

PhD in Computer Science

Research line: Artificial Intelligence

Research Plan for the PhD Thesis:

Improving Simulation Model Calibration for Cost-Effectiveness Analysis via Bayesian Methods

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Abstract

The use of mathematical simulation models of diseases in economic evaluation is an essential and common tool in medicine aimed at guiding decision-making in health. Cost-effectiveness analyses are a type of economic evaluation that assess the balance between health benefits and the economic sustainability of different health interventions. One critical aspect of these models is the accurate representation of the disease’s natural history, which requires a set of parameters such as probabilities and disease burden rates. Most of these parameters are obtained from scientific literature or expert consensus, but they often need calibration to fit the model’s expected outcomes, such as disease incidence or mortality in a specific context. However, the calibration process can be computationally expensive and traditional optimization methods can be time-consuming due to relatively simple heuristics that may not even guarantee feasible solutions.

In this thesis, we investigate the use of Bayesian optimization to enhance the calibration process by leveraging domain-specific knowledge and exploiting inherent structural properties in the solution space. Specifically, we examine the effect of additive kernel decomposition and constraint handling for efficient search. Our preliminary results show that this enhanced Bayesian optimization procedure leads to faster convergence and better solutions for larger models, improving the calibration process asymptotically.

Keywords: Cost-effectiveness analysis (CEA), simulation modelling, optimization, Bayesian optimization, constrained optimization, gaussian processes, additive decomposition, artificial intelligence

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# Introduction

Cost-effectiveness analysis (CEA) is a widely used approach to evaluate alternative medical strategies and guide decision-makers towards more efficient healthcare practices. CEA relies on simulation models that mimic the progression of a disease of thousands or millions of individuals transitioning through different health states. The aggregated effect of the cohort then calculated in terms of costs and benefits, allowing comparisons between different health interventions. These transitions occur because of various events such as disease development, medical procedures, and treatments. Simulation models for CEA (from now on CEA models), which include decision trees, Markov models, microsimulation models, dynamic transmission models, and other methodologies, provide outputs that encompass measures of effectiveness and cost. Additional computable outputs of interest can also be obtained based on the specific objectives of the analysis.

These simulated health strategies are parameterized by values obtained from scientific literature or expert opinions. These parameters include probabilities (e.g., probability of getting the disease), rates (e.g., recurrence rates), costs (e.g., treatment expenses) or utility values (e.g., utility of the disease health state), among others. Accurately identifying these parameters is essential before simulating the strategies and drawing reliable conclusions. However, these models are simplifications and abstractions of reality, and parameters are uncertain, therefore the outputs may not perfectly match the observed or expected data. To ensure the accuracy and reliability of simulation models, calibration becomes crucial. During calibration, the model parameters are adjusted to minimize the discrepancy between the model's outputs and the real-world data. This iterative process involves comparing the simulated results with actual data, making adjustments to the model inputs or parameters, and running the simulation again to assess the updated outputs. The goal is to find the combination of parameter values that best reproduces the observed behavior or meets the desired criteria. The calibration procedure can be seen as an optimization problem, which, due to its high dimensionality and other characteristics, can be a challenging problem for conventional methods such as Nelder-Mead or Simulated Annealing. In some cases, a single calibration can take weeks of computational time.

To illustrate, we will consider a study focusing on the cost-effectiveness analysis of lung cancer preventive strategies at a population level [1]. The study examines the health and economic implications of single and combined primary (brief and intensive smoking cessation) and secondary (screening) preventive strategies for lung cancer, , considering factors such as age, frequency, and coverage. The findings indicate that an intensive smoking cessation intervention at ages 35, 40 and 45, combined with screening every three years between the ages of 55 and 65, represents the most cost-effective strategy compared to no intervention. However, prior to obtaining these results, the model underwent iterative calibration processes to address occasional discrepancies between the calibrated parameters and medical evidence, such as a decreasing probability of dying as the cancer progresses. These iterative calibrations demanded considerable computational and human resources.

Therefore, in this work we propose innovative approaches for calibrating cost-effectiveness models, aiming to achieve improved models with enhanced efficiency and flexibility.

# Research Objectives

The aim of this thesis is to investigate and apply novel methodologies to enhance the calibration of cost-effectiveness models. The potential improvements encompass various aspects, and to accomplish the overarching goal, we need to fulfill the following objectives:

* **Exploration and analysis of the solution spaces of cost-effectiveness models**

While exploring optimization methodology, we first need to explore the cost-effectiveness models that we are trying to optimize and their behavior in order to identify which structural patterns in their solution space we can exploit. By analyzing different CEA models, we can detect similarities and shared behaviors that we could integrate in the optimization process.

