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# "All Models Are Wrong"
# Models & Simulations for Medical Devices

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Many disciplines such as weather forecasting, financial markets, and architecture routinely use models and simulations. Models and simulations are crucial elements of any new medical device development effort. A useful definition of a model is that it is a simplified yet accurate representation of reality that helps simulate a process, understand a complex situation, predict an outcome, or analyze a problem. One thing to keep in mind is a quote from George E. P. Box:

> *Essentially, all models are wrong, but some are useful.*[1]

Let us explore some of the ways investigators use models for developing medical devices and determine how wrong or useful the model might be. As a prelude, we will see that verification and validation, which are similar to leadership and management, respectively, are important concepts to understand usefulness of models. We will also look at Food and Drug Administration (FDA) activity in the use of modeling and simulations to show safety and efficacy of medical devices. Finally, we will look at the innovative area of biomimetic devices and their use for organ replacements, drug discovery, or models.

## Reasons for Models

Even though they are not completely accurate, models are still beneficial in representing reality for many reasons:

- Save money – try out different concepts on a less complex model before moving on to more expensive representations
- Save time – a less complex model can be built and modified in less time than a more elaborate representation
- Less restrictive – easier to experiment with than an animal model
- Physical scaling – a larger scale model can help better visualize the reality and a smaller scale representation can be less wieldy to manipulate

Different audiences can benefit from models and simulations:

- Convince financial stakeholders of the device's merits
- Verify engineering requirements for Design Controls per FDA[2]
- Validate clinical and user requirements for Design Controls
- Show desired and undesired physiological effects for physicians and other end users
- Determine endurance and reliability for warranties
- Provide education and practice for users
- Show benefits to potential customers for Sales and Marketing
- Demonstrate that a device is better than competitors for Sales and Marketing
- Convince a regulatory body (FDA or Notified Body) that the device is safe and effective

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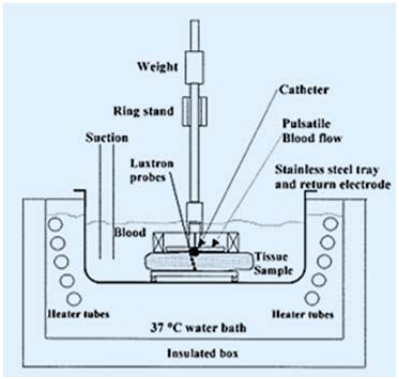
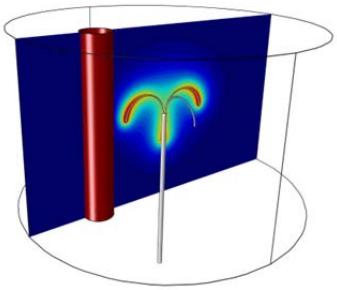
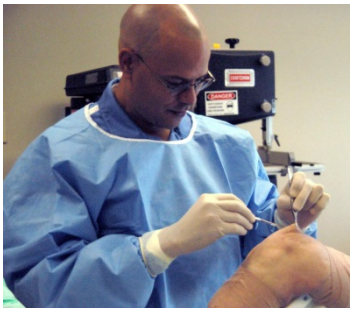
[1] *Box, G. E. P., and Draper, N. R., (1987), Empirical Model Building and Response Surfaces, John Wiley & Sons, New York, NY*

[2] 21 CFR Ch. I § 820.30

Table 1 shows examples of several types of models. Each one has its particular benefits and deficiencies with respect to parameters such as cost, time, restrictions, and accuracy.

