

Multi-state modelling in R: A stochastic approach to modelling pregnancy outcomes

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Focus

- To demonstrate an alternative approach to modelling the effects of previous pregnancy events (outcomes) on subsequent pregnancy events
- Current methods use regression based models. These incorporate the time component of pregnancy histories as a covariate in the model
- The approach presented today uses multi-state modelling

Context

- According to the ABS (1997) $\frac{1}{3}$ of all known pregnancies end in miscarriage
- The impact of having a miscarriage can have profound psychological and physical effects
- Numerous risk factors have been attributed to miscarriage: age, depression, smoking, previous pregnancy outcome
- The time between pregnancy events – the inter-pregnancy interval (IPI) - has gain considerable attention as a risk factor

Data

- Australian Longitudinal Study of Health and Relationships (2005)
- Random sample of women (4366) and men (4290) aged 16-64 (RR 57%)
- Women who had ever been pregnant (3485) provided a detailed history of pregnancy events:
 - Age at time of pregnancy
 - Multiple pregnancy
 - Outcome
 - Assisted pregnancy (ART)

Pregnancy Outcomes

- 4 main pregnancy events of interest:
 - Never being pregnant
 - Live births
 - Terminations
 - Non-live birth pregnancies (miscarriage, ectopic pregnancy, and still births)

Multi-state Modelling (MSM)

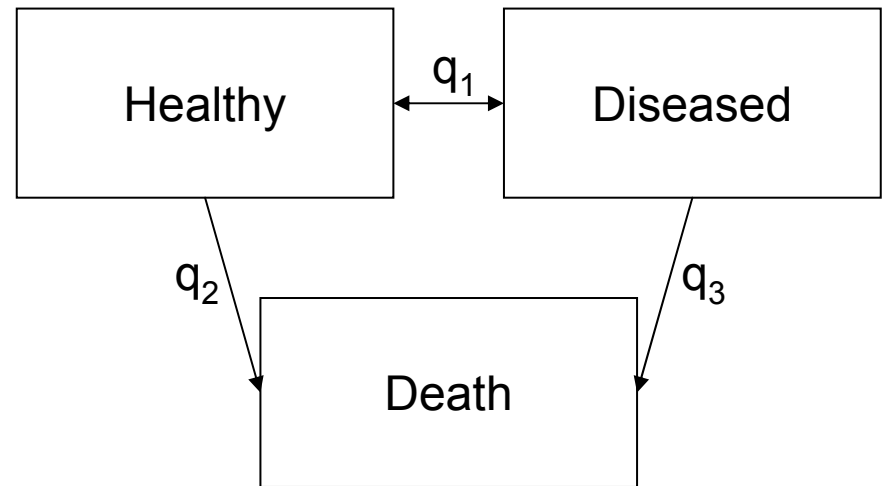
- MS models are an extension of survival analysis methods
- Are appropriate for analysing populations that move through discrete states:
 - non-disease → disease → dead (*disability model*)
 - not pregnant → pregnant (*pregnancy model*)
- Are apt for modelling both discrete time and continuous time data

MSM

Two primary components of MSM:

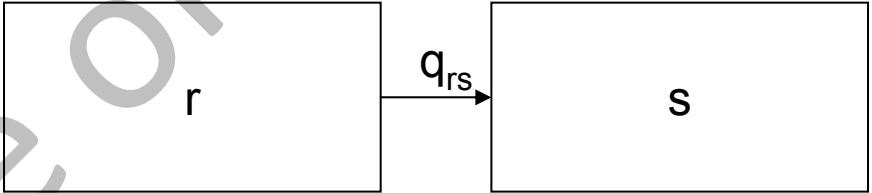
1. States – describe the condition or events
 - States are either transient or absorbing
2. Transitions – are the valid/plausible paths between states (e.g. q_{rs})

According to Hougaard¹ the best state-structure is Markovian – it can be represented graphically and model assumptions are clear



¹Hougaard, P. (2000). *Analysis of multivariate survival data*.

