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Improving healthcare decisions

Model Calibration in R

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ISPOR Short Course Program 2023 (Virtual)

Tuesday and Wednesday, 25-26 July 2023

Learning Objectives

At the end of this workshop, participants will gain an understanding of the following:

- Concept of model calibration and when it is needed
- Steps and decisions involved in setting up a model calibration
- Different model calibration algorithms and their strengths and weaknesses
- Bayesian model calibration (day 2)
- Implementation of a model calibration in R
  - Can be adapted to calibrate your own models (if using R)
  - Can use as a template for any programming language

The DARTH Workgroup

- Materials for this workshop were developed in part by the Decision Analysis in R for Technologies in Health (DARTH) Workgroup
- For more information
  - www.darthworkgroup.com
  - Twitter: @DARTHworkgroup

Why R?

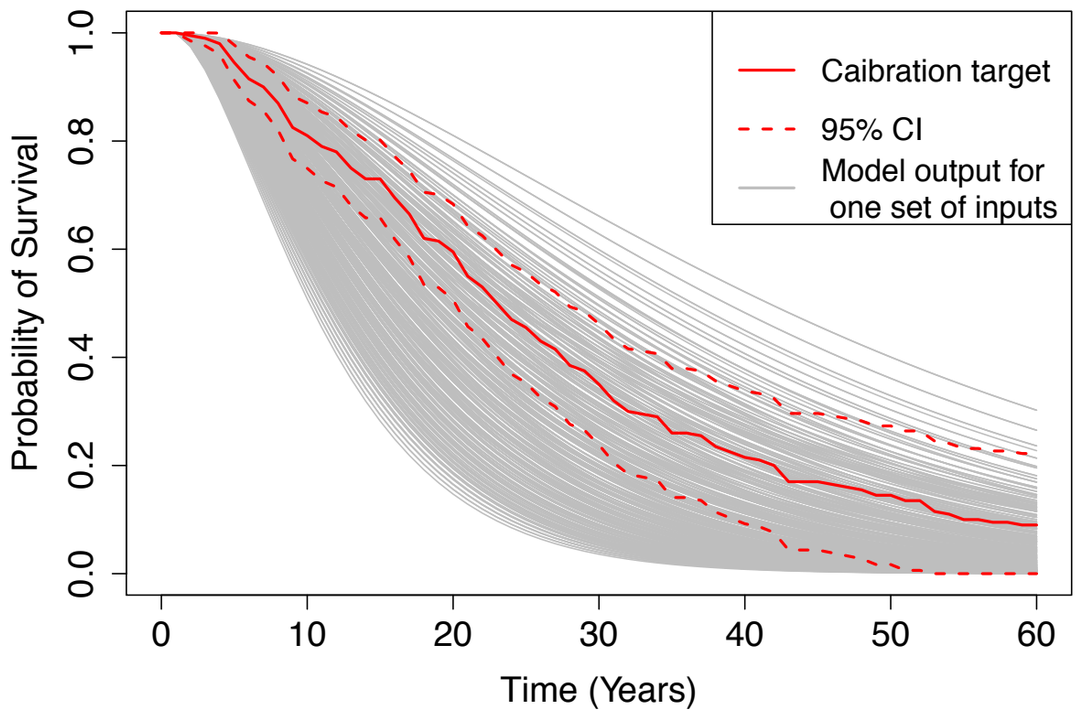
- Open-source, freely available
- Flexible
- Computationally efficient
- Existing packages that implement needed algorithms
- Many other programming languages have these advantages!
  - Can use the calibration framework presented here to write code in your favorite language

