University of Auckland

Department of Engineering Science

Part IV Project

Optimal Experimental Design for Understanding Burn Injuries

LITERATURE REVIEW AND STATEMENT OF RESEARCH INTENT

Author:
Marah Shahin

Supervisors:
Oliver Maclaren
Ruanui Nicholson
Vinod Suresh

October 30, 2020

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1 Background and Motivation

Skin is a multi layered organ with varying thermal properties. The structure of skin can be classified into three main sections, starting from the surface: the epidermis, dermis and hypodermis (fat). The thickness of each layer averages at 0.1 mm, ≤ 1 mm and 0.1 to several cm for the epidermis, dermis and hypodermis layers, respectively [1]. For simplicity, in the past, many attempts to study the properties of skin have adopted a one layer approach to capture the complex structure [2, 3, 4]. However, recent studies, more often than not have incorporated multiple layers in their models to more accurately classify the behaviour of skin [5, 6].

1.1 Burn Injuries

One parameter of interest, which varies across skin layers, is the thermal diffusivity. Still, the optimal experimental design for measuring such a property is yet to be established [5]. Whether the added complexity of a multi-dimensional and multi-layered model produces significant results is uncertain. In general these experiments typically mimic a burn to skin.

Burn injuries are ranked in four different degrees. A first-degree burn is considered the least severe, only affecting the skins epidermis, while a fourth-degree reaches past the skin, fat layer, muscle and bone [7]. Burns caused by heat are of the most common [8], thus are of the highest interest to investigate.
To enhance understanding of these conditions, experiments have been conducted using various attributes, such as the use of heated water, infrared lasers, porcine (pig) skin or phantom models [5, 6].

1.2 Inverse Problems

The objective of an inverse problem is to best determine parameters of a governing model where direct observation is not possible. A famous inverse problem is the measurement of the Newtonian gravitational constant, G. Although, G is one of the most fundamental values in physics and over 200 experiments have been conducted to observe the constant [9, 10], there is still uncertainty around the exact value [11]. This lack of precision highlights the complexity of inverse problems and their dependency on experimental methods. Consequently, experimental designs that have considered parameter inference are best suited for inverse problems and are critical for success.

The inverse problem posed in this project is the estimation of the thermal diffusivity from temperature measurements. The inverse problem is solved by repeatedly solving the forward problem until a *good* match between the temperature measurements (observables) and the corresponding model outputs is found, where model outputs are computed based on an input thermal diffusivity (parameter of interest). For example, unknown parameters can be estimated as a non-linear optimisation problem.
For inverse problems, however, there is no guarantee that the parameter that leads to the best fit to data is close to the true parameter. This can happen due to ill-posedness: lack of existence of a good solution (no parameter gives a good fit to the data), lack of uniqueness or *identifiability* (multiple parameters may give equivalent fits to data), and/or stability (small amounts of noise in the data can lead to very different parameter estimates) [12]. These issues can be analysed by considering inverse problems as statistical estimation problems, in which the uncertainty in estimates is also considered [12, 13]. However, to do so first requires a mathematical model of heat transfer (the forward problem, in this case). Methods for possible forward problems is discussed in Section 2.

1.3 Computational Experimental Design

Different experimental designs aimed at parameter inference for the same target parameter can lead to different levels of uncertainty in estimates, and can even lead to different conclusions [14]. The area of optimal experimental design [15, 16, 17] aims to determine the best choice of design and observation types for a given goal. This can be

considered an extension of inverse problems theory, where here some degree of choice exists in which experimental data to collect.

When working with an inverse problem, collecting specific types of data may be of more use than other types. For instance, a 2015 geothermal reservoir model study indicated that collecting data including injection pressure and matrix temperature yield lower uncertainties than others when estimating parameters [18]. Therefore, it is often more worthwhile to collect one type of data than another, particularly when inferring parameters.

2 Mathematical Modelling: The Forward Problem

Dym (2004) proposes that mathematical modeling can be condensed into a set of concepts formulated as questions on objectives and approaches to modeling. It is not a complete concept, nor a rigid method or formula, but instead a way of structuring and directing thoughts as the mathematical model is created. A diagram, found in Appendix A, shows ideas for developing clear forward and inverse models [19].

