Markov Models at the Intersection of Pharmacometrics and Health Economics

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Opportunity at the Intersection

- Better Inform Drug Development Decisions
- Better Inform Economic and Outcome Decisions
Markov Models (MM) in Health Economics Analyses

**QALY**\(^a\): measure of benefit, dependent on number of individuals and/or duration in any state

**ICER**\(^b\): cost per QALY

**Static Markov Models in HE Analyses:**
Approach based on discrete-time and proportion of individuals

Proportion of individuals in the population move across the states according to a set of transition probabilities only once per time interval (sometimes lengthy “Markov cycle”)

Time-dependent covariates possible

\(^a\) Quality-Adjusted Life Years, \(^b\) Incremental Cost-Effectiveness Ratio
A cost-effectiveness analysis of denosumab for the prevention of skeletal-related events in patients with multiple myeloma in the United States of America
Static Markov Model

Figure 1. Depiction of model health states. 1L, first line; 2L+, second line or later; Abbreviations. MM, multiple myeloma; OFF SRE Prev Tx, patients not receiving treatment to prevent SREs; ON SRE Prev Tx, patients receiving treatment to prevent SREs; SRE, skeletal-related event; Tx, treatment.

Deterministic Sensitivity Analysis

Figure 4. One-way deterministic sensitivity analyses of key variables from (a) the societal perspective and (b) the payer perspective. Ranges for parameters were as follows: annual efficacy discount rate = 0.00–0.05; percentage of patients not eligible to receive zoledronic acid = 0.05–0.15; annual crude denosumab = 0.55–0.64; annual crude SRE rate of zoledronic acid = 0.58–0.67; real world adjustment SRE rate = 2.01–4.01; SRE rate ratio for zoledron treatment = 0.42–0.82; zoledronic acid cost of administration = 189–231; denosumab number of cycles = 0.79–0.97; zoledronic acid number of cycles post-progression utility decrement = 0.57–0.72; QALY decrement SC = 0.0009–0.0014; QALY decrement IV = 0.0017–0.0025; QALY decrement vertebral = 0.05–0.15; QALY decrement non-vertebral fracture = 0.05–0.15; MM second-line treatment duration = 9.66–9.36; percentage of potential savings in treatment used in the cost-effectiveness analysis = 0.40–0.60; second-line MM treatment monthly costs = 16,430–20,081; third-line MM treatment number = 16,530–20,204. Abbreviations. 2L, second line; 3L, third line; CE, cost-effectiveness analysis; IV, intravenous; MM, multiple myeloma; RR, relapse; SRE, skeletal-related event; SRE rate ratio zoledronic acid vs no treatment; SRE, skeletal-related event; Tx, treatment.
Dynamic Markov Models: Infectious Disease

Haeussler et al. BMC Medical Research Methodology  (2018) 18:82
https://doi.org/10.1186/s12874-018-0541-7

A dynamic Bayesian Markov model for health economic evaluations of interventions in infectious disease

Katrin Haeussler¹,²*, Ardo van den Hout¹ and Gianluca Baio¹
Infectious Disease Health States

Fig. 1 Model structure of a hypothetical chronic sexually transmitted infection. The arrows represent the possible transitions. These are governed by the parameters $\phi_{r,s}$ with indices $r, s \in S$ representing origin and target states, respectively. The replenishment of the pool of susceptibles by newborns proceeds at a rate $\chi$. 
Infectious Disease Health States: Static MM

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Infectious Disease Health States: Dynamic MM

**Fig. 1** Model structure of a hypothetical chronic sexually transmitted infection. The arrows represent the possible transitions. These are governed by the parameters $\phi_{rs}$, with indices $r, s \in S$ representing origin and target states, respectively. The replenishment of the pool of susceptibles by newborns proceeds at a rate $\chi$.