Motivation

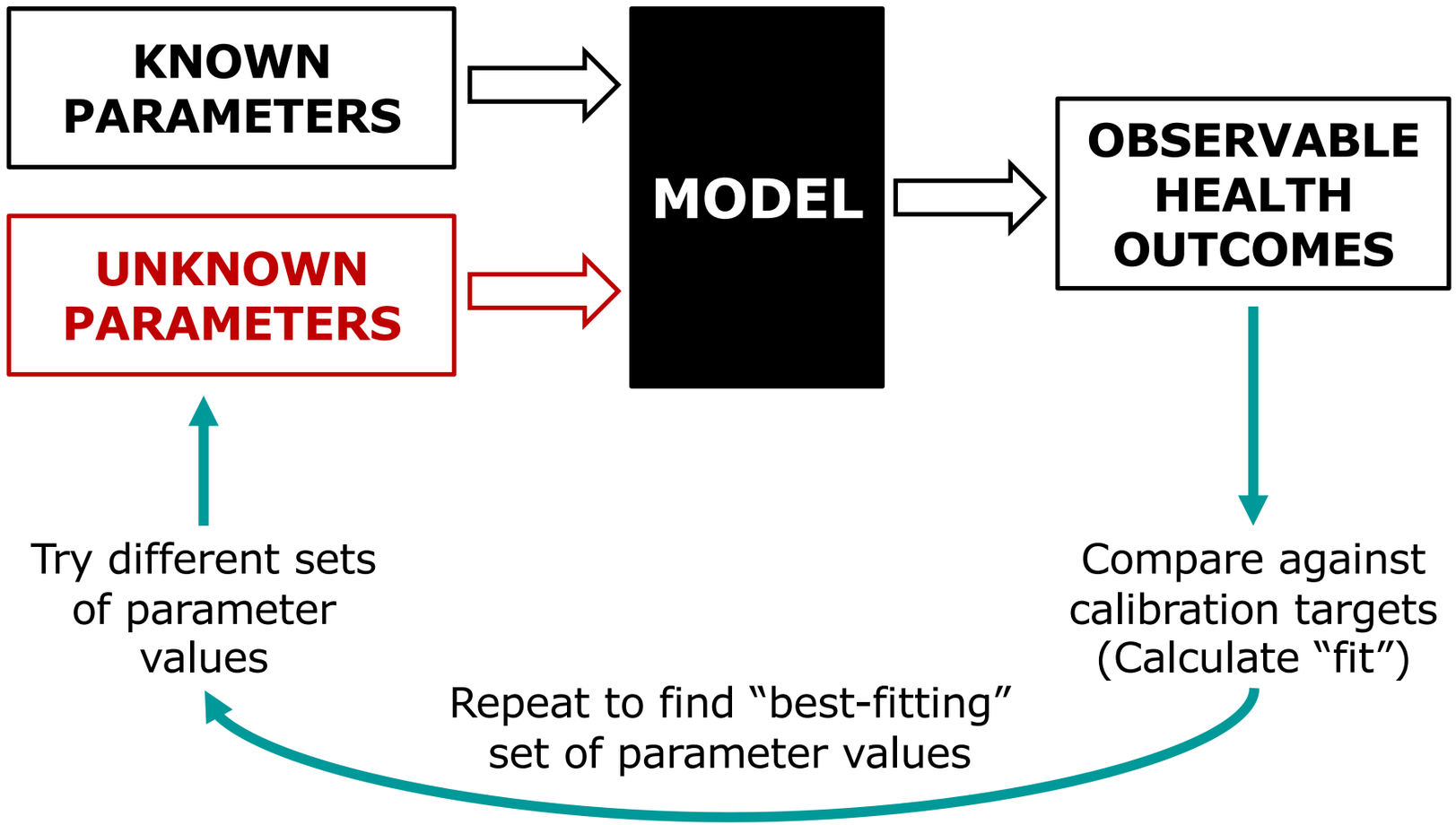
- Mathematical models of disease often involve a subset of parameters whose values are unknown
- Common reasons include physical, feasibility, and ethical limitations
- Estimate values for these parameters by matching model outputs to observed outcomes
  - Model calibration

Calibration definition

- Process of adjusting model input parameter values to match data on an outcome of interest (e.g., survival, prevalence, or incidence)
- Outcome(s) of interest = “calibration targets”



Calibration process



Calibration targets

- Empirical data to be replicated by the model
- Summary statistics (e.g. mean age of cancer diagnosis) or series of observations (e.g. age-specific incidence)
- Can calibrate to multiple targets (e.g. survival and prevalence) simultaneously
- Model should be able to output the outcomes of interest

Calculating “fit”

- Goodness-of-Fit (GoF) is the quantitative measure of how the model is replicating the target data
- Different ways to measure GoF
  - Distance
  - Likelihood
- Notation
  - M : a mathematical model (e.g., Markov model)
  - θ : Set of K parameters to be calibrated
  - $\phi = M(\theta)$: Model output for parameter set θ
  - y : Values of T calibration targets

Distance GoF measures

- Sum of squared errors

$$SSE(\theta) = \sum_{i=1}^{T} \left(y_i - M_i(\theta)\right)^2$$

- Weighted sum of squared errors
  - Assign different weight to different targets (w_i)
  - Often, $w_i = \frac{1}{\sigma^2}$

$$WSSE(\theta) = \sum_{i=1}^{T} w_i \left(y_i - M_i(\theta)\right)^2$$

Likelihood as GoF

- How likely is the observed data to have come from a model M with set of parameter values θ ?
- Assuming targets are independent, overall likelihood is the product of individual likelihoods

$$L(y|M(\theta)) = \prod_{i=1}^{T} L_i(y_i|M(\theta))$$

- Generally, we work with log-likelihood

$$\mathcal{L}(y|M(\theta)) = \sum_{i=1}^{T} \log L_i(y_i|M_i(\theta)$$

Commonly used likelihoods

- **Normal distribution**

$$\log L(y_i, \sigma_i | M_i(\theta)) = -\frac{1}{2}\log\left(2\pi\sigma_i^2\right) - \frac{1}{\sigma_i^2}\left(y_i - M_i(\theta)\right)^2$$