**Table 1. Examples of Different Model Types**

| Model Type, Pros & Cons | Example | Notes |
|---|---|---|
| **Engineering test**<br>↑ Known and controlled variables<br>↑ Repeatable<br>↑ Useful for design verification<br>↓ Oversimplifies the actual environment |  | Also called bench test.<br><br>**Example**<br>A test fixture models compressive and tensile forces in a hip implant component.<br><br>SOURCE: Bose ElectroForce 3510 instrument with hip implant fatigue fixture http://www.azom.com/article.aspx?ArticleID=10683 |
| ***In vitro***<br>↑ Known and controlled variables<br>↑ Uses biological material in a simplified environment<br>↓ May require considerable design, fabrication, instrumentation, and validation effort |  | Also called wet lab; performed with biological tissue outside its normal environment<br><br>**Example**<br>Radiofrequency ablation for treating cardiac arrhythmias is modeled using biological tissue in a blood environment.<br><br>SOURCE: He, DS; Bosnos, M; Mays, MZ; Marcus, F.; Assessment of Myocardial Lesion Size During In Vitro Radio Frequency Catheter Ablation, IEEE Trans Biomed Eng., Vol. 50, No. 6, JUNE 2003 |
| **Computer Simulation**<br>↑ Many good software analysis packages available<br>↑ Easy to modify<br>↑ More sophisticated packages model multiphysics and changing parameters, situations common in biological modeling<br>↑ Reduces expensive prototyping and testing<br>↓ Expensive software<br>↓ Requires high skill level to use<br>↓ Difficult to verify |  | **Example**<br>Radiofrequency tumor ablation near arterial blood flow acting as a heat remover is modeled with finite element analysis (FEA) using a multi-physics software package.<br><br>SOURCE: www.comsol.com/press/gallery/ |

| Model Type, Pros & Cons | Example | Notes |
|---|---|---|
| ***In vivo***<br>↑ Closest physiological model to patients<br>↑ Provides good feedback from end users<br>↓ Anatomical and physiological differences<br>↓ Administrative hurdles for proper animal handling and approval process |  | Also called pre-clinical or animal model. Effects of various biological entities are tested on whole, living organs<br><br>**Example**<br>A device for the treatment of aortic aneurysms is tested on a porcine model.<br><br>SOURCE:<br>magazine.uc.edu/issues/0408/designing_for_doctors.html |
| **Cadaver**<br>↑ Closest anatomical model to patients<br>↑ Provides good feedback from end users<br>↓ No modeling of physiological processes<br>↓ Administrative hurdles for proper specimen handling and approval process |  | **Example**<br>An orthopedic impant is tested in a cadaver knee.<br><br>SOURCE:<br>www.mscspace.com/laboratories/ |
| **Simulated Environment**<br>↑ Explore procedural issues<br>↑ Check for proper interfaces with other devices<br>↓ Expensive |  | **Example**<br>A measuring device is tested in a simulated environment with a medical mannequin.<br><br>SOURCE<br>"Simulation Centers: Selection and Tips from the Field" by Linda Pellegrino and Laurie Reed of Farm Design, Inc.<br>http://www.hfes.org/web/HFESMeetings/HCSPresentations/hcs2013pellegrino.pdf |
| **Usability**<br>↑ Check for proper interfaces with other devices, users, and environment<br>↓ Expensive<br>↓ Scheduling difficulties with users (especially physicians) |  | Required by regulatory agencies.<br><br>**Example**<br>Researchers and clinicians at a teaching hospital assess the usability of a medical device.<br><br>Source<br>www.hopkinsmedicine.org/lp/armstrong_usability_evaluation/why.html |

**Validation and Verification Are like Leadership and Management (respectively)**

Peter Drucker, noted leader and author on management theory, has written:

> *Management is doing things right; leadership is doing the right things.*

Let us paraphrase this for modeling:

> *Verification, like management, is ensuring the investigator designed the model the correct way; validation, like leadership, is ensuring the investigator used the correct model.*

To better illustrate verification and validation of a model, let us look at a somewhat realistic example. The medical device is a radiofrequency ablation system to treat cardiac arrhythmias. It consists of a generator (RF energy source) and an insulated catheter with a temperature-sensing metal tip (energy delivery probe). The generator controls its output power with a feedback loop to maintain a steady, pre-set temperature at the tip. The catheter is snaked into an internal chamber of the heart to heat a pinpoint region to a temperature greater than 65 °C to cause coagulation (necrosis). The temperature must also be kept to less than 100 °C to avoid harmful blood clotting. An *in vitro* test fixture (Figure 1) contains bovine blood heated to 37 °C. A pedestal in the blood holds a bovine myocardial tissue sample. A pump continuously circulates blood across the tissue sample to simulate convective heat loss at the ablation site. A stand supports the catheter such that the force of the catheter on the tissue sample is constant. A temperature-sensing device (thermocouple) placed into the tissue sample near the probe contact area and temperature continuously recorded at this site during ablation.

