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**Chapter 42: In Vitro Analogies: Simulation Modeling in Biomedical Engineering Sciences**

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**Abstract**

This chapter focuses on a novel class of models used in frontier research in the bioengineering sciences – in vitro simulation models – that provide the basis for biological experimentation. These bioengineered models are hybrid constructions, composed of living tissues or cells and engineered materials. Specifically, it discusses the processes through which in vitro models were built, experimented with, and justified in a tissue engineering lab. It examines processes of design, construction, experimentation, evaluation, and redesign of in vitro simulation models, in general, as instances of *building* the source analogy (as distinguished from *retrieving* an analogy), which figures prominently in creative frontier scientific research. Building the analogical source is a bootstrapping process, which furthers the articulation, as well as the solution of the problem.

**1. Introduction**

A major epistemic practice in biomedical engineering sciences (hereafter, BMES) is to use engineering concepts, theories, methods, and materials to create living in vitro models, composed of cells or tissues and engineered materials, that serve as epistemic tools (Knuuttila, 2011) for probing and learning about the behaviors of selected system components under controlled experimental conditions. Such models are epistemically and ontologically hybrid. These in vitro simulation models (often called “devices”) provide BMES researchers with a means to investigate the dynamics of normal and disease processes in biological systems. They aspire to understand the phenomena sufficiently to enable medical, clinical, and pharmaceutical researchers to develop treatments to mitigate or prevent disease processes. Frontier biomedical engineers formulate problems with respect to phenomena that customarily have not been investigated by bioscientists, such as the effects of forces of blood flow on cardiovascular cells and tissues or network learning in neurons. These are systems for which there are no general biological theories of the phenomena under investigation that can provide a resource from which to begin research, so bioengineers frame the problem from an engineering perspective and models are built from the ground up with the aid of engineering concepts, theories, materials, and methods. Modeling the dynamics of such systems comprises iterative and incremental processes of design, construction, evaluation, experimentation, and redesign, that is, cycles of *building* models to discover (Chandrasekharan and Nersessian 2015; Nersessian 2022).

A central epistemic aim of the practice of in vitro simulation modeling is to build models that provide the basis for inference about the target system, that is, to build an analogical source. BME researchers aim to build models that allow them to transfer inferences that derive from experiments they conduct with in vitro models to target in vivo phenomena as candidate understandings and hypotheses. As a researcher explained about her model: “*We typically use models to predict what is going to happen in a system [in vivo]*. *Like people use mathematical models to predict... what’s going to happen in a mechanical system? Well, this is an experimental model that predicts what would happen – or you hope that it would predict – what would happen in real life.”* Such prediction is a form of analogical transfer. Building is a bootstrapping process in which models are developed towards becoming an analogical source. Once developed and justified, in vitro models provide structural, behavioral, or functional analog systems through which researchers can reason not only about the model, but also about the real-world system by transferring inferences as hypotheses. Developing the warrant for such transfer is an important dimension of model building. This chapter will focus on the analogical dimension of modeling, which has largely been overlooked in the philosophical literature on models (Bailer-Jones 2009; Harré 1970; Black 1962; Hesse 1963 are notable exceptions). That literature has tended to focus on the representational nature of models, but when we look at models, generally, from the perspective of iterative and incremental investigative tools for building understanding, the dimension of analogical inference comes to the fore, which, of course, has representational implications as well.

My research group’s twelve-year cognitive-ethnographic investigation of model-building practices in two pioneering BMES university research labs – one in tissue engineering and one in neuroengineering – has provided a wealth of data on numerous dimensions of the nature of these epistemic practices. Importantly, in collecting field observations, interviews, and archival data (grant proposals, paper drafts, PowerPoint presentations, and so forth) over a sustained period, we were able to track the formation of problems and goals; to log the various methods, steps, and iterations of building; to ascertain specific concepts, theories, methods, and materials in use; to probe the decisions and judgements behind the development and alteration of a specific model; to examine how and what kind of inferences an experimental simulation with such models enables; and to note interactions among researchers relevant to the problem-solving process (Nersessian 2022). Here I draw on that material to examine the analogical nature of models. In particular, I focus on an important aspect of analogical reasoning that has been overlooked in both philosophy of science and cognitive science but is widespread in frontier science: building the analogical source (Nersessian 2008). In these labs, most of the reasoning we have observed is focused on the model, especially its capabilities and limitations, as well as on how to make it a better analogical source, which requires researchers to think not only about the biological target, but also about the resources available for building, including the constraints of the materials and methods. In both labs, cellular systems are seen as providing design possibilities that feed into various design options. Research in both labs revolves around engineering living cell cultures into simulation models – wet “devices” with experimental potential that is constrained both by the cellular systems and by the engineered artifacts with which they interlock. Since it builds the easiest bioengineered model for the non-specialist to comprehend, I focus on the tissue engineering lab.

