Appendix D: Constrained Optimization Modeling

Introduction

Constrained optimization (CO) modeling has been applied for over 100 years. It was initially used to improve work efficiency in various industrial settings. It is currently applied in healthcare for very diverse purposes, including for capacity management, clinical decision making, and optimal allocation of resources (Crown et al., 2017).

The focus in this appendix is on using CO modeling to determine whether new vaccination programs are cost-efficient which means obtaining the best outcome for the limited resources/cost available. The model therefore provides information on how to optimize health outcomes with the different intervention options and the different constraints, the latter mainly on budget and logistics. CO is used to derive the optimal levels of each available intervention to be selected.

Papers on the use of CO for decisions about communicable disease programs were first published in the 1970s (Sanders, 1971; Sethi, 1974) and for allocating healthcare resources across all diseases by the end of the 1990s (Stinnett et al., 1996; Petrou et al., 2000). These methods were used when the budget, intervention types, and the desired outcomes for specific health and healthcare domains like diabetes, AIDS, cancer, for instance, could be clearly delineated.

For CO, a distinction must be made between model construction and the analysis method used to evaluate the model.

The basis for the model construction is mathematical programming that assembles different components (variables) among which relationships are found. These relationships are expressed as mathematical equations that quantify the problem through input and output variables and the parameter values selected. The results of the model (the output) can be validated using observational data to test the accuracy of the model construct. Four elements are needed to develop the mathematical construct:

1. The objective to be optimized must be presented as a maximization or minimization value of an output variable.
2. The decision variables selected must influence the value of the output variable.
3. The objective function (relationship between the decision variables and the objective) must comply with a set of constraints, such as budget limits, logistic constraints, or both.
4. A list of parameter values must quantify the relationship between the decision variables and the objective and constraints.

Regarding the analysis method for CO, the simplex method is one of the most commonly used in very diverse industries, such as agriculture, forest management, fisheries, information technology, and healthcare (Dixit, 1990; Buongiorno et al., 2003). It should, however, be noted that many optimizing real world problems may be too complex to use the simplex method. Some examples of the more complex models include having multiple objectives instead of one, consideration of a very large number of decision variables, with many constraints, or having a nonlinear relationship between the decision variables and the objective or objectives and constraints that vary over time. Because those more advanced problems, where linear functions cannot be derived for all the relationships in the mathematical model, cannot be solved with the simplex methods, heuristic methods (neural networks, genetic algorithms, simulated annealing, etc) are then used. With today's computing power, new software to search for the best allocations to these problems exists. However, problems can grow in size such that solving is computationally very exhaustive. Consultation with experts is an absolute prerequisite before engaging in such analysis methods.

A good general reference is *Optimization Modeling: A Practical Approach* (Sarker and Newton 2008). A recently published overview on the application of CO in healthcare has been prepared by the International Society for Pharmacoeconomics and Outcomes Research Task Force on Constrained Optimization Methods (Crown et al., 2017).

CO has also been used to identify the best approaches for managing certain infectious disease problems having access to different intervention types. For instance, it was used to identify the most effective combination of interventions to prevent malaria, such as bed net use, in-house insecticide spraying, preventive drug use, treatment, and vaccination (Walker et al., 2016). CO has also been applied to determine the best combination of screening and vaccination to prevent human papillomavirus infection and cervical cancer with (Demarteau et al., 2012, 2014).

An approach closely related to CO to set priorities for developing and introducing new vaccination programs is the Strategic Multi-Attribute Ranking Tool developed by the Institute of Medicine in the United States (Madhavan et al., 2012, 2013; IOM, 2012). Weniger et al. (1998) and Becker and Starczak (1997) previously used a similar approach.