* **Exploration and development of novel optimization methods**

The final goal is finding a method that allows a cost-effectiveness analyst to calibrate a model as efficiently as possible. Although the objective should be focused on CEA models, the application for more general problems can be considered as well.

* **Tests and comparison of optimization methods**

The results of the methods explored in the previous objective must be assessed and compared to the conventional methods used for the same purpose. Different aspects should be evaluated, such as execution time, number of function evaluations, or interpretability, possibly among others. As mentioned before, it could be interesting to evaluate the performance of this method on other problems beyond cost-effectiveness analysis.

# State of the art

Current calibration procedures in CEA models commonly rely on manual trial-and-error or simple methods such as Nelder-Mead or Controlled Random Search (CRS) [2]. However, due to the intricate relationships among the model parameters, finding a set of values that align with domain knowledge can pose challenges.

These classical methods use simple heuristics to find global optima, but other alternatives provide a more sophisticated and flexible approach. Sequential Model-Based Optimization (SMBO) is a state-of-the-art methodology used to optimize expensive functions, with success in areas such as hyperparameter tuning in machine learning [3]. As the name implies, SMBO uses a surrogate model to guide the optimization process using principled inference steps to be more efficient and minimize the number of evaluations of the target function.A popular choice for a surrogate model is a Gaussian Process [4]. These non-parametric regression models allow great flexibility by specifying a kernel function that determines their expressiveness [5], and they can be used to take advantage of the properties of the kind of functions that we want to optimize.

There are diverse ways in the literature to add constraints in Gaussian processes [6][7], usually by modelling the constraints in a separate model and integrating this knowledge in the overall inference step. Similarly, usual complications arising in optimization problems due to high dimensionality can be mitigated using techniques such as additive kernels [8][9], input prior specification [10], dimensionality reduction [11] or matrix factorization [12], among others [13].

As mentioned before, SMBO is generally applied to expensive functions due to the method's significant overhead while doing the inference step in each iteration. To reduce the impact of this overhead and enable the reasonable use of this method in less expensive functions other techniques have been developed: batch learning [14][15], parallelization [16] or GPU-friendly approaches [17][18], for example.

Among all these techniques, the initial focus will be on implementing Gaussian Processes with Orthogonal Additive Kernels suitable to our specific problem. This will involve integrating constraint support through auxiliary surrogate models within the inference process. Firstly, as demonstrated/shown by Duvenaud et al, additive kernels offer enhanced efficiency in identifying patterns within high-dimensional problems, similar to the one under consideration in this project. Furthermore, as mentioned in the introduction, our problems often entail significant constraints that can pose challenges for conventional methods primarily focused on eliminating invalid solutions. Nevertheless, the SMBO method can be substantially improved by leveraging these constraints and guiding the process toward optimal and valid solutions.

# Research methodology and work plan

* 1. **Research methodology**
* **Literature review**

Initially, an extensive literature review will be carried out encompassing mathematics, statistics, and computer science to explore optimization techniques for black box functions. This comprehensive review will specifically target methods and strategies aligned with the nature of CEA models requiring optimization, considering their unique characteristics and requirements.

* **Analysis**

Prior to undertaking extensive development and testing, preliminary analysis of the CEA models will be performed to assess the suitability of the researched methods for our specific problem. This analysis may also provide valuable insights for refining search terms in a subsequent literature review.

* **Design and development**

Following the review and analysis of the CEA models, our plan entails adapting the identified methods to our specific problem and implementing a solution capable of generating conclusive results.

* **Evaluation**

Upon obtaining results, a comprehensive evaluation and comparison can be conducted, assessing them against various alternatives or conventional methods.

* **Dissemination**

This work is planned to be published in prominent journals focusing on artificial intelligence (for technical contributions) and healthcare indexed journals (for solution contributions), based on the relevance of the results within each respective field. A preliminary list of potential publication ideas is as follows:

1. Bayesian Optimization method for high-dimensional and highly constrained cost-effectiveness models
2. Application of previous method in a cost-effectiveness analysis situation
3. Comparison between different calibrated values and its impact on the cost-effectiveness result

In addition, seminars such as the annual IIIA Doctoral Consortiums, and conferences will be used to further disseminate the findings of this work.

