

## 4 Interlude: Building “the Lab”

In the preceding chapters on the BME labs, and in the ones on the ISB labs to follow, I examine each lab’s practices around modeling and how models are built toward accomplishing the lab’s epistemic aims. We have seen, in the BME case, how labs in different fields use the practice of in vitro simulation modeling to build the cognitive-cultural resources, primarily material and conceptual, they need to investigate specific aspects of complex biological systems. In this chapter I have a different objective. In the course of our BME investigations we came to realize that the devices themselves drive much of the direction in which a lab develops, especially through posing problems or opening new avenues of research, which in turn leads to new technologies and practices, all of which shape the student researchers as scientists. Getting a grasp on the evolving, historical dimension of this kind of a distributed cognitive-cultural system requires a different kind of analysis—of how the system, in effect, builds itself.

“The lab” is often associated with those physical spaces that house the research-specific technologies, instruments, artifacts, and workbenches. “The lab” is also used to designate a research agenda: the problems and groups of people associated with it. In the latter case, it is often referred to as “the X lab” where “X” is the name of the principal investigator/director. And, as in the case of lab A, the tissue engineering lab, it can also be referred to, internally and externally, by a salient research object, in this case, “the flow-loop lab.” This designation directs attention to the kind of epistemic practices through which the lab carries out its research, while also signaling that these practices are sufficiently known in a broader community to be a meaningful designation. For lab A, this is the epistemic practice of in vitro simulation modeling of mechanical forces in blood vessels by means of in vitro devices. In chapter 2, I dubbed such objects “signature artifacts” and examined in detail how

they and the warrant for their use as in vitro simulation models are built in both labs. In this chapter, I examine the function of these devices as providing what William Wimsatt (2013a,b) has called “structuring constraints” for future development within an ecosystem. In particular, I examine the role the signature artifacts in lab A played in *building the lab* into a distributed cognitive-cultural system comprising researchers, artifacts, problems, and practices, all with intersecting developmental trajectories.

As discussed in chapter 1, our analysis of research labs cannot simply apply the framework of D-cog as developed initially through studies of highly structured problem-solving environments. In such environments, participants carry out largely routinized tasks that use existing technologies and bring to bear knowledge that is relatively stable, even as used in novel situations. In contrast, the BME research lab is an innovation community where researchers do not have established methods, technologies, and well-defined problems in advance of beginning the research. Although there are loci of stability, there are equally important features of these labs that are continually undergoing development and change. These features include the ongoing development of the technologies, methods, and problems; the formation of social practices and systems; and the development of the researchers as they learn to be bioengineering scientists in the processes of carrying out a research agenda of a lab director at a stage of his or her research program. At each slice in time, “the lab” comprises the current state of these, its features.

As I discussed earlier, D-cog’s customary use of the adjective “distributed” is past tense, which signifies a process of distribution already completed. To study scientific practice, however, requires we attend to how cognition is actively distributed as a system is built, that is, attend to what Rogers Hall has called the dynamic processes of *distributing cognition*. As he explains, drawing on his research group’s examinations of the research practices of scientists and mathematicians, “the word *distributing* is a verb, operating in an ongoing present, and shifts our attention to studies of how cognition . . . is produced historically out of human activity” (Hall et al. 2010, 226; emphasis original). In this chapter I examine the research lab as a dynamic environment that *builds itself* as a D-cog system “historically out of human activity” with specific affordances and limitations for problem-solving as it furthers its epistemic aims. I focus, in particular, on the role of the signature devices in these processes.

In the following sections I examine how the signature artifacts of lab A not only provide a platform for current problem-solving, but also create structural constraints and affordances for research potentialities not yet envisioned, and how these build “the lab.” I then discuss the wider ecosystem that has been designed to turn the student researchers into the hybrid bio-medical-engineers envisioned by the senior researchers to populate and build a novel twenty-first-century version of the field of BME.

#### 4.1 Creating Epistemic Infrastructure: The Laboratory for Tissue Engineering

The director of lab A, as with many of the pioneers in biological engineering, had an unusual career trajectory. In an interview I conducted with him as he was closing down the lab (approximately ten years after we concluded our research), he characterized that trajectory as “*from astronauts to stem cells*”—a trajectory inconceivable to him at the outset. Starting in the late 1950s, the future director of lab A trained as a mechanical engineer and then worked in an aeronautical engineering lab for the space program. Since he received funding from NASA for his research, they drafted him to help study how the effects of vibration along the axis of the Saturn launch vehicle and during reentry in the Apollo capsule (“pogo stick vibration”) affect the cardiovascular system of astronauts. They tapped him because of his knowledge of the physics of launch and reentry forces. He reported that he did not know “*anything about biology and medicine*,” but that he felt an obligation to try to help them, and the problem was interesting. He discovered that no one had examined the effects of even the natural physical forces of blood flow through the cardiovascular system. He came to suspect that the mechanical forces, in the first instance, shear, would most likely impact the endothelium—the innermost layer of cells in a blood vessel—and decided to shift his own research program to this focus. First, though, he needed to learn some cell and vascular biology.

He spent a year as a visitor in a vascular biology lab that conducted research with an interdisciplinary team of medical and engineering researchers, and then left research in aeronautical engineering entirely for biomedical engineering. By then he was a tenured full professor, and he leveraged his engineering faculty position to begin research into how natural and aberrant blood flow through the arteries could affect the blood

vessels in animals and to learn as much about the biology of endothelial cells as needed to conduct research on the effects of the flow on the cells. Since no biologists would collaborate with him, he conducted this research in a veterinary lab at his institution (research discussed in chapter 2). He then moved to a new university, where he had a largely administrative role, while continuing the animal research long distance. The laboratory for tissue engineering (lab A) dates from 1987, when the director moved to another university to take advantage of the opportunity to begin research in the emerging area of tissue engineering and to create a new department of biomedical engineering. Importantly, the change provided the opportunity to move out of animal studies and “*take the research in vitro.*”

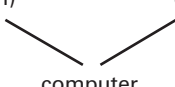
When we met the director in 1999, he was widely recognized as a senior pioneer in biomedical engineering. As we have seen in chapter 2, the epistemic practices of lab A center around creating in vitro devices, assembling them in various model-system configurations, and performing in vitro simulations under various controlled experimental conditions. The lab began with the flow loop, at that time a large device, cobbled together but precisely engineered in its flow components, which simulated blood shear forces on cells on slides. Flow experiments were still a significant portion of the lab’s activity when we arrived, but by then the initial device had been replaced by a redesigned compact version that could be assembled under the sterile hood to limit contamination and placed in an incubator to keep the cells alive. A new tissue-engineered device, the construct, had been introduced, and it was playing a central role in building the lab at that time, and throughout our investigation.