**2. Building in vitro models in a tissue engineering lab**

The tissue engineering lab (lab A) had been in existence for nearly twenty years when we entered. The director and the graduate student researchers had backgrounds in mechanical engineering, and the students were working towards degrees in bioengineering or in the biomedical engineering educational program under development. We conducted interviews, field observations, and collected archival data intensely for two years, and then continued to follow the graduate student researcher projects for another five years. The director was, by then, a widely recognized pioneer in tissue engineering and BMES, more widely. His research program started from a problem he had encountered as a mechanical engineer conducting aeronautics research. NASA tapped him to help them understand the effects of the forces of launch and re-entry (“pogo stick vibration”) on the cardiovascular systems of the astronauts. He reported not knowing “*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. In our initial interview with him, he formulated the insight he had then that would transform his research into a biomedical engineering program as: “*characteristics of blood flow [mechanical stress/strain forces]* *actually were influencing the biology of the wall of a blood vessel. And even more than that… the way the blood vessel is designed is… it has an inner lining, the endothelium. It’s a monolayer – it’s the cell layer in direct contact with flowing blood. So, it made sense to me that, if there was this influence of flow on the underlying biology of the vessel wall, that somehow that cell type had to be involved.”*

Lab A director’s research, thus, started with an engineering framing of a biological problem and a goal to understand complex biological processes of the cardiovascular system in terms of mechanical engineering concepts and methods.The hypothesis that mechanical forces were “*influencing the biology*” was radical at a time when the nascent field of vascular biology was focused on biochemical processes, and biologists initially rejected it. His statement also reveals the design perspective on biology of an engineer, which pervaded his investigative program. This engineering framing provided a means to manage the complex biological problem of the nature and effects of the dynamical processes within blood vessels by reducing it to understanding the effects of flow (mechanical forces) of blood on a specific cell type. The director proposed a novel hybrid “placeholder” concept (Carey 2009), *“arterial shear*,” that is, the frictional force of blood on the endothelium as it flows in the parallel plane through the lumen (the inner space of the arterial tube), and the aim of articulating various dimensions of this concept drove the research for over forty years. His research began with using cows as animal models to investigate the effects of stenosis that researchers induced surgically in their arteries. However, that mode of research did not allow sufficient controls and also required the animals to be sacrificed. He decided to see if it would be possible to “*take the research in vitro,”* by which he meant launching a program to study the impact of shear stress flow on cultures of endothelial cells in bioengineered models. Such models would isolate and control the relevant features of the target, cells, and blood flow, while (hopefully) producing relevant and useful understanding of the processes and effects of their interactions. Building in vitro simulation models would open the possibility of controlled experimental studies, amenable to qualitative and quantitative analysis, of the impact of both normal and pathological flow processes on cardiovascular cells and tissues. In this section, I provide an overview of the development of the main in vitro model-systems lab A researchers developed to instantiate features they deemed to be relevant – and feasible – of such processes, including some of the reasons and justifications researchers advanced for specific design decisions.

**2.1 The flow-loop—cells-on-slides model-system**

At the outset, researchers need to determine what abstractions might be feasible from a biological perspective for designing an in vitro model, while yielding relevant and significant information about the dynamical processes of interest. As one lab member expressed, the design process: “*as engineers we try to emulate that environment [in vivo]*, *but we also try to eliminate as many extraneous variables as possible, so we can focus on the effect of one or perhaps two, so that our conclusions can be drawn from the change of only one variable.*” In one major abstraction, the director decided, in line with his initial insight, to isolate and study only the endothelial cells and not include other components of the blood vessel. The researchers reasoned that this abstraction is warranted because these cells line the inner blood vessels, and so are in direct contact with the blood flow forces and bear the brunt of the frictional force. Further, as one researcher justified the choice, *“cell culture is not a physiological model; however, it is a model where biologic responses can be observed under carefully designed and well-defined laboratory conditions*.” This fact enabled them to derive reliable quantitative measures. Another important abstraction was to begin with studying laminar flow, which is steady and uniform in contrast to in vivo blood flow, which is turbulent and pulsatile along much of its pathway. The in vitro model system is, thus, greatly simplified, but to investigate just the response of endothelial cells to laminar flow would at the very least provide baseline information on biological responses of cells to fluid forces.