  - In R: `dnorm(x=`y_i`, mean=`$M_i(\theta)$`, sd=`σ_i`, log=T)`

- **Binomial distribution**

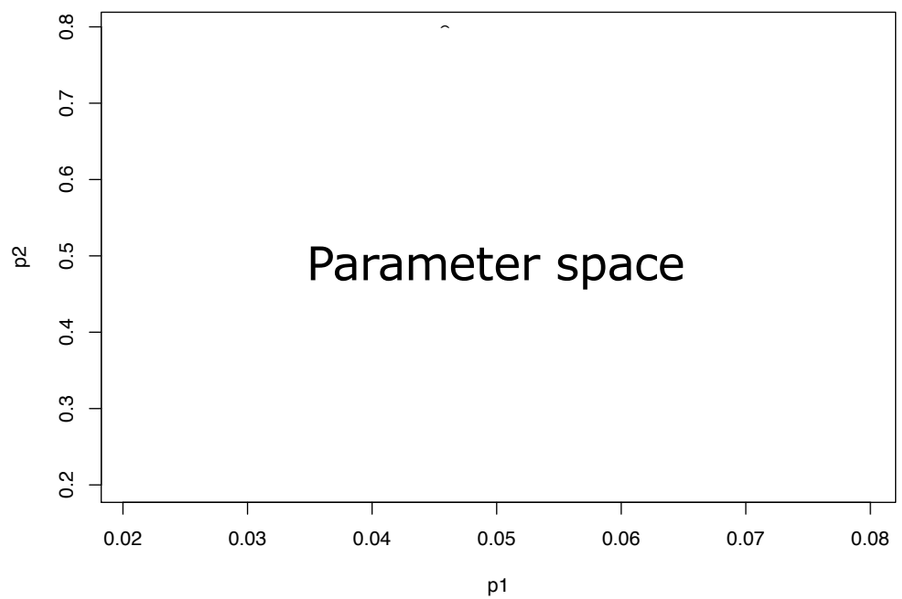
$$\log L(y_i, n_i | M_i(\theta)) = \log\left(\binom{n_i}{y_i}\right) + y_i \log\left(M_i(\theta)\right) + (n_i - y_i)\log\left(1 - M_i(\theta)\right)$$

  - In R: `dbinom(x=`y_i`, size=`n_i`, prob=`$M_i(\theta)$`, log=T)`

- **Multinomial distribution**
  - In R: `dmultinom(x=`y_i`, prob=`$M_i(\theta)$`, log=T)`