#### 4.1.1 Ontology of Artifacts

Shortly after we entered the lab, we conducted a sorting task in which we asked the researchers to put the names of the material artifacts they used to conduct their research on index cards and sort them into categories of their own devising. Their agreed-upon classification in terms of “devices,” “instruments,” and “equipment” is shown in figure 4.1.

Based on additional ethnographic interviews and observations, we formulated working definitions of the categories, with which the researchers concurred. *Devices* are hybrid bioengineered facsimiles that serve as in vitro models and sites of simulation. *Instruments*, some shared with other labs, extract and process information and generate measured output in

**Ontology of artifacts**

<b>Devices</b>	<b>Instruments</b>	<b>Equipment</b>
flow loop	confocal	pipette
construct	flow cytometer	flask
equi-biaxial strain	mechanical tester	water bath
pulsatile bioreactor	coulter counter	refrigerator
	"beauty and beast"	sterile hood
	LSM 5 (program)	camera
		
	computer	

**Figure 4.1**

Sorting task of lab A artifacts

graphical, quantitative, or pictorial form. *Equipment* assists with manual or mental labor. I focus on the devices here, since they drive the lab-building process, but the equipment and instruments also play important roles in the cognitive-cultural system. In fact, when we asked the researchers to tell us what is the most important artifact, the novice researchers settled on the pipette, to the astonishment of the lab director. He, and the more experienced student researchers, said it was a toss-up between the flow loop and construct. When I discuss cell culturing practices, it will become apparent why the novices made this choice. This ontology also underscores the fact that all of the cognitive artifacts are part of the material culture of an epistemic community, though the reverse does not hold. Here, only the devices and instruments perform cognitive functions.

The flow loop and construct were the signature devices of the lab. These devices, which were built in-house, provided structuring constraints for the evolution of a range of cognitive-cultural practices in the complex system that is "the lab." These artifacts are what Wimsatt called "generatively entrenched" in the evolution of a complex ecosystem (Schank and Wimsatt 1986; Wimsatt 2007, 2013a,b; Love and Wimsatt 2019). Briefly, an artifact or entity is generatively entrenched if it acts as a constraint on the future direction of development of a complex dynamical system, which,

in Wimsatt's account, includes cultural systems as well as the biological systems for which the notion was developed originally.<sup>1</sup> As we will see, the requirements of, and opportunities afforded by, these two devices led to the development of virtually all of the lab A cognitive-cultural structure as we encountered it and during the course of our investigation.

Most off-the-shelf purchases made by the lab fall into the equipment category. All of the equipment, except for the computer and camera, was used for cell culturing, which is critical to the research. The researchers noted later that they had forgotten the incubator, which is essential to keep the cells and constructs alive. The water bath and incubator are designed with biological knowledge of the requirements to keep the cells and tissues healthy—or as the researchers would say, “*happy*.” Unhappy cells become contaminated or dead, which can spell disaster for the research project under way. Researchers set the incubator's temperature and atmospheric content to what is optimal for growing cells. The water bath, which is the medium that surrounds the constructs (“*water for cells*”), includes nutrients that are optimal for cell life. Importantly, culturing cells is a prelude to building the construct models needed for most research projects. Because all the researchers need to build their own constructs, learning to culture cells had supplanted learning how to operate the flow loop as the entry point into the lab research and culture when we began our investigation. Cells on slides could be prepared by a lab manager, but constructs need to be built by a tissue engineer. So, as a senior researcher told us, learning to culture cells was “*baseline to everything*.” That is, it provided entry into the problem space and cognitive-cultural practices of the lab and, so, incorporated the new member into the community.

Learning to set up and manipulate the flow loop is a relatively easy task for an engineer; learning to culture cells and build constructs is not. For new researchers, this is often the first contact they have had with biological materials, concepts, and procedures. How much care and maintenance are needed to support the viability of a cell culture amazed and constantly frustrated them. The consequences of failure are high: when cell cultures die, experiments are ruined. As a result, mentoring within the lab usually began around learning to culture cells, which started with harvesting them from the animal arteries donated to the lab from a nearby veterinary school. It was quite common for us to observe the new member and the mentor huddled close together scraping cells off arteries or learning embodied

techniques of culturing under the sterile hood. Although there are written protocols for the steps, culturing is also a performance art that needs considerable practice to acquire. It is a highly embodied skill in which an incorrect angle of the hand with the pipette can lead to disaster.

The discourse of the lab frequently centered on keeping the cells “happy,” calling them “pets,” being told to “*think of them as children*” and bemoaning long weekends lost to “*babysitting*” them. As one way to address the tragedies of failure with cells, more senior researchers shared war stories about the recalcitrance of cells to respond in the ways they desired, and how they had emerged victorious, eventually. In such episodes, we witnessed how the researchers began to build resilience in the face of obstacles or failures, which are a constant in their pioneering research, and in all the labs we studied. The general ethos of the lab reflected the attitude that failure or impasses provide opportunities to learn. This attitude was reinforced by a broader community that purposefully promoted opportunities for structured and unstructured interaction among students and faculty from different labs where research impasses as well as successes could be shared and discussed. What is especially interesting is that we did not encounter any situations in either lab where an *in vitro* model, once broadly envisioned and in the process of being built, or once selected from the existing ones as the means to pursue a research problem, was abandoned in the research. Impasses or failures usually led researchers to make modifications to the model or model-system or to the scope of what might be investigated using it. Significantly, everyone in the labs when we were there conducted sufficient research to graduate, and they went on to academic or industry positions. Although lab directors encouraged practices for cultivating resilience in many ways, the most unusual was lab A director’s policy of handing out a compilation of what he called “The Rules of Life: The Planet Earth School,” which listed aphorisms about how to thrive in research and in life, to each new member—and to me, as I started this risky research on his lab.

During the process of learning to culture cells and make constructs, new members explored the research of the lab and the roles of various instruments and devices in informal conversations with more senior researchers. Through these conversations they came to understand how the research largely involves working with the constructs as “*modeling tools*.” This learning experience, too, began to build an interdisciplinary epistemic identity, shifting it from engineer to bioengineer (Osbeck and Nersessian 2017). As

one researcher put it, when we witnessed the scene of her joyously dancing around the lab with her first success in getting cells to do what she wanted after nearly a year of repeated failures in every approach she had tried, *“I’m a bio-bioengineer.”*

In the instrument category, the confocal microscope, flow cytometer, and Coulter counter are large, expensive instruments that have been purchased by the department for all the labs to use. Everyone in lab A uses these instruments. LSM 5 (laser scanning microscope) is the program used with the confocal microscope and enables user-directed image manipulation and analysis of how the cells behave and change as a result of the in vitro simulations, which is likely why the researchers singled it out. “Beauty and the beast” was a nickname they gave to the large computer (beast) and camera (beauty) setup that had been designed for analysis (including the software) by a researcher who had just wrapped up her research when we entered. Her project had been to develop a better substrate for proliferating endothelial cells on slides, which she thought might also be used to help the cells migrate in the constructs. It provides an example of technology still residing in the lab but no longer used. It remained, taking up lab space, throughout our research. The other researchers could explain what it does. Old technologies tended to hang around since they have the potential to be repurposed in new lines of research.

