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A Framework for the Economic Evaluation of Sequential Therapies for Chronic Conditions

Background

- Cost-effectiveness models often evaluate a sequence of treatments
- Downstream implications of a sequence should be captured
- Compare sequences within standard economic evaluation framework

Problem

- For conditions such as rheumatoid arthritis, an optimal treatment sequence has not been identified[1]
- Large number of sequences requires excessively large computational time (estimate cost and QALYs estimated for every sequence)
- Computation time increases when using individual patient simulation
- Evidence for a fully sequential model is not likely to be available

Problem description

Compare sequences to maximise net monetary benefit for a given threshold (λ). Identifying an optimal sequence is an optimisation problem:

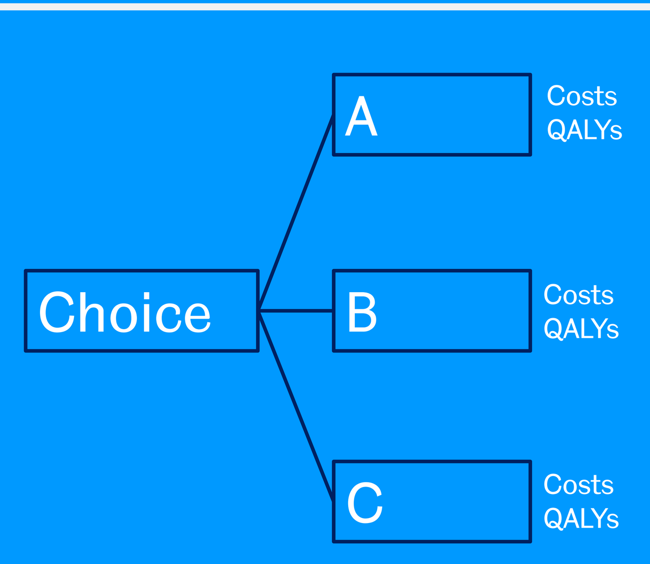
$$\max_{x \in X} g(x)$$

Where $x \in X$ represents a vector of input variables x from the potentially feasible space, X. Therefore x is a particular permutation of sequences from all feasible sequences X. $g(x)$ is the objective function, which cannot be determined analytically, but instead must be estimated via simulation.

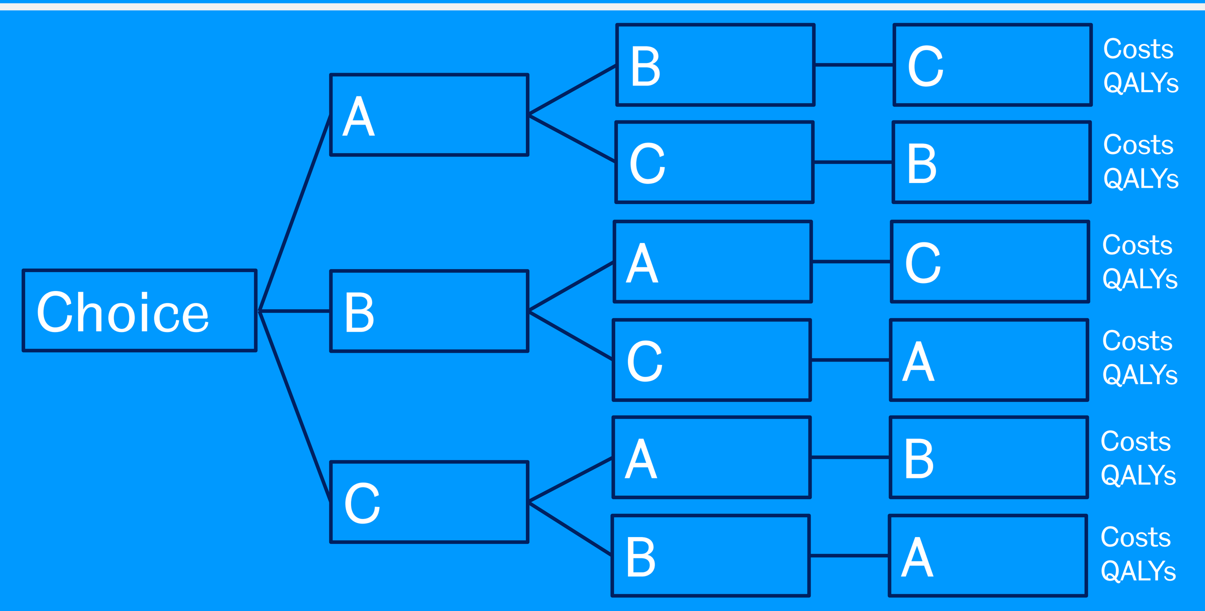
A simulation model provides an expectation of the objective function:

