled in the crafting of structural knowledge.

As life scientists increasingly 'give body' (Hopwood, 1999) to molecular biology, the methods of the ethnographer must keep pace. Diane's acquired feeling for the molecule clues us in to some of the complex corporeal practices that are involved in 'thinking intelligently about structure'. Crystallographic protein modeling is a time-consuming process of constructing models from experimental data using interactive materials, both physical and virtual. This paper aims to show that it is through the 'body-work' of crystallographic model-building, that is, through the labor of constructing, manipulating, and navigating through protein models onscreen, that researchers are literally able to come to grips with – and so make sense of – molecular forms and functions. Thus in addition to the intensive labor required to conduct X-ray crystallographic experiments,[5] and other tacit knowledges[6] involved in the wet lab work of protein science, three modes of body-work are brought into relief in the field of protein crystallography. I term these the body-work of *incorporation*, *communication*, and *reasoning*, in order to foreground the role of the body in learning, relaying, and interpreting the specificities of protein forms and functions.[7] As I demonstrate in the paper, the slow, reiterative, interactive work of crystallographic modeling enables researchers to incorporate molecular models in their embodied imaginations. Once embodied, these models come alive in the performative gestures researchers use to communicate protein forms and mechanisms in conversations within and outside of the laboratory, and in conference presentations and classroom lectures. Throughout the paper, I draw on Diane as an exemplar and as a guide to help pose new questions about the role of researchers' bodies in life science practice. While she may appear to be an exceptional case – she could be construed as an unusually 'expressive' scientist, having studied chemistry and drama as an undergraduate in the 1980s – interviews with her male and female students and colleagues, and with researchers in the wider field of structural biology, show that her 'feeling for the molecule' is in no way exceptional; indeed, it is part of a significant and widespread phenomenon observable among experienced protein modelers. That a 'feeling for the molecule' is widely observable among experienced modelers raises significant questions for social studies of pedagogy in science, as the face-to-face transfer of the tacit knowledge through modes of body-work in protein modeling pose challenges for training a new generation of structural biologists (see also Kaiser, 2005).[8]

This study is based on 4 years of ethnographic fieldwork among contemporary protein crystallographers, and other structural biologists in the fields of biological engineering, protein folding, and electron microscopy. My primary fieldsite was a large, private research university on the east coast of the USA. My informants were at various stages in their training and they included principal investigators, course directors, postdoctoral researchers, graduate students, teaching assistants, and undergraduate students. I conducted in-depth interviews and observations of laboratory work, and attended weekly lab meetings. I also observed full semester-long graduate

and undergraduate courses, including lecture courses on macromolecular crystallography, biomolecular kinetics, protein folding, introductory biology and biological engineering, as well as a hands-on laboratory course for biological engineering majors. In addition, I attended several professional protein crystallography meetings, numerous public lectures on structural biology and biological visualization, and interviewed a number of structural biologists working at other institutions on the east and west coast of the USA.

Though the history of structural biology is rich with accounts of model-building, limitations in the historical record make it difficult to study model-building in practice. In addition to providing insights into contemporary protein crystallography, this ethnography offers a re-reading of the accounts of early protein crystallographers. In historical and contemporary cases, I examine the role of corporeal knowledge in crystallographic modeling in both physical and virtual media, attending to how early developers of interactive molecular graphics sought to preserve the tangibility of virtual models. Throughout, I pay attention to what protein researchers do with their bodies in order to acquire and communicate embodied knowledge of molecular structure. What I find is that crystallographic model-making is not only a means of building molecular models, it also offers a training ground for the modeler. In this sense, model building is a means of reconfiguring researchers' embodied imaginations with knowledge of protein forms and movements. Working with and building multidimensional models of proteins are practices that rearticulate modelers' bodies (see also Latour, 2004; Prentice, 2005). Exploring the nature of such *molecular embodiments*, this paper offers a contribution to the history and anthropology of science, with insights into the role of researchers' bodies in the visual cultures of the computer-mediated life sciences.

Biology Thick and Thin: Methods for a 'Thick Description' of Molecular Biology

> If ideas cannot be comprehended without a history of the gestural knowledge and the objects through which they came to be expressed, and to which the terms of their expression most directly refer, then history of scientific ideas is a poor history indeed. (Griesemer, 2004: 435)

Proteins are substances with a long history in the life sciences (Cambrosio et al., 1993; Kay, 1993; Rheinberger, 1997; Tanford & Reynolds, 2001; Creager, 2002; de Chadarevian, 2002). Through the 1930s and 1940s, and up until the determination of the structure of DNA, these molecules were thought to be the material basis of heredity, and intensive effort was invested in determining their structures, chemical specificities, and cellular activities (Kay, 1993). Biophysical and structural studies of proteins, first initiated in the 1930s, came to dominate the field that mathematical physicist Warren Weaver termed 'molecular biology' (Law, 1973; Kay, 1993). W.T. Astbury was a member of

this 'protein community' (Law, 1973), and among the first to popularize the field (Stent, 1968). In 1951, Astbury insisted that molecular biology was to be understood as the 'predominantly three-dimensional and structural' study of the biophysical and chemical properties of molecules (cited in Stent, 1968: 390).

By 1967, however, the definition of molecular biology was already changing. In his widely cited lecture 'That Was the Molecular Biology That Was', Gunther Stent forecasted the decline of the structural school of molecular biology. While Stent defended the structural school's 'down-to-earth', 'physical' approach, which promoted the 'idea that the physiological function of the cell' could be understood 'only in terms of the three-dimensional configuration of its elements' (1968: 391), at that time Stent did not see how these contributions could be 'revolutionary to general biology'. After all, it had already taken more than 20 years to determine the structures of merely two 'respiratory proteins': hemoglobin and myoglobin (Stent, 1968: 391). The revolution was, according to Stent, going to be led by the 'one-dimensional' or 'informational school', whose 'intellectual origin' in the emerging computational cultures of cybernetics and cryptography in the 1950s and 1960s was 'diametrically opposite' to the physical understandings of molecules championed by the structural school (Stent, 1968: 391; see also Kay, 2000). While structural biology did not disappear, the field did lose traction during the sequencing craze of the molecular genetics and genomics revolutions (Kay, 2000) which, particularly during the 1980s and 1990s, produced a kind of 'genetic fetishism' that swept over the life sciences (Haraway, 1997).[9]

Through the discourses and practices of genetics and genomics, biological molecules have been figured most prominently through the tropes of 'information' and 'code'. These analogies have flattened the complex three-dimensional forms of molecules into one-dimensional strings of nucleotides and amino acids (Kay, 2000). Since the late 1990s, however, with the completion of the genomes of humans and other organisms and the ramping up of post-genomic investigations, many researchers are facing the limitations of genetic sequence data for accessing the multi-dimensional problems that biology poses. One of the central problems is that protein structures defy reduction to metaphors of code and scriptural analysis. This is in part because the three-dimensional conformation of a protein, and the paths through which a peptide folds into its active form within the cell, have yet to be successfully predicted entirely from DNA sequence: no one has yet discovered a 'code' that can predict protein form. Structures thus have had to be determined empirically for each protein, and their mechanisms of function interpreted indirectly.

This shift in attention from reading and writing DNA sequences to modeling protein forms has methodological implications for social studies of practice and visual cultures in science. Tracking the movements of the metaphor of code closely, analyses of molecular biology have tended to focus their interpretations at the level of the language that scientists deploy in their texts (see, for example, Doyle, 1997). However, social and historical studies whose methods adhere too closely to this metaphor, and rely entirely on text-based readings of the rhetoric

of code, miss out on a wider range of practices that have contributed to the making of molecular biology. The current intensification of protein structure research, with its elaborate modeling techniques that draw on intuition and trial and error, and demand performative modes of body-work, makes it clear that an exclusively rhetorical analysis is inadequate to the task: the production and deployment of protein models by life scientists defy reduction to text. Pointing to the wide-dispersion of three-dimensional models in scientific practice and the challenges they present to historical analysis, James Griesemer (2004: 435) suggests that a history of modeling must include a history of the 'gestural knowledge' through which models are made and used. For him, studies of scientific representations must take into account 'gestural as well as symbolic knowledge and the variety of means and modes of making, experiencing, and using models' (p. 435). Accessing a 'thick description' (Geertz, 1973) of representational forms and practices in molecular biology thus requires more than decoding the textual productions of scientists; in addition to the semiotics of modeling, it requires attending to the *corporeal* and *affective entanglements* of researchers with available concepts and modeling media, and with the visualization machinery they entrain on living substances.[10] Taking embodiment seriously in protein modeling demands that the ethnographer attend to the 'enactment' (Mol, 2002; Barad, 2003) of models in the process of building, using, and reasoning through their forms, so that she or he can in turn develop a *feeling* for scientists' movements, gestures, and affects as they work with their objects.[11] These are practices that can be difficult to record and relate, and so to convey the subtler dimensions of the craftwork, tacit skills, and creativity of scientific practice, ethnographers and historians need to develop new competencies for tracking bodies and embodiment. To remedy analyses that flatten both molecules and practices, this study aims to flesh out the 'liveliness' (Haraway, 1997: 137) and 'body-fullness' (Haraway, 2001) of life science practice that structural biologists, such as Diane, perform.

The Body-work of Molecular Model-making: A Brief History

Physical, three-dimensional models are essential visualization tools for teaching, learning and research in the life sciences. They have had a long and varied history in biology, and the stories surrounding their construction and use have recently captured the attention of scholars tracking the material cultures of the sciences (see for example Star, 1992; Francoeur, 1997; Hopwood, 1999; Daston, 2003; de Chadarevian & Hopwood, 2004). One of the key claims of this growing literature is that a focus on model-making reframes practices of scientific visualization and representation. More than visual traces, marks or inscriptions, three-dimensional physical models explicitly blur the boundaries between automated machinic productions and the skilled work of scientists, and between the intellectual and physical labor of research. I argue that modeling practices challenge narrow conceptions of 'thinking' as a cerebral activity, and make visible the craftwork, creativity, and embodiment of scientific reasoning (see also Hopwood, 1999). Three-dimensional models

are improvised, handcrafted artifacts that articulate scientists' intuitions; they are recursively made and remade in attempts to conceptualize and actualize new hypotheses and new modes of inquiry. Moreover, such models – whether physical, virtual, or embodied – are *interactive objects*; as such they demand participation and so are subject to continual transformation.