The mechanical tester is the most interesting instrument for understanding the central place of the construct model in building the lab, and provides an example of such repurposing. The design of the construct was continually under revision toward being both a better model and a viable implant. The properties of every new design needed to be examined and evaluated. The mechanical tester was used to examine the mechanical strength of various iterations of constructs. The original mechanical tester was an unused instrument in another lab that conducted tests on the strength of native tissues. An enterprising lab A researcher saw its potential, with suitable redesign, to be used to evaluate the mechanical strength of their engineered tissue. When we entered, it was a clunky, cobbled-together instrument that had been modified incrementally ever since the construct had been introduced. The testing process, at the time, was as follows. After constructs are “stimulated” in tubular form by the forces produced by various simulation devices, they are cut into rings and beads are glued at various intervals to examine local distension. The rings are placed in the liquid



chamber of the tester, and each side of the ring is attached to the tester's hooks. At this point the ring is pulled apart until it breaks, while the process is videotaped (a quite recent modification). The tester can measure stress, strain, and ultimate tensile strength.

Interestingly, while we were there, they decided to buy a machine made by Instron because of its increased range of forces and sensitivity, but despite having spent a considerable sum on it, the researchers never used it for mechanical testing. Although it could do much more than their tester, to them Instron tester was a black box that did not, in particular, fit into their practice of placing the rings into the liquid chamber—a feature missing from the Instron—to keep the rings from sticking together before attaching them to the hooks. The machine had been built by Instron to test a range of materials, but it would need to be modified to work with the lab's practices with constructs. The researchers noted they had been "*avoiding this thing [Instron], because no one wants to design something that'll work.*" To make it work they would either have to redesign the Instron to hold open the rings or redesign their practices for preparing the constructs to be tested. With many mechanical engineers in the lab, the former is something they could likely have done quite readily. However, despite being a jumble of parts and difficult to use, their mechanical tester had evolved alongside the lab's practices and had become entrenched in ways the Instron proved unable to dislodge. Later, researchers new to the lab would appropriate the Instron and modify it for the completely different purpose of developing a device to simulate the effects of compression on stem cells (Harmon and Nersessian 2008).

All the *in vitro* simulation models fall into the category of devices. The flow loop preceded the construct; together they constituted the primary model-system of the lab. As we saw in chapter 2, the researchers considered it unnecessary to undertake a considerable redesign of the flow loop to accommodate the construct's tubular design. Instead, the constructs were cut open and flowed flat when subjected to shear stress forces of the liquid. To accommodate the thickness of constructs, as compared with the cells on slides for which the flow chamber had been designed, a spacer was added to the flow chamber. Although "just" a spacer, it did require some redesign of the chamber to comply with the physics of the behavior of the flowing liquid. The baboon model-system experiment, discussed in chapter 2, was the first time it became necessary to maintain the tubular form of the construct. The researchers anticipated they would undertake a significant

redesign of the flow loop, but as we saw, A7 was able to attach a shunt to the flow chamber and connect the construct to the shunt tubing, just as she had done with the animal—an ingenious method that saved them considerable time and expense.

The lab's evolving understanding, goals, and problems in relation to the construct opened new lines of research and led to building new *in vitro* models through which to manipulate and examine construct properties under various conditions. The researchers built the other devices listed in the ontology to explore mechanical properties of the tubular constructs other than shear (stress, strain, pressure). The research into these properties was directed especially toward strengthening the construct to meet the requirements of the application goal (vascular implant) opened by its introduction into the lab. This research led to new conceptual resources related to arterial stress, strain, and pressure.

To be either a functional model or an implant requires (among other things) that the cells that are embedded in the scaffolding material replicate the capabilities and behaviors of *in vivo* cells so that higher-level tissue functions can be achieved, such as expressing the right proteins and genetic markers. Further, a vascular implant needs to be strong enough to be able to withstand the *in vivo* blood forces of a pumping heart, and so understanding what creates mechanical strength and integrity in native tissue became prime concerns. All of the experiments with the tubular construct required a silicon sleeve because it could not withstand the forces itself. The sleeve could be made to varying criteria that included thickness, elasticity, “stickiness” in holding onto the construct, and with or without a collagen coating. The researchers hoped through their investigations into mechanical strength to find a way not to use the sleeve, both because it “*added a level of doubt,*” to their simulation results and, of course, because “*a surgeon would actually want to suture the construct [sans sleeve] into the patient.*” To address the issues of mechanical strength and integrity, researchers created two devices to simulate mechanical forces of pressure in the tubes (the pulsatile bioreactor) and strain on the cells (the equi-biaxial strain device, or EBSAD).

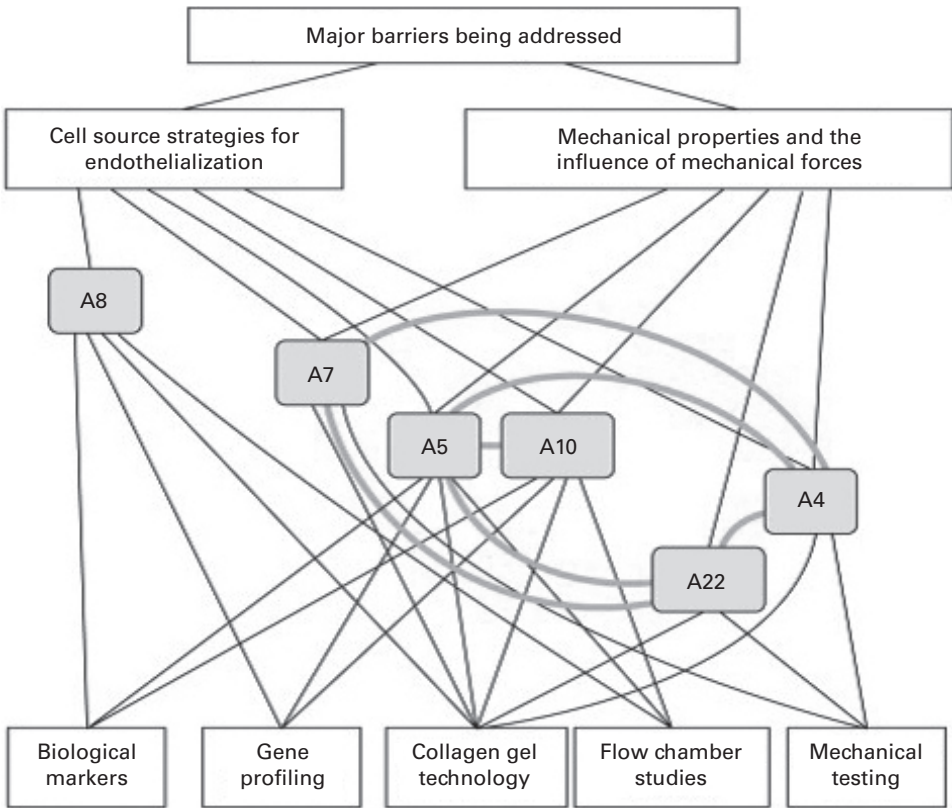
Finally, a vascular implant requires a high-yield source of endothelial cells, most desirably derived from manipulation of the patient's progenitor cells or marrow stem cells to prevent immune rejection. We saw in chapter 2 how A7 built a model-system with the construct and an animal model to examine a hypothesis about how progenitor cells function (more on that in