A more recent example of the use of CO modeling to make decisions about new vaccination programs is the Portfolio Management of Vaccines model (Standaert et al. 2017). This model helps setting priorities for introducing a vaccination program when different vaccines are available in the market but no implementation plan is in place because of local constraints. The constraints might be budgetary or related to feasibility and logistics, such as labor force availability, cold-chain maintenance, or transportation or delivery facilities. The model ranks the introduction of different new vaccination programs in a multiyear budget plan to maximize one or more outcome measures (e.g. QALYs gained, hospitalizations or medical visits avoided, or medical costs or mortality rates reduced) of interest to the decision maker.

Decision Problem

CO involves the construction of an optimization model and the selection of an optimization analysis method. The optimization model requires an objective function that is presented in a mathematical equation relating how the disease of interest is managed through different interventions in the presence of specific constraints (Earnshaw et al., 2003). The analysis method predicts the change in the outcome of the objective function by searching for the best allocation among the possible interventions while considering the constraints using an optimization algorithm (see section on Model Structure and Assumptions).

A simple example of the use of CO is the knapsack problem (Sarker and Newton, 2008). A decision needs to be made about which items to put in a knapsack but the weight of what can be carried has a limit. The selection of items to be in the knapsack is also based on a criteria of being most useful expressed through a value index. Each item can therefore be chosen through its weight and specific value index. The optimization algorithm searches for the highest value to be transported in the knapsack by selecting the best combination of items within the maximum weight affordable for the knapsack as a constraint.

In the context of disease management, the knapsack's weight limit is analogous to the budget limit for managing a disease, and the items to place in the knapsack are the intervention options available. Each intervention has a different cost and impact (value index) on the diseases. The objective function is to maximize the reduction in disease incidence within the budget constraint by selecting and combining interventions in a way that maximizes the impact.

Another type of decision problem can also be addressed with this model. It is to identify the minimum budget required to achieve a certain impact goal, such as reducing a disease's incidence by 35% within 5 years using a combination of interventions that has the lowest overall budget.

Perspective

Applying CO to a vaccination program is most useful from the perspective of a budget holder as decision maker who will select a mix of interventions to address a specific healthcare problem, such as all infectious diseases or a specific infectious disease. The budget holder's perspective might be limited to healthcare costs and disease prevalence, or it might include a broader range of inputs, outputs, and constraints to make it more comprehensive. For example, the ministry of finance might want to learn about a vaccine's ability to reduce work absenteeism rates while optimizing tax revenues.

Time Horizon

At least two-time horizons should be considered for CO. One depends on the disease model used to simulate its natural history with the impact a new intervention under study will have. The time horizon is that period during which a person remains at risk and during which the selected intervention will influence that risk. For example, many infectious diseases that can be prevented with vaccines in children are health risks for the first 5 years of life. Therefore, the time horizon of the CO model such that the outcome measure can quantify health gains through the selected interventions should include at least the first 5 years of life.

The other time horizon to assess is the one linked to the application of specific constraints. For example, a budget holder could have a fixed budget over a number of years to fund the new intervention. The time horizon of the analysis for that budget holder is then defined by the years the budget is available.

Model Structure and Assumptions

The structure of a constrained optimization model should be built in three steps, described below.

The first step is to express or translate the decision problem into an optimization task. Specifically, the outcome measure to be maximized or minimized needs to be identified for the diseases under study through specific interventions (= the decision variables). The type of outcome measures can be, for instance, QALYs gained, DALYs avoided, mortality reduction, cases avoided, or costs spent on preventing and/or treating the disease. The decision variables are the different interventions to be selected to achieve the objective. They may include treatment, screening + treatment, vaccination, etc. The optimal selection of these interventions is determined based on their contribution to the objective being optimized and the constraints on these interventions included in the decision problem.

In a second step, the decision problem is expressed as a mathematical function (objective function). The outcome measure to be optimized (single objective) is related to the different decision variables considered. Sometimes, more than one objective can be optimized within the same model. For example, a multi-objective model might aim to maximize the number of QALYs gained and avoided hospitalizations, whereas a single-objective model might aim to maximize the number of QALYs gained only or avoided hospitalizations only.

