Modelling red blood cell survival data

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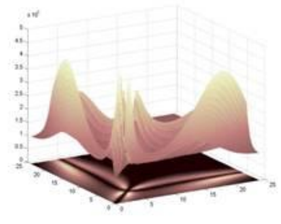

Background

- Survival of red blood cells (RBCs) is decreased in anaemia of chronic kidney disease (CKD) due to either:[1]
  - increase in random destruction.
  - accelerated senescence.
- Commonly, only a mean RBC lifespan value is determined based on RBC labelling experiments.[2]
  ⇨ Better insight into the processes of RBC destruction is desirable.
- A statistical model for the survival time of RBCs has been developed based on the plausible physiological processes of RBC destruction:[3]
  - Early destruction of unviable RBCs, reduced lifespan of misshapen RBCs, random destruction and senescence.
- The model accounts for short-comings associated with known RBC labelling techniques, such as random labelling with radioactive chromium (^{51}Cr).[4]

Objectives

- To apply the previously developed model for RBC survival to clinical data.
- To investigate differences in the RBC lifespan in anaemic CKD patients compared to healthy controls.

Materials & Methods

- Available RBC survival data using ^{51}Cr labelling method:[5]

Table I: Demographics	CKD group (n = 14)	Controls (n = 14)
Age (years) ±SD	57.2 ± 8.6	57.3 ± 7.9
Sex (M:F)	8:6	8:6
Haemoglobin* (g/L) ±SD	122 ± 12	143 ± 10

*p < 0.0001

- Two estimation scenarios were considered based on the model:
  - Estimating the main parameter controlling senescence.
  - Estimating the parameter controlling random destruction.
- Two analysis methods were used:
  1. A classical two-stage approach using generalized least squares.
     ⇨ Preference towards one of the scenarios across the individuals?
  2. A full population approach using MONOLIX 1.1.[6]
     ⇨ CKD and sex tested as covariates.
- Goodness of fit was assessed based on objective function value and visual predictive checks.
- Wald test and likelihood ratio test were used to assess significance of the tested covariates.

Results

1. Two-stage approach:
   - Estimation of random destruction preferred in majority of individuals (11 out of 14 in both groups).
   - Significant reduction in RBC survival in CKD patients: -28% compared to healthy controls (p = 0.0002).

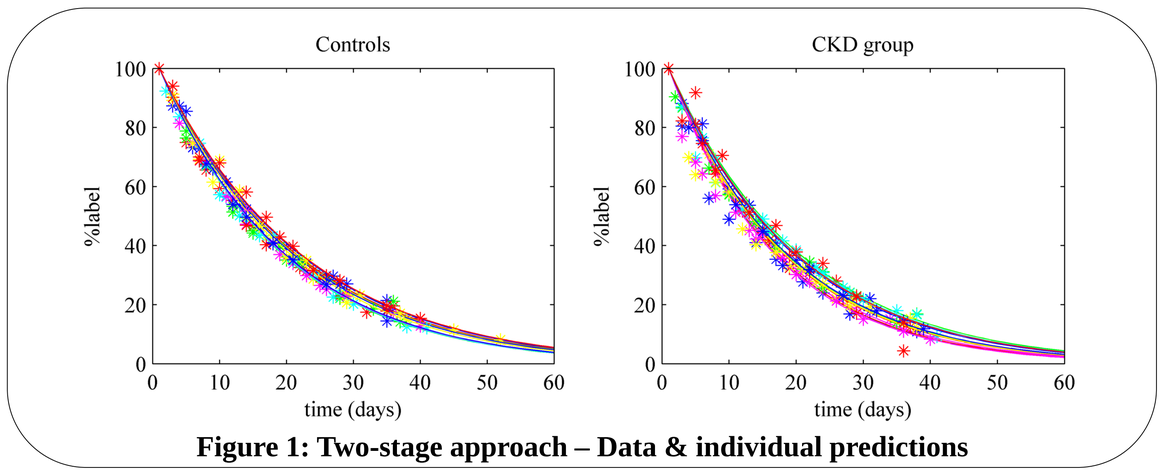

Figure 1: Two-stage approach – Data & individual predictions

2. Population analysis:
   - A combined error model best described the data.
   - Preference for estimating random destruction confirmed.
   - Only CKD was found to be a significant covariate in the full model.
   - Mean RBC lifespan in CKD = 56.2 days, controls = 69.4 days.

Table II: Population Approach Results	$\hat{\theta}$	Ω	Mean LS	$CV\%_{prop}$	σ_{add}^2
Base model	0.0133 days^{-1}	0.1296	56.0 days	2.27	0.0234
Full model	0.0106 days^{-1}	0.0721	69.4 days	2.05	0.0256
with covariate effect	0.0170 days^{-1}	(-44%)	56.2 days		

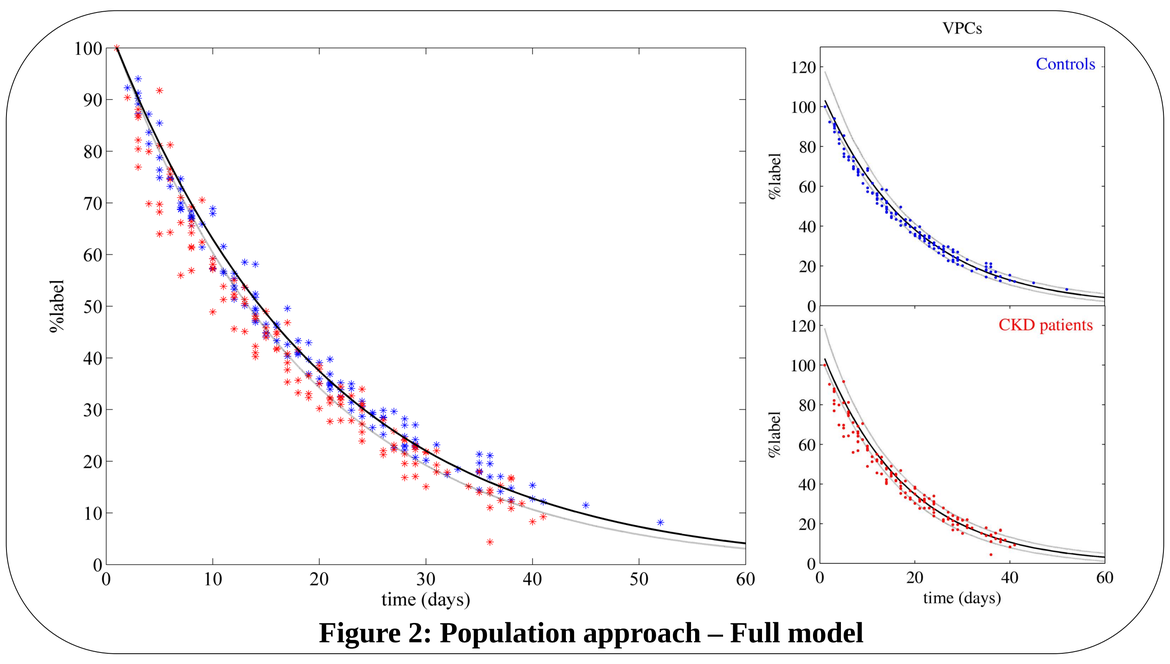

Figure 2: Population approach – Full model

Conclusions

- RBC survival in CKD patients decreased by 20-30%.
  ⇨ Increase in random destruction the preferred underlying mechanism.
- Initial over-prediction due to non-specific loss of label.
  ⇨ Care should be taken when interpreting RBC lifespan values.

References

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