Continuous Time Multi-State Models and Microsimulation

Devin Incerti

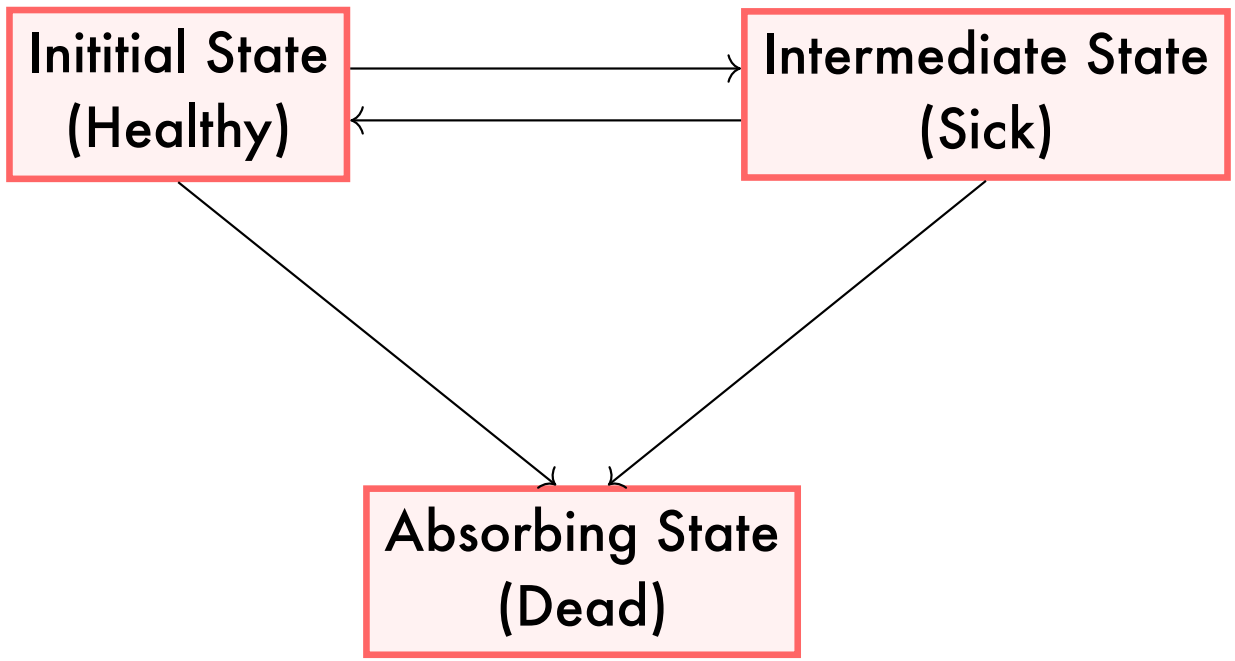
Overview

1. What are multi-state models?
2. How can multi-state models be estimated?
3. How can an estimated model be used to derive quantities of interest for health technology evaluation?

What is a Multi-State Model?

- Model of how individuals move through multiple states in continuous time
- 3 types of states
  - Initial state
  - Intermediate state
  - Absorbing state
- *Competing risk* models are a special case with one initial state and several mutually exclusive absorbing states
- *Survival analysis* is a special case with one initial state (alive) and one absorbing state (dead)

Canonical Example: The (Reversible) Illness-Death Model



Advantages for Parameter Estimation

- Properly accounts for competing risks
  - Individuals experiencing an event are no longer "at risk", which decreases transition intensities
- Flexible modeling of hazard rates
  - **Time homogeneous markov models**: transition intensities are constant over time
  - **Time inhomogeneous (clock-forward) markov models**: transition intensities depends on time since entering the initial state
  - **Semi-markov (clock-reset) models**: transition intensities depends on time since entering the current state

Advantages for Health-Economic Modeling

- Model is in continuous time
  - Predicts exact length of time in states
  - Do not need to worry about multiple events occurring during intervals
- Model is at the individual level
  - Can account for treatment heterogeneity
  - Transition intensities can depend on prior history $\rightarrow$ fewer states than in cohort models

