# Plan for Comparative Methods Study on Penalisation Methods for Multi-State Models

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## Overview

Multi-state models (MSM) are useful for prediction of complex clinical settings where patients may transition through several intermediate states before experiencing a terminal event [1][2][3][4][5]. A challenge of MSMs is the combinatorial complexity in models as the number of chronic conditions being modelled grows. This increases computation time, but also risks overfitting of some of the transition models within the MSM, especially those with fewer events/ observations.

One potential solution to this is to share parameters between transitions within the model [5]. For example, one could assume that certain groups of transitions share a common baseline and/or predictor effects. The properties of doing this in a prediction context (of multi-morbidity) are unknown. Likewise, in a prediction context, penalisation methods are often advocated to help minimise the risk of overfitting. Therefore, it is of interest to examine the impact of penalisation methods on this situation with or without sharing of parameter terms across the transitions. While the use of shared parameters across transitions to reduce the parameter space is well-documented, the concept of penalisation in this context is less well-studied.

## Definitions

We broadly define the terms relevant to this review:

MLE – Maximum likelihood estimate

LASSO - least absolute shrinkage and selection operator

CPRD – Clinical practise research datalink

Fold – A fold refers to the subset of the dataset that is used for training and validation.

Cross validation loop – A cross validation loop is the process by which a dataset is split into k folds. The model would then be trained and validated k times and using a different fold as the validation set each time.

Horseshoe prior – A type of Bayesian prior distribution, designed to encourage shrinkage of parameter estimates toward zero while allowing for the possibility of some parameters to remain large.

Metropolis-Hasting method – A Markov Chain Monte Carlo method (MCMC) used for generating a sequence of random samples from a probability distribution.

Burn-in period – The initial phase of the simulation where the Markov chain is allowed to converge to the target distribution.

Bootstrap sampling – A sample made by randomly drawing observations with replacement from the original dataset. This creates new datasets of the same size as the original but with some observations omitted and others repeated.

## Methodology

All analysis for this study will be conducted using R (version 4.3.1) in the RStudio environment under the MacOS Ventura operating system on a MacBook Pro (with Apple M1 Pro processor). Code for simulations and models will be provided on GitHub to ensure reproducibility.

### Scope of the Study

This study aims to compare current penalisation methodology for multi-state models. We will be considering the following methods of implementing the penalisation within prediction models:

* MLE no shrinkage
* MLE with uniform shrinkage factor applied to each transition
* LASSO penalised likelihood
* Fused-LASSO penalised likelihood [5]
* Reduced-rank methods [6]
* Bayesian approach with penalising prior to pull coefficients down towards an overall model-level value [7]

These methods will be applied to simulated data, and then applied to CPRD data [8].

### Data Simulation

We will start by simulating data for a simple illness-death model. From this, we will expand the model to change the number of states (and consequently, the number of transitions) using the *mstate* package (see Table 1). We will do this in a way such that the number of states and transitions will be determined by a parameter that we can vary across our simulation study.

Due to restrictions in packages we plan to use, data will need to be passed in a long data format. We will first simulate the model in wide format for ease of computation, and transpose this to create the long format we require.

### Penalisation Methods

Since we are using simulated survival data, a Cox proportional hazards model will be implemented using each of the penalisation methods in turn.

#### MLE No Shrinkage

In order to apply the MLE without shrinkage the *penalized* package will be used.

#### MLE with Uniform Shrinkage Factor Applied to Each Transition

To apply a uniform shrinkage factor to each transition we will specify a shrinkage factor prior to fitting our model. In the model we will multiple each covariate by the shrinkage factor, allowing the shrinkage factor to be applied uniformly to both covariates across each transition in the model. This will be fitted using the *mscoxph* function from the *mstate* package.

#### LASSO Penalised Likelihood

In order to apply the LASSO penalised likelihood, we will first concentrate on finding the optimum tuning parameter for the LASSO. This will be done using cross-validation:

1. Split the dataset into 10 folds.
2. For each potential value of the tuning parameter, perform a cross-validation loop.
3. Choose the tuning parameter that provides the best model performance across all folds.