the next section). The researchers further speculated (they explicitly denied it was a hypothesis) that compression forces might be the mechanism through which endothelial progenitor cells differentiated into endothelial cells *in vivo*. During the last part of our research (and so not on the ontology list), two newly arrived researchers were working on two compression bioreactor devices using confined and unconfined compression to examine the effects of these forces on progenitor and bone marrow stem cells. This provisional research aimed to determine whether a speculation could be turned into a hypothesis worthy of pursuit and, ultimately, to see whether the needed endothelial cells could be created by either of these methods. For the confined compression bioreactor, the researchers modified the rejected Instron mechanical tester. The unconfined bioreactor was in the planning stage when we concluded our research. This emerging research project provided us with a glimpse of how a new line of research and the requisite infrastructure derive from the then-current cognitive-cultural system of the lab.<sup>2</sup>

#### 4.1.2 Configuring the Problem Space

The representation drawn by the director when we asked him to draw a picture of the lab research partway through our study (figure 4.2) depicts, in our terms, the configuration of lab A as a distributed problem space. We gave him no instructions for how to do this. He declined to draw it while we were present, but said he would think about how to approach it and would work on it during a flight he was about to take. When he gave it to us, he said he had wanted to depict how his research “*barriers*” (listed at top), researchers (middle section), and technologies (listed at bottom) are interconnected. The diagram on paper is a static representation, but the word “*being*” marks his intention to capture the configuration of the lab’s ongoing research. In line with it as a dynamic depiction, I interpret it as a schematic of “the lab as an evolving distributed cognitive-cultural system with epistemic aims”—a dynamic constellation of interrelated problems, researchers, simulation models, methods, instruments, and other technologies. The picture depicts the hybrid nature of the interdisciplinary problem space of BME, as we will see in unpacking it. Each of the barriers references the interlocking of biology and engineering.

The diagram references the five graduate student researchers and one post-doctoral researcher (A8) in the lab at the time. A notable feature of the lab,



**Figure 4.2**

Lab A director's representation of how he envisioned "the lab." The original figure was drawn by hand, and we have redrawn it without alteration to make it easier to see.

not depicted, is that five of the researchers were women (A10 the lone man). I found the composition of the lab striking, coming myself from physics and philosophy, where women are underrepresented, and I asked the director about it. His response was that he chooses only "*the most qualified applicants.*" We were later to discover that although the proportion in lab A was unusual, BME has a high number of women in the field.<sup>3</sup> Although the director did not include himself on the diagram, he is, of course, an integral part of the system even though his visits to the physical space of the lab were rare. He spent a significant amount of time on the road to promote the research and to obtain the financial resources to conduct it, in addition to administering an interdisciplinary center, and building and promoting

an interdisciplinary educational program. He held lab meetings at varying intervals whenever he was in town, as well as individual meetings with each researcher when needed.

In this section I use the diagram to examine some of the research lines and their associated epistemic infrastructure that participated in evolving the lab as the researchers addressed the barriers.

At the top of the diagram the director categorized the “major barriers” with which the research was dealing. In lab A, the researchers addressed “barriers” by formulating research problems that interconnected the basic biological research of the lab and its medical application aims, and pursued these problems through developing technologies for in vitro investigation. To address the barrier of “mechanical properties and the influence of mechanical forces” required researchers to formulate problems directed toward understanding basic biological processes of arterial shear, stress, and strain and their role in normal and disease processes. It also required all the researchers to address the problem of developing a construct with desired in vivo biological and mechanical properties. The lab did not aspire to create an implant, but rather to solve the problems that would further that application goal. In particular, this meant bringing the research closer to understanding the requirements to create an implant with the requisite functional properties. As part of that goal, the lab undertook research directed at the barrier of “cell source strategies,” by which the director meant research to find an appropriate source of endothelial cells, such that a tissue-engineered implant would not be rejected by the recipient’s body. This research took the novel direction of investigations into the possible role of mechanical forces on cell differentiation and maturation. It opened lines of basic biological research for the researchers, such as on the role of forces in adult stem cell differentiation (A8) and in the maturation of progenitor cells (A7), which in the latter case led to the lab’s first animal model-system.

The lab-built devices are designated by “collagen gel technology” (construct), “flow chamber studies” (flow loop), and “mechanical testing” (pulsatile bioreactor and equi-biaxial strain device). “Mechanical testing” also indicates the lab-built instrument for testing mechanical strength of a construct. The kinds of investigations along the bottom of the diagram implicate both the devices and the technologies through which researchers could examine simulation outcomes from experiments conducted with

them. For instance, after a flow chamber simulation in which the construct is subjected to various controlled shear stresses, the researchers examine the effects on the endothelial cells for various biological markers with instruments or through gene profiling. These kinds of studies implicate a range of technologies, many external to the physical space of the lab, such as the confocal microscope used to study morphology and migration or the DNA microarray technology used to study gene expression.

The director used the thick lines to denote interconnections among the individual research projects, especially with respect to the researcher (A7) designated to build the animal model-system that would integrate findings from all these projects. He represented a postdoctoral researcher (A8) as unconnected to the students because she had just started the new line of lab research into the possibility that stem cells might be made to differentiate into endothelial cells by means of mechanical forces, and thus provide a cell source. Her project did become more central in the research after she was successful, and later led to the new researchers' project to examine compression effects mentioned in the previous section. At the time of the diagram, she did interact with other lab members about her and their research through conversations in the course of the lab activities and at lab research meetings. Although the research projects were carried out by individual lab members (sometimes assisted by an undergraduate or MS student), we witnessed frequent joint problem-solving episodes within the lab and at all the lab meetings. Each individual research project and its associated problem-solving processes formed a D-cog system. Each of these subsystems contributed to and was constrained by the lab's dual basic and applied research problems and goals. The diagram depicts the interconnected subsystems that constituted the configuration of the lab's problem space at that time and the direction of the lab's evolution. Together they constituted "the lab" as an evolving distributed cognitive-cultural system with epistemic aims.

