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[1,2]. Large numbers of sequences requires excessive 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 (T): Identifying an optimal sequence is an optimisation problem:

\[ g(x) \]

Where \( x \in X \) represents a vector of input variables \( x \) from the potentially feasible space, \( X \). Therefore \( g(x) \) is a particular permutation of solutions 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:

\[ g(x) = E_x[g(x, w)] \]

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

Combination Simulation Optimisation (S-O) Algorithm

Combinatorial Simulation-Optimisation Algorithm
- START
- RETURN MODEL OUTPUT
- RUN SIMULATIONS
- CANDIDATE SEQUENCE AS MODEL INPUT
- CONSIDER CANDIDATE SEQUENCE(S)
- GENERATE NEW CANDIDATE SEQUENCE(S)
- STOP?
- YES
- END

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 \( \sum_1^{14} x_1 = 93,928,269,313 \) (94 billion) potential sequences
- Identify a near optimal sequence of treatments for RA
- Evaluate the performance of the metaheuristics methods and their generalisability

Systematic Review of combinatorial S-O Methods

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<th>Class</th>
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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 neighbours
- Ensure both simulation model and optimisation model have appropriate stopping rules

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 for each method 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

References

Acknowledgements and funding
Jonathan Tosh is funded by a National Institute for Health Research (NIHR) Doctoral Research Fellowship. This article presents independent research funded by the NIHR. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. Conflicts of Interest: None Declared