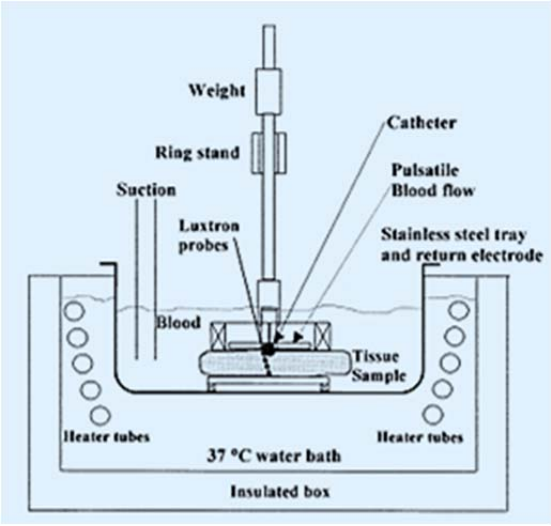



**Figure 1. *In vitro* test fixture to model radiofrequency ablation in the heart (identical figure as in second row of Table 1) same**

Investigators verified the test fixture by correlating the system set-point temperature with both the thermocouple and observed tissue changes (tissue permanently changes color above its coagulation temperature). They noticed a verification error in that the metal of the thermocouple influenced the

tissue coagulation pattern. They switched to a different type of temperature sensor containing no metal parts (Luxtron optically based temperature measurement system, www.lumasenseinc.com). Verification tests now showed that temperature measurements aligned with tissue effects and the erroneous influence of the temperature sensor disappeared.

During animal studies, the investigators noticed large and rapid temperature swings that exceeded the danger area of 100 °C. They determined there was a validation error. The design optimized the feedback control algorithm for the continuous flow of the test fixture and could not maintain a stable temperature in the pulsatile flow of the animal model. The investigators found that they had to tune the feedback control algorithm differently for the pulsatile blood flow condition when they used pulsatile blood flow in the test setup. They found that they could accurately tune the feedback control algorithm in the easier environment of the *in vitro* test fixture rather than the more difficult *in vitro* animal environment.

**Table 2. Summary of Radiofrequency Ablation Model**

| Assessment of Model | Business Equivalent | Description |
|---|---|---|
| Verification | Management<br>(Do things right) | Design model so temperature measurement system does not affect tissue coagulation outcome |
| Validation | Leadership<br>(Do the right thing) | Use correct model attribute of pulsatile blood flow rather than continuous flow |

## The FDA and Computer Simulations

In the medical device industry, investigators have used computational modeling and simulation mainly to aid in development, design optimization, training, and competitive benchmarking. The FDA's Center for Device and Radiological Health (CDRH) is seeing a growing number of submissions for medical devices that include a simulation-data component.[3] The main purpose of a submission is for the FDA to assess how well a device will do what it claims with minimal risk of harm to the patient. The FDA has recently issued a draft guidance document for submissions containing computational models.[4] Importantly, the FDA now recognizes that computational modeling and simulation studies, together with bench, non-clinical *in vivo*, and clinical studies, are appropriate tools to evaluate the safety and efficacy of medical devices. The FDA requires the following in submissions with computer simulations:

- a rationale for the assumptions and simplifications, comparing it to the actual device and environment
- details regarding how the assumptions and simplifications might affect the output of the computational model, the interpretation of the results, and the relevance to the purpose of the study
- method(s) used to assess the accuracy of the computational model (e.g., *in vivo* or *in vitro* comparator)
- details that describe how the measurements were taken from the comparator and used to assess the accuracy of the predicted numerical output

[3] www.mdtmag.com/articles/2013/04/simulation-now-recognized-fda-essential-medical-device-evaluation
[4] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM381813.pdf

## Replacing One Model with Another: Organs-on-a-Chip

Some researchers are developing biomimetic devices or so-called organs-on-a chip[5]. These exciting devices are fabricated using computer microchip manufacturing techniques to form intricate three-dimensional structures. Animal or human cells of different types are layered on these structures and the cells mimic some of the functions of a real organ much better than the cells without the structure. One such device models the functional alveolar-capillary interface of the human lung[6] (Figure 2). These biomimetic tissues have the potential to replace organs such as lungs, liver, and kidney. Investigators are also exploring their use to drug candidates, reducing animal trials that take more time and investment.