When the researchers noted in figure 4.2 entered the lab, the flow-loop model was a well-established technology of research, but several of them formulated research problems that would require some redesign of it. The construct model was a recent addition, and all the researchers played significant roles in furthering its design in directions related to their specific projects. A22's research focused on developing the collagen gel technology

toward improving the mechanical strength of constructs, although at the time she was still in the process of figuring out how she would approach the problem. She was the newest member in the lab, who started as an MS student, and she decided to transition to a PhD student only shortly before we concluded.<sup>4</sup> A4's research was to examine specific biological markers in relation to controlled mechanical stimulation of constructs by stretching with the pulsatile bioreactor, as compared with their behavior in native tissue, thought to be stimulated by pressure forces *in vivo*. A5's research was to correlate the development of arteriosclerosis with the genetic behavior of the endothelial cells and progenitor endothelial cells that circulate in the bloodstream by simulating normal and abnormal flow conditions with the flow loop. She, along with A10, introduced new biological methods and tests related to gene profiling.

It's interesting for our purposes to have a glimpse of A10's project because he introduced a new kind of construct, which in turn required him to build a new simulation device to pair it with. A10's project was to investigate the effects of shear stress on the function of the aortic valve. Stenosis *in vivo* is a frequent problem, and there has been a long history of largely unsuccessful attempts to replace the valve. A10's research aimed both to understand normal and diseased valve functioning and to contribute to the goal of a tissue-engineered replacement. He built a novel aortic construct and used valvular endothelial cells harvested from animal valves. Valvular endothelial cells experience forces different from those that line the arteries; in particular, they undergo significant stretching due to their proximity to the pumping heart. Understanding what creates mechanical integrity and strength in native valves was a primary concern for him. He hypothesized that the effects of stretching on the cells might be what strengthens the extracellular matrix. To follow out this hypothesis he decided to build a new device. The only device in the lab that simulated repeated stretching of the construct was the pulsatile bioreactor, which was an inadequate design because it simulated stretching along only one axis of the tube, so different parts of the construct, and thus the cells, experienced different stretches. A10 wanted to look at cellular behavior where *"it's critical to make sure you are doing the same things to every single cell."* He saw a design for a biaxial strain that another mechanical engineer at a university in distant state had built for different purpose. A10 initiated a collaboration with him, and they

redesigned and built the EBSAD for use on valvular constructs. This device could simulate the strain (deformation from stress) experienced by a vessel as blood flows through it.

Interwoven with the engineering task, A10 worked to develop the biological knowledge and expertise to determine whether the cells, when exposed to the simulated in vivo stretching by the EBSAD, would produce biological markers that indicated strengthening. He struggled for quite a while to figure out what to analyze as markers, deciding on the proteins that make up the extracellular matrix, which binds the cells in the tissue. He reasoned that *“the cells secrete protein. . . I surmise that the valvular cells, because they are in a highly dynamic flexing environment . . . have to constantly remodel the matrix they’re in to kind of repair it.”* His research, thus, again led to new biological methods being introduced into the lab practices: the gene microarray studies to compare protein generation in stretched and nonstretched cells. He chose that method because *“there may be characteristics from the gene profile that suggest that they [proteins] will interact with the matrix in a certain way that may strengthen it.”* Both the time and financial investment of the lab into building the EBSAD and the costs of establishing a collaboration with a nearby university to conduct the complex gene array studies represented a gamble. His hypotheses about strengthening through stretching and the gene profile characteristics *“very well may not hold.”* As with virtually every research project the lab undertook, it represented a significant risk to invest in building out in a specific direction.

As indicated by the thick lines on the diagram, all of the system’s components are connected to A7. All of the research projects undergird the construct-baboon model-system designed by A7, which she called interchangeably an ex vivo (meaning outside the animal’s body) or in vivo experiment, that we discussed in chapter 2. In an early interview A7 noted that she had been designated as *“the person who would take the construct in vivo.”* This meant that she would need to create a model-system in which a construct would be connected to the vascular system of a living animal. To be successful, as she said, the project would need to *“obviously integrate the results of colleagues here in the lab.”* At the start, she was quite unclear about just what she would study with the model. Once she decided on a specific animal, she devoted considerable time to designing a means of connecting the fragile construct to the animal without it rupturing (and in an animal-friendly way). As her research project evolved, it became clear that it would



connect the two “barriers” by investigating whether shear stress conditioning of endothelial progenitor cells with the flow loop would make them function as mature endothelial cells in the production of thrombomodulin (a protein that prevents platelet formation) when attached to an animal circulatory system.

For her investigation, she designed a model-system (figure 2.6) that could connect the teflon-scaffolded construct to the bloodstream of a baboon by means of an exterior shunt between the femoral artery and vein of the animal. The *ex vivo* simulation was designed to be run in real time through a gamma camera to provide functional imaging. Conducting a simulation with this model-system under the requisite experimental controls was the most complex problem the lab had undertaken. As A7 noted, *“In the lab we can control . . . exactly what the flow is like. . . . But when we move to an animal model, it’s more physiologic—the challenge then is that it is a much more complex system.”* Importantly, she was able to determine that preconditioning the progenitor cells with flow-loop shear at the normal human *in vivo* blood flow rate enhances the ability of progenitor cells to express anticoagulant proteins within the model-system, but not at lower rates. This finding made a significant contribution both to the research community’s understanding of the effects of arterial shear, along with further articulation of that concept, and to the problem of finding endothelial cell sources for a vascular graft. With respect to the latter, it demonstrated that mature endothelial cells can be created by mechanical forces from progenitor cells, which gave a boost to the lab’s research in that area. A7’s research was completed just at the end of our follow-up investigation, so it took approximately five years of concentrated work, but it was predicated on nearly thirty years of building the lab.

Although not represented explicitly on the diagram, the barriers, technologies, and researchers implicate both lab history and research potentialities. One potentiality is seen in the, then, less-integrated line of A8’s research. Her novel investigation into the effects on mechanical forces on adult stem cells as a strategy for producing endothelial cells—if successful—could lead to more research along those lines. In fact it was successful, and it did open other lines, including the line we mentioned above in connection with the Instron mechanical tester. The two new researchers would be connected to A8 in carrying on her project on cell differentiation by means of forces but, in their case, compression on bone marrow stem cells

and progenitor cells. They modified the Instron to carry out confined compression studies and were building a new device to carry out unconfined compression studies. Their research also required they make modifications to the collagen gel technology.

