Gaining insight into red blood cell destruction mechanisms using a previously developed semi-mechanistic model[1]

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Background

- Assessment of the physiological mechanisms underlying red blood cell (RBC) survival is of interest in pathological conditions that affect RBC survival.
- A semi-mechanistic model for the survival time of RBCs has been developed previously[2] based on plausible physiological processes of RBC destruction:
  - Early destruction of unviable RBCs, reduced lifespan of misshapen RBCs, random destruction and senescence.
  - These mechanisms are described by five fixed effect parameters.
- The model was shown to be fully identifiable provided that the available clinical data on RBC survival is sufficiently informative.[3]
- Random labelling of RBCs using biotin is presumed to be close to flawless and should provide informative RBC survival data.[4]

Objective

- To assess whether the proposed RBC survival model in combination with informative data is able to provide deeper insight into RBC destruction mechanisms.

Methods

- RBC survival data based on the biotin labelling method was digitally extracted from literature.[5]

Demographics	Non-diabetic subjects	Diabetic subjects	Total population
Number of subjects	6	6	12
Male : Female	2 : 4	3 : 3	5 : 7
Age [years] (mean ± sd)	50.0 ± 10.0	49.0 ± 6.6	49.4 ± 8.1

- Non-linear mixed effects modelling (NLMEM) was conducted using the SAEM algorithm implemented in MONOLIX 1.1.[6]
- The number of estimated fixed effects parameters was increased in a stepwise manner until the addition of a further estimated parameter became statistically insignificant based on the likelihood ratio test or until parameter estimation became unstable when using different sets of initial estimates.
- The non-estimated fixed effects parameters were kept fixed at their default values as determined in Korell *et al*. (2011a).[2]
- Diabetes mellitus was tested as a covariate in the final model on the main parameter controlling senescence as well as the parameter controlling random destruction.

Results

- Three fixed effect parameters were estimable, relating to random destruction, senescence and destruction due to delayed failure.

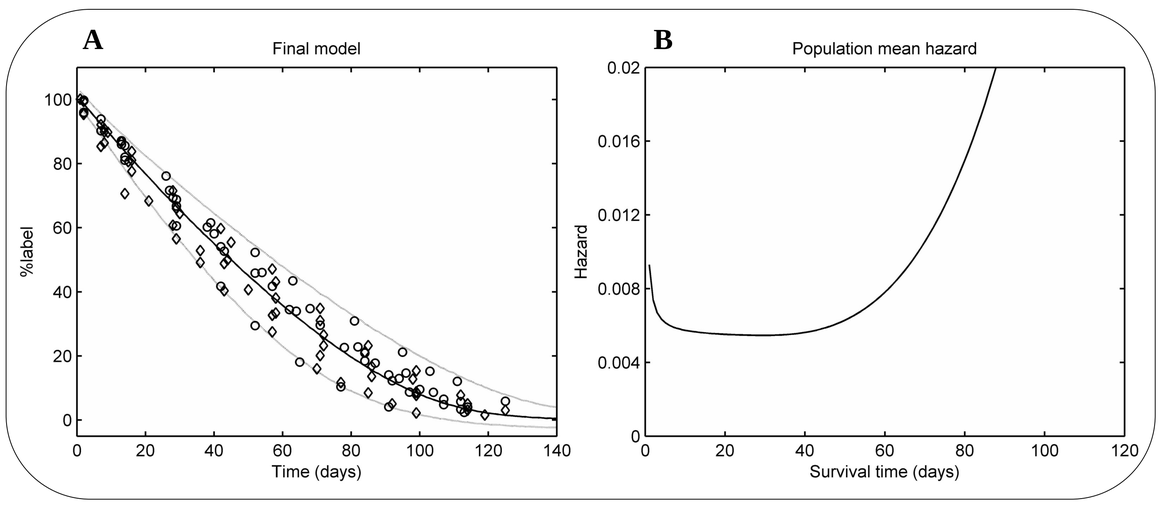

Figure 1: A) VPC for the final model: non-diabetic subjects (○), diabetic subjects (◊), median (—), 5th & 95th (---) percentiles of the model predictions. B) Hazard function for RBC survival based on the population mean parameter estimates of the final model.

- Diabetes mellitus was not a significant covariate on RBC survival.
- Large between subject variability in the individual mean RBC lifespan was observed: 50 – 90 days (median 76.7 days).
- Three subjects showed a decreased RBC survival: individual mean RBC lifespan <61 days:
  - All three showed differences in the underlying RBC destruction mechanisms: increased random destruction in #9, accelerated senescence in #3, and a combination of both in #8 (Figure 2).

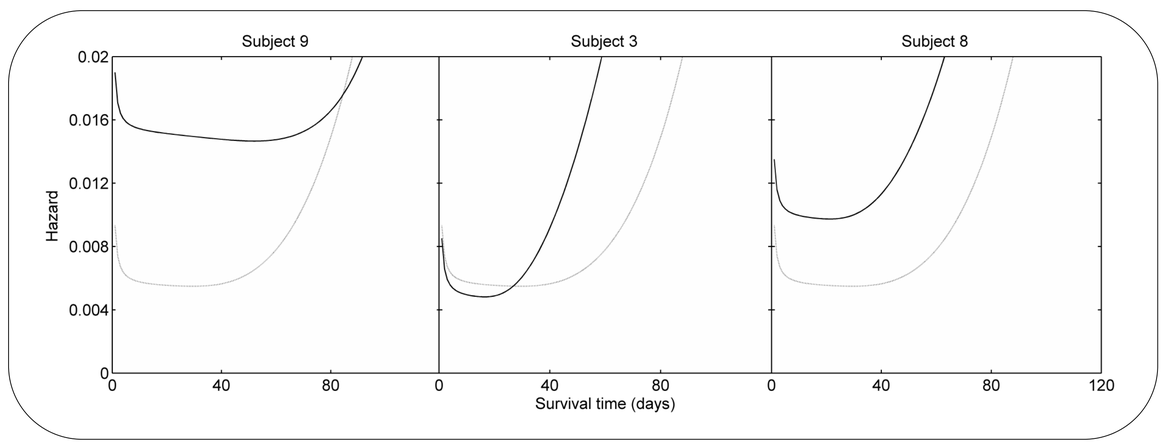

Figure 2: Individual hazard functions for three subjects with decreased survival (—) in comparison to the population mean hazard function (---).

Conclusions

- The proposed RBC survival model can provide insight into RBC destruction mechanisms on a population as well as individual level when applied to informative clinical data in a NLMEM framework.

References

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