Some of the most striking features of the wide range of three-dimensional models used in the life sciences are their tangibility, manipulability, and amplification to a human scale. This is perhaps most apparent in the case of molecular models, those playful ball-and-stick 'Tinker-toys' representing atomic structures familiar from high school chemistry laboratories (Francoeur, 1997). Structural biologists have built and used models of protein structures from crystallographic data since the late 1950s (de Chadarevian, 2002; Francoeur, 1997). Eric Francoeur (1997, 2000, 2001; Francoeur & Segal, 2004) has documented the history of molecular models in chemistry and biochemistry, detailing how they have been improvised, standardized, and disseminated. Made from metal, plastic, cardboard, Styrofoam balls and toothpicks, balsa wood and elastic bands, three-dimensional models have amplified the molecular world to sizes, and in styles and forms manageable and imaginable for their users and admirers (see also Bassow, 1968). And beginning in 1963, structural biologists produced molecular models that flickered on analog computer screens, creating an entirely new medium for molecular representation (Levinthal, 1966; Francoeur & Segal, 2004).

While molecular modeling media have changed significantly over the years, these materials have consistently been selected for their tangibility and manipulability. Francoeur (1997: 14) shows that a special feature of molecular models is that they 'embody, rather than imply, the spatial relationship of the molecule's components'. Such models can be manipulated and analyzed:

> Like many other types of object handled by scientists in the field or the laboratory, they can be touched, measured, tested, dissected or assembled, and tinkered with in many different fashions. In other words, they act as a material analogy. (Francoeur, 1997: 14)

Building physical analogues of molecules thus requires physical handling and spatial thinking. As Francoeur (2000: 6) notes, the 'working out' and 'sorting out' structures with physical models is a kind of 'thinking with the hands' that has long been an integral part of the work and knowledge of chemists and biochemists. This practice of 'thinking with the hands' is well exemplified by a canonical story often told in the history of structural biology. Linus Pauling is remembered for his exceptional skills in modeling proteins in three dimensions: his 'discovery' of the structure of the alpha-helix, while lying in bed with the flu in Oxford in 1948, has become legend (see also Nye, 2001). Max Perutz was at that time competing to determine the same structure. In an obituary for Pauling, Perutz (1994:670). describes how Pauling figured out the alpha-helix. Apparently he worked

out the structure while laying in bed amus[ing] himself by building a paper chain of planar peptides' until he 'found a satisfactory structure by folding them into a helix' (670). This process of 'discovery' required him to improvise with ready-to-hand materials. 'Giving body' to molecular form, he fleshed out the molecule in order to figure out the spatial organization of atoms (see Hopwood, 1999).[12]

In the history of three-dimensional modeling practices, such work has not been easy. Molecular modeling in three dimensions requires concerted effort and great patience. In his account of the 'discovery' of the helical structure of DNA in the early 1950s, Watson (1969: 62) reminisced that his and Crick's 'first minutes with the models' were 'not joyous'. 'Even though only about fifteen atoms were involved, they kept falling out of the awkward pincers set up to hold them the correct distance from one another' (p. 62). Indeed, he had to keep 'fiddling' with the models to get them to hold together (p. 122). As he and Crick got closer to determining the structure, they sometimes spent whole afternoons 'cutting accurate representations of the bases out of stiff cardboard' (p. 123) to produce models of nucleotide pairs that could be shuffled in and out of different pairing possibilities. This was an improvisational practice that eventually enabled them to give form to the DNA molecule and figure out how the nucleic acids adenine and thymine, and guanine and cytosine, could

FIGURE 2
Building the 'sausage model', the first crystallographic model of a protein molecule. This screenshot was obtained from a movie produced in Kendrew's laboratory in Cambridge, UK. Used with permission from the MRC Laboratory for Molecular Biology, Cambridge, UK.

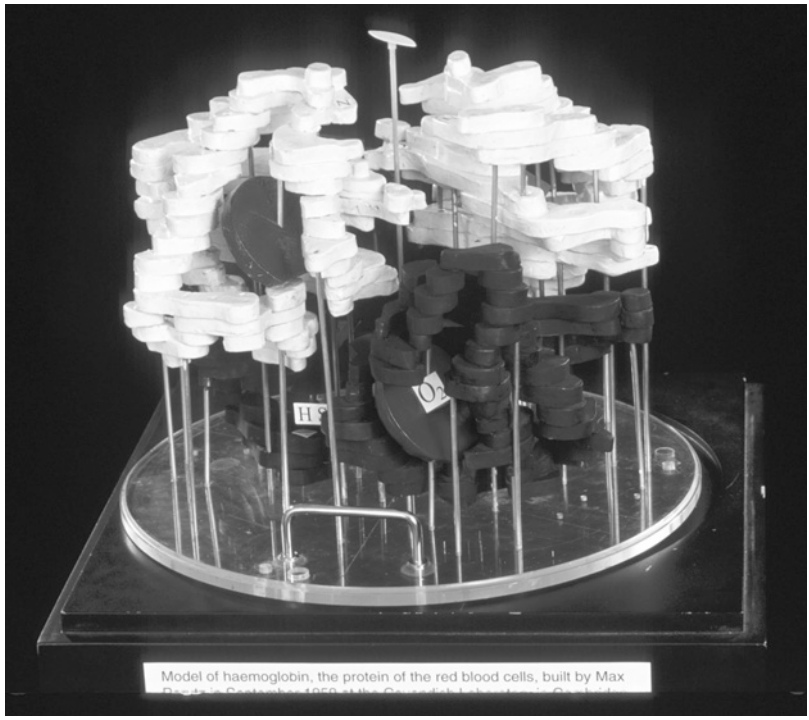


FIGURE 3
Max Perutz's low-resolution model of hemoglobin made with thermo-setting plastic. Used with permission from the MRC Laboratory for Molecular Biology, Cambridge, UK.

pair to form the double helix. Molecular model-building with physical materials is thus a time-consuming, trial-and-error-ridden process that requires physical engagement and exploratory interaction with often-finicky materials.

Models of complex biological molecules were built in a range of different media, each of which afforded particular kinds of bodily interaction and manipulation. Some of the materials even revealed the work of their makers. In 1957, John Kendrew's laboratory in Cambridge, UK, produced the first model of a protein. Made out of thick tubes of black Plasticine and supported on wooden pegs, it was nicknamed 'the sausage model' (see Figure 2). As this frame, shot from an 'in house' movie of the making of the sausage model at the Laboratory for Molecular Biology (LMB) reveals, the model-builder appears not to have been Kendrew, but one of the many women who were employed in his laboratory.[13] In addition to providing what was a shocking and 'visceral' view into the molecular realm,[14] this model also offered a record of the performance of the modeler. That is, the pliable Plasticine medium recorded the movements and gestures of the modeler's handiwork. When attempting to build his earliest models of hemoglobin in the early 1960s, Max Perutz also tried Plasticine, but when this material proved too unstable for his more complex molecule, he resorted to cutting thermo-setting plastic into topographical sections that he stacked one on

top of each other, baking the model to set it permanently into shape (de Chadarevian, 2002: 143) (see Figure 3). However, this rather clunky, low-resolution model did not articulate the fine detail of hemoglobin's atomic structure, nor could it be used to demonstrate the subtle movements of hemoglobin's molecular mechanism. With better crystallographic data, Perutz was later able to produce atomic-resolution models with standardized, machined parts. Adjustable links between the atoms along the polypeptide chain provided the opportunity to manipulate the model. The mechanical properties of such models could be engaged dynamically, and performatively, as a means to make arguments about molecular function.[15] In a video interview conducted towards the end of his life, Max Perutz can be seen moving a ball and stick version of his hemoglobin structure in and out of different conformations, demonstrating with delight the effect of oxygenation on the structure of the heme group.[16] Thus, analyses of scientific models must take into consideration the various media used, not only to understand how modelers represent protein molecules (which would be a concern with how the resulting models look), but also to understand how these distinct media engage modelers' bodies in different ways.[17] Different materials afford different modes of interaction and manipulation, and different kinds of insight into the molecular realm.

Where films of early protein modelers enacting their molecular models are scarce, ethnographic research among contemporary protein modelers adds depth to these historical accounts and provides access to the performance of models in practice. Jim Brady is a prominent professor of biology at the same university where Diane Griffin teaches. While lecturing in a course on protein structure and folding, he demonstrates the value of 'thinking with the hands' by playing on the double meaning of the verb 'to grasp'. He picks up an old and worn physical model (which was built at the Laboratory for Molecular Biology in Cambridge, UK, and brought to this campus about 40 years ago) and holds it up in front of the class. It is a colourful ball-and-stick model of the amino acid alpha-helix, a key secondary structure within protein molecules. He warns the class: 'Now … This is not easy to grasp, and that's why it's so important to *grasp* these structures' (his emphasis). Grabbing hold of the model, and using his fingers to walk along the spiraling peptide backbone, amino acid by amino acid, he directly invokes his hand and its grasping motion in seeing and understanding. However, he does not only posit a direct relation between his hands and understanding; in his lively lectures he pulls his entire body into play to demonstrate specific protein folds. To animate the packing alpha-helices within a protein, he draws his arms in towards the core of his body and curves his torso inwards. With his arms crossed at the forearms to specify the precise angle at which the helices meet, he signals the strength of the atomic forces between the helices by varying the tension he holds in his muscles (see Myers, in press, a). As Diane's performance also exemplifies, molecular models are not just the product of handiwork; produced and propagated through lively body-work, they clue their users' entire bodies into the intricate structures of proteins.