Constraints on the decision variables or other jurisdiction-specific inputs that the objective function must satisfy should be listed and defined in the third step. Examples of constraints are available budget, observed treatment or prevention adherence rates, and feasibility or minimally acceptable rates of participation in a medical intervention. Constraints can be expressed as equality/inequality functions (e.g., equal (=), less than or equal to (≤), or greater than or equal to (≥) a certain predefined value). Constraints may also be mathematically presented as “either-or” or “if-then” statements. As an example a budget holder is interested in funding health care interventions such that the maximum number of QALYs is accrued. The number of interventions given is no more than the number of individuals in the population who are eligible for the interventions. The budget holder has a limited budget to spend. To construct the model, first, we define the variables and parameters. For this example, we have:

Decision variables:

x_i = number of intervention *i*’s to be funded where *i* = 1 to *n* interventions

Parameters:

p_i = QALYs accrued when funding one unit of intervention *i* where *i* = 1 to *n* interventions

c_i = cost of one unit of intervention *i* where *i* = 1 to *n* interventions

B = budget holder’s budget

P = population eligible for the interventions

Table D1 lists how the model structure could be developed.

Table D1: Defining the model structure of a constrained optimization model.

Step	**Mathematical formulation**	**Description of equations**
Objective function	Max $\sum_i^n p_i x_i$	Maximize the number of QALYs accrued
Intervention selection constraint	$x_1 + x_2 + x_3 + x_4 \ldots\ldots + x_n \leq P$	Number of interventions selected can be no larger than the number of individuals eligible for the interventions
Budget constraint	$c_1x_1 + c_2x_2 + c_3x_3 + c_4x_4 \ldots\ldots + c_nx_n \leq B$	Funded interventions can cost no more than budget B
Decision variables	$0 \leq x_1, x_2, x_3, x_4 \ldots x_n$	Number of individuals receiving each intervention must be 0 or greater
Parameter values	$c_1, c_2, c_3, c_4 \ldots c_n, p_1, p_2, p_3, p_4 \ldots p_n \geq 0$	Cost of and QALYs able to be accrued by each intervention unit must be 0 or greater

The example above is structured as a continuous linear, constrained optimization problem. These forms are the most straightforward and easiest to solve. However, the real world may not occur in this format. The objective function and/or constraints could be nonlinear/dynamic and the decision variable might need to be restricted to integer values. In these cases, the formulations are the same. It is the analysis method used to find the optimal allocation that will be more complex.

Comparators

In CO modeling, no comparison is made. The exercise finds the best combination of interventions to optimize a health objective given the constraints. However, a budget holder might use a CO analysis to determine whether and how much the selected optimal mix is superior to any other alternative that does not apply the optimization algorithms. The comparator could then be a mix of interventions randomly chosen versus those chosen using the optimization exercise.

Sometimes, new interventions can only be introduced one at a time because of budget limits. If so, the optimization exercise can result in a ranking of interventions to introduce sequentially in a way that allows health objectives to be achieved most efficiently within pre-specified timeframes. The interesting comparator could then be the introduction of interventions not following the optimization process. They are introduced in a random fashion or an order determined by the decision maker or budget holder without considering optimization concerns.

Data Requirements and Sources

Many of the data required for CO are the same as for any other economic analysis of a new vaccination program (see Appendix C and E). Specifically, data must be collected on resource use, cost of current and new interventions as well as the disease(s) outcomes with each intervention.

CO differs from cost-effectiveness analysis and fiscal health modeling as it has a list of constraints that the analysis process needs to take into account. The constraints to include will come from budget holders as decision makers, or operational managers taking care of the logistic consequences of the program such as maintaining a cold chain, developing stockpiling, ensuring feasible levels of each intervention based on resource and behavior constraints among others.