Transition intensities

$$q_{rs}(t) = \lim_{\delta t \rightarrow 0} \frac{\pi_{rs}(t, t + \delta t)}{\delta t}$$


- r is the transient state; s is the destination state
- q_{rs} is the probability of being in state s at time $t + \delta t$ given previously being in state r at time t
- The probability that a particular state s is the destination state from r is given by:

$$\pi_{rs} = q_{rs} / q_{rr}$$

- Explanatory variables (z) can be fitted: $q_{rs}(t, z(t))$

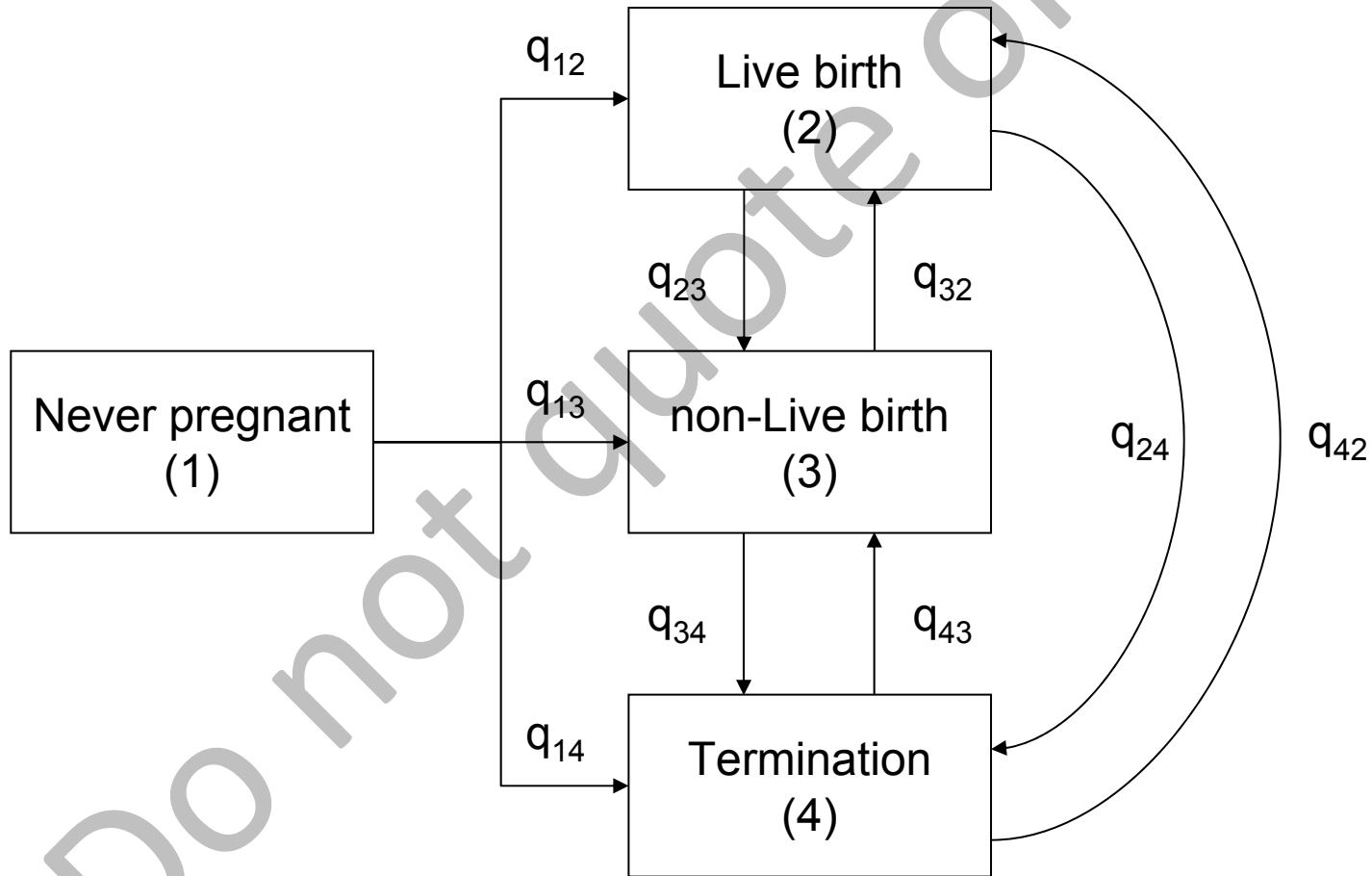
Transition intensities matrix

$$\mathbf{Q} = \begin{pmatrix} q_{11} & \dots & q_{1k} \\ \vdots & \ddots & \vdots \\ q_{k1} & \dots & q_{kk} \end{pmatrix}$$

- Q is the combined information of all transition intensities between states (1...k) where the diagonals q_{rr} are defined by:

$$q_{rr} = -\sum_{r \neq s} q_{rs}$$

MSM model for pregnancy data



Data preparation

Id	Event order	Outcome	IPI	Event age	Age first sex	Age first pregnant	Current Age
1	0	not pregnant	0	20	20	30	38
1	1	non live	120	30	20	30	38
1	2	non live	132	31	20	30	38
1	3	non live	138	31	20	30	38
1	4	live	144	32	20	30	38
2	0	not pregnant	0	16	16	23	26