In R, this will be done using the *glmnet* package, using *cv.glmnet* to perform the cross-validated LASSO, and the *glmnet* function to fit the final model with the optimal tuning parameter using the lambda argument of the function, and the *family* argument to specify the Cox model. To indicate to the *glmnet* function that we are using LASSO penalisation, we will set the *alpha* argument to 1.

#### Fused-LASSO Penalised Likelihood (Shared Parameters)

Just like in the LASSO penalised likelihood, we will first find the optimum tuning parameter for the fused-LASSO penalisation. When using the *cv.glmnet* function, we will set the *alpha* argument to 0.5 to indicate a fused-LASSO approach.

#### Reduced-Rank Method

To implement the reduced-rank method of penalisation, we will use the *redrank* function of the *mstate* package. We will choose the value of *R* (the rank of the matrix used for the reduced-rank problem) based on cross-validation and choose the rank that minimizes prediction error on unseen data.

#### Bayesian Approach with Penalising Prior (Shared Parameters)

We have decided to use a horseshoe prior as described in Beesley (2020). A horseshoe prior is a continuous shrinkage prior, that strongly shrinks moderate and weak signals to zero, while still allowing very large signals. The prior takes the form:

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where smaller implements a greater global shrinkage, and indicated the half-Cauchy distribution. and can be sampled in turn using the Metropolis-Hasting method. As we are applying the horseshoe prior to a multi-state model, we will define separately for each transition.

We will be using the *brm* function from the *brms* package to implement this type of penalisation. We will specify priors for the intercept, standard deviation, and each covariate in the model. The models using the simulated data will not be complex, so we will only use 2 chains. We will start with 2000 (with a burn-in period of 1000 iterations) iterations, as this provides a good balance between computational efficiency. Using trace-plots and the Gelman-Rubin statistic we will assess convergence; if these diagnostic tools show that insufficient convergence has occurred, we will increase the number of iterations.

### Packages to Use

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| Package | Use |
| mstate | Contains functions needed for data preparations, description and hazard estimation for multi-state models [9]. This includes reduced rank proportional hazards model for multi-state models. |
| tidyverse | A collection of packages for preparing, wrangling and visualising data [10]. |
| genSurv | Generation of survival data with one (binary) time-dependent covariate [11]. |
| penalized | Used to fit penalized regression models for lasso and fused lasso penalties [12]. Also used for the MLE penalisation with no shrinkage. |
| shrink | Used for uniform (global) shrinkage [13]. |
| brms | Used for fitting a Bayesian Cox model with a horseshoe prior [14]. |
| glmnet | Used for providing efficient LASSO penalisation [15]. |
| Table 1: A list of packages and their uses. | |

## Validation

### Internal Validation

Bootstrapping will be used for internal validation of our models on the simulated data [16]. We will create multiple bootstrap samples. For each penalisation method, we will fit multiple models using each bootstrap sample in turn, using the same model specification as we used in the original analysis.

For each model fitted using the same penalisation method, we will calculate the following performance measures:

* Time-dependent ROC curves [17]
* C-Index [18]
* Calibration plots [19]

We will then aggregate the results, to calculate the average and confidence internals across all the bootstrap samples. This will be compared with the performance measures of the original model to check that the results are consistent with those of the bootstrapped samples.

### External Validation - Use on ‘Real World’ Data

Using the CPRD dataset, we will start by pre-processing the data to be of a similar format to the simulated data. This will include using complete case analysis to handle missing data, as our simulation did not have missing data. We will also ensure that any categorical variables are encoded in the same way as the simulated dataset, and that all variables present in the Cox models are present in the CPRD dataset.

After the data has been pre-processed, the Cox models for each of the penalisation methods will be applied using the same coefficients and specifications obtained from the original models. We will then calculate the following performance measures:

* Time-dependent ROC curves [17]
* C-Index [18]
* Calibration plots [19]

We will compare the performance of the models using ‘real world’ data to their equivalent models that used simulated data. If any model’s performance using the CPRD dataset [8] is significantly different from its performance on the original dataset we will consider refitting the model based on the new dataset.

## Author Contributions

CC and GM contributed to the conception and design of the study. All authors contributed to discussions around updates to the protocol.

CC wrote the protocol.

CC performed the data simulation and method implementation, iteratively updating the protocol where necessary.

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