An in vitro model of the target system requires at a minimum that it can replicate the shear forces of blood on the cells. The channel flow device (“*flow loop*”) is a functional model of that process, which enables controlled experimentation directly on endothelial cell cultures, thus creating what the researchers call a model system. A specific model system can be the locus of an experiment or just one step in a multi-model experimental process. The flow loop in use at the time of our investigation was the result of several iterations of the design. The important modeling parts of the flow loop comprise a peristaltic pump, a liquid, and a channel in which the liquid flows over cells. The speed at which the pump operates reflects a range of potential blood flow in vivo, and the pulse dampener allows control over the constancy of the flow, for instance, it can turn pulsating flow into laminar flow. Both normal and abnormal flows can in principle be studied. The channel through which an incompressible fluid flows over the endothelial cell cultures on slides is engineered to exact geometrical specifications in a physiologically meaningful range. The liquid medium has the viscosity of blood, a cell-friendly Ph, and other in vivo features. The flow loop in use was the product of iterations of design and redesign, dating back twenty years.

The initial flow loop was designed in 1981 with the capacity only to produce laminar (steady, uniform) flow. However, the mechanical features of blood flow in vivo vary with the distance from the heart, as well as with respect to topological features of the arteries, especially constrictions. The flow loop was redesigned in 1989 to allow “*studies in which fluid mechanic conditions can be systematically varied,*” which include pulsatile and oscillatory flows, in order “*to determine the extent of any such flow effects*” that can occur in vivo. It was a large bench-top device and contamination was a constant problem because the viability of cell cultures requires that they are maintained at appropriate CO2 levels and a specific temperature range, which was impossible with this model. Over fifty percent of their experiments failed because of contamination.

New technology made a significant redesign of the flow loop to address the contamination issue possible in 1995. In an interview, a recent graduate of the lab chronicled the process (see, Kurz-Milcke, Nersessian, and Newstetter, 2004) of “*model-revising this design to go into the incubator*,” which made long-term experiments possible. This was important because it takes twenty-four hours for the effects of flow on the cells to be seen, and contamination increases with time. “*Model-revising*” entailed a redesign of the model to replace the heating function of the coils with the incubator and to use a pump rather than a pressure difference to derive flow. The revision also made the components sufficiently decomposable to allow for independent redesign if needed as the research program advanced. In fact, minor modifications continued to take place throughout our investigation. The redesigned flow loop could be assembled under a sterile hood, operated in an incubator, and had an integrated peristaltic pump. The geometry of the flow channel, where cells-in-culture interface with mechanical parts, was left unchanged. This redesign of the flow loop device was central to its function in the model system because its viability as an in vitro model is totally dependent on the ability of the endothelial cell cultures to resist contamination. To determine the response of the cells to the applied forces, the researchers remove them from the chamber and examine them with various instruments, including the Coulter counter and confocal microscope, which provide information about proliferation, alignment, alive/dead status, morphology, migration, and so forth in the form of numerical and visual (graphical, diagrammatic, color-coded) representations. This information can be related directly to the controlled shear stresses and quantified.

The flow loop, then, is a dynamical model that when in operation has the possibility to simulate normal and pathological forces of blood flow, laminar and pulsatile, through the lumen of an artery. In most experiments, however, the process instantiates the shear forces of a steady (constant speed), laminar (straight stream lines) flow over a flat surface (cells on slides). The flow is two-dimensional and unidirectional. The researchers listed all of these features as contributing to their assessment that the model system “*emulates*” in vivo shear to a “*first-order approximation... as blood flows over [sic] the lumen.*”[[1]](#endnote-1) They argued that instantiating this process with only characteristics of first-order flow is justified because it provides a “*way to impose a very well-defined shear stress across a very large population of cells such that their aggregate response will be due to”* it and enables them to *“base... conclusions on the general response of the entire population*.” Experiments flowing cell cultures on slides continued to be conducted throughout the period of our investigation, but investigations with a more complex vascular wall model, the construct device, were, by then, the focal point of lab research.