The general method for mathematically modelling burn injuries is the heat equation, originally developed by Joseph Fourier [20]. The parabolic heat equation in a one dimensional homogeneous medium is given by:

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2}, \tag{1}$$

where D is the thermal diffusivity of the medium [21]. Thermal diffusivity is a constant calculated from density, ρ, thermal conductivity, λ and the specific heat capacity, c where:

$$D = \frac{\lambda}{c\rho}. \tag{2}$$

To solve this partial differential equation (PDE), boundary and initial conditions must be specified, e.g. boundary conditions:

$$u\left(0,t\right) = 30, \qquad \frac{\partial u}{\partial x}\left(L,t\right) = 0, \tag{3}$$

initial condition:

$$u\left(x,0\right) = 0. \tag{4}$$

There are numerous applications for the heat equation in this context. A range of assumptions can be relaxed to introduce new terms or additional layers of skin. A common assumption experiments make is neglecting the heat loss to the blood supply, the blood perfusion. The heat flux condition specified at the boundary (i.e. equation 3) between the blood and skin often reflects this heat loss. In most studies, including Simpson (2018), this term is assumed to be insignificant [22, 5, 2]. Accounting for this thermal transfer adds a source term to the heat equation, thereby making it more complex. However, this decision to exclude blood perfusion could be detrimental to the results and thus, considered a limitation of the experiment.

2.1 Basic heat transfer models

Here, previously applied modelling approaches are presented.These are based on [5], which are discussed in more detail in the following section.

2.1.1 Heat Equation: Two Layers

$$\frac{\partial T_1}{\partial t} = D_1\frac{\partial^2 T_1}{\partial x^2}, \qquad 0 < x < l_1, \tag{5}$$

$$\frac{\partial T_2}{\partial t} = D_2\frac{\partial^2 T_2}{\partial x^2}, \qquad l_1 < x < l_2. \tag{6}$$

Separate boundary conditions need to be applied to each equation.
Boundary conditions:

$$T_1(0,t) = T_h, \qquad \frac{\partial T_2}{\partial x}(l_2,t) = 0. \tag{7}$$

Continuation condition:

$$T_1(0,t) = T_1(0,t), \qquad D_1\frac{\partial T_1}{\partial x}(l_1,t) = D_2\frac{\partial T_2}{\partial x}(l_1,t). \tag{8}$$

Initial condition:

$$T_1(x,0) = 0, \qquad 0 < x < l_1, \tag{9}$$

$$T_2(x,0) = 0, \qquad l_1 < x < l_2. \tag{10}$$

2.1.2 Heat Equation: Blood Perfusion

Including a blood perfusion term is illustrated as:

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} - k(T^*(x,t) - T_{ref}), \tag{11}$$

where k is the thermal loss rate to the blood and $T^*(x,t)$ is the temperature at location x and time t. The model assumes heat losses are equivalent to the difference between $T^*(x,t)$ and a reference temperature, T_{ref}.

2.1.3 Adapted Pennes Bio-heat-transfer Equation

An non-Fourier heat modelling approach is a combination of the Beer–Lambert law and the Pennes bio-heat-transfer equation:

$$\rho c\frac{\partial T}{\partial t} = \nabla\cdot(\lambda\nabla T) - \rho_b c_b \omega_b (T - T_b) + Q_r + Q_m, \tag{12}$$

where T is the medium temperature, Q_r is equal to the absorbed light intensity (study uses lasers), Q_m is the medium heat generation rate, b relates to properties of the blood and ω is the perfusion rate.
Here, three of the most relevant studies - which use the are considered in relation to their mathematical models and improvements.