Input data about disease outcomes with the alternative interventions for CO models that are used to address infectious disease problems can come from separate disease models developed independently of the CO model. This allows the analyst to avoid complexities in finding the optimal solutions based on dynamic disease models that capture indirect effects of vaccination programs. Including the dynamic disease models in the objective function directly could make it difficult to find an exact solution for the optimum combination of interventions. Running the dynamic model and the CO model in parallel is a more elegant way to obtain results while keeping the optimization analysis method simple.

Outcome Measures

CO can use single or composite measures to be maximized or minimized, depending on how the problem is formulated. Single measures that are frequently used include life expectancy gains; mortality reductions; avoided hospitalizations, medical visits, or disease cases; reductions in disease-related costs; and maximized net present value. Composite measures that can be selected include QALYs and combined endpoints, such as reductions in hospitalization and mortality rates. For a composite endpoint, each component should be weighted by a specific factor. The process to identify the weighting should be well defined and clearly reported.

Discounting

No recommendation for discounting in CO for health care has been issued to date. However, whether to use discounting is likely to depend on the outcome measure selected in the objective function and the time horizon for the budget analysis (i.e. whether it is short term or extended). For example, discounting is needed when the net present value of a new vaccination program with a longtime horizon is optimized. If the analysis focuses on a time horizon of no more than 3 years and the outcomes occur within this period, discounting should not be used. The literature on CO in healthcare, including on the Strategic Multi-Attribute Ranking Tool for vaccines already mentioned in the introduction, shows that a discount rate for clinical outcomes and for cost of 3% per year is used for studies with a long time horizon with sensitivity analyses performed for discount rates between 0% to 5% (Madhavan et al., 2012).

Analysis Method

Many CO models use linear programming to define the objective function if the problem can be expressed as a continuous, linear function with constraints that are also expressed as linear functions. The simplex method can then be used to solve the equations, and the results can be presented in tabular format. The simplex method finds the optimized allocation after iterations of integrating each decision variable one by one into the allocation process. The decision variable with the greatest influence on the outcome variable is selected first, and the next iteration uses the next most influential decision variable.

Linear programs that include variables with integers instead of continuous values may pose problems in finding appropriate allocations when using the simplex method. Different alternative methods have been proposed to ensure an allocation is possible. One method includes solving the integer, linear program as a continuous, linear program using the simplex method then rounding the non-integer allocation. However, the optimal allocation to the continuous linear programming model with rounded allocation is not guaranteed to be optimal or even to be feasible. With today's computing power, the "branch-and-bound" approach (Sarker et al., 2008) can be used to solve an integer linear program to optimality. However, if the number of potential allocations is large (> 20), computation time can be extensive or the optimal allocation may not be able to be found in a reasonable amount of time.

If complex optimization models with more than one objective to be reached or with multiple decision variables and many constraints or that have nonlinear/dynamic features are constructed, it will be difficult to reach exact allocation. In these situations, heuristic approaches that apply more sophisticated analysis methods such as neural networking, fuzzy logic, genetic algorithms, etc. will be chosen to solve the problem. Under such circumstances it will be important to check the validity of the allocations proposed by those sophisticated analyses methods. Expert advice in those matters will be more than welcome to better develop an appropriate analysis plan (Gilli et al, 2003, Wenker et al, 2004).

Uncertainty Analyses

When solving continuous, linear constrained optimization models using the simplex method via an available software package, a form of sensitivity analysis is outputted along with the results (Earnshaw et al., 2003). Specifically, the solution output provides us with conditions

around the objective function coefficients under which decision variables will remain and become part of the optimal allocation. This includes the range over which the objective function coefficients for specific decision variables may change while the current allocation remains optimal or how the objective function coefficients of a specific decision variable (reduced cost) must change in order for this decision variable to be part of the allocation. Change in the limits set on constraints is also presented as one can understand the range over which this limit can vary such that the current allocation stays optimal. Slack or surplus can indicate how much of the constraint limit is still available to be used. Shadow prices are helpful for understanding to what extent an increase of one more unit of a constraint's limit will improve the outcome of the objective function.
Like other modeling exercises, univariate analyses for specific variables and parameters or specific scenarios can be developed as well. Stochastic methods could also be applied. However, they are less well defined. Specifically, development of a full analysis with stochastic instead of deterministic values is limited. Research continues to identify how to apply these methods in optimization (Tanner et al., 2008).