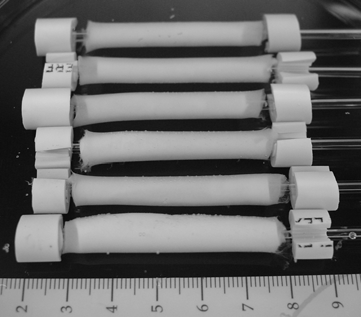
**2.2 The flow-loop—construct model-system**

Improving the devices and model systems so as to instantiate additional relevant features is an ongoing part of the research. Although an extended discussion is not possible here, this process can be understood as one of “de-idealization,” especially involving processes of reformulation and concretization as discussed by Tarja Knuuttila and Mary Morgan (2019). As they argue for immaterial models, processes of de-idealizing a material model are not a straightforward reversal of any prior idealization process. Lab A's research began with building a simplified model that focused on one causal interaction that “made sense” to the director as the most important for his purposes. Reformulating a model to instantiate (make concrete) additional features, in the case of in vitro models, depends on an assessment both of what other features might be causally relevant and of what it is feasible to do with the biological materials and the engineering materials and technologies at hand, which changes over time.

Simulations with the endothelial cells in isolation from other components of arterial tissue enable a basic, provisional understanding of cell response to shear, but the researchers were fully aware that “*cell culture is not a physiological model*” of the blood vessel wall. It leaves out many features of the blood vessel and, thus, produces limited understanding of their target problem of the effects of mechanical forces on the blood vessel wall, which has other components. In a first attempt to add relevant features, they created a “*co-culture*” of endothelial and smooth muscle cells, but the limitations remained much the same since it does not capture their structural relations in the tissue of a blood vessel. Specifically, as the director noted, *“putting cells in plastic and exposing them to flow is not a very good simulation of what is actually happening in the body. Endothelial cells… have a natural neighbor, smooth muscle cells. If you look within the vessel wall you have smooth muscle cells and then inside the lining is [sic] the endothelial cells, but these cell types communicate with one another. So, we had an idea: let’s try to tissue-engineer a better model-system for using cell cultures.”* Their aim became *“to use this concept of tissue engineering to develop better models to study cells in culture;”* that is, to work towards building *“a more physiological model”* – one that would instantiate more features and have the functionality, eventually, of an in vivo vessel along mechanical, physical, and biochemical dimensions. With this more complex model, they could study the effects of shear on more components of the blood vessel wall, as well as the interactions of different cell types. But the “*the big gamble*” the lab took to try to build a model that instantiated more of the relevant features of a blood vessel wall was only possible because new tissue-engineering techniques and materials had been developed. If successful, building the construct model could also open a novel application potential: to turn the model into a vascular graft to repair diseased arteries in vivo. Within the lab, this tissue-engineered model was referred to, variously, as “*the construct*” device, the “*tissue-engineered blood vessel wall model*,” and, underscoring its application potential, the “*tissue-engineered vascular graft*.”

An in vivo blood vessel is tubular in shape and comprises several layers: the lumen where the blood flows; a first, mono-layer of endothelial cells that sit on collagen; an internal elastic lamina; a second layer of smooth muscle cells, collagen, and elastin; external elastic lamina; and an additional layer of loosely connected fibroblasts. The construct is grown on a specially designed structure that comprises tiny silicon tubes, which allow cells to attach and grow on them, and then be slipped off (Figures 1a and 1b). To function as a model of the target arterial system, the materials used to grow them must coalesce in ways that mimic the properties of native tissues, and the cells that are embedded in the scaffolding material must replicate the capabilities and behaviors of native cells so that their higher-level tissue functions can be achieved. Depending on the goals of an experiment, the in vitro model can be constructed to instantiate some or all of the in vivo features. It is possible, for example, to use only collagen and not add elastin, or to seed it with either endothelial cells or smooth muscle cells. Thus, the construct forms a *family of models* that can be designed for different experimental purposes.