$$g(x) = E_{\omega}[G(x,\omega)]$$

The performance measure estimated via the simulation model $G(x,\omega)$ is stochastic, with ω the randomness exhibited in each run of the simulation. Therefore a combinatorial simulation-optimisation (S-O) problem



Three treatment model



Three treatment sequential model

Systematic Review of combinatorial S-O Methods

Methods

- Reviews of methods require bespoke search methods[2]
- Citation pearl growing search conducted, an effective search method for methodological literature[3]
- A bespoke framework considered the development, theoretical basis and applicability of each paper
- Excluded were multi-objective, naïve, local search and non S-O methods

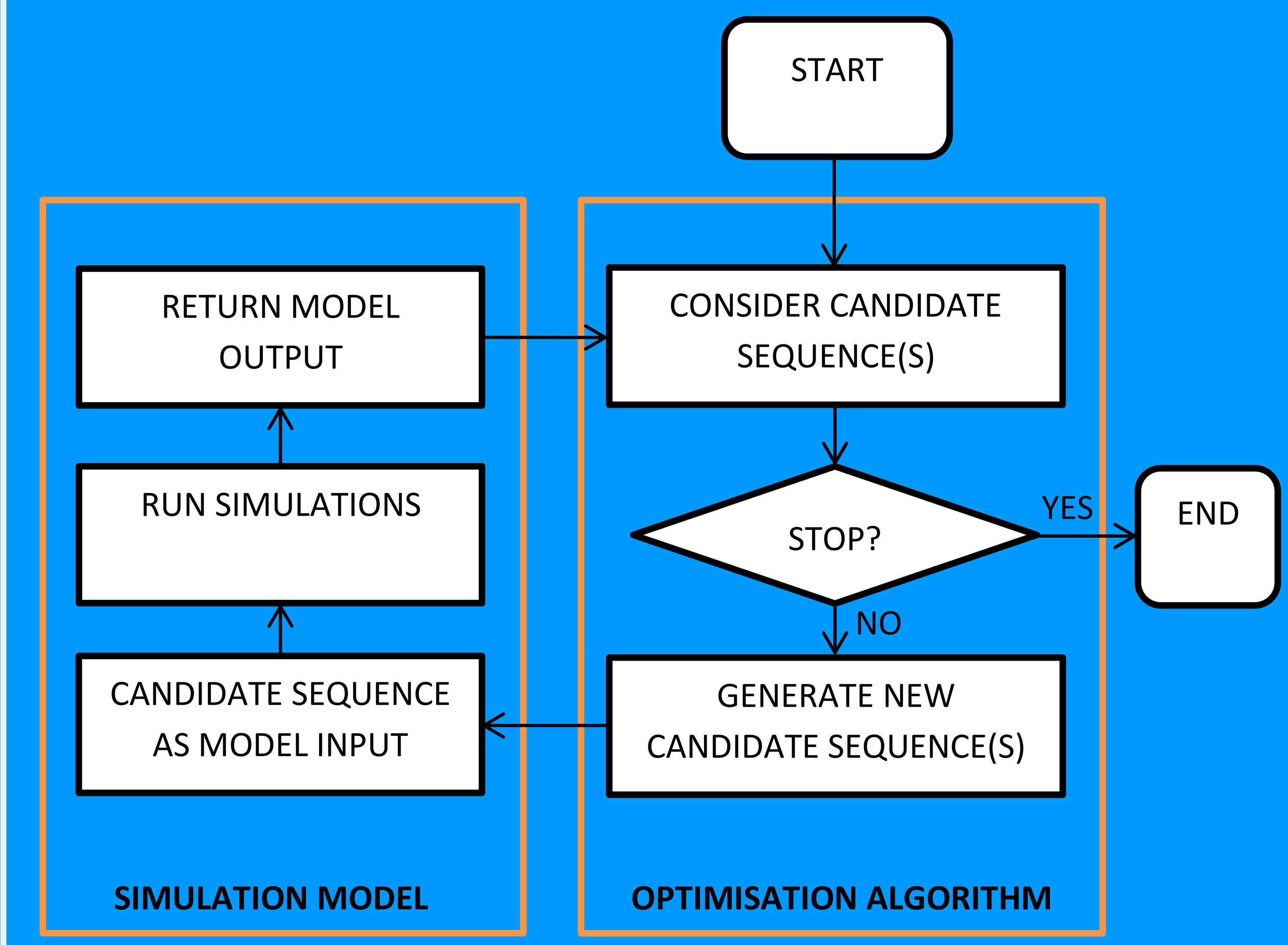
Results

- 28 papers were identified, either developing or applying a method for a combinatorial S-O problem
- 17/28 (61%) were metaheuristics, which are generalisable and applicable to many S-O problems.
- Statistical methods identified were concerned with estimating how many simulations to run, and how to prove superiority between solutions in the presence of noise
- Metaheuristics which allow the balancing of 'exploration' of the global search space, and 'exploitation' of local areas of interest, were likely to be most appropriate

Conclusions

- Simulated Annealing (SA) and Genetic Algorithms (GA) selected for implementation, due to their generalisability, and being the two most commonly used methods for combinatorial S-O problems.

Combinatorial Simulation Optimisation (S-O) Algorithm



Model considerations

- Include all eligible treatments, with clear rules regarding where they can be used in a clinically legitimate sequence
- Sequences automatically tested for eligibility before simulation
- 'Neighbourhood' based on solutions one perturbation away (see table below)
- Apply metaheuristic optimisation algorithm alongside simulation model
- Estimate near-optimal solution in reasonable time
- Ensure both simulation model and optimisation model have appropriate stopping rules

Neighbourhood representation for permutations	Example sequence	Details
Adjacent pairwise interchange	51432 → 15432	Swap two adjacent elements
Insertion operator	51432 → 54312	Select element and insert in new position
Exchange operator	51432 → 51234	Two selected elements are swapped
Inversion operator	51432 → 52341	Invert sequence between two elements

Class	Category	Method
Random Search	Random Search	Random search hill climbing