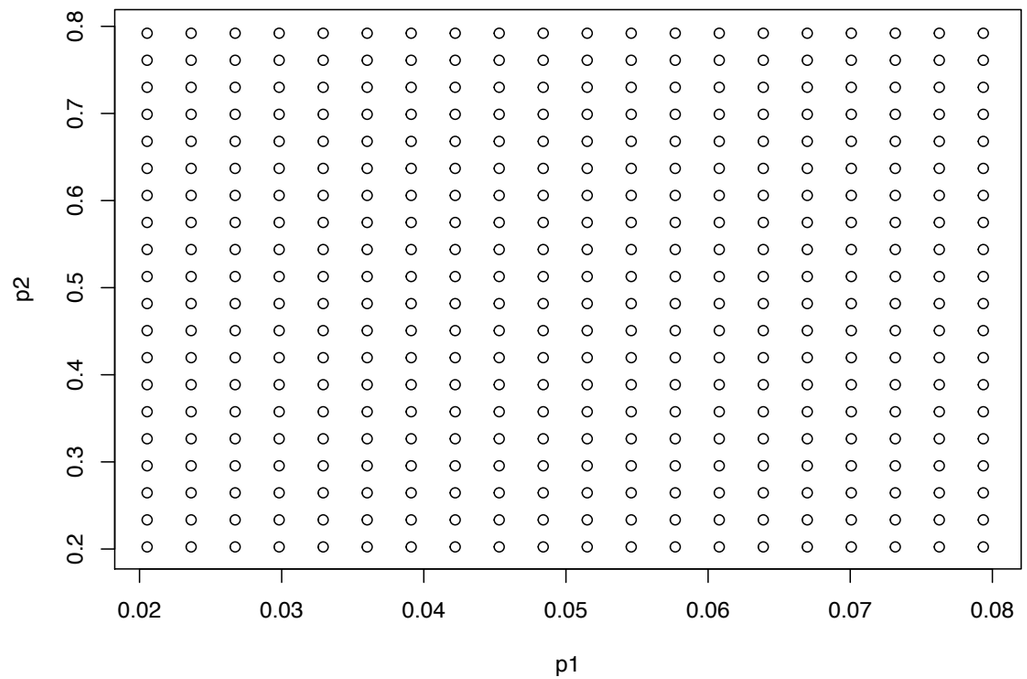
Search Strategy

- Define plausible ranges for parameter whose values are unknown
- Use a search strategy to “search” through the input parameter space
  - Run the model for sets of parameter values generated by search strategy



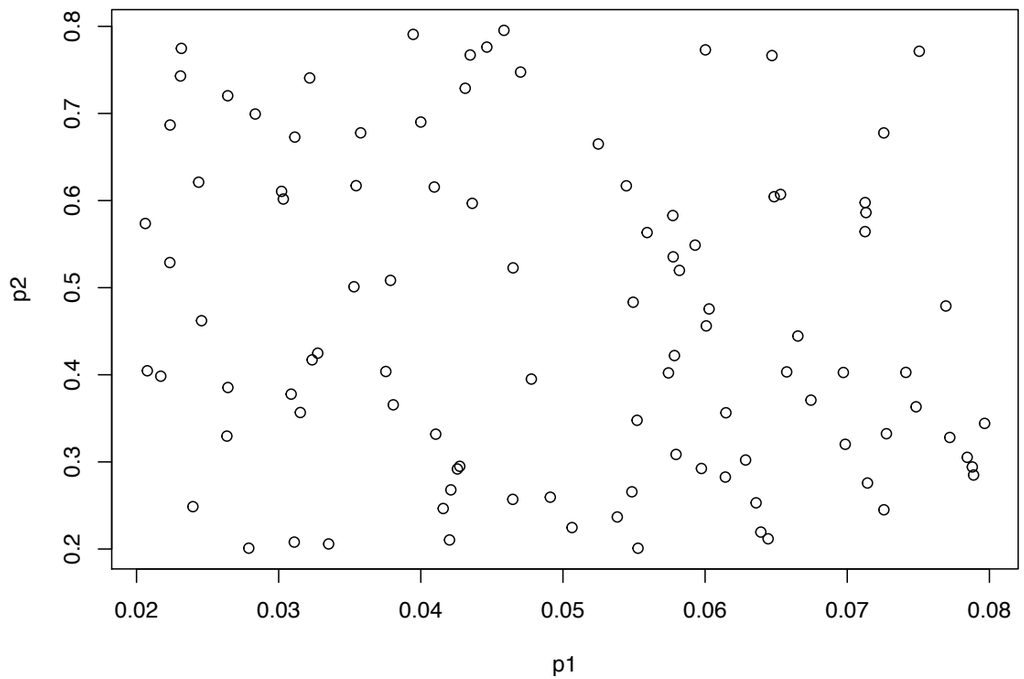
Grid Search

- Run model for all possible combinations of parameter values
- Often infeasible



Random Search

- Randomly sample a large number of parameter value sets from probabilistic distributions
- Use "Latin hypercube sampling" (LHS) to ensure sample captures the full parameter space