2.2 Two-Layer, Simpsion (2018)

Simpson et al present a model of heat transport during burn injuries, and this forms the basis of much of our work. The experiment uses porcine skin as it is similar to human skin [23]. The mathematical model considers two layers: the fat layer and combined epidermis and dermis layers. This is modelled by the equations shown in Section 2.1.1. This experiment found there were issues identifying the diffusivity in the second layer. This was shown in their parameter profile, Figure 1, as a large space of viable options for this parameter. In this situation, a heat source is applied on one side, there's a continuation term and there is no transfer of heat on the other side. The heat flux condition is referred to as a Neumann condition whereas a Dirichlet boundary condition is one with direct temperature values [5].
It is noted that there is no perfusion term included and thus, a possible improvement. Other limitations of the study include: combining the two top layers of skin, dis-

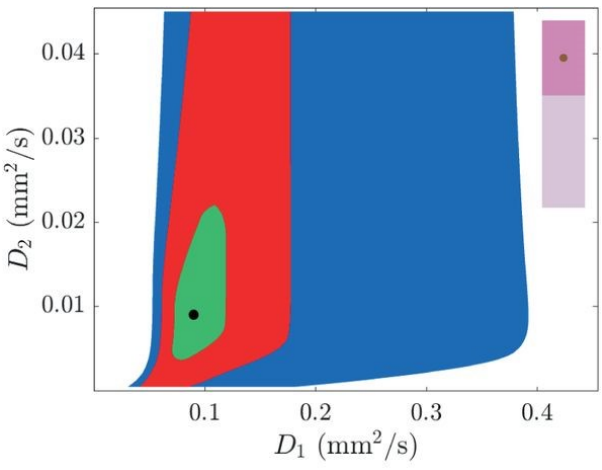

Figure 1: Viable parameter space for two diffusivity parameters.
Extracted from [5]

regarding experimental variability and use of known parameter estimates (uncertainty around *true* values of parameter).

2.3 One-layer, Simpsion (2017)

This model is similar to Simpsion's 2018 experiment in that it also used porcine skin and the heat equation to solve for parameters. However, the significant difference in this study includes the blood perfusion term. The heat equation for this model is given in Section 2.1.2.

The study concluded that the addition of this term did not make a substantial difference [4]. Though, the goal of this experiment was not to explicitly decide if it's best to include the blood perfusion term so the topic remains ambiguous. The model also uses a one layer approach with a thin layer of skin and does not measure temperature across the skin. Instead the model uses a depth average equation to simplify the heat equation [4].

2.4 Three-layer, Cho et al. (2018)

This study uses the Beer–Lambert law and the Pennes bio-heat-transfer equation combined rather than the heat equation for a three layered agar gel model. The equation is given in Section 2.1.3.
The assumption was made that the relationship between heat generated, Q, and gel depth was decreasing exponentially. Additionally, the study aimed to measure only one set of parameters from the known thermal and optical properties whereas in practical applications this may be unrealistic [6].

3 Solving the Heat Equation

There are various methods to solve the PDE. Where differential equations cannot be solved, such as the heat equation or e.g. $\frac{dy}{dx} = y\cos(ye^{-y}) - \tan^{-1}(xy)$, one can only approximate the solution using numerical solutions. The solution however, will always be prone to some scale of error (as it is an approximation).

3.1 Finite Differences

Finite differences solves the PDE by approximating the equation using Taylor series. Implicit or explicit schemes can be derived from the approximation. Each method has its respective trade offs. Explicit methods are easier to implement and come at a lower computational cost compared to implicit methods. Although, explicit methods have conditionally stability, meaning the solution may not converge, whereas implicit methods do not. Overall, it isn't clear which method would be fitting in every situation. Each method should be examined and used based on the specific problem.

3.2 Finite Element Method

The finite element method (FEM) was considered as it is able to handle complex skin properties such as blood perfusion, its inhomogeneous structure, multiple spatial dimensions (if considered in the FEM formulation) and time-varying and/or Neumann boundary conditions with ease. FEM's unique method allows complex, unconventional or irregular geometries to be analysed accurately and without difficulty [24]. Generally, in this case, FEM is implemented to reduce the heat equation to an easily solvable system of equations [25]. Employing FEM to solve the forward problem would allow flexibility when simplifying model assumptions made - these can be relaxed or reinstated without drastic changes to the solver. Hence, due to the methods robustness, FEM was considered the most promising method of solving this project's forward problem.

4 Experimental Design and Measurement

This project involves both collecting real data and using computational methods to design experiments. These are briefly reviewed next.