2	1	live	84	23	16	23	26
3	0	not pregnant	0	17	17	19	42
3	1	term	24	19	17	19	42
3	2	term	48	21	17	19	42
3	3	term	120	27	17	19	42

msm package

- Allows a general Markov multi-state model to be fitted to longitudinal data
- accommodates data where *exact* time of events are known or *arbitrarily* determined
- Able to model transition rates
- Calculate sojourn time in a state
- Accommodates censored data
- Fit additional covariates

Jackson, C (2007) Multi-state modelling with R: the *msm* package (Ver. 0.7.4)

msm code

`msm(formula, subject = NULL, data = list(), qmatrix [,other arguments])`

Other arguments can include:

- If exact times of events are known (`exacttimes`)
- Censored data (`censor`)
- Absorbing states (`death`)
- Specification of a hidden Markov model (`hmodel`)
- Covariates to be accounted for (`covariates`)

msm pregnancy code

```
pregnancy<-msm(outcome~ipi, subject=id, data,  
  qmatrix=crudemat, exacttimes=TRUE)
```

Where

```
crudemat<-crudeinits.msm(outcome~ipi,id,data,  
  qmatrix=twoway4.q)
```

Where

- `twoway4.q<-rbind("nev_preg"=c(0,1,1,1),
 "l_birth"=c(0,0,1,1), "nl_preg"= c(0,1,0,1),
 "term"=c(0,1,1,0))`