Our analysis shows that lab history is implicated in current problems, technologies, methods, and researchers. A7's account of how her understanding of how it was possible she could now use the construct in an animal experiment provided in an interview in her third year in lab illustrates the *hands-on role of history* in the research: "*One of the main limitations of the collagen gel construct is its mechanical strength. And like over the course of research in our lab, A1 had looked at things like mechanical conditioning to increase the strength, and of course A12's work has focused on how he could integrate elastin. Well, with his integration of the elastin sleeve we've now actually made enough progress in the area of mechanical strength that we have a strong enough construct to put in an animal.*"

This account characterizes constructs as products of communal activity around a problem, the lack of mechanical strength. Her sketch of its historical trajectory thus far in the lab gives the artifact meaning through its relationship to two prior members and their roles in this ongoing problem-solving effort. One person looked at mechanical conditioning as a possible source of strength, while the other added a new component to the construct. A7 identified the current problem situation and her future work and lab role as yet another chapter in the building of the construct and of the lab. The historicity of the construct served to create a thread that binds the activities of lab members within its developing cognitive-cultural fabric. Such accounts by members of the lab-built technologies were commonplace in our interviews and informal discussions. In chapter 2, I provided their account of history of the flow loop, as recounted by several members. These accounts led us to understand the importance of the historical dimension of building the lab is a resource for current and future research (see, e.g., Kurz-Milcke et al. 2004). The agenda of design and redesign makes history a resource that is intellectually hands-on; that is, history is meaningfully related to present work with lab technologies, devices in particular. Devices, inherited and new, need to be (re)designed for the current problem situation. To avoid past pitfalls requires, among other things, knowing why and how a certain problem situation has led to the realization of certain design options and what about those options worked or did not. The historicity of

the artifacts is a resource for novel design options in the present. In practice it is not an easily accessible resource, but becomes more available as a researcher's participation in the community develops.

Finally, a central component of the epistemic and sociocultural infrastructure of the lab is not explicit in the diagram. It is the educational infrastructure at the institutional level that was under development at the same time and was directed specifically at creating a new kind of interdisciplinary researcher in BME—a program designed to move the research field beyond the problematic collaborations of researchers in different disciplines by designing hybrid BME researchers. A central dimension of our research was to use our findings about their epistemic and learning practices in the context of research to aid in the development of their curriculum to enhance that kind of research. We dubbed our approach a “translational strategy.” I had long worked informally with K–12 science education researchers, which reinforced my strong belief that philosophers of science could—and should—make a contribution to the improvement of science education. This research provided an exciting opportunity to contribute to building a practice-informed educational program from the ground up. But I also saw that the funding we received from the educational directorate at the US National Science Foundation for developing a novel, practice-informed education in BME would also provide the means to collect the data of the sort needed to address the problem of cognitive-cultural integration in the epistemic practices of science.

#### **4.1.3 Designing Educational Infrastructure for Hybrid Researchers**

In the BME labs, graduate students are simultaneously learning to be scientists and pioneering researchers. Thus, the development of student learners into BME researchers is a significant component of building the lab. These BME communities see themselves as conducting cutting-edge research on the frontiers of science, engineering, and medicine. The lab ethos is infused with an open-ended sense of possibility, as well as a tinge of anxiety about how little is known in their area and whether PhD research projects will work out. The researchers place a high value on innovation in methods, materials, technologies, and applications. Obstacles and impasses are omnipresent, as are lab-devised support structures for dealing with them. These structures help student researchers to see failures along the way are viewed as opportunities for learning. During our investigation, we saw several

instances where “big gambles” led to high payoffs, which sustained this attitude, despite the fact that most of the researchers engaged in high-risk research are doing it for their dissertation projects. The sociocultural fabric each lab built, along with the supports developed in their local community, has been successful in helping students to graduate.

Our labs resided in a BME community that decided to place high value on what it calls “*interdisciplinary integration*” at the level of the individual researcher. For them this meant to move beyond problematic collaborations, which stem from the numerous differences between the practices and epistemic norms and values of engineers and of bioscientists, to the extent possible, and cultivate the individual researcher as a hybrid bio-medical-engineer from the outset. The nature of the research requires lab members, who arrive predominantly with engineering backgrounds, to develop equal facility with wet-lab techniques and in vitro engineering design, as well as to develop a selective deep knowledge of the biology of their research targets. Although it was clearly possible to, as the lab A director expressed, “*learn the biology as they go along,*” the lab directors knew from their own experience that this was often an arduous and haphazard process, and so sought to develop an educational program to facilitate systematic hybrid learning.

The lab A director and other senior colleagues felt the lab context and interaction with wider research communities were not sufficient to provide the infrastructure for students to develop fully as researchers. They saw it as their challenge to design and build a new educational environment in which to develop their students into a new breed of researcher, better-equipped to meet the demands of an emerging field and become leaders in it. This new breed would move beyond the faculty’s own experiences of being educated as engineers who later moved into biomedical research—they would be educated as hybrid biomedical engineers from the outset. In conducting research, they would be able to integrate engineering and biological concepts, methods, and materials to address, mainly, medical problems.

As a consequence, the faculty determined they would build a pioneering educational program that would firmly establish BME as an “*interdiscipline*” that integrated all three components in its research and education.<sup>5</sup> So, in this framing, to address biomedical problems within an engineering framing did not require the BME researcher to establish collaborations with biologists or integrate them into the research, although they could do so. The graduates of this program would be able to collaborate fluently with

other hybrids or with disciplinary colleagues in each area, thus mitigating much of the “interactional complexity” of interdisciplinarity (Wimsatt 1974). They would be equally able to move into academia, medicine, public health, industry, or government.