Software for Estimating Multi-State Models

- Nearly all of it is written in R
- Prominent R packages
  - *mstate*: non-parametric and semi-parametric models
  - *flexsurv*: parametric models
  - *msm*: missing information (e.g. do not know exact time of each transition)

A Liver Cirrhosis Example

- To illustrate methods, lets consider a clinical trial where patients received "Placebo"" or "Prednisone"
- Reversible illness death model with 3 states
  - State 1: Normal prothrombin levels
  - State 2: Low prothrombin levels
  - State 3: Death
- 4 possible transitions
  - Normal to Low
  - Low to Normal
  - Low to Death
  - Normal to Death

Examining the Data

- A patient treated with Prednisone

id	from	to	trans	Tstart	Tstop	years	status	treat
33	2	1	3	0.00	0.25	0.25	1	Prednisone
33	2	3	4	0.00	0.25	0.25	0	Prednisone
33	1	2	1	0.25	9.21	8.96	0	Prednisone
33	1	3	2	0.25	9.21	8.96	0	Prednisone

- Summarizing the transitions

	to				
from	Normal	Low	Death	no event	total entering
Normal	0	272	100	117	489
Low	313	0	179	32	524
Death	0	0	0	279	279

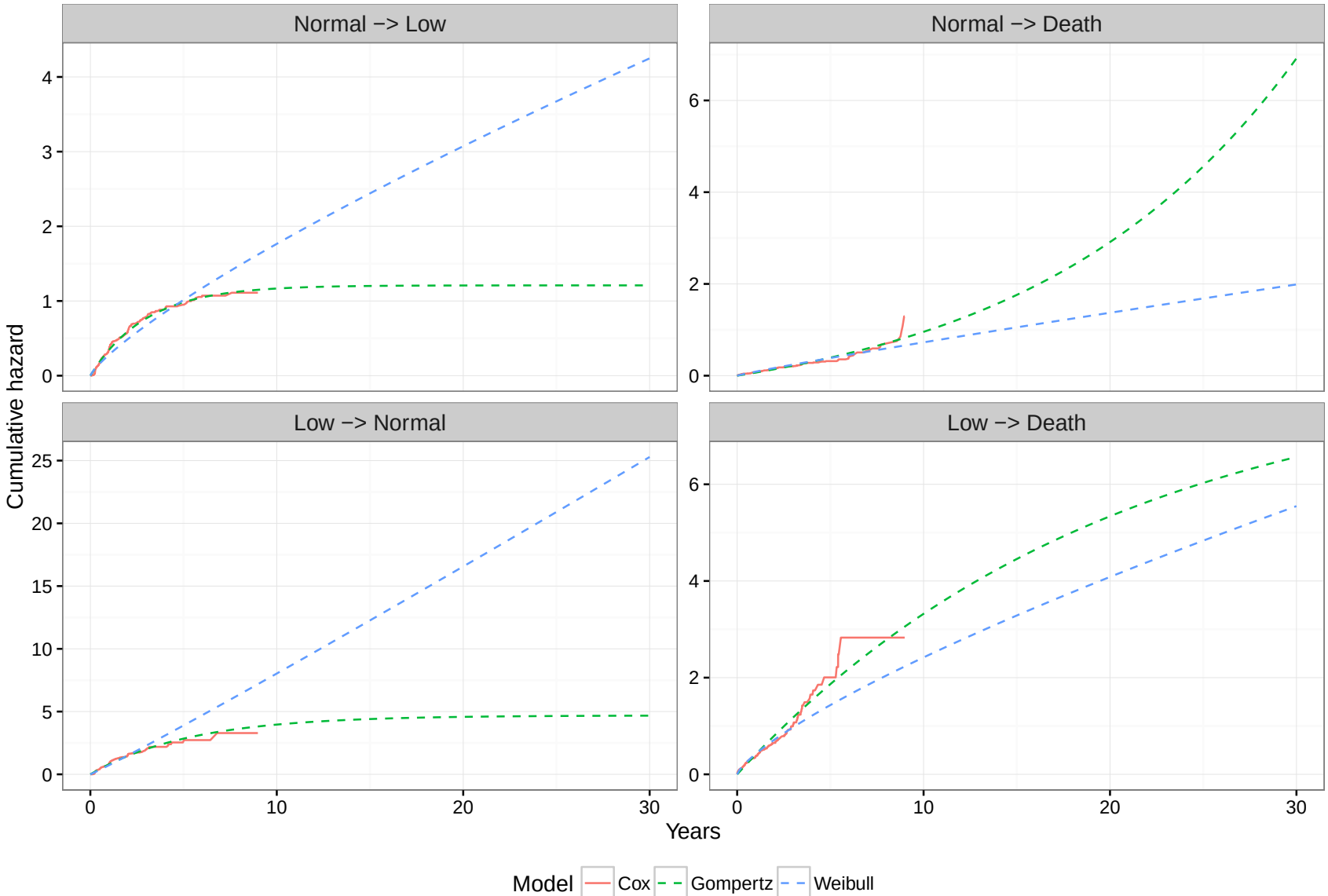
Fitting Multi-State Models

- Joint model if constraints in parameters across transitions; otherwise transition specific models are more computationally efficient
- Individuals entering "competing" states treated as censored
- Types of models
  - *Non-parametric*: fit separate Cox model to treatment and control
  - *Semi-parametric*: clock-forward or clock-reset Cox models
  - *Parametric*: clock-forward or clock-reset model with standard survival distributions (e.g. Weibull, Gompertz)

Why do we Need Parametric Models?

- We have Kaplan-Meier curves and Cox models so why use parametric models?
- Some advantages of parametric approaches
  - Extrapolation beyond time periods in data
  - Prediction for new individuals
  - Less prone to overfitting
  - Faster simulations
  - Time dependent effects (e.g. non-proportional hazards)
- Estimates from flexible parametric models are very similar to non-parametric and semi-parametric alternatives
- Model checking is essential though!

Some Model Checking



Transition Probabilities in Multi-State Models

- A transition probability is the probability of being in state $X(T) = s$ at time T given that an individual is in state r at time t_0

$$P_{rs}(t_0, T) = P(X(T) = s | X(t_0) = r) \tag{1}$$

- Given discount rate, $\beta(t)$, and quality of life weight, $q_s(t)$, discounted QALYs in state s given being in state r at time t_0 are