The Digital Materiality of Interactive Molecular Graphics

The contribution of researchers' bodies to model-building was not lost with the transition to virtual media. Indeed, interactive computer graphics aimed to facilitate modes of embodiment more conducive to model-building. As crystallographers improved their techniques, acquiring higher resolution data, and modeling increasingly complex proteins, the use of physical materials for molecular modeling became more challenging. Material models became far too large and cumbersome to build, subject as they were to the unfortunate effects of gravity and mechanical stress. This was a lesson learned by one group of molecular modelers based in Manchester, UK, in the early 1960s. After their elaborate model of a protein made of balsa wood and elastic bands collapsed in the dry and dusty basement in which they were working, they went so far as to contemplate building their model underwater in a swimming pool to cancel the effect of gravity (Francoeur & Segal, 2004: 412). Following his failures to model proteins in balsa wood at Manchester, C. David Barry, one of the members of this group, joined MIT biologist Cyrus Levinthal at Project MAC to help develop the first interactive computer graphics work station for visualizing, manipulating, and predicting protein structures (Levinthal, 1966; Francoeur, 2002). Between 1963 and 1967 Levinthal, in collaboration with Barry and others, developed an interactive molecular graphics machine they jokingly nicknamed 'The Kluge' (see Francoeur & Segal, 2004). This interface made use of a 'crystal ball' (an early mouse) and light pen to enable control of rotation and the selection of specific coordinates of the structure. Offering an improvement over the swimming pool option, this interactive graphics workstation could be thought of as the first practical zero-gravity chamber for molecular modeling.[18]

Once interactive graphics had already begun to take hold of the molecular modeling community, Robert Langridge, a key supporter of Levinthal's work at Project MAC, articulated the benefits of molecular graphics over working with physical models. In a 1981 paper reviewing advances in computer graphic modeling he writes:

> Space filling or wire models are satisfactory up to a certain level of complexity, but purely mechanical problems cause serious difficulties since the model on the bench and the list of [atomic] coordinates in the computer are not necessarily closely related (*especially after the model is degraded by many curious hands*). Particularly difficult is the restoration of a structure after simple modifications. With computer graphics, the display and the data are directly related, storage of prior configurations is simple, and pieces do not fall off. (Langridge et al., 1981: 661; emphasis added)

As it turns out, the very pliability of physical molecular models was both their greatest virtue and greatest limitation as working tools. The 'haptic' dimension involved in the manipulation and handling of physical materials was key for the production of models that could give modelers a sense of the structure and dynamics of the molecule, and offered a means for researchers to use their bodies to incorporate structural knowledge. However, once available to 'curious hands', these toy-like structures invited continuous reworking and tweaking, eventually leading to conformational

distortion. Motivated to overcome the challenges faced in working with physical models, while inspired by the tangibility they offered, crystallographers and computer scientists collaborated to develop interactive computer graphics technologies for building protein models onscreen.

Early researchers' accounts of the development of computer hardware and software in interactive molecular graphics reveal how they approached the problem of preserving the tangibility and manipulability of models in making the transition from physical to virtual modeling. What becomes clear from their accounts is that an intimate relationship between user and computer had to be engineered into a workstation in order to make it interactive enough to keep the modeler physically engaged in model-building. Interactive computer graphic techniques aim to intimately couple the modeler to the computer screen through an array of input devices that mimic some of the aspects of physical model-building. Eric Francoeur and Jerome Segal's (2004) history of the emergence of interactive molecular graphics makes it clear that while this interactive technology offered a medium distinct from the physical models previously used to investigate structures, these tools preserved a kind of tangibility that modelers had come to rely on to do their work. This tangibility, and the embodied nature of this early interactive graphics technology was not, however, immediately obvious to the uninitiated. At a Gordon conference in 1965, Robert Langridge presented the Kluge system to an unenthusiastic audience. As he recalled, one crystallographer 'objected that a graphics display would simply not do as a substitute for physical models, since he had to have his hands on something, something physical, so that he could understand it'. For Langridge,

> standing up at a conference and showing 16 mm movies, in the early days, was really not a good substitute for sitting in front of the computer and actually using it. When you first got your hands on that crystal ball at Project MAC and moved the thing around in three dimensions it was thrilling. There was no question. (Langridge, quoted in Francoeur & Segal, 2004: 418)

The early developers of these programs sought to generate the 'smooth handling' of graphic models in 'real time' on the computer screen. They aimed 'to produce an illusion (a hand-eye correlation) strong enough that the operation required to manipulate the model via the computer' could become 'instinctive' (Barry et al., 1974: 2368–69). In this way the molecular graphics 'map and model' could be 'manipulated almost by hand' (Tsernoglou, et al., 1977: 1379). For Langridge, the 'smooth rotation of three-dimensional objects is one of the most important elements in making use of the display seem "natural" to persons used to handling "real" molecular models' (Langridge, 1974: 2333). He explained that there was, however, 'no precise definition of the terms real-time and interactive: the difference between interactive and noninteractive uses of computer graphics depends on how long you are willing to wait to see a result' (Langridge et al., 1981: 666). 'Satisfactory' interactions demanded advancements in the speed of computer processors, but also patience on the part of the user (p. 666).

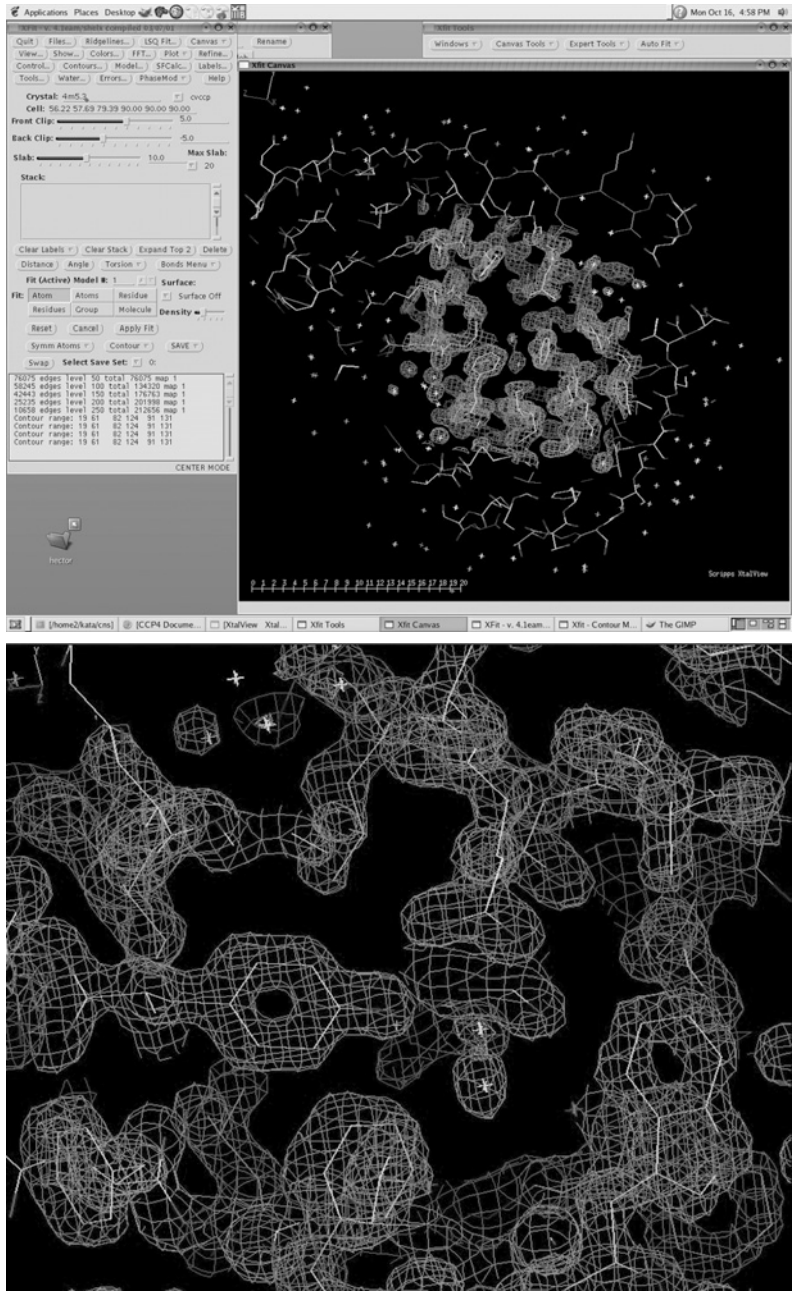


FIGURE 4
Contemporary tools for crystallographic model-building. (a) A screen-shot of an interactive computer graphics interface used for building a molecular model into a computed electron density map (b) A close-up of an interactive graphics electron density map showing the skeleton of a molecular model built into regions of electron density. The user can freely rotate this composite map and model onscreen, and zoom in and out to observe and manipulate it at different scales. Images used with permission from an anonymous ethnographic informant.

In the hardware systems that emerged later, a whole new array of input devices was developed and used to enhance the human–computer interface in the simulation of a 'real-time', interactive modeling experience.[19] Switches, knobs, joysticks, tablets – and a range of apparatuses to generate the experience of '3D vision' through stereoscopic technologies – connected the user to the maps and models they could manipulate on screen.[20] Remarkably, what interactive computer graphics developers achieved was more than an illusion of connection between modeler and model: the interactive graphics workstation became a prosthetic extension of a physically engaged modeler into an interactive and so tangible world of graphic molecules. Ensuring that protein researchers experienced the physicality they had come to expect from their molecular modeling work, interactive molecular graphics developers offered a successful alternative to modeling with physical materials. In the process, they also produced a new kind of tangibility for virtual objects.

In 1977, Tsernoglou and his collaborators reported the successful modeling of a protein entirely through interactive graphics technologies. The complete transition from physical to digital models did not, however, take place overnight. Physical models retained pedagogical value, and some physical modeling techniques were held over for teaching purposes. For example, in the early days of protein crystallography, Perutz, Kendrew, Dorothy Hodgkin, and others built large-scale three-dimensional electron density maps out of physical materials. They traced slices of electron density on transparency paper and stacked these between Plexiglas sheets, building up a physical model of the electron density map layer by layer (Kendrew, 1964; de Chadarevian, 2002).[21] In the 1960s, Diane's advisor, Susan Fielding, participated in building one of the first models of an enzyme protein using these early techniques. Diane trained in Susan's lab in the early 1990s. At that time, interactive computer graphics programs were readily available for constructing three-dimensional electron density maps onscreen,[22] yet Susan insisted that her graduate students first learn how to build models of electron density using the old Plexiglas sheets she kept stored in her lab just for this purpose. Diane explained Susan's rationale for this pedagogical exercise: digital graphics could only present small pieces of the map at a time, so that physical modeling was the best way to get a feel for the map and the molecule as a whole. At the same time, this pedagogical practice served to provide a material reference for novices just beginning to work in digital media, so that when the students went to use the virtual tools, they already had a sense of the physicality of the electron density topographies they were navigating onscreen (see Figure 4a,b).