* 1. **Work plan**

This project will be developed through a series of iterative sprints, each spanning four months. Each sprint will begin with a comprehensive literature review, followed by an analysis phase to assess the applicability of the identified strategies to our models. Subsequently, the selected strategy will be implemented during the design and development phase. Lastly, the outcomes will be added into a comprehensive compilation of results for evaluation. Throughout these stages, meticulous documentation will be maintained to facilitate the writing process of writing during the final dissemination stage.

The expected duration of the project is four years. The plan for each year is as follows:

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **TASK** | **MONTH** | | | | | | | | | | | | |
| Development of calibration using Bayesian optimization | YEAR | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 |
| 1st year |  |  |  |  |  |  |  |  |  |  |  |  |
| 2nd |  |  |  |  |  |  |  |  |  |  |  |  |
| 3rd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 4th year |  |  |  |  |  |  |  |  |  |  |  |  |
| Implementation of Orthogonal Additive Kernels | YEAR | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 |
| 1st year |  |  |  |  |  |  |  |  |  |  |  |  |
| 2nd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 3rd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 4th year |  |  |  |  |  |  |  |  |  |  |  |  |
| Implementation of constraints in Bayesian Optimization | YEAR | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 |
| 1st year |  |  |  |  |  |  |  |  |  |  |  |  |
| 2nd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 3rd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 4th year |  |  |  |  |  |  |  |  |  |  |  |  |
| Test and validation of calibration on simplified lung model | YEAR | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 |
| 1st year |  |  |  |  |  |  |  |  |  |  |  |  |
| 2nd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 3rd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 4th year |  |  |  |  |  |  |  |  |  |  |  |  |
| Test and validation of calibration on endometrium model | YEAR | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 |
| 1st year |  |  |  |  |  |  |  |  |  |  |  |  |
| 2nd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 3rd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 4th year |  |  |  |  |  |  |  |  |  |  |  |  |
| Test and validation of calibration on external model | YEAR | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 |
| 1st year |  |  |  |  |  |  |  |  |  |  |  |  |
| 2nd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 3rd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 4th year |  |  |  |  |  |  |  |  |  |  |  |  |
| Conference submissions and presentations | YEAR | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 |
| 1st year |  |  |  |  |  |  |  |  |  |  |  |  |
| 2nd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 3rd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 4th year |  |  |  |  |  |  |  |  |  |  |  |  |
| Manuscript submissions and publications | YEAR | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 |
| 1st year |  |  |  |  |  |  |  |  |  |  |  |  |
| 2nd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 3rd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 4th year |  |  |  |  |  |  |  |  |  |  |  |  |
| Thesis writing and defense | YEAR | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 |
| 1st year |  |  |  |  |  |  |  |  |  |  |  |  |
| 2nd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 3rd year |  |  |  |  |  |  |  |  |  |  |  |  |
| 4th year |  |  |  |  |  |  |  |  |  |  |  |  |

* + 1. **Detailed work plan for the current academic course (2023-2024)**

During the current academic year, the sprints will focus specific aspects outlined in the previous section. The initial eight months will be focused on identifying, implementing, and testing efficient methods for constraint handling within the previously developed Bayesian Optimization method. Two reference models will be used as calibration benchmarks: a published endometrial cancer model[19], whose calibration is more complex than the lung cancer model used in the first year, and an external reference model yet to be determined. The results of the first year will be presented at 2023 CCIA, while the progress of the second year will be presented at the 2024 IIIA Doctoral Consortium.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **TASK** | **MONTH** | | | | | | | | | | | |
| M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 |
| Development of calibration using Bayesian optimization |  |  |  |  |  |  |  |  |  |  |  |  |
| Implementation of constraints in Bayesian Optimization |  |  |  |  |  |  |  |  |  |  |  |  |
| Test and validation of calibration on endometrium model |  |  |  |  |  |  |  |  |  |  |  |  |
| Test and validation of calibration on external model |  |  |  |  |  |  |  |  |  |  |  |  |
| CCIA & CSIC seminar presentations |  |  |  |  |  |  |  |  |  |  |  |  |

1. **Conclusions**

We have outlined the general research plan for the first academic year. Since the scope of this work involves a healthcare perspective, other concerns besides purely computer science criteria have to be considered, so unexpected modifications to this plan may occur.

As a summary, the objective of this thesis consists in an efficient way to calibrate CEA models while considering and taking advantage of knowledge from a healthcare domain. This endeavour will prove useful for healthcare professionals in the development of new medical strategies to improve the quality of life of the population in an economically sustainable basis.

# Conferences

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