\[
\frac{dn_1(t)}{dt} = \chi [n_1(t) + n_2(t) + n_3(t) + n_4(t)] - \rho_{1,2}(t)n_1(t) - \rho_{1,5}n_1(t)
\]

\[
\frac{dn_2(t)}{dt} = \rho_{1,2}(t)n_1(t) - \rho_{2,3}n_2(t) - \rho_{2,5}n_2(t)
\]

\[
\frac{dn_3(t)}{dt} = \rho_{2,3}n_2(t) - \rho_{3,4}n_3(t) - \rho_{3,5}n_3(t) \quad (1)
\]

\[
\frac{dn_4(t)}{dt} = \rho_{3,4}n_3(t) - \rho_{4,5}n_4(t)
\]

\[
\frac{dn_5(t)}{dt} = \rho_{1,5}n_1(t) + \rho_{2,5}n_2(t) + \rho_{3,5}n_3(t) + \rho_{4,5}n_4(t).
\]
Bayesian Posterior Predictive Distribution

Fig. 2 Calibration results on the number of high-risk females in the states following a systematic probabilistic calibration approach. The results of the Bayesian models are similar, with a slightly higher number of high-risk females in the states \textit{Infected} and \textit{Asymptomatic} estimated by the Bayesian ODE-based model. In contrast, the deterministic ODE-based model results in a lower estimate on the number of high-risk females in the states \textit{Infected} and \textit{Asymptomatic}; however, the outcome on the state \textit{Morbid} is reversed.
Linking PMX and PE: Xanthine Oxidase Inh. & Gout

Individual-Level PKPD Modeling and Simulation

Integration of Pharmacometrics and Pharmacoeconomics to Quantify the Value of Improved Forgiveness to Nonadherence: A Case Study of Novel Xanthine Oxidase Inhibitors for Gout.
Daniel Hill-McManus; Scott Marshall; Elena Soto; Dyfrig A Hughes
Simulation: Response vs. Adherence

- Simulation-based comparison of febuxostat and hypothetical analogues
- Varied clearance, potency, for analogues
- Informed by adherence RWE

Simulation: Pricing vs Response

Curve of estimated pricing to achieve cost effectiveness versus febuxostat 80 mg with probability of 50% and 10% at a willingness to pay threshold of £20,000 per QALY.
Multi-Scale Systems Pharmacology Models

- Osteoporosis
- Primary Hyperparathyroidism
- Hyperparathyroidism Secondary to Chronic Kidney Disease
- Estrogen Modulators
- Bisphosphonates
- Parathyroid Hormone
- RANK-L pathway
- Wnt Signaling
- Bone Biomarkers
- Bone Mineral Density
- Fracture

Peterson, MC and Riggs, MM. Predicting Nonlinear Changes in Bone Mineral Density Over Time Using a Multiscale Systems Pharmacology Model
Fracture Rate MSSP/Model-Based Meta Analysis

Fracture Hazard Ratio by Treatment

**Fig. 3** Hazard ratios for each treatment relative to placebo calculated and density plots for this calculation over the posterior distribution of parameter estimates are represented, for the model with both drug–BMD interaction and additional drug effect.

Linking MSSP/Fracture Model & Pharmacoeconomics

Early Development ICER ($/QALY) Predictions

- New drug, target
- New dose, regimen
- Combination therapies
Benefits, Challenges and Potential Strategies of Open Source Health Economic Models

William C. N. Dunlop¹ · Nicola Mason² · James Kenworthy¹ · Ron L. Akehurst²

- To apply the model in its existing form with minor changes to inputs
- To modify the model structure for a new decision problem
- To be able to fully audit and check the model
- To use the model for teaching purposes
- To learn technical aspects of the model for use in a different disease area or decision problem
- Other
Probability of Success: **Outdated Thinking**

vs. placebo
Probability of Success: Evolving Thinking

vs. active control
Probability of Success: **New Opportunity**

- vs. future competitor
- informed by predicted ICER
- in Real World treatment population
- Continuously updated and re-assessed as development programs and standard of care evolve
Summary

● Markov Models in Health Economics

● Utility of static vs dynamic Markov Models

● Value of open science in HE Analyses

● Opportunities at the intersection of Pharmacometrics and Health Economics
Thank You