Results

Estimated transition intensities for pregnancy outcomes

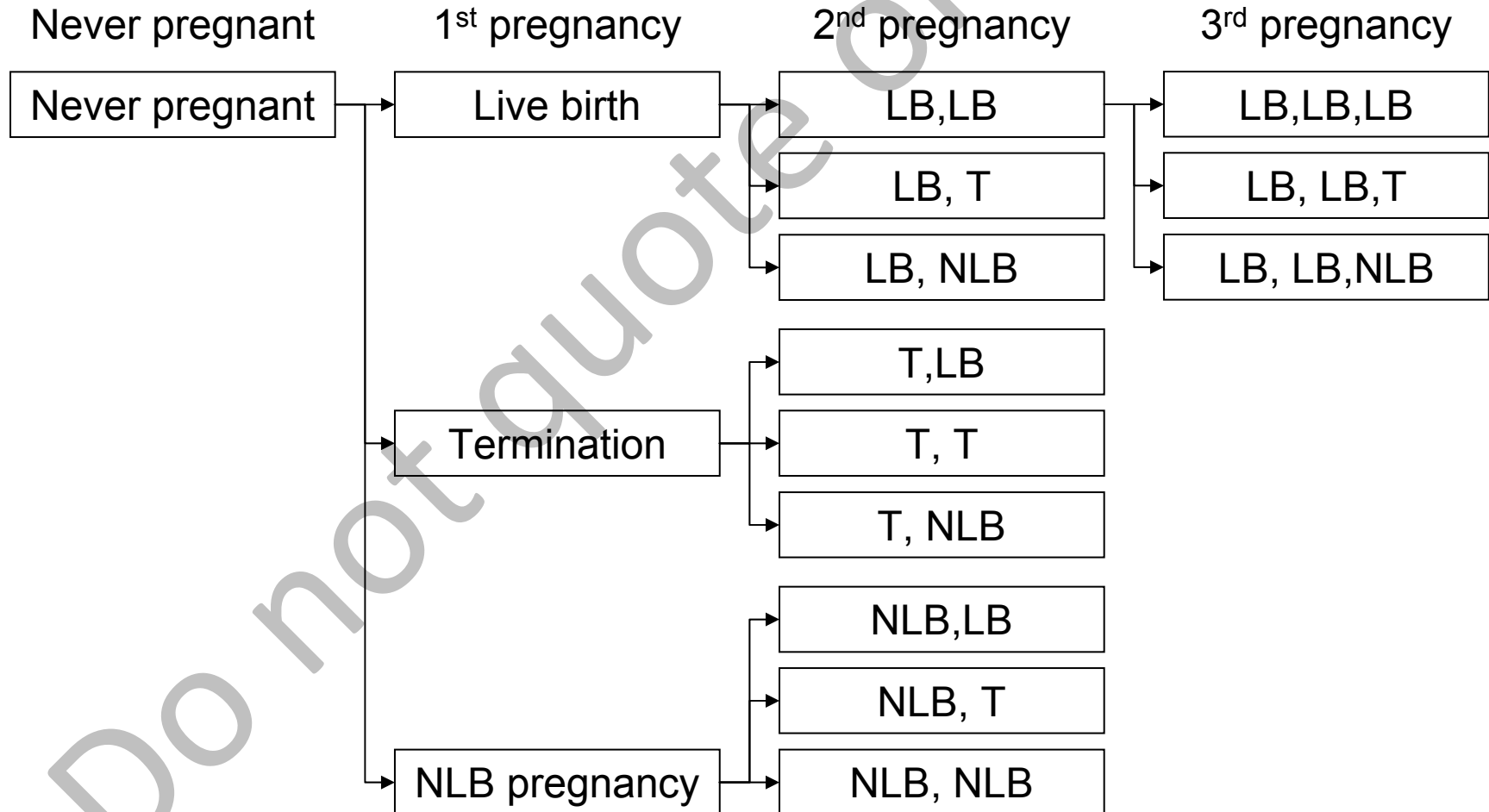
		NP	LB	NLBp	Term
NP	q_{rs}	-0.0145	0.0107	0.0021	0.0017
	CIs	(-0.015,-0.014)	(0.0103,0.0111)	(0.0019,0.0022)	(0.0016,0.0019)
LB	q_{rs}		-0.0054	0.0041	0.0014
	CIs		(-0.0058,-0.0051)	(0.0038,0.0044)	(0.0012,0.0015)
NLBp	q_{rs}		0.0351	-0.036	0.0009
	CIs		(0.0327,0.0377)	(-0.0386,-0.0336)	(0.0006,0.0014)
Term	q_{rs}		0.0102	0.0023	-0.0126
	CIs		(0.0091,0.0115)	(0.0018,0.003)	(-0.0139,-0.0113)