	Adaptive Random Search	Balanced Explorative and Exploitative Search
		Convergent Optimisation via Most-promising-Area Stochastic Search
Metaheuristics	Metaheuristics	Simulated Annealing (SA)
		Genetic Algorithms (GA)
		Tabu Search
		Ordinal Optimisation
		Nested Partitions
		Particle Swarm Optimisation
Statistical methods	Sampling methods	Sequential Stochastic Comparison
		Adaptive Sampling
	Approximation	Sequential Multipoint Linear Approximation
	Metamodelling	Neural Network Metamodel
Hybrid and other methods	Hybrid methods	Averaging framework for SA
		Empirical Stochastic Branch-and-Bound

Simulated Annealing

- SA is a local search metaheuristic with the capacity to escape a local optima
- Mimics the annealing process of a crystalline solid
- An initial solution is randomly selected as 'current best', and a neighbour identified
- The algorithm selects a better neighbour solution as 'current best', but also allows the selection of worse neighbour solution based on a stochastic process
- As the algorithm iterates, the probability of selecting a worse neighbour (the temperature) is reduced
- Balances exploration / exploitation
- Simple to implement when a clear neighbourhood function is designed
- Algorithm requires careful user tuning of temperature and stopping parameters
- The systematic review found SA to have good performance for combinatorial S-O problems

Genetic Algorithms

- Population based metaheuristics
- Maintaining a pool (population) of potential solutions
- 'Parent' solutions are selected and evolutionary operations are applied to create offspring solutions
- These operations maintain good characteristics of parents, and allow an escape from local optima
- GA are complex to compute, due to the evolutionary processes
- GAs have been found to perform well for combinatorial S-O problems, but are potentially slow to run due to the evolutionary operators

Next steps

- Implementation of SA and GA methods for a sequential rheumatoid arthritis (RA) model
- 14 RA treatments $\sum_{x=1}^{14} x!$ = 93,928,268,313 (~94 billion) potential sequences
- Identify a near optimal sequence of treatments for people with RA
- Evaluate the performance of the metaheuristics methods and their generalisability

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Conflicts of Interest: None declared

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(Reviewed studies available on request)

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