Protein modelers today almost exclusively use digital media; however, physical models are still used in some protein crystallography labs. In her office, Diane shows me one small molecular model she sometimes uses to make a particular argument about a chemical interaction. However, she explains that models like this are rare. Fernando, a fifth-year PhD student in her lab, mourns this loss of physical models, which he sees as the best means to provide students with a tangible object that can stand as the primary referent for the graphic models they manipulate onscreen. He would

prefer that a culture of physical modeling be maintained alongside computer graphics to help crystallographers-in-training gain experience with manipulating three-dimensional objects. He has observed that molecular modeling kits are also less prominent in chemistry classrooms and tutorials at his university, and sees this as the product of an intellectual culture that devalues physical models, treating them as toys rather than as serious tools. My observations in lecture courses and teaching laboratories in the field of structural biology do show evidence of the use of some physical models, though these are often ancient artifacts (such as the one described above that Jim Brady demonstrated for his protein-folding class), and they are always used in conjunction with interactive graphics, two-dimensional renderings, and rich rhetorical analogies (Myers, in press, a).

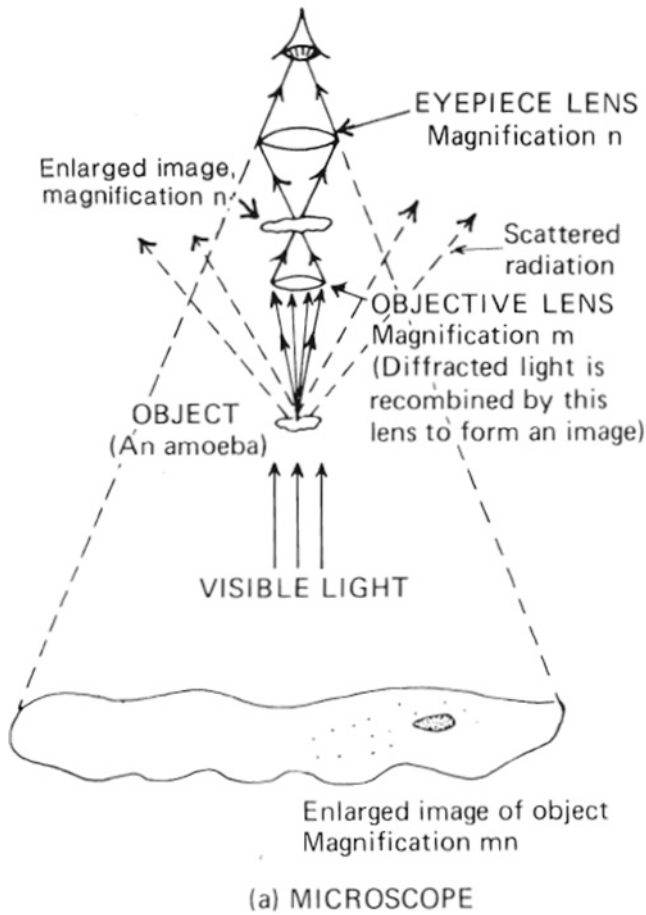
In some senses, interactive graphics reconstitute what it means for a digital object to be tangible; and this is not so easy to 'grasp' for first-time users. In pedagogical contexts, novices do have a hard time experiencing the tangibility of interactive graphics. However, over time and with the experience of constant interaction with virtual objects, they eventually acquire a feeling for the tangibility of digital media. Katherine Hayles (1999) argues against prevailing assumptions that users are drawn out of their bodies, or disembodied, when they work with virtual media. Indeed, what I have observed suggests that rather than 'dematerializing' the molecule into some bodyless virtual reality space, over time the interactive graphics workstations used for crystallographic model-building enable a particularly effective kind of handling. Digital models acquire a materiality and tangibility through their manipulation onscreen. Diane clarifies the embodied nature of computer modeling work when describing her experience building crystallographic models onscreen. She invokes the same language and gestures one might use to describe model-building with physical materials:

> And physically you are sitting at your computer, often with the stereoglasses on. And you are *physically dragging* pieces of protein structure, like amino acids, and sticking them in. You drag it in and you stick it there. And then with your dials or your mouse, you are adjusting it, moving the pieces to get it to fit. So you are *physically building* with the stereoglasses and the mouse. You are physically building in a model into this electron density.

As Diane describes building the model, she stretches her arms out in front of her and mimes the activity of modeling. She uses her hands to act out her work at the computer. Through elaborate gestures, she carves out the space of the computer screen, the amino acids and the shape of the electron density map. With her hands clasped and pulsing around invisible objects, she conveys the density and textures of the molecules, and their inter-molecular associations, while in the open, gestural space in front of her she builds a model 'onscreen'. Through this elaborate body-work she expresses how tangible the graphic model is for her.

When I observe crystallographers building protein models onscreen, the protein model is never left still: it is kept in motion through constant

and restless gestures of the mouse and the quick-paced and sometimes clumsy tapping out of keyboard commands that pull up new windows and views. In one window, data will be streaming up the screen, and in another, the crystallographer holds the skeleton-like interactive rendering of a model. She keeps it alive in space and depth, rotating it onscreen and zooming in and out, keeping it visible at multiple angles, constantly shifting her visual and haptic relationship to it. This dynamic practice of seeing in motion appears to offer a means for the modeler to keep the three-dimensionality of the model visible and tangible. But more than the crystallographer's hands and eyes are in play. Though more subtle than their hand movements, I observe that their bodies become *affectively entangled* in the task of manipulating the model onscreen: with movements initiated at the head and neck, they move as they rotate the model, leaning in, pulling away, and even peering around behind obstructions in order to see and feel their way through the model. Moreover, as they parse the thicket of this dense visual field for a curious, novice onlooker, or another expert viewer, they pull the model off the screen through elaborate gestural choreographies



(a) MICROSCOPE

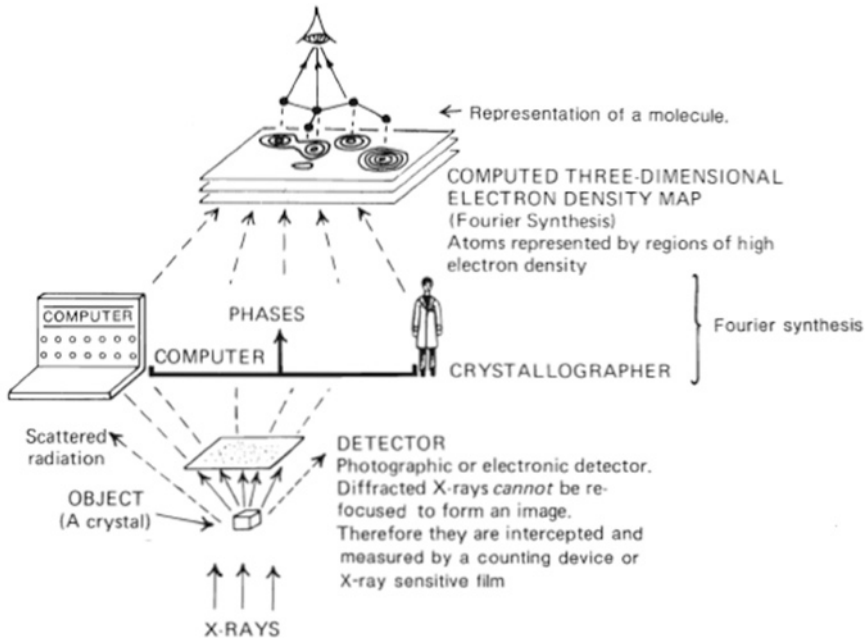


FIGURE 5
An analogy between microscopy and crystallography. (a) Microscopy. (b) Crystallography, Glusker and Trueblood (1985: 5) use this pair of diagrams to show how the 'crystallographer' and 'computer' are coupled form a kind of microscope lens that can recombine the diffracted X rays into an electron density map in order to generate a model of the atomic structure of a molecule. The original caption reads: '… X rays cannot be focused by any known lens. Therefore the recombination of the diffracted beams that is done by a lens in the microscope must, when X rays are used, be done mathematically by a crystallographer with the aid of computer' (p. 5). Used with permission from Oxford University Press.

that animate the structure's intra-molecular forces, functional mechanisms, and movements. Thus, for experienced users, virtual models become tangible interactive objects. For novices who haven't yet experienced the embodied interactivity of the graphics interface, these models can be fleshed out and relayed through expert modelers' gestures and movements; in so doing, expert modelers give body to otherwise virtual objects.

The Human–Computer Lens

Protein crystallographers make use of an elaborate set of computer-mediated techniques in order to build atomic-resolution models of proteins. This practice is intensely time-consuming, and physically and intellectually demanding.[23] According to Diane, to be a crystallographer you have to be 'a molecular biologist and a protein biochemist, you have to be a little bit of a physicist, you have to be a computer jock, *and* you have to be an artist'. The

model-building process is itself a rite of passage into becoming a protein crystallographer. The common lore in the lab is that even if well versed in crystallographic theory, a crystallographer remains a novice until they have fully built their own structure. Working in the tangible medium of interactive computer graphics, modelers-in-training learn how to see, feel, and build protein structures through their embodied interactions with the data. Model-building is thus a kind of training ground for crystallographers to acquire their 'feeling for the molecule', to develop the tacit skills and craft knowledge required to visualize proteins and 'think intelligently about structure'. As I show below, the well-trained crystallographer's molecular intuitions form an integral part of the technological 'lens' that draws proteins into view.

Approaching crystallography as an optical system – that is, a technology for visualizing molecules – crystallographers often compare and contrast X-ray crystallographic techniques to microscopy (see Glusker, 1981; Glusker & Trueblood, 1985). Diane adapts this canonical analogy in her introductory lecture to students in her macro-molecular protein crystallography class, and presents a hand-drawn schematic on an overhead based on Glusker and Trueblood's diagram (see Figure 5 a,b). As their diagram outlines, in contrast to the optical systems of microscopes that make use of visible light, X-rays cannot be focused with the aid of lenses. In place of a microscope lens, crystallographers have devised an intricate system to couple the modeler with an assemblage of computer technologies and mathematical functions. This assemblage simulates the function of a 'lens' that can actively resolve models of protein structure. This *human–computer lens* in effect provides the resolving power for an 'X-ray microscope'.