Random sample

Random Search

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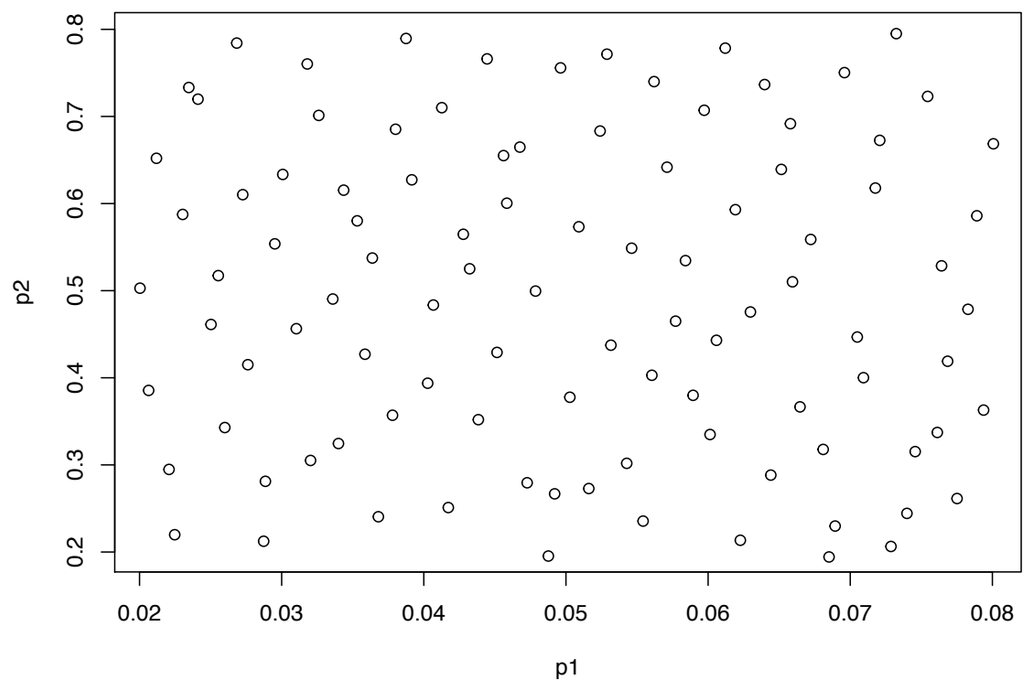
- Use "Latin hypercube sampling" (LHS) to ensure sample captures the full parameter space



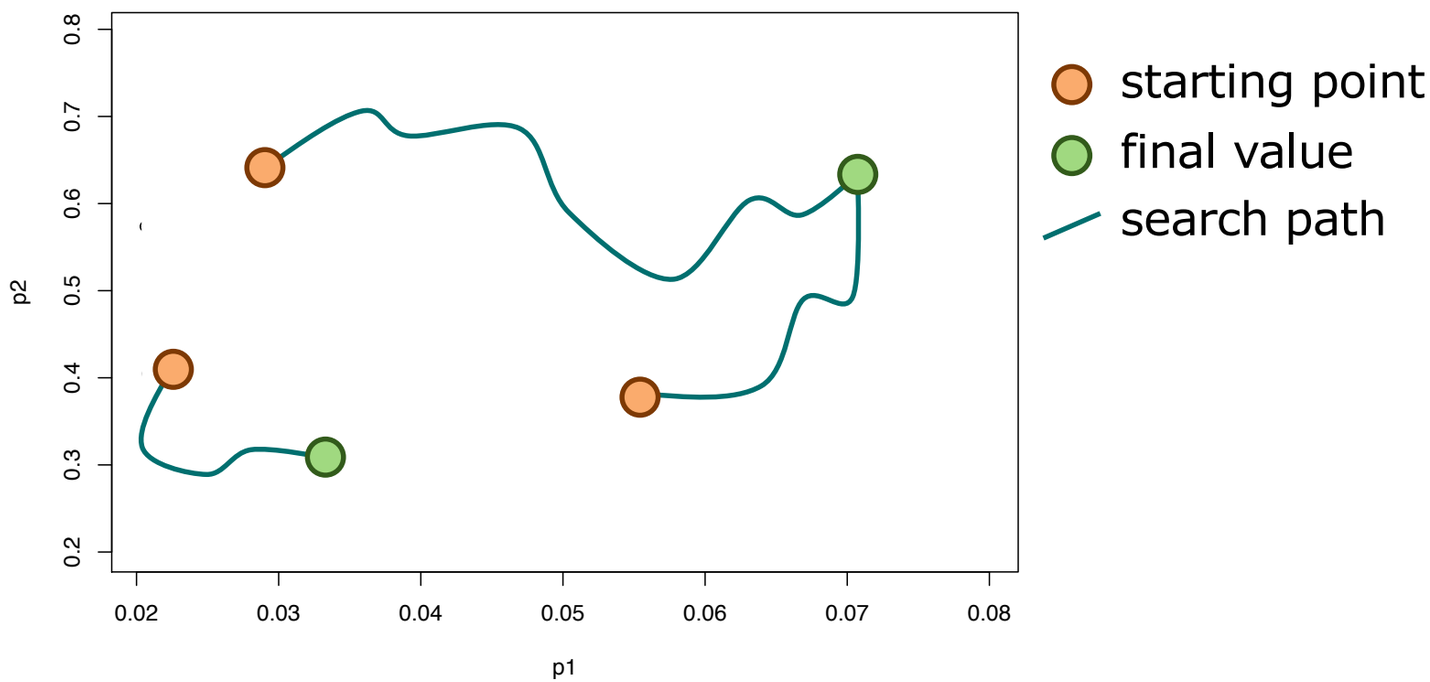
LHS sample

Iterative Search

- Use fits of past input values to determine which input values to try next
- Directed methods
  - Nelder-Mead (simplex method)
  - Gradient–descent and others
- Meta-heuristic algorithms
  - Genetic algorithms
  - Simulated annealing