While our discussion here on modeling has been limited to medical devices, organs-on-a-chip may seem out of scope. However, biomimetic devices will be a new class of medical devices containing inorganic structures and living cells, much like combination products that are both devices and drugs (such as drug-eluting stents). Additionally, biomimetic devices have the potential use as models to test medical devices, especially combination devices.

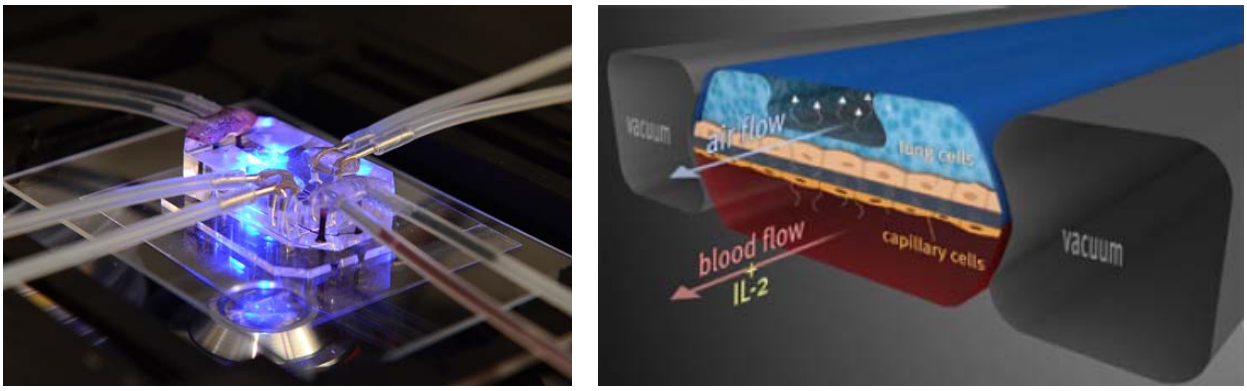



**Figure 2. Biomimetic Microfluidic Device Reproduces Lung Function to Study Disease[7]. Left: Actual device. Right: Diagram**

## In Closing

A robust modeling program is a key way to communicate progress and attributes of medical devices to a broad audience from financial stakeholders, marketing and sales teams, end users, and regulatory agencies. We have seen that all models have shortcomings and investigator must fully understand the strengths and weaknesses of the models they use. Regulatory agencies require that investigators verify and validate models to prove design robustness. The FDA is taking a more active role in providing guidance about use of computer simulations to evaluate safety and efficacy. A semi-hypothetical example showed us that verification and validation of a model could sometimes be a trial-and-error process. There is a wealth of knowledge on models used for medical devices that investigators can

[5] Dongeun, H; Matthews, BD; Mammoto, A; Montoya-Zavala, M; Hsin, HY; Ingber, DE; Reconstituting Organ-Level Lung Functions on a Chip, *Science*, 25Jun2010, **328**, pp. 1662-68.

[6] wyss.harvard.edu/viewpressrelease/36/living-breathing-human-lungonachip-a-potential-drugtesting-alternative

[7] www.medgadget.com/2012/11/biomimetic-microfluidic-device-reproduces-lung-function-to-study-disease.html

leverage for their particular applications. Experienced investigators can create new models for new devices. We briefly explored biomimetic devices that have a potentially great future to replace diseased organs, to simplify drug discovery, and to use for test models. While modeling can be expensive and time consuming, a well-run test and simulation program can add great value to the engineering, financing, user acceptance, and marketing of a medical device development effort.

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