Rheumatoid Arthritis disease progression in a South African cohort: Multistate chronic dynamic disease modelling.

Musenge E (PhD), Hodkinson B (PhD), Ally M (MD), Meyer PWA (PhD), Anderson R(PhD) and Tikly M (PhD)
Outline

• Definition of Rheumatoid Arthritis
• DAS28 and HAQ-DI
• Prior and posterior modelling
• Disease progression multistate models
• Great study and analysis
  – Fitting the no covariates model
  – Fitting model with covariates
  – Model goodness of fit
• Concluding remarks
Definition of Rheumatoid Arthritis

- **Rheumatoid arthritis (RA)** is a chronic disease, that affects many tissues and organs, but mainly flexible joints making them tender or swollen.
- This can lead to permanent disability or substantial loss of functioning and mobility if not adequately treated.
- Arthritis is the most common physical reason for people, especially the elderly, becoming disabled and encountering difficulty in performing activities of daily living (ADL)
DAS28 and HAQ-DI

• Disease activity in Rheumatoid arthritis (RA) patients is measured by a 28 joint disease activity score (DAS28):

\[
DAS28 = 0.56 \sqrt{\text{TENDER JOINTS}} + 0.28 \sqrt{\text{SWOLLEN JOINTS}} + 0.70 \ln(\text{ESR/CRP}) + 0.014 \times \text{VAS}
\]

  – Patients on treatment generally move from high disease activity (DAS28 >5.1) to moderate, low disease activity and eventually remission (DAS 28 <2.8).

• Functional disability as measured by the health assessment disability index (HAQ-DI) is a function of disease activity early in the disease.
A priori and a posteriori methods

Sir Ronald Ross (1857-1932)

Ross, (July 15, 1915), An application of the theory of probability to the study of a priori pathometry. (Page 205)

“The whole subject is capable of study by two distinct methods which are used in other branches of science, which are complementary of each other, and which would converge towards the same results – the a posteriori and the a priori methods. In the former we commence with observed statistics….fit analytical laws to them and so work backwards to the underlying cause…..and in the latter we assume a knowledge of causes, construct our differential equations on that supposition….and finally test the calculated results by comparing them with the observed statistics.”
A priori and a posteriori models
SIR model (time homogeneity)

A Priori model

\[
\begin{align*}
\frac{dS(a)}{da} &= -\lambda S(a) \\
\frac{dI(a)}{da} &= \lambda S(a) - \sigma I(a) \\
\frac{dR(a)}{da} &= \sigma I(a)
\end{align*}
\]

Hepatitis A from Bulgaria, Keiding (1991)

Data

A Posteriori model

\[
\begin{align*}
\pi_i &= 1 - e^{-\int \lambda da} \\
Y_i &= \begin{cases} 
1 & \text{sero} + \pi_i \\
0 & \text{sero} - \pi_i
\end{cases} \\
Y_i &\sim B(\pi_i)
\end{align*}
\]

My focus is on priori models for disease progression using frequentist and later develop Bayesian inference procedures.
Disease progression multistate model & intensity matrix

Jackson et. al (2003)

\[
Q = \begin{pmatrix}
q_{11} & q_{12} & 0 & 0 & \cdots & 0 & q_{1n} \\
q_{21} & q_{22} & q_{23} & 0 & \cdots & 0 & q_{2n} \\
0 & q_{32} & q_{33} & q_{34} & \cdots & 0 & q_{3n} \\
0 & 0 & q_{43} & q_{44} & \cdots & 0 & q_{4n} \\
\vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
0 & 0 & 0 & 0 & \cdots & 0 & 0
\end{pmatrix}
\]
Model specification

\[ q_{rs} = q_{rs}(t, \mathcal{F}_t) = \lim_{\delta t \to 0} [\Pr \{ S_i(t + \delta t) = s | S_i(t) = r, \mathcal{F}_t \} / \delta t]. \]

- Time homogeneous and Markov, Komogorov forward and backward equations
- Independent of time and observation history
- Below is the transition rate when we add a covariate

\[ q_{rs}(t, z(t)) = q_{rs} \exp \{ \beta_{rs}^T z(t) \}. \]

- Adopting the Bayesian approach, we can introduce priors in the modelling of the rates

\[
\text{Probability (process, parameters|data)} \propto \text{Likelihood} \\
\times \text{(data|process, parameters)} \times \text{Probability (process|parameters)} \\
\times \text{Probability (parameters)}
\]

\[
\pi(\Theta, \xi, \eta|y) \propto \pi(y|\Theta, \xi, \eta)\pi(\eta|\xi, \Theta)\pi(\xi, \Theta)
\]
Great study cohort