$$\int_{t_0}^{T} q_s(t)\beta(t)P_{rs}(t_0, t)dt \tag{2}$$

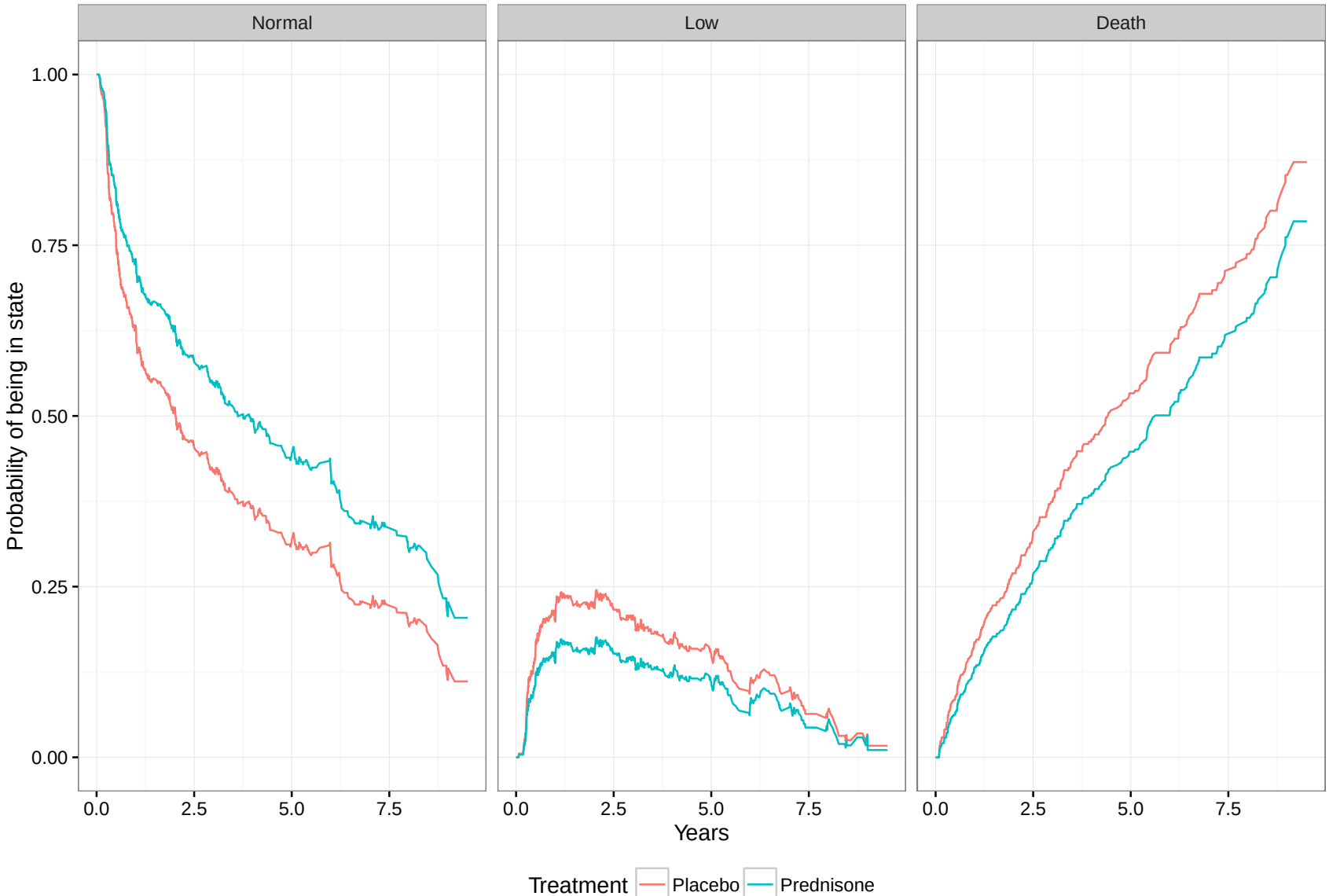
- Total QALYs are calculated by adding up QALYs in each non-absorbing state

Estimating Transition Probabilities

- Illness-death model example:
  - Probability of transitioning from state 2 at time t_0 to state 3 at time T is given by multiplying:
    1. Probability of transitioning to state 3 at some time before T
    2. Probability of remaining in state 2 until making the transition to 3
- General case for Markov models
  - Transition probabilities can be estimated by solving the *Kolmogorov forward equation*
  - Solution can be approximated by the *Aelen-Johansen estimator*
- Simulation needed for Semi-Markov Models
  - Aelen-Johansen estimator does not apply because transition probabilities from intermediate states depend on when the state was entered