**Fig. 1a**: Constructs seeded into mandrels **Fig. 1b**: Cross-section of a construct.

(A Teflon sleeve is used to strengthen it for a specific experiment).

The flow loop – construct model-system provides insight into how multiple in vitro models can interlock in experimental simulations. Because of the geometry of the flow chamber, the researchers would have needed to undertake a major redesign of it to accommodate the tubular shape of the construct. Instead, they decided to cut open the construct so it would lie flat in the existing chamber. They justified using the flat constructs by arguing that since the cells are so small with respect to the construct, the shear forces they experience would be the same as if they were in a curved vessel. As one researcher explained their reasoning, from the “*cell’s perspective*” a cut-open construct is not an approximation because “*the cell sees basically a flat surface. You know, the curvature is maybe one over a centimeter, whereas the cell is like a micrometer…. It’s like ten-thousandth the size, so to the cell – it has no idea that there’s actually a curve to it.*” That is, flowing the fluid over a flat construct instantiates the force the cell experiences in vivo, because the cell is so small with respect to the arterial wall, the cell’s in vivo experience is as though it lives in a flat world.

As with all in vitro models, the iterative and incremental construct design is based on what is understood at the time of the biological environment of endothelial cells and vascular biology, on the kinds of materials available, and on the tissue engineering techniques developed in the lab and in the field thus far. The lab’s ongoing research sought to advance all these aspects through numerous iterations. Thus, with the move to tissue engineering, the lab’s major research question became: *“The big, big question is how do our constructs act like a modeling tool, how do they respond to – or biological markers respond to – mechanical stimulation. So is there a certain correlation to the stress and strain and the distribution being applied to these constructs to certain biological markers... Does it respond in the same manner? That’s the big, big question.”* To “*respond in the same manner*” means, among other things, that it expresses the in vivo proteins and genetic markers, and possesses the in vivo mechanical properties.

For any device to perform as a “*modeling tool,*” researchers must understand both how it represents in vivo phenomena (device qua model) and how it is an object in its own right (device qua device), an environment for biological experimentation with constraints and affordances due to the nature of the design, the materials, and the engineering challenges. Also, with respect to the former, although these modeling tools are highly specific in the details of their construction, they are understood to represent generic biological systems – systems of that kind (e.g., cardiovascular systems) – rather than a specific system. All these factors need to be taken into account when researchers plan experiments, evaluate outcomes, and make inferences about what to transfer as hypotheses to the in vivo target system.

**2.3 In vitro models as built analogical sources**

In vitro models are the primary means through which BME researchers gain epistemic access to complex biological phenomena. As we have seen in the brief overview of two model systems, researchers build epistemic warrants for a model through the principled decisions and rationalizations they make in the processes of building it. Researchers design and perform in vitro simulation experiments with devices in processes they claim to “*parallel*” or “*mimic*” salient aspects of in vivo situations. The warrant for using these kinds of models as epistemic tools is connected to how the models function as dynamic representations; that is, how they are built to instantiate and simulate in vivo features. What I consider now is that to fathom how the practice can achieve its epistemic aims through model-based reasoning, we need to understand the epistemic affordances of the models as built analogies.

**2.3.1 Building the analogical source**

The BME epistemic practice of building devices and model systems is, fundamentally, an analogical practice. The researchers aim to design models to provide analogical sources that can enable them to gain understanding and control of complex biological systems. This analogical practice is quite unlike any considered in the customary philosophical and cognitive science literatures. Usually, analogy is cast as a process of making sense of what we do not understand (target) in terms of what we do (source). Here little is understood about either source (model) or target (real-world phenomena) at the outset. Customarily, in analogical problem solving, the reasoner retrieves a previously solved problem that provides a source analogy, determines a mapping between source and target, transfers features from source to target, and evaluates inferences with respect to the target domain. Mary Hesse (1963), whose account has been most influential in both philosophy and cognitive science, called the features that form the mapping “positive,” if they match the target, “negative,” if they do not match, and “neutral,” if their status is unknown.[[2]](#endnote-2) On her account, the neutral features provide a resource for further development. Recently, Tarja Knuuttila and Andrea Loettgers (2014) have shown that for retrieved analogical sources used in synthetic biology, negative features can also lead to further development. With built analogies in BMES, as illustrated above, researchers are well aware at the outset of negative features not instantiated in a model, and these negative analogies, indeed, provide opportunities for development.