• Longitudinal data used were from patients enrolled in an observational cohort in Johannesburg and Pretoria, know as the Gauteng Rheumatoid Arthritis Trial (GREAT), a prospective study of early (less than 2 years) disease-modifying anti-rheumatic drugs (DMARD) naive RA
  – There were 171 patients average age 47(±12.5), majority 82% females and 23% smokers.
  – The average years in school were 8.9(±3.2) and 11.7(±7.0) months duration of illness before treatment.
  – About half (48.7%) had moderate / low disability i.e. HAQ-DI <1.5
Fitting the MLE no covariates Model

```r
> ###Transition Matrix for a no covariates model
Call:
msm(formula = das_cat ~ duration, subject = patid, data = cav1,
     qmatrix = twoway4.q, death = 4, ....)

Maximum likelihood estimates:
Transition intensity matrix

<table>
<thead>
<tr>
<th></th>
<th>State 1</th>
<th>State 2</th>
<th>State 3</th>
<th>State 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>State 1</td>
<td>-1.701</td>
<td>1.686</td>
<td>0</td>
<td>0.01471</td>
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<tr>
<td>State 2</td>
<td>1.89</td>
<td>-8.979</td>
<td>7.084</td>
<td>0.005192</td>
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<td>State 3</td>
<td>0</td>
<td>1.194</td>
<td>-1.492</td>
<td>0.298</td>
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<tr>
<td>State 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-0</td>
</tr>
</tbody>
</table>

-2 * log-likelihood: 556.9172

> ###Transition probability Matrix at time=1 (month)

<table>
<thead>
<tr>
<th></th>
<th>State 1</th>
<th>State 2</th>
<th>State 3</th>
<th>State 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>State 1</td>
<td>0.30138501</td>
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<td>0.4808407</td>
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<td>0.13914678</td>
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<td>0.5811509</td>
<td>0.17369439</td>
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<td>State 3</td>
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<td>0.09796933</td>
<td>0.5919288</td>
<td>0.21925667</td>
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<tr>
<td>State 4</td>
<td>0.00000000</td>
<td>0.00000000</td>
<td>0.00000000</td>
<td>1.00000000</td>
</tr>
</tbody>
</table>
```
GREAT’s multistate transition matrix

- The average time patients spent in remission, moderate (mild) or severe was 7.0 (-1/-1.701), 1.3 and 8.0 months respectively.
- A patient starting with moderate disease is 3.75 times (7.084/1.89) more likely to be get worse than get better.
- The likelihood to die is about 20 fold (0.298/0.01471) in those who with severe disease compared to those with low disease.
- Based on the higher forces from moderate to severe compared to remission it is desirable to keep patients remitting state.
RA prevalence plots by state
Effect of HAQ-DI and model improvement (model with a covariate)

- As the HAQ-DI score increases by 1 unit the likelihood of a person in remission dying is 1.6.
- Addition of HAQ-DI improved the model significantly.

```r
> hazard.msm(cav.msm22)
$haq

<table>
<thead>
<tr>
<th>State 1 - State 2</th>
<th>HR</th>
<th>L</th>
<th>U</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0.8360627</td>
<td>1.908538e-01</td>
<td>3.662493e+00</td>
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<tr>
<td><strong>State 1 - State 4</strong></td>
<td><strong>1.5617821</strong></td>
<td><strong>1.028507e+00</strong></td>
<td><strong>2.371558e+00</strong></td>
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<tr>
<td>State 2 - State 1</td>
<td>1.0447772</td>
<td>6.114683e-01</td>
<td>1.785145e+00</td>
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<tr>
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<td>1.210189e-01</td>
<td>1.004201e+00</td>
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<tr>
<td>State 2 - State 4</td>
<td>1.1898887</td>
<td>5.556062e-04</td>
<td>2.548271e+03</td>
</tr>
<tr>
<td>State 3 - State 2</td>
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<td>2.067787e-01</td>
<td>9.866259e-01</td>
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<tr>
<td>State 3 - State 4</td>
<td>0.8637799</td>
<td>4.462549e-06</td>
<td>1.671950e+05</td>
</tr>
</tbody>
</table>

> lrtest.msm(cav.msm1, cav.msm22)
-2 log LR df p
  cav.msm22  35.07  7 1.085068e-05
```
HAQ-DI Covariates model figures

Rheumatoid Arthritis disease progression transition rates

State 1

State 2

State 3

State 4
Concluding remarks

• Better functionality was associated with good and faster progression from severe to remission.
• In conclusion we advocate that patients should be treated until the disease activity score is in remission or lowest possible to enable greater physical functionality whilst alleviating disability and mortality due to RA.
• We also motivate for public health and interventions for people to present early at most within two years of onset of disease before much bodily damage is incurred to enable better response to treatment.
• The model fits can be improved using the Bayesian approach allowing use of other parametric distributions.
References


