Background

One of the main goals of biomedical research is improving the quality of life and extending the life expectancy of the population by developing new medical advancements such as medicines, medical procedures, or other novel medical interventions. However, budgetary constraints in the different health systems mean that not all available interventions can be included in healthcare plans. Health economics models, and specifically cost-effectiveness analysis, can help to assess both the health and economic impact of these interventions to inform decision makers what strategies are cost-effective and could be included in healthcare plans.

Many cost-effectiveness analyses (CEA) in healthcare use simulation models that mimic a disease process to evaluate the aggregate effects of thousands or millions of individuals participating in different intervention strategies. These simulations can be implemented using different types of models depending on the strategy complexity, including decision trees, Markov models or microsimulation models, among others. Irrespective of the type of model chosen, the two crucial outputs of simulation models to evaluate the cost-effectiveness of different strategies are the estimates of lifetime costs (in currency units) and effectiveness usually expressed as quality-adjusted life years (QALYs). The incremental cost-effectiveness ratio (ICER), which represents the economic value of an intervention compared with an alternative, has become a popular methodology in CEA to summarize the cost-effectiveness of a health care intervention. An ICER is calculated by dividing the difference in costs (incremental cost, ∆C) by the difference in the health benefit (incremental effect, ∆E) to provide the ratio of “extra cost per extra unit of health effect” for the more expensive intervention versus the alternative. Interventions are usually considered cost-effective if the ICER lies below a cost-effectiveness threshold that represents the Willingness To Pay (WTP) of a specific country or region for the life expectancy improvement.

Simulation models consist of several components such as system entities, input variables, performance measures, and functional relationships. Generally, the knowledge of these components is extracted from the scientific literature or expert consensus using values such as probabilities, rates, ratios, or costs. Often, these values are only approximations of the needed parameter due to model assumptions or lack of data availability that add uncertainty to the model that will later be reflected in the simulations in an uncertain way. Sensitivity analysis (SA) are usually performed to test the robustness of the models against uncertainty and to evaluate the impact of slight parameter variations in the results. SA can be deterministic (DSA) if parameter values are manually changed from a pre-specified range or probabilistic (PSA) if they are sampled from statistical distributions. In univariate sensitivity analysis one parameter is varied at a time, whilst in multivariate sensitivity analysis more than one parameter is varied simultaneously. Despite its limitations, univariate SA can be useful to see the marginal contribution of single parameters to the results. However, multivariate SA allows exploring parameter interactions and is of particular interest when the parameters are highly correlated, such as sensitivity and specificity of diagnostic tests or utility of pre- and post-progression health states.

PROject AIM

The final execution time for all these simulations, especially during a SA, can quickly grow and lead to a combinatorial explosion. For example, a single model execution might require the simulation of thousands of individuals, each execution might have to be replicated thousands of times for a single SA and this process might have to be repeated for a hundred different subsets of parameters. of parameters computationallyThe efficient identification of parameter subsets of special interest in a single multivariate SA would be a very useful tool in the evaluation of these models.

Usually, subsets are defined with previously identified parameters in univariate analyses, but this subset can leave out parameters that could be influential in interaction with others already included or it could include some parameters that would be dispensable when correlating with others. Small, meaningful, and cohesive subsets are preferable for interpretation purposes.

Therefore, SA can quickly become unwieldy given the potential number of combinations of parameter values to test concurrently, this along with the relative complexity of the model and the number of simulated individuals. At the same time, this kind of analysis implicitly generates comprehensive datasets, of at least several dozens of variables including inputs and outputs. These datasets are often underutilized in current CEA usual practices, which focus mostly just in ∆C and ∆E. Artificial Intelligence (AI) and Explainable AI (XAI) techniques can leverage all this data to help researchers understand the impact of the different parameters in different ways and identify the subset of them that would actually have a large influence on the results. Different ideas to contribute to CEA modeling in this manner are outlined next.

1. A possibility to handle the mentioned parameter subset selection is the use of artificial neural networks (ANNs). Using a single hidden layer, proper training and ensuring an adequate fit to the simulation model, the fitted network parameters could give us insight into promising subsets. More hidden layers could detect more complex hierarchical relationships. but at the cost of a more difficult interpretation.
2. Another useful tool would be the generation of causal diagrams representing the model using directed acyclic graphs (DAG), with the addition of intermediate outputs of interest generated by the model (e.g. observed incidence, observed mortality, number of unnecessary treatments, ...). These diagrams would show the causal relationship between the inputs, outputs and these intermediate variables. These relationships could lead us to unexpected but true causal effects, confirm expected relationships or point out possible mistakes, either within the model implementation or its conceptualization.
3. An additional recurrent problem in SA happens when some values for a small subset of parameters have an extreme effect on the results. Once these outliers are identified, a further step would be to discover why these sets of parameters are so different from the rest of simulations using XAI techniques such as LIME.