Although models have pride of place in contemporary philosophy of science, scant attention has been directed towards the analogical dimension of models. I venture this stems from the fact that the literature focuses on models derived, at least partially, from theories, which draws attention to the traditional “realism” issues associated with thinking about theories. However, starting from the other direction, that of building models “from the ground up” in the absence of a theory of the phenomena under investigation, underscores how models and analogies are tightly bound (see, e.g., Nersessian 1992; 2008; 2022). This analogical relationship has importance, thus far not addressed, for models derived from theories since analogical inference provides a means to transfer prediction, explanation, and understanding from model to world. Additionally, as Hesse (1963) pointed out, the source model is always a “false” representation in that it cannot accurately or adequately represent all the features of the target. With her, I contend that “true” and “false” are not the appropriate categories for thinking about models. However, in the case of in vitro models, neither is Hesse’s, and the customary, notion of similarity. These models must instantiate features with the same biological properties and functions as those features selected from the real-world system in order to perform properly as a living system, and so similarity is also not an appropriate category for the representational relation between in vitro simulation models and the in vivo target. In general, BMES researchers strive to design in vitro models that both refer to and instantiate features of the in vivo biological system germane to their epistemic goals. As will be discussed in the next section, the notion of exemplification, advanced by Nelson Goodman (1968) and extended to scientific practices by Catherine Elgin (2018), can best capture this representational relation between source and target.

Although what we customarily understand as analogy occurs in science, for frontier research problems there is often no pre-existing analogical source. Rather, the source itself needs to be created in interaction with the goals and constraints of the target problem – a bootstrapping process that furthers the articulation of the problem as well as its solution. There are several sources of data on scientific problem-solving, including historical, think-aloud protocol, and ethnographic (see, e.g., Nersessian 1984, 2008, 2022), that provide evidence of this important *representation-building* aspect of analogy. My analyses of data from all these sources provide a list of features that are relevant to understanding in vitro models as built analogies:

* building processes are goal-directed
* building processes are iterative and incremental
* interaction between source and target is ongoing in the building process
* elements used in building analogies can derive from more than one domain (“hybrid analogies”)
* various abstractive processes are used in selecting features and merging target, source, and model constraints
* mappings are established during the building processes, so in most cases, mappings develop/evolve over time
* models are built towards instantiating features germane to the epistemic goals
* models are evaluated based on whether they do exemplify features germane to the problem
* features not exemplified can provide a resource for further development
* analogical transfer requires that a model instantiate relevant features, and leave out nothing essential to that inference

It is important to note that although the word “abstraction” is commonly used for a separate process alongside “idealization” and other abstractive notions, this is confusing. It is better to reserve “abstraction” for a comprehensive notion comprising various processes, including idealization, approximation, simplification, omission, limiting case, and generic modeling. All of these abstractive processes can play a role in model building.

As we saw, BME researchers aim to build physical simulation models to the degree of specificity they believe sufficient to examine an aspect of the in vivo phenomena in a cognitively tractable manner. This goal is informed by an assessment both of the current state of understanding of the phenomena and of how the available materials and technologies constrain and enable design possibilities. Given the frontier nature of the research, all of these factors change over time, thus the building process is incremental, as a satisfactory representation is developed. Additionally, models are hybrid bioengineered constructions and there is tension between the constraints on the design and functionality of a device that derives from biology and those from engineering. Some selections are made in order to merge these constraints and need to be considered in assessing the warrant for transferring any inferences.