Nelder-Mead Algorithm

- Downhill simplex method
- Must be run multiple times for different starting points to avoid local extrema



Example:
Calibrating a 3-state cancer model

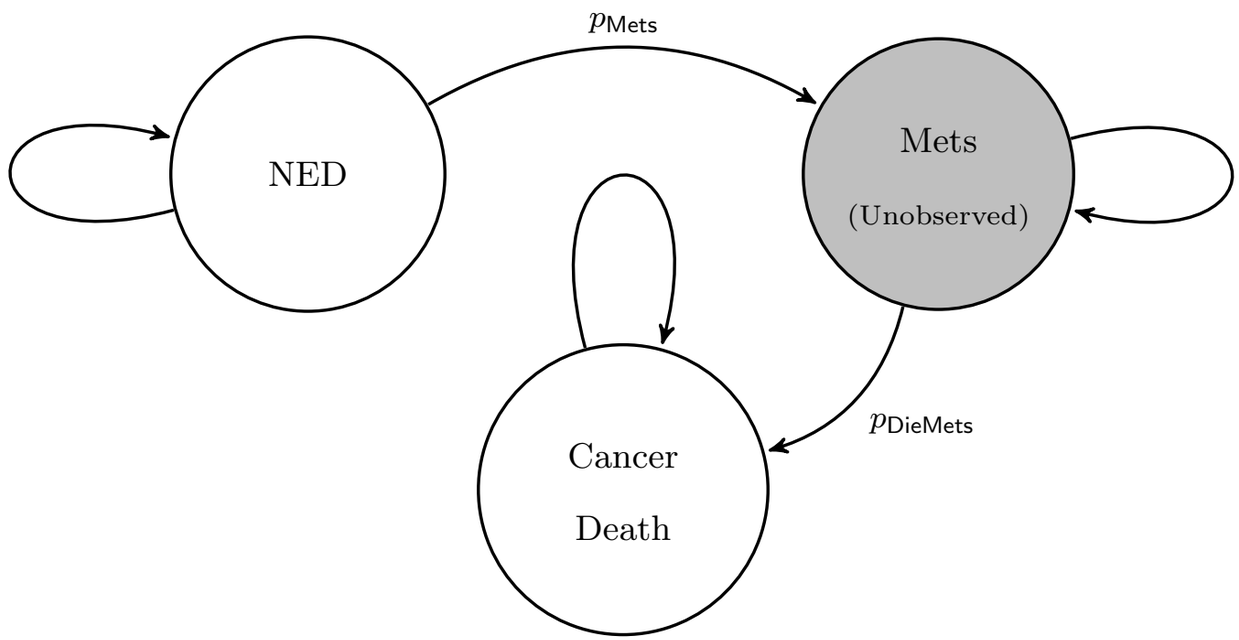
3-state cancer model

- Relative survival as reported by the Surveillance, Epidemiology, and End Results (SEER) Program, represents cancer survival in the absence of other causes of death
- Cancer Markov models often have a distant metastasis state, a state not directly observed in SEER, from which cancer deaths are presumed to occur
- These models are used to model interventions that affect transitions to and from this state

Alarid-Escudero F, Maclehose RF, Peralta Y, Kuntz KM, & Enns, EA. Non-identifiability in model calibration and implications for medical decision making. *Medical Decision Making,* 2018;38(7):810–21.