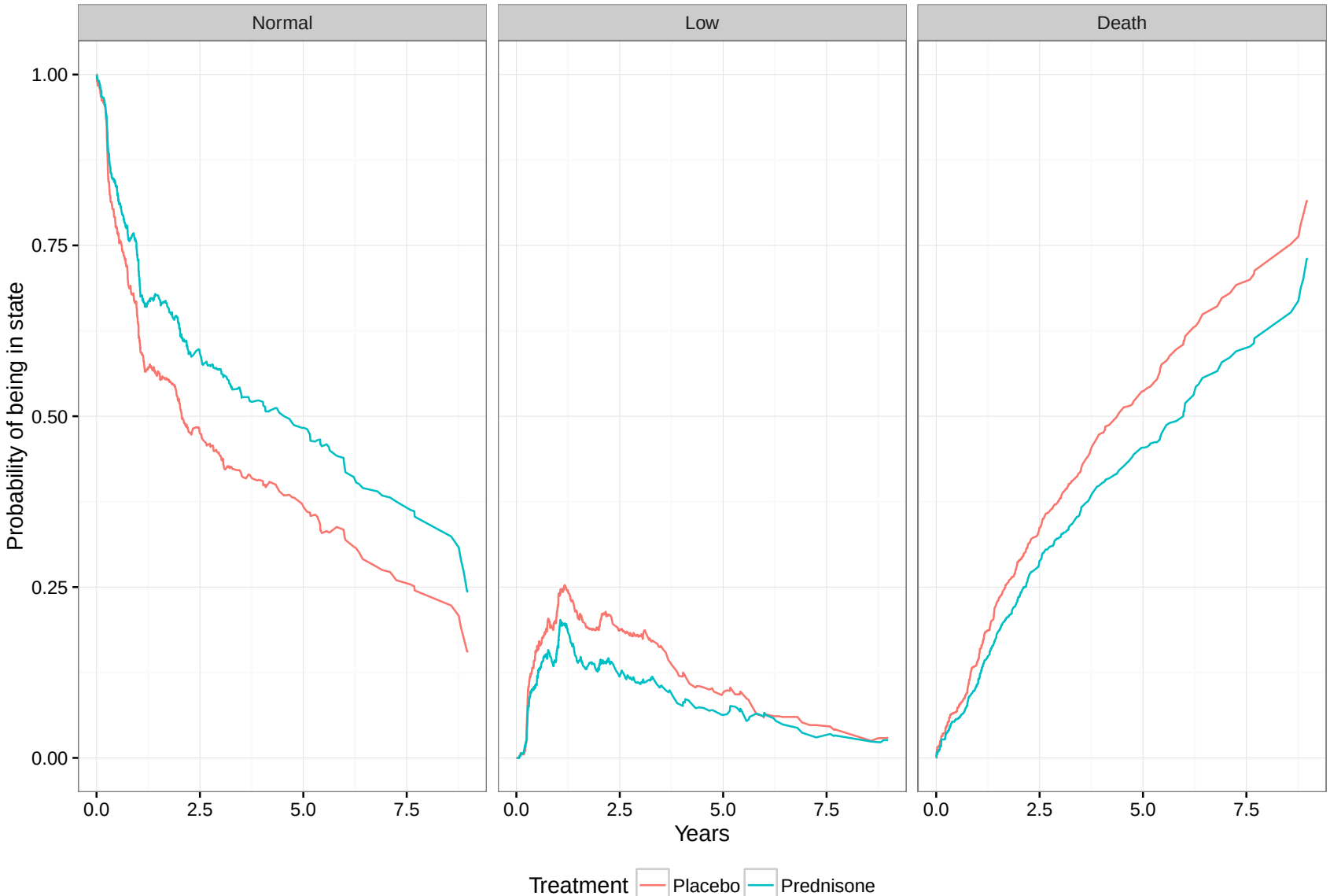
Transition Probabilities in Clock-Forward Cox Models

Using R function `probtrans` from *mstate* package



Transition Probabilities in Clock-Reset Cox Models

Using R function `mssample` from *mstate* package



Lifetime Simulation

- Parametric models can be used to simulate outcomes beyond time in data
- I've created function `simMS` for parametric Semi-Markov models
  - Time (and age) move forward as individuals jump from one event to the next
  - Simulates outcomes for a population of individuals with differing covariate values
  - Simulation stops when all individuals reach absorbing states or time has reached preset ending time
  - Can be used with any distribution by supplying a function to generate random numbers and using the custom distribution framework in *flexsurv*
  - Allows analyst to specify different distributions for each transition
  - Only valid for semi-Markov models; use `probtrans` for clock-forward Markov models

Benefits of Simulation

- Can calculate standard quantities of interest
  - Discounted QALYs (dQALYs)
  - Length of stay (LOS) in each state

	Placebo		Prednisone	
	LOS	dQALYs	LOS	dQALYs
Low	1.21	1.06	0.86	0.76
Normal	4.59	3.95	6.26	5.23

- Don't need analytical expressions to estimate other more complicated quantities
- Assess uncertainty (e.g. probabilistic sensitivity analysis)

```
                              mean 2.5%  50% 97.5%
dQALYs using Prednisone 6.12 5.14 6.07  7.34
```

When Can Multi-State Models be Used?

- Requirements
  - Individual time to event data must be available for each transition
- Scenarios in which it is most useful
  - Individuals spend a lot of time in each state
  - Risks of new events depend on time in state
  - Chance of multiple events within an interval
  - Need estiamtes for representative patient populations
- Some examples
  - *Transplantation*: functioning transplant $\Leftrightarrow$ failed transplant $\Rightarrow$ death
  - *Oncology*: surgery $\Rightarrow$ local recurrence, distant metastasis $\Rightarrow$ death