During our investigation in both labs, the researchers’ concerns about a model’s relation to the real-world system informed decisions about design and redesign, as well as their evaluations of experimental simulation outcomes. Importantly, in vitro models are dynamic systems and a model needs to instantiate those features that enable the cells and tissues to behave in an experimental simulation as they would in the in vivo phenomena under those conditions. A major epistemic task, therefore, is to determine what those features might be and whether or how any abstractions made can impact behavior. For instance, a flow-loop simulation instantiates first-order (laminar) blood flow. This is a counterfactual situation because there are always higher-order effects in vivo, but for their initial epistemic goal to understand in what ways forces can affect the morphology and proliferation of endothelial cells, the researchers argued that there is no need to capture the full complexity of the in vivo blood flow at the outset. The reasons researchers gave for this choice included such considerations as: there are places of laminar flow in the circulatory system as the flow gets further away from the heart, laminar flow enables them to impose a well-defined shear on a population of cells, and if indeed the cells functioned differently in significant ways in vivo (e.g., gene expression), the device design affords (or can be redesigned to) the possibility to simulate higher-order effects. These reasons (in order) are of the following sort: the model instantiates a germane feature of a part of the in vivo system of interest, the model achieves an important engineering goal that reduces the complexity of the analysis, and the model can be made to instantiate other features of the system if in vitro biological function is importantly different. They did use the flow loop’s capacity to simulate higher-order effects in later research when it became technologically possible to examine gene expression, which made it worthwhile to investigate these effects.

Importantly, redesign is continual with in vitro model building. Some redesigns have to do with improving the engineering and others are made for practical purposes, such as enhancing the viability of cells. The most important redesigns, however, are to improve the nature of the parallelism to the biological phenomena of interest, if only in minor ways, as they are made to provide better or different exemplifications. Redesign can be driven by a change in understanding of the phenomena or of the problem or by a change in technological and material capabilities as the research progresses. At any point in time, in vitro models are in different stages of development. Thus, exemplification, here, is a historical process. During the period of our investigation, the flow loop was quite stable, the construct was still undergoing design changes, aimed mostly at improving its mechanical strength. Once the kinks have been worked out of a design and the researchers assess that it has met their epistemic goals, change is largely incremental. In vitro systems are meant to be sites of long-term investment so as to enable systematic experimentation.

Negative analogies are a major driver of model development and redesign. For instance, in the design of the flow loop, researchers were aware of a negative analogy from the outset: flow loop simulations are “*something very abstract because there are many in vivo environments and many in vivo conditions within that environment*.” Things change constantly in human bodies over the day and over lifetimes; including physiological flow rates. These changes had been a significant problem in the director’s earlier animal studies and motivated his move to in vitro. The first flow loop could produce only laminar flow, but when redesigned, it had the capability to produce a range of flow rates. Flow-loop simulations could instantiate higher-order effects if there were reasons to do so, such as “*if there’s a whole different pattern of genes that are upregulated in pulsatile shear.*” In this instance, however, for many years there was no way to investigate possible salient differences in gene regulation. That potential came quite late in the research program when gene array technology was developed. The prior basis for partial comparison of their results was provided by studies of morphology and proliferation in vascular biology and whatever biological markers were available from biochemical studies. The possibilities for comparison of a model with biological research are always fluid and incomplete.

Two other negative analogies were important to furthering the lab’s research program. First, the flow loop model exemplifies only one of the in vivo mechanical forces: shear stress. This is the force with the greatest impact on the endothelial cells. Blood vessels are also subject to strain forces from the blood pressing on the vessel wall, but to instantiate this force requires a model system that instantiates the topology of the vessel. A second negative analogy concerns the use of slides with endothelial cells in culture in flow loop simulations. The researchers recognized that this model system does not provide “*a physiological model.*” This simulation does not instantiate some of what they knew to be relevant mechanical and biochemical features of blood flow through the lumen of an artery and thus limits the understanding obtained. For one thing, endothelial cells have a “*natural neighbor*,” smooth muscle cells. It was not until the technologies to engineer complex tissues started to develop in the 1990s that it became feasible for the lab to attempt to build a blood vessel wall model that could also instantiate smooth muscle cells and other in vivo components, i.e., build the construct family of models. These models enabled simulations and assessments of the shear forces of blood flow that more closely mimic the in vivo system. They also led to researchers building other model systems to investigate the forces of pressure and strain, the other negative analogy (see Nersessian 2022, chap. 4).