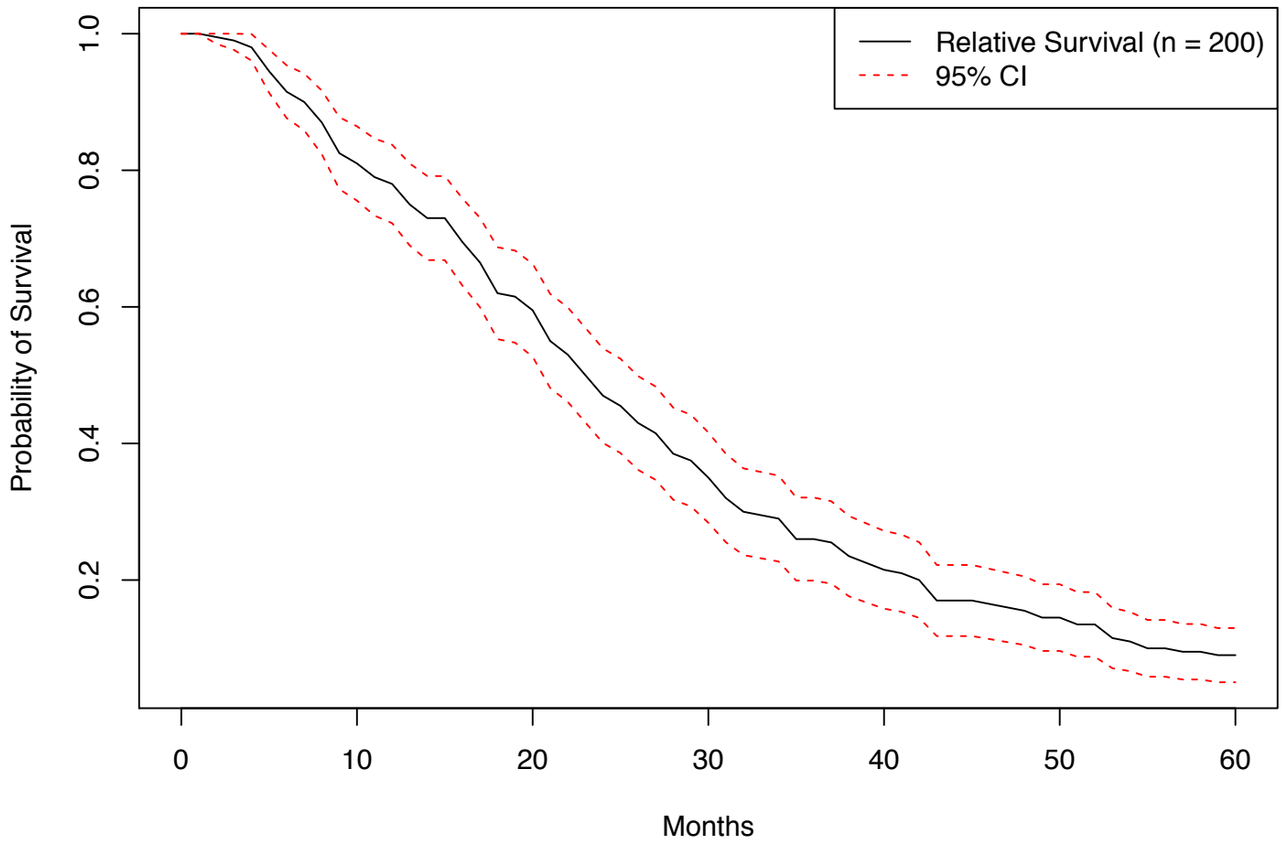
3-state cancer model

- Two unknown transition probabilities
  - p.Mets: Monthly risk of developing distant recurrence, range = [0.04, 0.16]
  - p.DieMets: Monthly risk of cancer death, range = [0.04, 0.16]



Target: Relative survival

- Data frame “CRS_targets$Surv” stored in data file “CRS_CalibTargets.RData”



Calibration R code template

```
### Load calibration targets ###


### Load model as a function ###


### Specify calibration parameters ###


### Calibrate ###


### Explore best-fitting input sets ###
```

R Session

Bayesian Calibration

Bayesian setup

- Instead of a single best-fitting value, we would like an estimate of uncertainty in model parameters, θ, given our observed targets, y
  - E.g. a posterior distribution $p(\theta|y)$
- Recall Bayes theorem

$$p(\theta|y) = \frac{p(y|\theta)p(\theta)}{p(y)}$$

  - $p(\theta)$ is the prior distribution
  - $p(y|\theta)$ has a "related" likelihood function $L(y|\theta) \propto p(y|\theta)$
  - $p(y) = \int p(y|\theta)p(\theta)\, d\theta$ is not a function of θ and often difficult to calculate

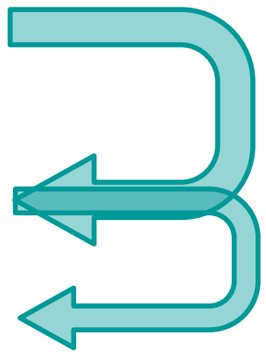
Bayesian setup

- A few steps of math...

$$p(\theta|y) = \frac{p(y|\theta)p(\theta)}{\cancel{p(y)}}$$

$$p(\theta|y) \propto p(y|\theta)p(\theta)$$

$$p(\theta|y) \propto L(y|\theta)p(\theta)$$



- Using this fact, we can sample the posterior distribution using the likelihood function, prior distribution, and some clever algorithms

Commonly used prior distributions for sampling n_s values

- **Normal distribution**

  In R: `rnorm(n=` n_s`, mean=`$\bar{\theta}$`, sd=`σ_i`)`

- **Uniform distribution**

  In R: `runif(n=` n_s`, min=` lb`, max=`ub`)`

- **Beta distribution**

  In R: `rbeta(n=` n_s`, shape1=`α`, shape2=`β`)`

- **Gamma distribution**

  In R: `rgamma(n=` n_s`, shape=`α`, rate=`β`)`

Pros and Cons of Bayesian Calibration

- **Pros:** We obtain distributions of parameters rather than only point estimates
- **Cons:** “Harder” to implement than other methods? Mmm not really!