Validation

The validation process should include a check of the reliability of the data sources, assumptions made in the model construct and subsequent results, and whether the disease model used to generate some of the data inputs in the optimization model (e.g. the impact of the vaccination program or other interventions on the outcomes of the objective function) fits the observed disease outcomes. It is also critical that the optimal combination of interventions identified by the CO meets any feasibility constraints and that their total cost is within the budget limit. The accuracy of the coding should also be evaluated.

The dual formulation (maximization or minimization of alternative objectives) facilitates the validation of a CO analysis. When this process is used, the results for the combination of interventions selected should be the same for both objectives (Sarker and Newton, 2008).

Transparency

Constrained optimization modeling is highly formulaic/mathematical in nature. Thus, a way to increase transparency is to present a layman's description of the decision variables, objective function, and constraints along with the formulation. Transparency is also increased when the number of decision variables and constraints are limited. As the number of decision variables and constraints in the equations increase or multiple or nonlinear objective functions are used instead of linear relationships (Tanner et al., 2008), the formulation can then be more difficult to follow.

Software Options

Many software options exist for CO, such as Solver in Microsoft Excel and standalone analysis tools for professionals. Which program to use depends on its price, the objective for using the software, the availability of technical support, the flexibility needed, its ability to handle many constraints and decision variables, how often the modeling approach is used, and whether extended sensitivity analysis is needed. The following websites describe programs available for CO:

- Optimizely (www.optimizely.com)
- AIMMS Prescriptive Analytics Platform (Aimms.com)

- O.R. & Analytics (www.informs.org)

Reporting

The Consolidated Health Economic Evaluation Reporting Standards should be used to report the results of all health economic analyses (Husereau et al., 2013). The question to answer must be specified in the report, as must the reasons for selecting the method used because many people might not be familiar with CO. The methodology section of the report needs to describe the objective function, decision variables, and constraints used as well as the perspective of the analysis (e.g. whether the perspective is that of one decision maker, the budget holder, or more than one decision maker). The sensitivity analysis should include scenario analyses as well as one-way or multi-way analyses so that readers can understand which input values have the most impact on the results.

The results section may include a graphical presentation if feasible, but it is unlikely when the optimization model is allocating among more than three interventions (i.e., decision variables). A tabular format will then be the main presentation form of the results. Finally, the discussion section should highlight why the selected method is a good approach for the problem to be analyzed, as stated in the introduction.

Strengths and Limitations of CO

CO modeling cannot be used in all conditions, but it does provide flexibility for assessing the ability to use a combination of different interventions to achieve a given objective (e.g., screening programs with different recall frequencies for early detection of cervical cancer). It also allows constraints to be included that are not necessarily quantifiable in other modeling approaches but can be measured qualitatively, such as by ethical and or equity considerations (Stinnett et al., 1996).

Constrained optimization modeling is a system of equations that can be graphically plotted in mathematical planes. However, once more than three decision variables are in the equations, it becomes challenging to present graphically the problem and the optimal allocations.

Also as problems grow in number of decision variables and constraints, solving to optimality will become more challenging. But with today's computing power, optimization software is able to facilitate the search for allocations.

Meanwhile, what makes constrained optimization modeling most attractive is the direct link between the availability of a budget and a health goal to be reached. When different options are available for reaching a certain objective, solving such a problem will enable one to understand the degree to which a new vaccination program should be used instead of or in addition to other available intervention while meeting budget and other constraints. The interconnections between the different interventions to be combined for reaching a health objective makes the price setting of each more transparent related to the budget constraint. It helps to prioritize the new and current interventions and promote a budget plan over several years.