Crystallographic Vision

Getting Lost and Found in the Model

> Imagine sailing for years through uncharted water, and then suddenly you see land rising on the horizon. And this model emerging was like this. So one morning in September in 1959, our results came out of the computer at the Cambridge Mathematical Laboratory: thousands of numbers, which we plotted on sheets of paper. And then we drew contours around them, and there emerged a landscape of peaks and valleys. So, I built this model. And then, suddenly saw this thing, you know, which I'd been working on for twenty-two years. And it was a fantastically exciting moment. I always say it was like reaching the top of a mountain after a very hard climb and falling in love at the same time. (Max Perutz[24])

In the many steps required to transform a protein from its in vivo form into models and animations of its structure and molecular movements, protein crystallographers make use of an array of computer-mediated visualization techniques including X-ray imaging, electron density mapping, molecular modeling, and tools for producing publishable figures and generating simulations. First, protein molecules must be purified from cells and crystallized. Forming viable crystals is often a major rate-limiting step, sometimes taking years in itself.[25] X-rays are then used to generate diffraction patterns of the

crystal. The series of patterns that are produced as the crystal is rotated in the X-ray beam correspond to the positions of the atoms within the proteins packed into the crystal. In ways similar to other three-dimensional visualization systems such as the Visible Human Project, PET scans, and confocal microscopy,[26] there is a 'tomographic' logic to this X-ray imaging system which builds up a three-dimensional image by slicing through the object at precise intervals and stacking these slices. As the crystal rotates in the apparatus, detectors pick up images of the scattering of X-rays at every degree of rotation. Each spot on the diffraction pattern, and each X-ray image, itself a slice through the molecule, becomes a data point for generating a map of the approximate position of the electrons in the molecule.

As Dorothy Hodgkin recounted in her 1964 Nobel lecture (the award was given for work done in the late 1940s and 1950s), while the techniques of structure determination can be 'formally' represented as a cycle of mappings followed by 'rounds of calculation' and modeling, 'the outline hardly gives an accurate impression of the stages of confused half-knowledge through which we passed' (Hodgkin, 1972: 75–76). A key problem that the crystallographer faces is that the pattern of light scattering is extremely cryptic. Each spot on the diffraction pattern is a product of the interaction of every

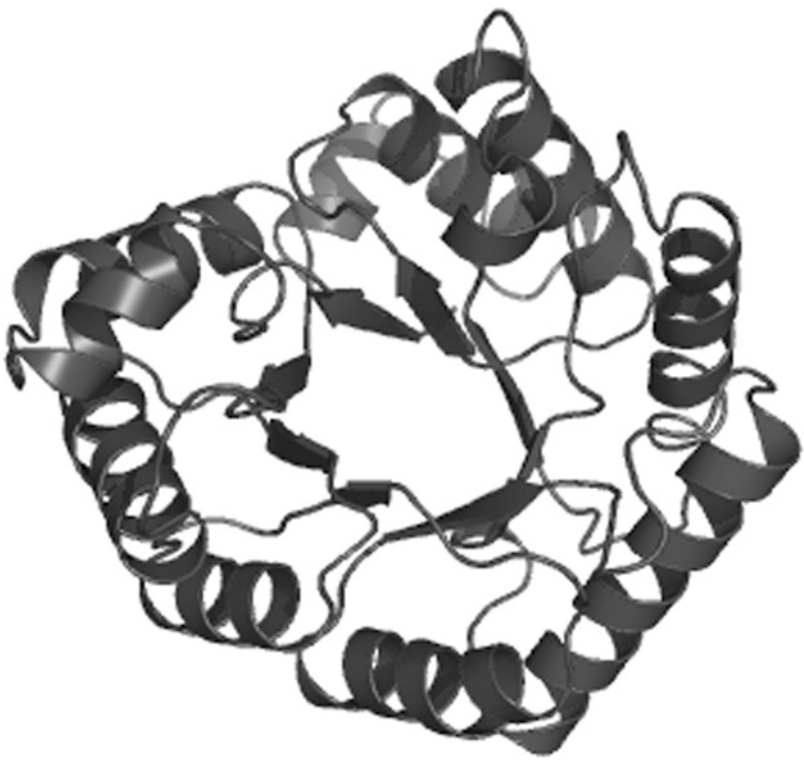


FIGURE 6
A ribbon diagram of a TIM barrel. Note the circular arrangement of alpha-helices. Used with permission from an anonymous ethnographic informant.

atom in the molecule, and every molecule in the crystal. The diffraction patterns produced must be analyzed and transformed through a series of complex mathematical functions, including Fourier transforms, in order to translate them into a form that is legible and interpretable. These conversions generate three-dimensional electron density maps of the molecule that indicate the approximate positions of the atoms within the proteins (see Figure 4). These maps are read almost like three-dimensional topographical maps, where 'peaks' of electron density mark the approximated positions of atoms.

Indeed, working in between maps and models over the long duration of model-building is an elusive and piecemeal practice, involving much trial and error. Crystallographic models are built slowly through a recursive and iterative interplay between increasingly refined electron density maps and models. Moving back and forth between different kinds of electron density maps that correct for various errors, crystallographers actively cycle between techniques of mapping and modeling. As they build more amino acids into the electron density, they use the model as a means to generate more refined electron density maps. Calculating backwards, they can construct hypothetical electron density maps of the models they are building, as a means to test the models against the observed data. Thus they move through rounds of mathematical refinements, recalculating the density peaks, re-fitting the model, and continuously comparing calculated electron densities with observed electron densities. Layered into this process is the corroboration of their model with the known sequence of the protein. Gradually, a clearer and clearer image of the map and model emerges.

Much of the difficulty in this work lies in the fact that the model is never self-evident from the map. Faced with an electron density map, the crystallographer has few clues as to which parts of the protein fit in which parts of the electron density. It is up to the crystallographer to recognize what amino acids fit into particular configurations of electron density. Dehlia, a fourth-year PhD student in Diane's lab whose first structures were already published in *Nature*, told me: 'And one thing I didn't realize when I started building is the extent that … you have to start making executive decisions.' Her lab-mate Amy, a fifth-year PhD student who had been having incredible difficulty solving the structure of a new protein she was working on, confirmed this in a separate interview. She emphasized that:

> A lot of guesswork goes into [building a structure]. And guesswork isn't the best word to use; maybe subjective would be the best word to use to describe it. And that's not something you can understand until you actually have a structure that you have done yourself, or are in the middle of doing. The first structure I did was an easy one. I was really surprised that it was up to me to put in [amino acid] residues. It was up to me to put the [polypeptide] backbone in. I was just really surprised. … That it was something that I could make a mistake and no one would know. It's kind of scary, and it makes you really wary about other structures sometimes.

To do their work well, students must cultivate sound judgments that demonstrate a respect for protein forms. According to Diane, crystallographers must rely on what she calls 'known knowledge' to 'interpret what otherwise would

be completely un-interpretable'. Sculpting a best-fitting model into the map through a wayward and intuitive process, the modeler must draw on embodied knowledge of allowable molecular geometries, including the distances and bond angles between atoms within the polypeptide chain, and the intramolecular forces that hold the whole molecule together. For Diane, model-building requires the modeler to be comfortable with the experience of meandering through the electron density map, never really knowing for sure 'where you are'. As crystallographers build, they must first get lost in the map, and feel their way around familiar and unfamiliar forms in order to connect up the model atom by atom, doing work that the computer alone cannot achieve.

Best known for his articulation of the role of tacit knowledge in scientific practice, philosopher of science Michael Polanyi (1958) offers insight into model-building. Indeed, as a physical chemist who used X-ray crystallographic techniques in his experiments, he developed elements of his thinking about tacit knowledge with reference to crystallographic practice. Drawing on Gestalt psychology, Polanyi found 'inarticulate manifestations of intelligence' beneath the surface of scientific practice, an intelligence that 'falls short of precise formalization' (1958: 53), wherein experimental progress is made incrementally, by trial and error, such that researchers must 'grope' their way toward insights (p. 62–63). Diane's experience maps onto this description well: for her, the structure can remain obscure for a long time, until a shift in perception opens it up to view. Once you have started building your model, she explains,

> Then you'll look at it and go, 'Okay, there's a big side-chain here. And three residues down there's something long. And this looks like an arginine [an amino acid] and down there, that looks like something big.' And you'll go through your sequence, and go, 'Okay, where are the arginines? What's four residues away? Oh, lysine [an amino acid]. That's no good.' And you will work your way through. And you'll sort of build some of it, and then go, 'Okay now I'm lost and I don't know where I'm going next … '
>
> And there are certain folds that people know. Like TIM barrels [see Figure 6]. One time I could see some helices in an early map, and I was putting a couple in, and I put a couple more in. And then, I think I got up for a minute and came back and just sort of saw from a distance what I had done. And I looked and there was a whole bunch of helices around in a row. And I said, 'That's a TIM barrel!' And there's got to be strands in the middle. And then I pulled in a TIM barrel and went, 'Okay, it's a little off, it needs some adjusting, but yeah, that's what it is.'
>
> And so, sometimes it takes a long time to recognize the fold, because sometimes it's not a very standard fold. And other times it can come out relatively quickly, you'll all of a sudden see the connections by how things are, or you'll find a region where you can see the density of beta-strands. And you know that you can pull in the model and try to get it to fit.

For Diane, model-building is like a 'detective story' where the crystallographer has to search for clues about their structures. She says, 'That's why you never know you are done until you are *done*. Because at the end stage you go, "Okay, if that's correct we should be able to connect [amino acids] five and six, and it's all there!"' Here Diane's account suggests that there is a gestalt shift in seeing that occur through immersion in the work of modeling, where the form of the folds jump out at her, emerging whole from a piecemeal process of building. Key here is that the interactive graphics systems that Diane uses can engage her in what early developers like Barry (Barry et al., 1974: 2368) had called 'the "intuitive, trial and error" style used with mechanical models': According to him these systems exploit an 'interactive mode' which is 'able to take advantage of the powers and versatility of the "*human computer*" for pattern recognition and inductive thinking' p. 2368, emphasis added).

The Craft Work of Computer Modeling

> We decided to develop programs that would make use of a man–computer combination to do a kind of model-building that neither a man nor a computer could accomplish alone. … It is still too early to evaluate the usefulness of the man–computer combination in solving real problems of molecular biology. It does seem likely, however, that only with this combination can the investigator use his 'chemical insight' in an effective way. (Levinthal, 1966: 49, 52)

Computers figure in crystallographic work in many other ways besides their role in interactive computer graphics technologies. Crystallographers were among the first life scientists to make use of computers, initially for alleviating the massive labor they faced with calculation, and later for reducing the physically laborious process of data collection and for facilitating computer graphic representation and manipulation (Siler & Lindberg, 1975; Tsernoglou et al., 1977; de Chadarevian, 2002; Francoeur & Segal, 2004). In each case, computers introduced important changes in modelers' work; however, in none have they completely replaced the modeler.