Results

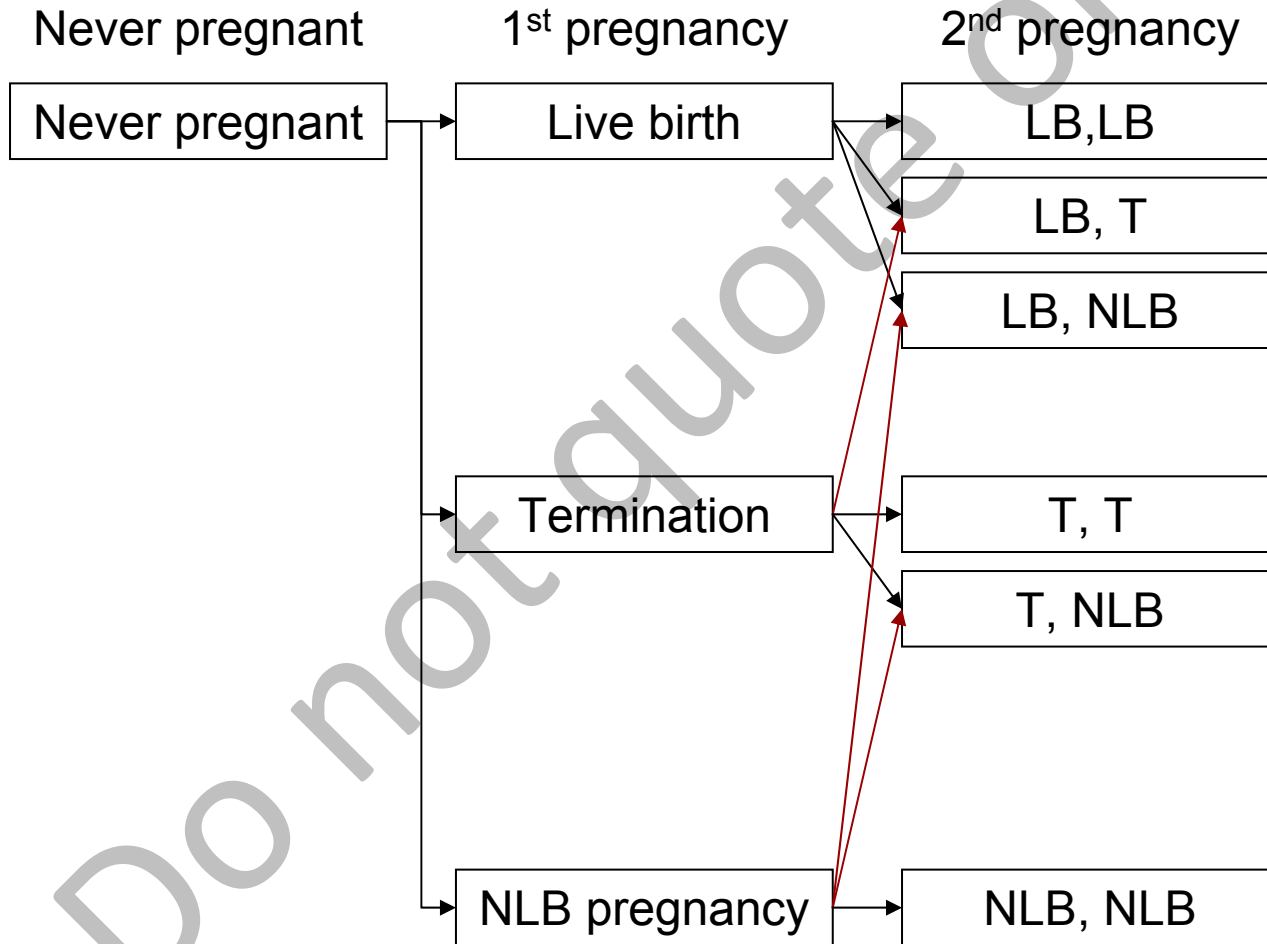
Odds ratio for transition intensities with age at first sex

		Odds Ratio	Lower CI	Upper CI
NP	LB	1.42	1.33	1.52
	NLBp	1.23	1.05	1.45
	Term	0.61	0.50	0.74
LB	NLBp	1.01	0.88	1.16
	Term	0.69	0.53	0.89
NLBp	LB	1.21	1.08	1.35
	Term	0.70	0.26	1.88
Term	LB	1.43	1.14	1.80
	NLBp	1.11	0.65	1.91

Desirable approach



Alternative desirable approach



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