4.1 Experimental Measurements

A parallel project carried out by [26] reviews the experimental literature in detail. In particular, both direct measurements of the constituent properties making up D, as shown in Equation 2, as well as temperature measurements to be used for solving the inverse problem, can be collected. Numerous studies aimed at direct calculation have been carried out as well as studies aimed at solving the inverse problem [5]. It is clear these values vary a great deal both in location of skin and between people. Table 1 (in Appendix B) shows the ranges of the thermal properties observed in various experiments.

4.2 Computational Framework for Experimental Design

Finding the optimal experimental design (OED) first means first being able to determine the "good" experiments from the "bad". One way to differentiate between the two is by computing the model or estimator covariance matrix and some scalar measure of this such as its determinant or trace. This value reflects the quality of the experimental design by quantifying the uncertainty of parameter estimates. [27].
A closely related quantity is the Fisher information matrix (FIM), which is essentially the inverse of the parameter estimate covariance matrix [28]. The FIM again allows quantification of the precision and variability of parameter estimates and hence can be used to quantify design performance [29].
Using the FIM, studies have confirmed the results of an OED are more accurate than other designs trialed [30, 31]. Other studies combine prior parameter information to reduce the pool of reasonable experiments to a set of superior experiments. These yield results that sit within close proximity of the prior and by using the FIM the optimal of these can also be found [32, 33]. Methods based on the parameter estimate covariance matrix or the Fisher information matrix are essentially linear approximations to uncertainty analysis. This can lead to difficulties in the poorly-identified case. Nonlinear uncertainty analysis can be carried out by computing a full likelihood function or a Bayesian posterior, depending on the inferential framework adopted, rather than just the implied Gaussian approximation associated with covariance-based methods. A recent example of estimation and design analysis for partial differential equation models in biology demonstrates how to carry out nonlinear analysis from both frequentist and Bayesian perspectives, using profile likelihood and Markov chain Monte Carlo (MCMC) methods, respectively [34]. Profile likelihood methods were shown to be reliable in the presence of poor identifiability, as well as much faster than MCMC. We discuss methods for computing uncertainties further below, in the context of inverse problems.

5 Solving as an Inverse Problem

To determine a point estimate of parameters, inverse modelling uses a numerical method of model calibration. Model calibration seeks to find the parameter, ϕ, value by minimising some objective function, $S(\phi)$, for the observations. Some optimisation methods may be better suited than other depending on the situation.

5.1 Least Squares

One of the most popular methods used for $S(\phi)$ is the least squares function [35]. For a given set of parameter values and model, $f(x;\phi)$ the prediction of the model is $y_i = f(x_i;\phi)$. However, this prediction will be wrong and

thus, the misfit is $\bar{y_i} - y_i$. Minimising the sum of these attempts to improve the model:

$$S(\phi) = \sum_{i=1}^{N} (\bar{y_i} - y_i)^2, \tag{13}$$

where N is the number of points. A weighted alternative can be implemented to add emphasis to points of interest. This places higher importance on some areas of the model over others. This is useful when areas are known to be associated with more uncertainty or if it is preferred the model fits one type of observation over others. The weighted sum of squares is given as:

$$S(\phi) = \sum_{i=1}^{N} w_i (\bar{y_i} - f(x_i; \phi))^2, \tag{14}$$

where w_i is the weight given to its corresponding observation $f(x_i; \phi)$. By modifying the parameter(s), ϕ, the model can be improved or worsened and is shown through the variation of the objective function, $S(\phi)$. Calibration methods are implemented to find the optimal parameter values that minimise the objective value.

5.2 Optimisation Methods

5.2.1 Gradient Descent

Gradient descent a widely known method but is currently seldom used due to its drawbacks and many recent advanced methods. The algorithm however, is profoundly simple in that, it can be seen as the basis for a great deal of optimisation algorithms. This method works in the following steps [36]:

1. Pick an initial guess, ϕ_0 of the parameter set.
2. Calculate the direction of steepest descent from ϕ_0.
3. Update estimate of the parameter that minimises the objective function, ϕ_{min}, by moving a step in the direction computed in step 2.
4. Repeat steps 2 and 3 to improve the estimate of ϕ_{min}. Given the step size taken in step 3 is small enough, each iteration will give a better objective function than the previous.