**2.3.2 Analogy and exemplification**

In the words of our researchers, devices are designed to “*parallel*” or “*mimic*” features of the in vivo phenomena. Their expressions can be interpreted to mean that in vitro physical simulation models are built to provide structural, behavioral, or functional analog representations of selected dimensions of complex in vivo biological systems. They provide a way to get a grip on the behavior of a biological system by creating a parallel or virtual world through which to conceptualize, control, and experimentally probe aspects of that complex dynamic system. Such models can only function as epistemic tools if they have been designed with an appropriate representation of what is understood about the biological facts. Importantly, unlike computational virtual worlds, in vitro models are composed in part of biological materials, so the cells and tissues have biological functionality that needs to be maintained as they interface with engineered materials and perform under greatly simplified conditions, all of which figure into how they function epistemically. And, to add a level of complexity, most model systems are *nested* analogies, that is, analogies within an analogy (Nersessian and Chandrasekharan 2009). For example, the flow loop provides an analogy to hemodynamics, the construct provides an analogy to the blood vessel wall, and the model system they constitute provides an analogy to blood flow in an artery. So, the considerations in play need to be not only about each model, but also about how the model system fits together.

What enables the researchers to have some assurance they are on a productive path with a device or model-system design? Despite their complexity, in vitro models are missing much of the in vivo target system. What we found in our data is that researchers were continually asking the question that can be phrased generically as: “Is the model of *the same kind as* the in vitro system along the relevant dimensions?” That is, are the features instantiated such that the researcher is warranted to infer that the behaviors of the model belong, along specified dimensions, to the same class of phenomena as those of the in vivo biological system? Answering that question requires an assessment of the relevance of both the features that are instantiated in the model to its behavior and those that have been left out. The best way to interpret that question is by asking whether the built analogy *exemplifies* the features relevant to the research.

In the sense advanced by Goodman (1968) and Elgin (2018), “X exemplifies Y” means “X instantiates relevant features of Y, and refers to Y by means of that instantiation.” The notion of exemplification captures the representational relation the researchers aim for as they build models to “parallel” or “mimic” in vivo phenomena. The flow loop, in performing, not only refers to shear stress forces in a process of blood flow through the endothelial cells in a blood vessel, but it also produces those shear stress forces. The liquid has what the researchers judge to be relevant fluid-dynamic features of blood as it flows over the endothelial cells' cultures or the construct device that has been designed to have relevant features of the blood vessel wall. The in vitro models, then, are successful exemplifications if, indeed, they possess the features of the in vivo phenomena germane to the problem at hand, and much of the research is directed towards determining if this is the case. Such determination requires the researcher to consider both the relevance of what is and what is not instantiated to the behavior of the system. What is not instantiated provides a potential resource for further development (negative analogy). Building in vivo models towards exemplifying features is an incremental, and thus, historical process in which models are *built towards* exemplifying the features determined to be relevant to the functioning of a target biological system – features that can change as research progresses.

Models that are satisfactory exemplifications provide the researchers with a warrant for the analogical transfer of hypotheses based on experimental findings, but with the proviso that what inferences are justified depends on the historical state of the model. So*, analogy and exemplification work together in model-based reasoning.*

**3. Conclusion**

In vitro simulation modeling is a significant epistemic practice in BMES. It has become even more widespread with the advent of the “next generation” tissue-engineered “organ on a chip emulation models.” These are in vitro simulation models the size of a memory stick, which instantiate the requisite structure and functionality of in vivo organs to be used in experiments aimed at understanding disease mechanisms or evaluating the therapeutic effects of drugs (Ingber 2022). Although the ethnographic investigations we conducted into the practice of in vitro simulation modeling ended several years ago, the data are still relevant to the fundamental epistemic issue: what justifies researchers in transferring inferences from in vitro simulation models to in vivo systems? As I have argued, these kinds of models are built to instantiate epistemically relevant features of the target system, in order to serve as source analogies. Exemplification, then, provides the criteria for assessing the affordances and limitations of an in vitro model – at a particular stage in its development – as an analogical source through which to investigate the target in vivo phenomena. These assessments enable researchers to determine for which inferences about the behaviors of the in vitro model there is epistemic warrant to transfer as hypotheses to the in vivo system.

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1. 1 That the researchers all use “*over*” instead of “*through*” the lumen (which is tubular in in vivo) is an interesting slip. I suspect they made the mistake because they were thinking in terms of the in vitro simulation, in which, as we will see, the tubular constructs are cut open and laid flat in the flow chamber. [↑](#endnote-ref-1)
2. 2 Hesse called these features “properties,” but “features” is a better expression to use since it captures the notion that properties, relations, and relational structures can be mapped. [↑](#endnote-ref-2)