This was the vision. They translated it into an explicit decision for how to build that vision with three main components: (1) two new buildings with architecture designed to promote interdisciplinarity among bioengineering, biosciences, and medicine, with one building dedicated entirely to the envisioned BME department; (2) a new joint department of biomedical engineering across two universities, with one university providing largely engineering and bioengineering expertise and the other medical expertise, with the biosciences drawn from each university; and (3) a new educational program (starting at the graduate level, but quickly adding an undergraduate degree) that would integrate the three components of the field throughout its curriculum and cultivate student identities as bio-medical-engineers. Together these components would serve to articulate and institutionalize the kind of interdisciplinarity they broadly envisioned. This pioneering educational program has since attained national and international recognition, as well as garnered major awards.<sup>6</sup>

When we became involved, the first two components were well under way and provided the institutional, material, and financial structures from which to develop an educational program. They were raising funds and consulting with architectural experts in building spaces for labs and offices and for developing community activities that would promote interdisciplinary interaction and community-building. They had few ideas, however, about how to build an educational program to achieve their vision, and there were no established curricula or textbooks that could be adapted to that vision in their estimation. Through a serendipitous circumstance they became interested in understanding what cognitive science might have to offer as a resource. At that time the US National Science Foundation had a requirement that any grant that included an educational program also needed to include a cognitive science dimension. The NSF, as with other funding agencies, often includes such requirements to further their own objectives, in this case to improve the quality of science and engineering education through incorporating cognitive science research on learning. The leaders of the BME initiative were applying for an engineering research center (ERC) that would include graduate training. I was director of the

Program in Cognitive Science, so they contacted me and asked if I could explain to them why the NSF would have such a requirement, which I interpreted to mean to explain what cognitive science has to offer education. My response to their request created a partnership between them and me and my colleague Wendy Newstetter, whom they would hire into the new department and who became the co-PI on our NSF-funded research.

Our NSF funding, in turn, led to our creating a research group to conduct the investigations into the cognitive and learning practices emerging in frontier bioengineering sciences research labs. CLIC: the Cognition and Learning in Interdisciplinary Cultures research group continued, with varying composition, for fifteen years. We proposed a “translational approach”: to study their cognitive and learning practices in authentic settings of research and translate our findings about the requirements to carry out BME research into classroom and instructional lab educational experiences. Our proposal to create what they called “a cognitively informed educational program” was a novel conception consonant with their novel objectives. If successful, it would put them on the map as leaders in education as well as research. Indeed, eighteen years from the time we began to develop it, the program received the highest award in educational innovation from the United States National Academies of Engineering, as well as other awards along the way.<sup>7</sup> The project, as envisioned, would also contribute pioneering research to cognitive and learning sciences, as well as to philosophy of science, since it provided the opportunity to examine cognitive-cultural integration as it occurs “in the wild” of science, as well as to investigate novel model-based reasoning practices as they emerge in interdisciplinary practice.

Much cognitive and learning science research has established that making students active participants in their learning is more effective than simply lecturing to them, and in the sciences especially, if they are engaged in attempting to solve authentic problems. In the K–12 area, there was by then a long history of educational initiatives based on “problem-based learning” activities. Given this and what we were finding about problem-solving in the labs, we were predisposed to find a way to make problem-based learning (PBL) central to the developing curriculum. Our choice was reinforced further by the fact that the method is widely used in medical education as a means of preparing students for the clinic, and thus familiar to the medical faculty. With medical PBL, small groups are presented with problems—rich and complex real-world medical cases—that enable them to engage in the

authentic practices of the field, with “scaffolding” created by the teachers (who act as “facilitators” to student problem-solving) to support the development of expertise in diagnostic practices. In the course of working to solve authentic medical diagnostic problems, students develop a deep understanding of the human body, diagnostic capabilities, and an identity as medical problem-solvers.

PBL, as used in medical schools, however, was designed to scaffold the kind of hypothetical-deductive and inductive reasoning needed for diagnosing ailments. Our research determined that problem-solving in BME is model-based. To scaffold biomedical engineering model-based reasoning (Nersessian 1992a, 2002, 2008, 2009) we needed to develop a different kind of scaffolding in collaboration with the faculty who would run the courses. The faculty, at first, did not understand what we meant by model-based reasoning, but given a few examples, they agreed our characterization of their practices is apt. To distinguish our problem-solving objectives from the medical field, we called the new PBL-informed method for BME education “problem-driven learning” (PDL). Over time, through several iterations, this method has become woven into the BME curriculum. It is still a dynamic curriculum, which has continued to evolve since our research grants ended. At that time, the graduate level had two core PDL classes, and at the undergraduate level there were three core PDL courses, two classes and one instructional lab, we helped to create in collaboration with the faculty (Newstetter 2006; Newstetter et al. 2010; Osbeck and Nersessian 2019). Notably, as the undergraduate level developed, the education provided began to create an outstanding pool of undergraduate researchers for the labs. Much of the rest of the curriculum at both levels, which we did not ourselves design and develop with them, contains significant PDL elements incorporated by individual faculty members who have been inspired by what they experienced as facilitators of the introductory PDL course (all faculty facilitate). They did continue to consult with Wendy Newstetter, our project co-PI, who had become a member of their department and who was also a facilitator in the introductory undergraduate course, in developing these courses. Thus PDL, as a method, has become generatively entrenched, in that it provides structuring constraints for course design.

The introductory course is taken by all incoming students, who work in groups of eight on the problem outside of class, and with one faculty or postdoc facilitator during the class periods.<sup>8</sup> The problems they work on are

carefully designed by the faculty, with the assistance of Wendy, to present complex, ill-structured health-care problems drawn from the real world, which encourage students to develop, integrate, and anchor their bioscience and engineering knowledge in the context of medical applications. For example, in a problem about cancer screening, student teams need to formulate and address questions concerning the biology of cancer, current screening technologies (e.g., CT scans or MRI), as well as envision future screening strategies (e.g., at the nanoscale), and to develop statistical models, among other topics of investigation. There is now a substantial repository of problems that faculty can draw from and modify to keep updated, as well as add new problems to.

It is important to underscore that the curriculum development is not a linear process. Hutchins has characterized learning as “adaptive reorganization in a complex system” (Hutchins 1995a, 289). The development of the BME educational program, too, fits the notion of *building* we have been using: designing, constructing, experimenting, evaluating, and redesigning incrementally through numerous iterations. This kind of iterative course development is called “design-based research” in the cognitive and learning sciences areas, and was pioneered in K–12 education (Brown 1992; Collins 1992). Our research group and the BME faculty were also learners, and much “adaptive reorganization” took place in the early years of this curriculum development. We were pioneers in attempting a translational approach to curriculum development. Further, there had been little cognitive science, educational, or philosophical research on the emerging research practices of biomedical engineering (or any field of engineering) when we began. Although university research laboratories are the main training grounds for future researchers, they have rarely served as sites in which to study situated learning. Our program of translational research focused on turning our findings about the nature of the epistemic practices and of the effective strategies that support problem-solving and learning in the setting of the research lab into educational experiences in the instructional settings.