Metaheuristics are now more commonly used. These algorithms, at their core, follow that above but have an aspect of randomness. The methods take an unrelated step every now and then to improve the likelihood of landing at a global optimum rather than a local. If run long enough, a few techniques (e.g. simulated annealing) are guaranteed to reach the optimal solution. Otherwise, these methods still find a *good* solution in much less time and computational effort. There is also a python library available for metaheuristics ready for use [37].

5.3 Uncertainty

It is usually desirable to provide an interval or some other measure of uncertainty, rather than simply provide a single point estimate. This is specifically useful for inverse problems and experimental design, as the parameter values are usually *uncertain*. Either frequentist or Bayesian approaches can be adopted; these are compared and reviewed in [13]. We largely take a frequentist approach here, where we use either estimator covariance matrices or likelihood functions to measure uncertainty and construct confidence intervals.

5.3.1 Parameter Uncertainty

Optimisation methods often require a initial guess to start off the search. When this guess is based on literature or personal expert knowledge, it is referred to as the *prior information*. Prior information can be used in both frequentist and Bayesian statistical frameworks, though a prior in Bayesian terms specifically refers to a probability distribution expressing expert information about the value of a parameter. In a frequentist or classical setting prior

information can also be incorporated in the form of constraints or plausible starting guesses for optimisation [38]. Inference is then typically based on the so-called likelihood function [39], discussed further below. Post-calibration, the result of a Bayesian analysis is a distribution referred to as the *posterior*. This distribution is a combination of the prior knowledge and relevant observations, where the latter enter through the likelihood contribution.

If the parameters are completely unknown (i.e. there is no expert knowledge or relevant literature [40]) then frequentist and Bayesian approaches typically give the same result, both being based essentially on the likelihood function only [39]. In the present context this is given by:

$$\mathcal{L}(\phi|y^0) = e^{-\frac{1}{2\sigma^2}\left((y(\phi)-y^0)^2-(y(\hat{\phi})-y^0)^2\right)}. \tag{15}$$

In particular, the posterior is proportional to the likelihood when a uniform prior is used. Frequentist confidence intervals can be formed by including all values above some threshold relative likelihood value, where this is typically calibrated via an approximate chi-squared sampling distribution [39]. Gaussian approximations to the likelihood (in terms of the parameter) lead to the covariance/Fisher-information-based methods discussed above in the context of optimal experimental design.

5.3.2 Parameter Sensitivity

Sensitivity analysis is closely related to uncertainty analysis and can help improve the validity of the model design (see Appendix A, "Valid?" question). A high sensitivity indicates good parameter estimation; Figure 2 shows the relation between identifiability, uncertainty and sensitivity.

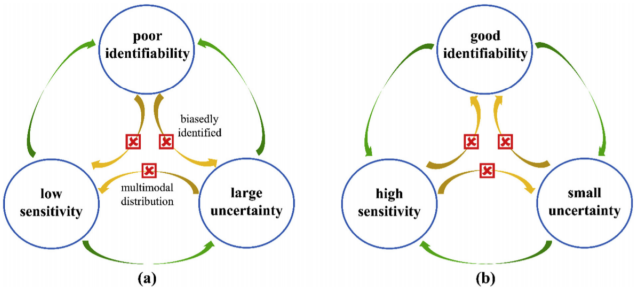

Figure 2: Relation between identifiability, uncertainty and sensitivity
Extracted from [41].

The concept of sensitivity addresses how large the output change in relation to a unit change in a parameter, $\frac{\partial y_i}{\partial \phi_j}$, where y is the ith output and ϕ is the jth parameter, corresponding to the $ijth$ item in the Jacobian matrix, J_{ij}. Where the model is expressed numerically, so are the sensitivities. Therefore:

$$J_{ij} f(x_i; \phi + \Delta\phi_j \epsilon_j) = \frac{-f(x_i;\phi)}{\Delta\phi_j}, \tag{16}$$

where ϵ_j is the unit vector, with direction ϕ_j, in parameter space. For fixed i and N parameters, N sensitivities can be calculated in $N+1$ model runs since $f(x_i;\phi)$ is constant across all J_{ij}. Parameter sensitivities can also be used to further understand the underlying physics of the model. The most sensitive parameters can be compared against the least once the model has been properly implemented.
Parameter sensitivity can also be in relation to the objective function, i.e. $\frac{\partial S}{\partial \phi_j}$. This is particularly useful for model calibration. A known single parameter can be adjusted rather than refining the lump of parameters. For instance, the estimate for density alone can change rather than thermal diffusivity - if this is what the sensitivities dictate. Sensitivity analysis and uncertainty analysis can be directly connected, where the sensitivities form a key input into linear uncertainty analysis [12].