Obtaining a Posterior Distribution

- Analytically
  - Not feasible for simulation models
- Markov chain Monte Carlo (MCMC)
- Sampling methods
  - Sampling Importance Resampling (SIR)
  - Incremental Mixture Importance Sampling (IMIS)

Markov chain Monte Carlo (MCMC)

- Simulates posterior distribution by **jumping** in the parameter space in a Markovian fashion
- The transition matrix of the Markov chain is proposed using a **proposal distribution**
- There are numerous MCMC algorithms, including **Metropolis-Hastings** (MH)
- R has some packages that implement MCMC algorithms
- Other R packages interface with external MCMC software, including WinBUGS, JAGS, and Stan

Markov chain Monte Carlo (MCMC)

- **Pros:**
  - Theoretically will eventually converge to the “true” posterior distribution

- **Cons:**
  - Computationally intensive
  - Autocorrelation is a problem with simulation models and therefore requires a high number of samples
  - Use of external software (WinBUGS, JAGS), requires implementing the model within that software’s syntax

Sampling Importance Resampling (SIR)

Used to simulate posterior distributions (Rubin 1988) with three basic steps

1. **Sampling:** Sample a large number, N, of parameter sets from prior distributions
2. **Importance:**
   1. For each parameter set θ_i $(i = 1, \ldots, N)$, run the simulation model and compute the likelihood
   2. Compute the (normalized) sampling importance weights w_i for each parameter set θ_i by dividing its likelihood value by the sum of likelihood values of all parameter sets,

$$w_i = \frac{L_i}{\sum_{i=1}^{N} L_i}$$

3. **Resampling:** Sample from the discrete distribution of $\{\theta(1), \ldots \theta(N)\}$ with probabilities w_i

Incremental Mixture Importance Sampling (IMIS)

- SIR can miss areas of high posterior probability as the number of parameter increases
- IMIS addresses limitations of SIR and was proposed by Steele at al. (2006)
- Starts with a modest-size SIR
- But in addition to SIR samples, add in samples from a multivariate normal distribution centered at the point with the highest importance weight
- Recalculate importance weights and sample a new sample of input parameter sets
- At the end, posterior becomes a mixture of multivariate normal distributions and of the prior distribution

Incremental Mixture Importance Sampling (IMIS)

1. **Initialization.**
   a) Sample N parameter sets from prior distribution
   b) For each parameter set, θ_i, calculate the likelihood L_i and compute the importance weights w_i
2. **Importance sampling**. Iterate for $k = 1, 2, \ldots$
   a) Choose parameter set with maximum importance weight as the mean of a multivariate normal (MVN) distribution, and compute covariance matrix from nearby parameter sets. Define $H_k = \mathrm{MVN}(\theta^k, \Sigma^k)$.
   b) Sample B new input sets from H_k
   c) Re-calculate importance weights, w_i^k, for all $N + Bk$ samples
   d) Repeat Step 2 until stopping criteria is met.
3. **Resampling**. Resample B_{re} input sets with replacement using importance weights from the last iteration, K. This is a sample from the posterior distribution.

Incremental Mixture Importance Sampling (IMIS) in `R`

- Function `IMIS()` from `IMIS` library takes the following inputs
  - `B`: sample size at each iteration of IMIS
  - `B.re`: number of draws from the posterior
  - `number_k`: maximum number of iterations in IMIS

- IMIS() also requires the following functions to be defined by the user
  - `prior(x)`: returns the prior density of x
  - `likelihood(x)`: returns the likelihood of x
  - `sample.prior(n)`: returns n samples from prior distribution of x

Incremental Mixture Importance Sampling (IMIS) Outputs

- `resamples`: `B.re` draws from the posterior distribution
- `stat`: diagnostic statistics at each IMIS iteration
  - `MargLike`:
  - `UniquePoint`: expected number of unique points among `resamples`
  - `MaxWeight`: maximum importance weight
  - `ESS`: effective sample size (the closer to `B.re`, the better)
- `center`: center of Gaussian components

R Session

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