Until very recently, few steps of the crystallographic modeling process have been fully automated. Though many computer scientists and mathematicians are developing algorithms with the aim of automating protein structure determination, their programs currently cannot, on their own, fully determine the large and complex configurations of protein molecules from sequence information, or perfectly fit a model to a map. Thus the crystallographer is an essential component of this visualization technology. The 'human' part of the human–computer lens – that is, the crystallographer – must sculpt a best-fitting model into the map through a practice that requires intimate knowledge of molecular form, keen eyes, intuition, and an intimate bodily engagement with the model as it is slowly built up over time.

As outlined in the diagrams comparing crystallographers and microscopists in Figure 5, while crystallographers may assume that microscopists rely on the 'mechanical objectivity' (Daston & Galison, 1992; Galison,

1998) of their technical apparatus to produce faithful microscope images of cells, these modelers explicitly theorize an entwined human–technological agency in their practice of drawing proteins into view. In this sense, crystallographers are explicit about the contributions of their own knowledge and labor to model-building. It is the embodied nature of crystallographic modeling that preserves for the crystallographer what might be called a 'critical epistemology of visualization'. Key here is that crystallographers value the intuitions and embodied knowledge they contribute to their work: they deem the craft nature of their practice a virtue that raises the epistemological status of their data (Turkle et al., 2005: Chs 1, 2, 5). By making so explicit their direct participation in model-building, protein crystallographers are always careful about qualifying the epistemological status of their various visual productions: their renderings are only ever 'models': imperfect but powerful representations of otherwise invisible molecular worlds.

Molecular Embodiments

> To get used to [things] is to be transplanted into them, or conversely to incorporate them into the bulk of our own body. Habit expresses our power of *dilating* our being-in-the-world, or changing our existence by approaching fresh instruments. (Merleau-Ponty, 1962: 143, emphasis added)

> We may say that when we learn [a] probe, or a tool, and thus make ourselves aware of these things as we are of our body, we *interiorize* these things and *make ourselves dwell in them.* (Polanyi, 1969: 148, emphasis added)

How do interactive molecular graphics technologies enable this physical experience of handling and manipulating structures? A phenomenological approach to the kinds of learning enabled within the training ground of crystallographic model-building draws out the fine details of this process. Exploring the prosthetic nature of tool use, Maurice Merleau-Ponty (1962) and Michael Polanyi (1958) offer insights on the intimate association of bodies and tools in learning. According to them, we learn to use new instruments by enveloping them within the folds of our flesh, and also by reaching our bodies outwards to meet the tool as an extension of ourselves. These insights into learning and embodied practice suggest that our bodies are open to the world, porous to new possibilities and adaptable to new kinds of tools. In this way, protein modelers can be understood to 'dilate' and extend themselves into the prosthetic technologies offered by computer graphics, and 'interiorize' the products of their body-work as embodied models of molecular structure. In a key moment during an interview with Diane, she offered this insight into her experience of incorporating molecular forms:

> The person who builds structure … they understand the structure in a way that I don't think anyone else ever will. And I try now as an advisor, I try to get inside the structure and really try to understand it at that level. And I have for a few of them, but it is really time consuming, I mean, to sort of have the structure in your head in *three dimensions*, which is how I felt about

> some of the other structures that I actually did build myself. And I would be at a meeting and people would be discussing a mechanism, and I would kind of close my eyes and try to think about it and go, 'No. Too far away.'
>
> And you know, it's really this vision that you have of the active site, and sort of this sense of how tightly packed it is and how much flexibility there might be and where those regions of flexibility are. To have this sort of sense that you have. And you can think about it then *moving* in a way because you sort of know something about what the density was, so that you know that part is definitely mobile right in there, but that this part would not be mobile. And this information is kind of like stored in your brain in some way, and it's not something that is easy to communicate, because, you know you can't explain something in three dimensions to someone … (her emphasis)

A number of striking insights emerge from Diane's description. In order to really 'understand' the protein model, she has to 'get inside of it'. As she describes in other conversations, by actively handling the model through interactive molecular graphics programs she can project herself 'inside' of it and figure out 'where she is' within the structure. She achieves this intimacy with the model by dilating her body-image to meet its form. But clearly, her learning body does not just extend outwards to meet it: she also envelops the model within her flesh. Although she indicates that she 'stores it' in her 'brain' and can rotate the molecule around in her 'head', while she describes the model, her whole body is engaged in descriptions of its flexibility, intramolecular forces, tensions and movements. Once it is inside her as an embodied model, she has both a 'vision' of the active site and a 'sense' or feeling for the forces within the molecule that exceed what could be described as a 'mental image'. It is through the dimensionality of her body that she is able to appreciate the full three-dimensionality and movements of the protein model, so that she feels the spatiality and temporality of the molecule by virtue of the spatiality and temporality of her own body. While she mourns the limitations of language for the communication of three-dimensional, structural knowledge, her body provides an articulate medium for vivid expression of the fine details of molecular structure: inflected and informed by the molecular models that inhabit her body, she demonstrates with clarity the twisting helices and the movements of the peptide backbone meandering through the molecule. Throughout our conversations, during class lectures, and in informal discussions with members of her lab, her gestures and affects animate the forms, textures, and tensions within the protein.

Diane's molecular embodiments are in no way exceptional. In-depth interviews with her male and female students, and with other crystallographers, show that those who have made it through the rite of passage of model-building, those that have 'solved' their own structures, can carry specific knowledge of the configurations and chemical mechanisms of their proteins in their bodies. For example, an interview with Brent, who had been a football player in college and was now a postdoctoral researcher in Diane's lab, revealed that molecular embodiments are not restricted to a stereotype of the 'expressive woman scientist'. When I asked him to describe one of the proteins he had modeled before, he proceeded with an

elaborate demonstration of its chemical mechanism. He leaned across the table between us, and drew his hands together, carving a small pulsing sphere out of the space in front of him. In order to describe the specific intra-molecular forces between a small cluster of amino acids in the active site of his protein, he tenderly drew the middle finger of one hand across an invisible force field on the palm of the other, indicating the exact site where charged amino acids interact with each other. Throughout his demonstration, he held a buoyant tension in his hands that extended through his arms, and into his whole body. He had cultivated a profound feeling for his protein in the course of building the model, and he performed what he hypothesized to be its chemical mechanism through gestures and affects that reflected the intimacy of his molecular knowledge.

Other students I interviewed were not yet inflected with such precise molecular affects. These were the graduate students and postdoctoral researchers who had not yet built their own structures, including: those who were new to the lab and to crystallographic practice; those who were still struggling to perfect what they often refer to as the 'voodoo magic' required to get their proteins to crystallize; and those stalled at the stage of trying to, as they say, 'massage' poor quality diffraction data into meaningful electron density maps. When I asked them to describe proteins whose structures and mechanisms they had learned in class, but not built themselves, they rarely used gestures. If they did use their hands to describe the form and movement of the protein, their gestures were often vague and imprecise, as if their hands loosely circumscribed the general form of an object they could only see at a distance. They were familiar with the model from the outside, but it did not yet 'belong' to them.

Among protein crystallographers there is a profound sense of investment of one's 'self' in the model: seen as a craft product of labor and love, a crystallographic protein model is an artisanal object. For Diane, and others I interviewed, the sudden emergence of the model after the arduous labor of construction warrants a 'birth announcement'. In an interview, Diane described it this way:

> I don't know, some other people say that they want birth announcements when the structure [is coming out] … because it is kind of like being in labor. … And often a building process will take nine months. And it is, it's sort of as it's coming out … you're all of a sudden, 'Oh! Look at where that conserved patch is … Yes! Oh! Oh! That makes so much sense! That other group was wrong about what those residues do.' And so it's sort of this unveiling. And then you finally give birth to your molecule. And what I've started doing is putting our structures on refrigerator magnets and so then for Christmas you can share with your family and friends. Everyone sends out their pictures of their kids and you send out pictures of your kids. It is kind of like that in a way.

The product of a crystallographer's labor is always figured by the modeler as 'my protein', 'my molecule'. As Brent recounted, it's not until you can produce crystals that diffract well, and start working on a model, that the protein becomes 'yours'. He explained that he always keeps a number of

projects running and maintains a kind of emotional distance until a protein shows promise by forming 'beautiful' and reproducible crystals that diffract well. For him, it is only once a project is well on its way that the protein becomes his own. He emphasizes his intense sense of ownership of the molecule and the model by drawing his arms powerfully into his chest and emphatically repeating the word 'mine'. This evocative gesture also served to remind me *how* the protein model belongs to him: the model is not the product of disengaged rationalization, and it does not hover in his head in some mental image. The model *belongs to his body* because in a sense, that is where his knowledge of it lives.

Thus the richest, most detailed model of the molecule resides in the modeler: the two- and three-dimensional renderings the modeler must produce to illustrate protein structures and mechanisms for others never fully convey the wealth of their embodied knowledge. Diane makes clear the frustration she feels about the limitations of the two-dimensional figures she must construct to communicate to others what she identifies as the most salient features of the structure. She insists that no one will ever understand the protein as intimately as those who built the model. And this is why, when new structures are presented in the literature or at meetings, she will never take the two-dimensional diagrams or descriptions of mechanisms at face value: she goes to the Protein Data Bank (PDB) and downloads the coordinates of the model into an interactive molecular graphics interface so that she can examine the model herself and get a feeling for its folds. The listing of a model's atomic coordinates in the PDB does not suffice: she must handle and manipulate the models as tangible, three-dimensional objects in order to get a glimpse into the knowledge that the crystallographer who built the model possesses.

Crystallographic modeling through interactive computer graphics is thus not only a practice that produces digital renderings as visual forms of data; it is also a pedagogical site for producing new protein crystallographers. The students who presented their misshapen models to Diane, and elicited a cry of pain, were crystallographers-in-training: they were in the process of acquiring a feel for the possible geometries, forces, and movements within their specific molecules, and proteins in general. All of the advanced students I interviewed recognized Diane's skills, but said they were still 'nowhere near' her 'level' yet. This was a skill they understood as her ability to look at a model and intuit that something was wrong. However, Diane's skill, as she says, to 'see what the structure is saying' does not merely rely on memorized mental images of what proteins should look like. Keen molecular vision is, for her, an embodied practice of observation and manipulation, where seeing is also a way of *feeling* what the structure is expressing in its form.