6 Solving The Design Problem

As discussed above, optimal experimental design seeks to develop the complex experiments that provide complete information content for the detection, estimation and discrimination of subsequent nonlinear model. Furthermore, we can solve the design problem by treating it as an extension of the inverse problem discussed above, in which there is some degree of choice in which data to collect. Thus the same basic methods discussed above can be used, after which uncertainties can be compared for different designs, either quantitatively or qualitative. A useful methods of comparison for linear uncertainty includes plotting experiment variances on the same set of axis [42]. This gives a visualisation on the average deviations each experiment observes; a factor to consider for determining the optimal experimental design. In more complex problems, full likelihood functions or posterior distributions may be required, in which case methods such as those discussed by [34] can be used.

7 Statement of Research Intent

This project investigates the optimal experimental design for measuring thermal proprieties in the layers of skin. The project's mian goal is to computationally and mathematically investigate various experimental designs which use phantom models for determining diffusitivity parameters from temperature measurements. This will be accomplished via the following associated goals:

1. Build a numerical PDE solver capable of solving both the basic model as well as being easily extendable to more complex cases (e.g. blood perfusion, inhomogeneous structure, multiple spatial dimensions, time-varying boundary conditions, etc)

2. Implement numerical methods for basic parameter estimation using nonlinear optimisation for fitting the forward model to data

3. Compare various experimental designs by analysing uncertainty, applicability, parameter identifiability and complexity.

4. Provide a basis for future work regarding useful mathematical models and uncertainty quantification techniques

This key purpose will be accomplished by two sub-projects working in parallel. One project will be completed by my project partner, Anthony Zemke. This sub-project will focus on developing a mimic of human skin based on varying gel concentrations and known thermal properties. Then the parallel experimental project will focus on various experimental designs. Some of these designs have been previously implemented, others may be new. The project will produce a number of distinct phantom tissues that will be mathematically modelled by the second sub-project.

The other project will be completed by myself. This project will apply appropriate mathematical models to the skin models produced in the first sub-project. The computational models will be written in python using suitable numerical solvers. The first model will be a 1D, one layer model solved using an explicit finite difference scheme and checked against a validated solution. Later models will adopt a finite element method to solve the model due to the robustness of the solver.
The mathematical model will then attempt to estimate the known thermal diffusivity from the model using optimisation techniques. Since the true value is known, the parameter value accuracy of each model will be known. Thus, this, in conjunction with uncertainty analysis, will indicate which design gives the most accurate parameter estimates.
Building on the Simpson (2018) study, the model will incorporate experimental variability through a comprehensive uncertainty quantification.

