A computationally-efficient method for probabilistic parameter threshold analysis for health economic evaluations

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BACKGROUND

Threshold Analysis is typically used to determine the threshold value of an input parameter at which a health care technology becomes cost-effective. **Currently**, threshold analysis is typically performed in a deterministic way. This approach assumes independence between input parameters and *may result in biased threshold values* if the relationship between input parameters and the measure of cost-effectiveness is non-linear. 2-level Monte Carlo approach is considered to be the gold standard and can provide unbiased threshold values. But it is computationally intensive and complex. However, probabilistic sensitivity analysis (PSA) might overcome the issues related to deterministic threshold analysis and 2-level Monte Carlo approach.

OBJECTIVE

Propose a probabilistic method for performing threshold analysis, namely **generalized additive model**, which accounts for the joint uncertainty in all input parameters, makes no assumptions about the linearity of the cost-effectiveness model, and is computationally-efficient at the same time. The estimated threshold values obtained from generalized additive models are compared with the threshold values from existing approaches.

REAL-WORLD EXAMPLE

A health economic evaluation comparing typhoid conjugate vaccination strategies in Gavi-eligible countries is chosen to compare the different approaches.

We focus on the input parameters:
- Typhoid mortality when hospitalized ($\Pr(die_{hosp})$)
- Probability of hospitalization with typhoid ($\Pr(hosp)$)
- Duration of illness for patients seeking medical care (DOI_{care} (in years))

Either 2 or 3 vaccination programs (d) are compared:
- No vaccination (No vacc)
- Routine vaccination at 9 months with a catch-up campaign up to 5 years (RC5)
- Routine vaccination at 9 months with a catch-up campaign up to 15 years of age (RC15)

D=2 (No vacc, RC5); D=3 (No vacc, RC5, RC15)

METHODS & RESULTS

Probabilistic parameter threshold analysis

The probabilistic threshold value, θ_i^*, is defined as:

$$\theta_i^* = \{\theta_i |\, d \neq d^*: E_{\boldsymbol{\theta}_{-i}|\theta_i}[NB_d(\theta_i, \boldsymbol{\theta}_{-i})] = E_{\boldsymbol{\theta}_{-i}|\theta_i}[NB_{d*}(\theta_i, \boldsymbol{\theta}_{-i})]\}$$

The term $E_{\boldsymbol{\theta}_{-i}|\theta_i}[NB_d(\theta_i, \boldsymbol{\theta}_{-i})]$ can be estimated via 2 ways:

Deterministic threshold analysis

1. Define the uncertain parameter of interest, θ_i.
2. Fix the remaining input parameters ($\boldsymbol{\theta}_{-i}$) at their base case value.
3. Vary the values of θ_i and record the cost-effectiveness.
4. The parameter threshold value θ_i^* is: $\{\theta_i |\, d \neq d^*: NB_d(\theta_i, E[\boldsymbol{\theta}_{-i}]) = NB_{d*}(\theta_i, E[\boldsymbol{\theta}_{-i}])\}$

2-level Monte Carlo approach

1. Outer level: Sample value from θ_i, obtaining $\theta_i^{(k)}$, with k=1,…,K.
2. Inner level: Obtain NB for each decision d.
   a) Sample value from $\boldsymbol{\theta}_{-i}$, obtaining $\boldsymbol{\theta}_{-i}^{(k,j)}$, with j=1,…,J
   b) Evaluate $NB_d\left(\theta_i^{(k)}, \boldsymbol{\theta}_{-i}^{(k,j)}\right)$ for each d
   c) Repeat a) and b) J times
3. Outer level:
   a) For each k and d, determine $NB_d^k = \frac{1}{J}\sum_{j=1}^{J} NB_d^{(k,j)}$
   b) For each k, determine the decision with the highest expected net benefit (d^k): $d^k = max_d NB_d^k$
   c) Repeat the outer level K times
4. When d^k is obtained for all $\theta_i^{(k)}$, determine θ_i^*.

Generalized additive model

Generally, a generalized additive model (GAM) looks as follows:

$$NB_d(\theta_i^s) = g_d(\theta_i^s) + \varepsilon^s$$

1. Define a set of S samples from the joint distribution of the model input parameters (also known as the PSA sample).
2. For each decision d, we fit a GAM: $g_d(\theta_i) = s_i(\theta_i)$
3. Obtain the fitted values, $\widehat{NB}_s(\theta_i^s)$, for each d.
4. The parameter threshold value is θ_i^*.

95% bootstrap CI are calculated to provide a measure of accuracy of the threshold value in the presence of possible model violations. Only the bootstrap samples that produce the same number of threshold values as the original PSA are used to calculate the 95% CI (Beff, out of 1000).

Deterministic threshold analysis					2-level Monte Carlo approach				Generalized additive model					
Parameter	**S**	$\boldsymbol{\theta_i^*}$	**Optimal d**	**Time (s)**	**K**	$\boldsymbol{\theta_i^*}$	**Optimal d**	**Time (s)**	$\boldsymbol{\theta_i^*}$	**Optimal d**	**Time (s)**	**95% CI**	**Beff**	**Time (s)**
Nicaragua, WTP=1000$, D=2														
$\Pr(die_{hosp})$	7000	0.0671	RC15	16.28	8	0.038	RC15	157.09	0.0430	RC15	1.31	0.0394-0.0486	921	409.70
$\Pr(hosp)$	7000	0.0678	RC15	18.03	8	0.042	RC15	150.13	0.0447	RC15	1.20	0.0423-0.0531	999	420.36
DOI_{care}	7000	No	No vacc	13.46	8	No	RC15	255.78	No	RC15	1.25		702	388.97
Nicaragua, WTP=1000$, D=3														
$\Pr(die_{hosp})$	10 000	0.1142	RC15	16.34	7	0.067	RC15	196.81	0.0733	RC15	2.05	0.0676-0.0842	989	694.66
$\Pr(hosp)$	8000	0.1209	RC15	18.99	8	0.074	RC15	218.92	0.0872	RC15	1.66	0.0786-0.1037	999	603.31
DOI_{care}	8000	No	No vacc	14.19	8	No	No vacc	188.80	No	No vacc	1.67		374	595.90
Uganda, WTP=800$, D=3														
$\Pr(die_{hosp})$	10 000	0.1037	RC15	18.27	7	0.056	RC5	216.68	0.0497	RC5	2.11	0.0451-0.0527	998	715.55
						0.069	RC15		0.0606	RC15		0.0555-0.0656		
$\Pr(hosp)$	10 000	0.1025	RC15	16.47	7	0.061	RC5	222.34	0.0549	RC5	1.90	0.0518-0.0590	941	787.08
						0.073	RC15		0.0654	RC15		0.0617-0.0694		
Cambodia, WTP=100$, D=3														
$\Pr(die_{hosp})$	10 000	0.1048	RC15	17.15	7	0.053	RC5	247.53	0.0551	RC5	1.90	0.0491-0.0596	994	686.61
						0.081	RC15		0.0834	RC15		0.0780-0.0915		
$\Pr(hosp)$	8000	0.0949	RC15	15.91	9	0.059	RC5	284.17	0.0613	RC5	1.73	0.0548-0.0645	998	789.37
						0.084	RC15		0.0897	RC15		0.0837-0.1016		

SUMMARY

1. GAM performs better than the deterministic threshold analysis.
2. GAM is faster in determining the threshold value compared to the other approaches.
3. Further research needs to be done on how to improve the precision of GAM.

REFERENCES

Bilcke, J et al. (2019). *Lancet ID* **19**; Strong, M et al. (2014) *Medical Decision Making* **35**