A number of specific protein models inhabit Diane's body – those models she worked on herself. These *molecular embodiments* are the product of her intense involvement with the modeling process over long periods of time. *Becoming molecular*, she is able to give what is otherwise a virtual structure a physical body, a place for it to dwell. The practice of building protein

models has thus *articulated* Diane's body with specific molecular knowledge (Latour, 2004; Prentice, 2005).[27] In other words, through an interactive practice of sculpting molecular models, the models themselves can act recursively to sculpt and reconfigure the modeler's body. Crystallographic model-building is thus a practice of learning through incorporation, of drawing the model into one's body as it is sculpted piecemeal onscreen through a graphics interface. In this sense, molecular embodiments are generated by 'infolding' the model into the 'flesh' of the modeler, where it comes to reside as a part of the modeler her- or himself (on 'infolding' see Haraway [2006] and Merleau-Ponty [1968]). Inflected and informed by the embodied models that get embedded in their tissues, researchers' bodies become expressive media for the expression of molecular forms.

Conclusion

Protein crystallography presents a visualization practice that challenges traditional notions of knowledge. It is as if protein crystallographers celebrate Ian Hacking's famous reformulation of representation 'as intervention' (1983): their visual facts are produced through techniques of manipulation, and they are candid about the contributions of tacit knowledge to their model-building practice. However, the human–computer lens of contemporary crystallographic modeling requires that crystallographers have more than 'good hands' (e.g. Heath, 1997): they must also carry their knowledge of protein forms, forces, and movements throughout their bodies. In addition to their hands, their arms, shoulders, torsos, necks, and even knees can be pulled into play. As they manipulate and build crystallographic models, they incorporate these unique and complex molecular forms into the folds of their flesh. In the process, they rearticulate and so entrain their embodied imaginations. Thus, in addition to revising conventional notions of scientific vision as a practice of disembodied objectivity (see Haraway [1991] for a critique of these), crystallographers' model-making reworks the relations between subjects and objects of scientific knowledge. Modeler and model are intimately entangled and co-crafted in this practice. Indeed, as the very substance on which their professional identities are formed, protein models belong to their modelers in a way that goes beyond concerns over intellectual property and scientific priority. To become a crystallographer, the modeler must become their model.

A thicker ethnography of protein modeling must extend beyond the model-building phase. Once built, the structure of a protein model remains to be interpreted. 'Thinking intelligently about structure' requires hypothesizing how a protein carries out its functions in the cell. This phase of research also depends on the trained intuitions and embodied knowledge of experienced crystallographers. As Diane demonstrates, the crystallographer carries the model within her body, but she also can 'get inside of it' in order to 'figure out' how it 'works'. Her goal is to have a three-dimensional atomic-resolution understanding of 'how nature has tailored' proteins to do chemical and biological 'work' within the cell. To do this, she uses her embodied

knowledge of the specific molecular geometry and chemistry of the protein in order to reason through possible biological mechanisms. In this sense, *figuring out* protein mechanisms requires another form of 'body-work', one that couples the body-work of incorporation to that of communication (see Myers, 2006). This wealth of embodied knowledge in turn shapes how proteins come to be figured, both materially and semiotically within scientific papers and in pedagogical and professional presentations (Myers, in press, a,b).

Yet, protein models also have a life that extends well beyond the immediate grasp of the modeler. Once a model is built, it is uploaded into the ever-growing PDB, where it becomes available to researchers in fields such as biological engineering, and rational drug design. Crystallographic models also feed into high-throughput proteomics initiatives that seek to amass catalogues of all proteins produced in a given cell, tissue, or species. Interactive graphics technology allows these researchers access to the folds and intricate chemical forms over which the crystallographer had long labored. This interactive object can thus be manipulated and incorporated by a larger audience, instructing others in the ways of its folds. However, as the models move out from the crystallography laboratory, and enter wider circulation, crystallographers voice some anxieties. PDB entries list the atomic coordinates of the protein model, include relevant statistics and experimental data, and provide files that can be uploaded into interactive graphics programs. Yet they do not carry the 'thickness' of the modelers' structural knowledge. For example, Edward, a postdoctoral researcher in Diane's lab, expressed concern that his model would be regarded by others as a 'static structure' rather than, as he described it, a 'breathing entity'. His embodied knowledge is thicker and livelier than the data that can be transmitted through the PDB: in a sense it is he who keeps his model alive, both in his trained embodied imagination, and through his lively performances of its form. Thus, in the process of distribution, much of the crystallographers' artisanal labor is obscured as their craft-productions are, in a sense, picked off the shelf and swept up in capital-intensive economies among drug developers and biomedical researchers. In my larger research project I examine face-to-face interactions among structural biologists and their collaborators and students in order to understand how embodied forms of structural knowledge are propagated in the various milieus of formal and informal lab meetings, conference presentations, and lectures (Myers, 2007).

In conclusion, this paper has aimed to articulate how attention to the 'body-fullness' of protein modeling can transform historical and contemporary conceptions of life science practice. In this study I have not only aimed to refigure the role of scientists' bodies in their work, I have also sought new ways of making sense of the objects of biological research. As protein molecules come to be figured *in, through, and as* bodies, the flattening tropes of information and code are no longer adequate metaphors to describe the practices of life scientists or the substances of life. Rather, molecular models, and the scientists who make and are made by them, form exceptionally animate assemblages that demand interpretive strategies with equally dynamic modes of attention.

Notes

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1. The Protein Data Bank (PDB) is an online database that stores the atomic coordinates of known protein structures, and is publicly accessible at <www.rscb.org>. When the PDB was first founded in 1971, fewer than a dozen protein structures had been determined and deposited. By 2000, 13,635 structures were available for viewers to download onto their computers and view through interactive visualization software. As of July 2006, there were 37,658 searchable structures in the database. The PDB thus offers a growing 'atlas of observables' (Daston & Galison, 1992) for life science researchers to compare and contrast protein configurations within and between species. This is an important research tool in the field of what is called 'structural genomics' or 'proteomics'. Researchers in this field aim to determine and catalogue the structures of all proteins produced by a given cell or organism. This work is being supported by corporations and government agencies, which have made huge investments into the determination of protein structures from crystallographic and nuclear magnetic resonance (NMR) techniques, as well as predictive molecular modeling by computers (see Wadman, 1999; Abbott, 2000; Smaglik, 2000; Jones, 2003). As a large-scale, high-throughput study of protein structures modeled on the industrial technologies and logics that organize genomics research, proteomics and protein structure prediction is making a major contribution to biomedical research, and pharmaceutical companies are using protein structures to facilitate the engineering and synthesis of drugs through rational drug design. Gathering together physicists, chemists, and computer scientists, this research fulfills long-standing desires to model, manipulate and re-make biological systems at the molecular level. In particular, structural biology has offered engineers a long-awaited entry into biology, giving them quantifiable, physical objects that they can model and manipulate as 'molecular machines' (see Myers, in press, b).
2. For readers unfamiliar with proteins, the following description may be helpful: proteins are 'macromolecules', large, very complex organic molecules made up of thousands of atoms. Reduced to their constituent parts, they are made up of smaller subunits called amino acids, linked end to end to form long polypeptide chains. A protein may be made of a single polypeptide, or several folded in together. Amino acids themselves are small molecules made up of varying amounts of carbon, nitrogen, oxygen, and hydrogen, and some contain other elements such as sulfur. There are 20 different kinds of amino acids. While they all share a common carbon backbone structure, each bears a different chemical side-chain that confers different chemical properties. Each species of protein has a unique sequence of these 20 amino acids, and polypeptide chains can vary greatly in length. For a protein to acquire biological function it must be folded correctly within the cell. Proteins fold into secondary structures, such as alpha-helices, and these

secondary structures pack together to form the tertiary structures of the active form of the protein. The active forms of some proteins are made up of two or more polypeptides, and when these pack together, proteins acquire their quaternary structure.

3. The names and locations of all ethnographic subjects have been changed. X-ray crystallography is one of the primary techniques that generates structural data from which molecular models of proteins are constructed. Other techniques such as nuclear magnetic resonance (NMR), electron microscopy, and predictive modeling are also widely employed, but not explored in this paper. All of these techniques demand intensive use of computers for model-building and display.
4. The term 'mental image' is widespread, and is often used to make sense of scientists' imaginations. See for example Meinel (2004) and Trumpler (1997). See also Sacks (2003) for an elaboration of the diversity and complexity of mental images.
5. From the arduous calculation and analysis of crystallographic data, to the physical labor of operating the machinery of experimentation, crystallography is a labor-intensive practice. Describing the intensely physical experience of conducting experiments and gathering data at synchrotrons, Diane jokes that researchers need to train at the gym to ensure that they're fit enough to handle the heavy doors that protect them from the high-intensity X-ray beams. On the issue of the intensive labor of crystallographic calculation, and the allocation of this work to women in the early history of crystallographic computing, see de Chadarevian (2002).
6. On tacit knowledge see, for example, Polanyi (1958), Collins (1992 [1985]), and Rheinberger (1997).
7. This is of course, an artificial parsing of what is a much more entwined process. For example, my observations suggest that the body-work of communication — the elaborate gestural expression of molecular form—is intimately involved in the process of reasoning. Researchers conduct 'body-experiments', much like 'thought-experiments', where they use their bodies to work through and reason through such dynamic phenomena as intra-molecular forces or inter-molecular interactions (see Myers, 2006). I would argue as well that these performative practices are also a mode of incorporation, a way for the modeler to learn possible molecular forms and movements.
8. My dissertation, 'Modeling Proteins, Making Scientists: Visual Cultures and Pedagogy in Structural Biology', explicitly takes up this problem of pedagogy and training. On the use of protein models in classroom pedagogy, see Myers (in press, a).
9. Donna Haraway (1997) offers crucial insight into the problematics associated with the fetishization of DNA as code. Drawing on Marxist, psychoanalytic and feminist analyses, she examines how technoscience produces a literalization of the trope of 'information' in the form of a fetishized object, which erases the labor that contributes to its production (1997: 133–37). In her example of 'genetic fetishism', 'life itself' is materialized in a malleable and marketable form through the tropes of code and information (Haraway, 1997: 137). See Myers (forthcoming b) for an analysis of how the cultures of engineering currently shaping concepts and practices in structural biology are producing a kind of 'machinic fetishism' that renders proteins as 'molecular machines', the pumps, gears, clamps, springs, motors, and levers at work on the factory floor of the cell.
10. Haraway's (1991, 1997) theory of 'material-semiosis' comes closest to an analytic modality that can account for the conjoined material and semiotic processes through which researchers combine words, gestures, and materials to give body and meaning to proteins in their construction of molecular models.
11. To further situate my approach, it is important to note that this paper presents interpretations of the body-work of molecular modeling based on a broad set of skills and modes of attention to bodies I have acquired through formal laboratory training in molecular genetics and developmental biology research, as well as through over 25 years of training in classical and modern dance. These skills afford a kind of 'situated knowledge' (Haraway, 1991) for observing and interpreting bodies in practice.
12. Nick Hopwood's (1999) treatment of the history of late-nineteenth century embryological modeling practices provides key insights into the relationship between modeling practices and embodied knowledge. Hopwood documents embryologist Wilhelm His's