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Appendices

A Modelling Design

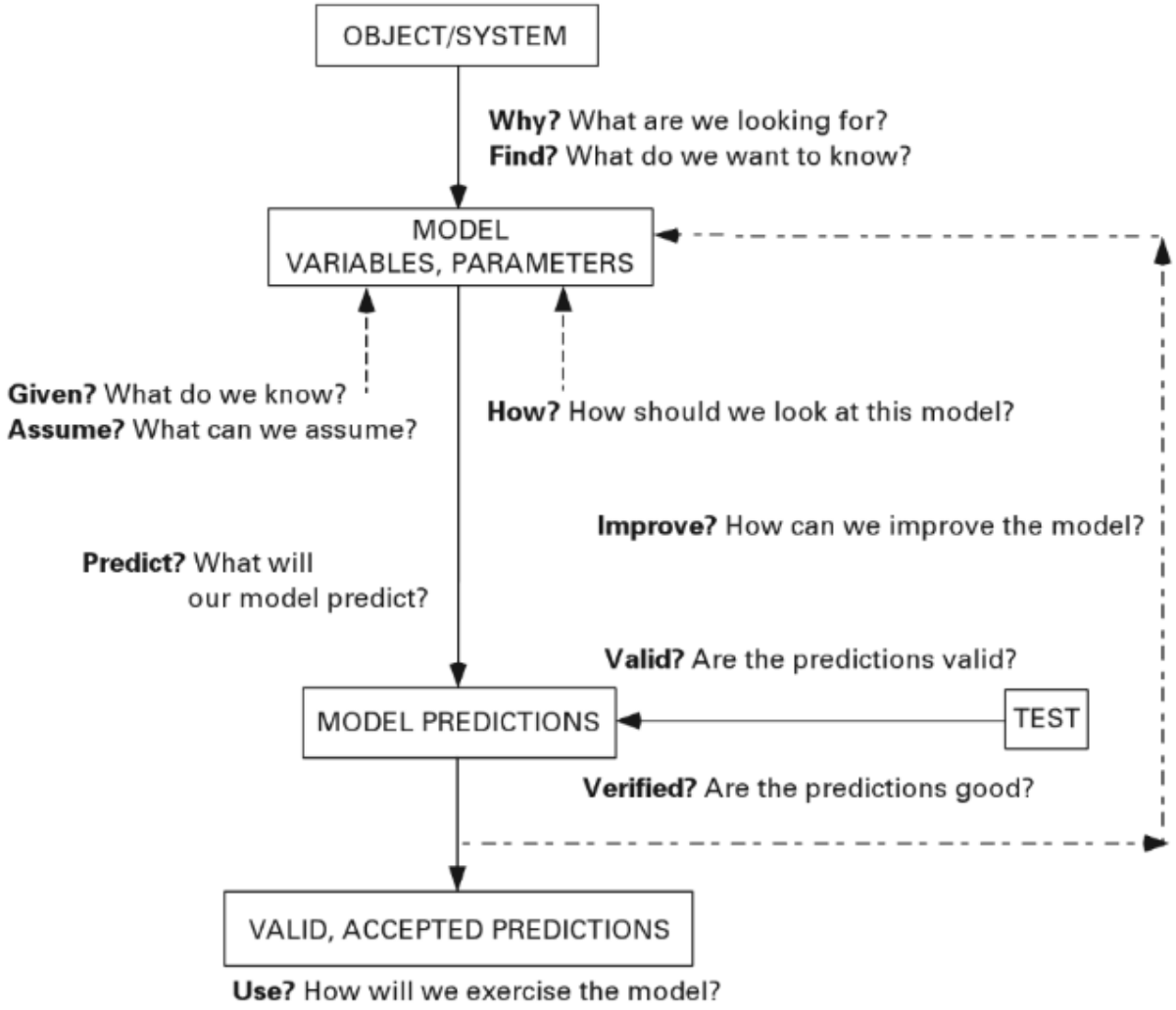

Figure 3: Ten questions for modelling design
Extracted from [19].

B Thermal Properties of Skin

Property	Units	Value Range
Specific Heat	J/kg • °C	
a) epidermis		3578 - 3600
b) dermis		3200 - 3400
c) sub-cutaneous		2288 - 3060
d) blood		3770
blood perfusion rate	$m^3/s/m^3$ tissue	
a) epidermis		0
b) dermis		0.00125
c) sub-cutaneous		0.00125
Thermal conductivity	W/m • °C	
a) epidermis		0.21 - 0.26
b) dermis		0.37 - 0.52
c) sub-cutaneous		0.16 - 0.21
d) single layer		
in vivo		0.48 - 2.8
in vitro		0.21 - 0.41
Thickness	m	
a) epidermis		80×10^{-6}
b) dermis		0.00200
c) sub-cutaneous		0.010
Body core temperature	°C	37
Body surface temperature	°C	32.5
Density	kg/m^3	
a) epidermis		1200
b) dermis		1200
c) sub-cutaneous		1000
d) blood		1060

Table 1: Ranges of skin layer thermal properties
Extracted from [43]. Further references include: [44, 45, 46, 47, 48, 49, 50]