In both our philosophical and cognitive science research we sought to understand the ways in which the social, cultural, material, and cognitive aspects of practice and learning mutually inform, and are informed by, the research setting. We analyzed the ecological features of the research labs—the cognitive, investigational, and interactive practices—that invite and support complex learning and used them to guide design principles for



instructional settings. Our findings led us to characterize the research labs as *agentive learning environments*, where student researchers are made agents of their own learning, unlike traditional passive instruction via lecture and the canned, recipe-driven instructional lab (Newstetter et al. 2004; Newstetter 2005). These findings reinforced our initial choice of problem-based learning as a pedagogical method through which to implement the design principles through numerous iterations. Presently, learning scientists<sup>9</sup> and experienced faculty work with incoming faculty, which, together with the repository of PDL problems, constitute what we call a “faculty incubator.” The environment of the incubator provides the cognitive-cultural scaffolding for new faculty to rapidly participate in what, for them, is usually a novel pedagogical approach and learning-centered BME ecosystem. Finally, through the engineering education outreach efforts of Wendy Newstetter, the BME faculty, and the PhD students of the program who have gone on to university appointments, significant elements of our novel PDL approach have become generatively entrenched in other BME programs in the United States and internationally.

#### **4.2 Summary: Lab A as “an Evolving Distributed Cognitive-Cultural System with Epistemic Aims”**

The brief glimpse of lab A practices sketched in this chapter and chapter 2 provide an illustration of our findings about how the devices researchers build in the course of specific problem-solving efforts in a lab largely drive the building of the lab as a distributed cognitive-cultural system. These artifacts possess possibilities that researchers can exploit to evolve the system further. At the outset, the lab A director did not envision his lab engaging in tissue engineering to make vascular construct models or conducting stem cell research and gene profiling. His initial epistemic goal was to understand the effects of the force of arterial shear on endothelial cells, which in turn might help to inform understanding about disease processes of the vascular system, such as arteriosclerosis. At the end of his career he expressed wonderment at the fact that his research program had spanned “*astronauts to stem cells.*”

The director began his research program with the problem of the effect of vibratory forces on the cardiovascular systems of astronauts by using his engineering knowledge to create mathematical models. Later, as he

transformed into a hybrid biomedical engineer, he developed those models with experiments on animals. The animal *in vivo* research provided insight into important dimensions of the effects of shear on the vessels, but lack of control and other limitations led him to build the first *in vitro* model-system, which comprised the flow loop and endothelial cell cultures on slides. The flow-loop device afforded more control and opened the possibility to examine selected features of arterial shear in relation to endothelial cells, which were isolated from other features of the *in vivo* system. Specifically, this model-system configuration both enabled and constrained the research to focus on structural properties and proliferation behavior of cells under shear. Significant problems in conducting the flow-loop simulations, especially with respect to contamination, led lab members to redesign it into a compact artifact that could be assembled and run in a sterile environment.

The researchers realized all along that the cell cultures provided a limited model of the vascular wall in relation to the blood mechanical forces, as well as that the flow loop offered the possibility to examine the relationships among different kinds of cells in the blood vessel wall, if they could engineer a living three-dimensional tissue model. With the advent of new technology for tissue engineering, the lab undertook to design the construct family of models, which provides a range of models that instantiate more of the physiological functionality of the blood vessel to use in flow-loop simulations. The construct device opened the application potential to create a vascular graft to repair diseased arteries and led the researchers to investigate the requirements of such a graft, which, in turn, opened the new problems and avenues of research into mechanical strength and integrity and began the quest to find out whether it is possible to use mechanical forces to develop a high-yield endothelial cell source. Importantly, the tubular shape of the construct supported the researchers in formulating new epistemic goals with respect to understanding the functional properties of blood vessels in relation to a range of mechanical forces. These goals required the researchers to build several new devices, for instance to examine pressure and strain, and an instrument to test mechanical strength, as well as to introduce new methods and technologies to examine experimental outcomes. Eventually, all of this led to the lab's ability to create a completely different kind of animal model than that of the director's initial research.

In sum, in vitro simulation devices provide structuring constraints for articulating the cognitive-cultural system that constitutes lab A as it develops over time. This system comprises researchers, goals, problems, models, methods, concepts, and epistemic norms and values, together with technologies for experimentation, visualization, and analysis and with socio-cultural practices. The material infrastructure, in particular, both drives the direction of and becomes *incorporated* into the D-cog system and subsystems of a research lab, and is essential infrastructure for its epistemic goals and accomplishments. In the BME labs we studied, signature devices, in particular, contain the potential for development of future cycles of building, which often proceeds in novel and unanticipated ways.

In an important sense, then, a core activity of the lab is building itself as a distributed cognitive-cultural system directed toward achieving the overarching epistemic and application goals of the research. The initial and persistent goal of lab A had been to understand the role of physical forces on biological processes in the vascular system. The flow loop was particularly generatively entrenched in that it served as a structuring constraint on nearly all of the research of the lab for all the years of its existence. It made possible taking the research in vitro because, with it, normal and pathological in vivo forces on cells could be replicated to a first-order approximation. It also had the potential to simulate higher-order effects, if these proved important. It was generatively entrenched on two levels. On a physical level, as a device, it has formed a component of most experimental model-systems. On a metalevel, it entrenched the practice of importing engineering concepts and methods of analysis pertaining to mechanical forces into the study of biological phenomena. Most importantly, its affordances and constraints served to direct the researchers in forming new problems and building novel technologies. What kinds of experimentation the researchers envisioned could be done with the flow loop led, for instance, to the novel construct family of models. The construct needed to be designed to interlock with the flow loop in experimental situations, which in some instances required modifications to the design of both. The construct device provided the lab with a more physiologically realistic model and opened an application possibility and, with it, a line of stem cell research. These features generatively entrenched the construct in the remainder of the lab's existence as it opened and drove new directions of research.

Although I have looked only at the tissue engineering lab in this chapter, the features of processes of “building the lab” I have discussed transfer robustly across lab D, and likely those other BME labs that use similar practices of in vitro simulation modeling. The signature artifacts of a lab provide the structuring constraints that afford ways of evolving the research program without rigidly specifying in advance what moves can be made. Further, frontier research areas, such as those in twenty-first-century bioengineering sciences, often require researchers located in universities to build educational infrastructure. The BME educational program, built to facilitate a specific kind of integrative interdisciplinary research, provides a demonstration of “the manner in which epistemic integration interacts with organizations and institutions” in interdisciplinary research (Gerson 2013, 515; see also Caporael 2014). Existing institutions adopted the idea that innovative BME research requires a more directed and richer epistemic integration of biology, engineering, and medicine than collaboration alone could produce. Following out this idea, in turn, required the creation of new institutions, new kinds of architecture, and new modes of organization. Most notably, it led to a novel educational program, generatively entrenched in a new kind of cross-university department aimed at creating hybrid researchers, themselves poised to work at the forefront of biomedical engineering and to extend the frontiers for the next generation.

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# **Interdisciplinarity in the Making Models and Methods in Frontier Science**

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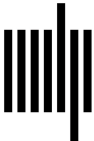
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