(1831–1904) techniques for sculpting scale models of embryos in wax. In defense of a mechanical theory of embryological development, His had developed a method for precisely reconstructing the form of embryos from the details derived from microscopic examination of tissue slices. In Hopwood's reading, His's insight into the mechanical processes of embryogenesis was gained through the physicality of building models. His 'had first to make his problem, to use his fingers', and it was by this method that he was able to '"to give body" to his views' (Hopwood, 1999: 466). In the process His developed an embodied knowledge of the phenomenon in the practice of making models, such that the problem of development became familiar to his body. As Hopwood argues, it was 'the experience of modeling' that was 'the most compelling evidence of the importance of mechanical principles in development' (p. 466). His thus learned the mechanical forces of embryogenesis by working with the forces of physical materials, and with the physics of his body.

13. In *Designs for Life*, Soraya de Chadarevian (2002) examines the history of women in protein crystallography laboratories, in particular the women technicians, or 'computors' who, before the advent of computer graphics, were responsible for most of the labor of computation in crystallographic experiments, measuring crystallographic data by hand and using punch-card computers. As this frame-shot shows, the women laboratory technicians were apparently also involved in the craft of model-building.
14. Indeed, the model was shocking to the scientific community. After the model had been built, Kendrew marveled at the 'unexpected twists the protein chain was performing' (de Chadarevian, 2002: 142). Biophysicists had expected proteins, substances that could form regular crystalline arrays, to be simple, symmetrical structures.
15. It is significant that different levels of resolution and different materials rendered proteins in very distinct ways. The sausage model portrayed the myoglobin as a 'rather vulgar' (Perutz, 1968) body; others rendered proteins with anatomies that could be 'dissected' (see de Chadarevian, 2002). High-resolution models built from standardized machined parts made proteins look much more machinic, with clean lines and movable parts, and made them available to be manipulated as chemical mechanisms. This shift has made it possible for proteins to be figured through the now pervasive metaphor of 'molecular machines' (see Myers, in press, b).
16. See interviews with Max Perutz online: 'Face to Face with Max Perutz' (Vega Science Trust <www.vega.org.uk/video/programme/1>). Also shown alongside Perutz and his mechanical model is a video clip of an interactive molecular graphics screen animating the same movements onscreen. Perutz's handling of the model is also described by de Chadarevian (2002).
17. Elsewhere (Myers, 2007), I distinguish between analyses of models as end-stage representations of nature, and models as enactments. Treated as representations, they are what Keller (2000: S82) calls 'models as nouns', 'separate entities' at the 'end of the process' of modeling. In my view, protein models are more than *representations of* molecules, and more than *representations of* scientific knowledge. Building on Keller's (2000: S82) notion of models as 'verbs', my aim is to theorize molecular models outside of the idiom of representation, so that they can be seen, not as objects that stand in for phenomena, but as *forms of knowing*, as knowledge in-the-making. I am interested in how three-dimensional models do not just represent things: they also *enact* them, and in the process produce new forms of knowing for the modeler. One way to effect this move is to shift from a discourse of representation – which too easily slips into the realm of 'model as noun' – to one of *rendering*, an idiom which can gather up the modeler and their media, and make tangible the very activity of modeling.
18. Thanks to Stefan Helmreich for this analogy. Interactive graphics does seem to offer a gravity-free, buoyant environment for protein modeling. Indeed, as Donna Haraway reminds me, interactive computer graphics may in some ways reproduce the watery worlds that support protein structures in their cellular environments.

19. In a paper called 'The Human Interface', M.E. Pique (1986: 13) writes:

    > Ideas spreading from Xerox PARC and Atari, through the Apple MacIntosh and the Commodore Amiga, will reach molecular graphics during 1986: pop-up windows, pull-down menus, more than one thing going on at a time. During the next 5 years, users and builders will make molecular systems more like video games, with mice and trackballs, some joysticks that are specialized by function, and the working system easier to use and more fun.

20. By the early 1980s, a number of technologies were available to produce stereo effects. Robert Langridge and his co-workers (Diamond et al., 1982: 286) describe one stereovision system, where 'left and right perspective views are presented alternately. When they are viewed through a synchronized shutter, each of the observers' eyes sees only its associated image, and the result is perceived as a stereoscopic image with a strong sense of depth of field.' Creating the three-dimensional effects and the 'illusion' of depth through stereoscopic techniques, however, assumes that the user has binocular vision. So attentive to the interaction between users' bodies and the graphics hardware, and aware that 'a good ten percent' of the population has difficulty seeing in stereo, a group of researchers at the Laboratory of Molecular Biology in Cambridge devised an elaborate optical system to simulate three-dimensional perception for 'one-eyed guys'. Reworking the physiology of vision for one- or two-eyed researchers, such innovations in stereoscopic techniques attest to their inventors' recognition of the embodiment of seeing.
21. Kendrew describes modeling from such stacks of electron density as a process of 'dissection', such that 'from the map it was possible to "dissect out" a single protein molecule' (Kendrew, 1964: 681). According to reviewers assessing developments in the field by 1975, this method proved 'almost unbelievably cumbersome' (Collins et al., 1975: 1049). This is particularly true since many different maps would have to be constructed and compared. Collins and his colleagues outlined how, in 1968 at Yale University, Frederic M. Richards came up with an innovation that radically transformed the work of mapping and modeling. The Richard's 'optical comparator', 'Richard's box', or 'Fred's Folly' as it came to be known, 'revolutionized the interpretation of protein electron density maps' (Collins et al., 1975: 1049). The device projected an optical illusion, making it appear as if a wire model was embedded within the three-dimensional electron density map through the use of a half-silvered mirror. The model could then be manipulated until its projected image fit within the electron density. The coordinates of the atoms would then have to be measured and calculated from the model itself. And while this 'arduous work' was both 'highly tedious and inherently inaccurate,' it was a step up from the method Kendrew first employed (Collins et al., 1975: 1049).
22. Novel systems of interactive computer graphics overcame the practical limitations of the solid structures generated by Plexiglas electron density maps and wire models. For example, they enabled the 'fitting' of a digital model directly into the electron density map, rather than having to 'dissect out' a structure from a solid object (Collins et al., 1975: 1049): 'Electronic Richard's boxes' allowed variously sized volumes of electron density to be displayed on the computer screen in stereo, enabling the user to 'superimpose' stereo images of atomic models 'in such a way that the latter [could] be translated and rotated until an optimum fit of the model to the map [was] achieved' (p. 1049). As such, 'fitting model to map … can be far more convenient and faster than the mechanical operations in the Richard's box' (p. 1049). An added benefit, and indeed what the developers saw as the most important feature of this interactive system, was that the coordinates of the constructed model could be recorded automatically. Replacing the time-consuming and error-prone work of trying to measure the atomic distances from scale models, the grid logic of the computer screen could accurately identify the location of each atom in the structure.
23. For example, it took Max Perutz 22 years to produce a high-resolution model of hemoglobin.
24. From an interview with Max Perutz by the Vega Science Trust in 2001: 'Face to Face with Max Perutz'. Streaming video of the interview is available at

<www.vega.org.uk/series/facetoface/perutz/>. Perutz was an avid mountain climber. The quote is taken from 5:17 min.
<www.vega.org.uk:8080/ramgen/face2face/perutz_haemoglobin_story.rm>.

25. These steps of protein purification and crystallization deserve careful ethnographic observation. According to Diane, even with today's technology, which greatly expedites the process, a graduate student may start a project and after 4 years still not have successfully crystallized a protein or a built a model. In the history of protein modeling, particularly during wartime years, protein purification was a messy task. Slaughterhouses provided some of the cheapest and most abundant sources of tissue. Currently, most proteins are purified from bacteria that have been genetically engineered to over-express the gene for a protein of interest. Crystallization poses serious challenges as some proteins are notoriously difficult to crystallize, or just do not form crystals. Crystallographers regularly joke that protein crystallization is a practice requiring 'voodoo magic'. They develop all kinds of rituals to ensure that once they find the 'magic potion' that can coax their protein to form crystals, they can reproduce their results. They will try anything to get their crystals to grow: from playing techno music while they mix their biochemical media; to donning a special sweater on crystallization days; and even talking to their crystals. One crystallographer recounted a story about a colleague of his who was able to get viable crystals up until the day he shaved his beard, after which he could do nothing to get his crystals to grow.
26. On the generation of three-dimensional images in confocal microscopy and the Visible Human Project, respectively, see Keller (2002) and Waldby (2000). Joseph Dumit's (2004) analysis of positron emission tomography (PET) calls for detailed descriptions of the apparatus of visualization to facilitate understanding of the kinds of mediation that an object, such as a brain, must undergo in order to render images that can travel as facts beyond the laboratory.
27. For a treatment of the training of 'articulate' bodies for scientific research, see Latour (2004). Drawing on Latour's exploration of articulation, Rachel Prentice (2005) develops the concept of 'mutual articulation' to describe researchers' development of effective computer simulations for teaching anatomy and surgery. In this case the designer must articulate the model-patient through algorithms, which once embedded in the simulator, in turn work to articulate the body of the surgeon who uses this interface for training. There is also a form of 'mutual articulation' going on between the molecular modelers I describe here, their computers, and the models they construct.

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