References

Becker NG, Starczak DN. Optimal vaccination strategies for a community of households. Math Biosci. 1997 Jan 15;139:117-32.

Buongiorno J, Gilles K. Decision methods for forest resource management. 1st ed. Academic Press, Elsevier Science; 2003.

Crown W, Buykkaramikii N, Thokala P, Morton A, Sir M, et al. Constrained optimization methods in health services research – an introduction: report 1 of the ISPOR Optimization Methods Emerging Good Practices Task Force. Value in Health. 2017,20;310-319.

Demarteau N, Breuer T, Standaert B. Selecting a mix of prevention strategies against cervical cancer for maximum efficiency with an optimization program. Pharmacoeconomics. 2012 Apr;30:337-53.

Demarteau N, Morhason-Belo IO, Akinwunmi B, Adewole IF. Modeling optimal cervical cancer prevention strategies in Nigeria. BMC Cancer. 2014; 14: 365.

Dixit A. Optimization in Economic Theory. 2nd ed. Oxford: Oxford University Press; 1990.

Earnshaw SR, Dennett SL. Integer/linear mathematical programming models: a tool for allocating healthcare resources. Pharmacoeconomics. 2003;21:839-51.

Gilli, M., Winker, P. A Global Optimization Heuristic for Estimating Agent Based Models. Computational Statistics and Data Analysis, 2003, 42, 299–312

Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) – explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guideline Good Reporting Practices Task Force. Value Health. 2013;16:231-50.

IOM (Institute of Medicine). Ranking vaccines: a prioritization framework: phase I: demonstration of concept and a software blueprint. Washington, DC: The National Academies Press; 2012.

Madhavan G, Kinpritma S. Ranking vaccines, a prioritization framework. 1st ed. Washington, D.C.: The National Academies Press; 2012.

Madhavan G, Sangha K, Phelps C, Fryback D, et al. Ranking vaccines. A prioritization sotfware tool. 1st ed. Washington, D.C.: The National Academies Press; 2013.

Murty K. Linear programming. New York: John Wiley & Sons, Inc; 1983.

Petrou S, Wolstenholme J. A review of alternative approaches to healthcare resource allocation. Pharmacoeconomics. 2000 Jul;18:33-43.

Sanders JL. Quantitative guidelines for communicable disease control programs. Biometrics. 1971 Dec;27:883-93.

Sarker RA, Newton ChS. Optimization modeling, a practical approach. 1st ed. CRC Press; 2008.

Sethi SP. Quantitative guidelines for communicable disease control program: a complete synthesis. Biometrics. 1974 Dec; 30:681-91.

Standaert B, Schecroun N, Ethgen O, et al. Optimising the introduction of multiple childhood vaccines in Japan: a model proposing the introduction sequence achieving the highest health gains. Health Policy, 2017 Dec; 121(12): 1303-1312.

Stinnett AA, Paltiel AD. Mathematical programming for the efficient allocation of health care resources. J Health Econ. 1996 Oct;15:641-53.

Tanner MW, Sattenspiel L, Ntaimo L. Finding optimal vaccination strategies under parameter uncertainty using stochastic programming. Math Biosci. 2008 Oct;215:144-51.

Walker P, Griffin J, Ferguson N, Ghani A. Estimating the most efficient allocation of interventions to achieve reductions in Plasmodium falciparum malaria burden and transmission in Africa: a modeling study. Lancet Glob Health. 2016;4:e474-84.

Winker, P., Gilli, M. Applications of optimization heuristics to estimation and modelling problems. Computational Statistics & Data Analysis. 2004, 47, 211–223.

Weniger BG, Chen RT, Jacobson SH, Sewell EC, Deuson R, Livengood JR, et al. Addressing the challenges to immunization practice with an economic algorithm for vaccine selection. Vaccine. 1998 Nov;16:1885-97.