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Modeling of Red Blood Cell (RBC) Life-span (LS) in a Hematologically Normal Population

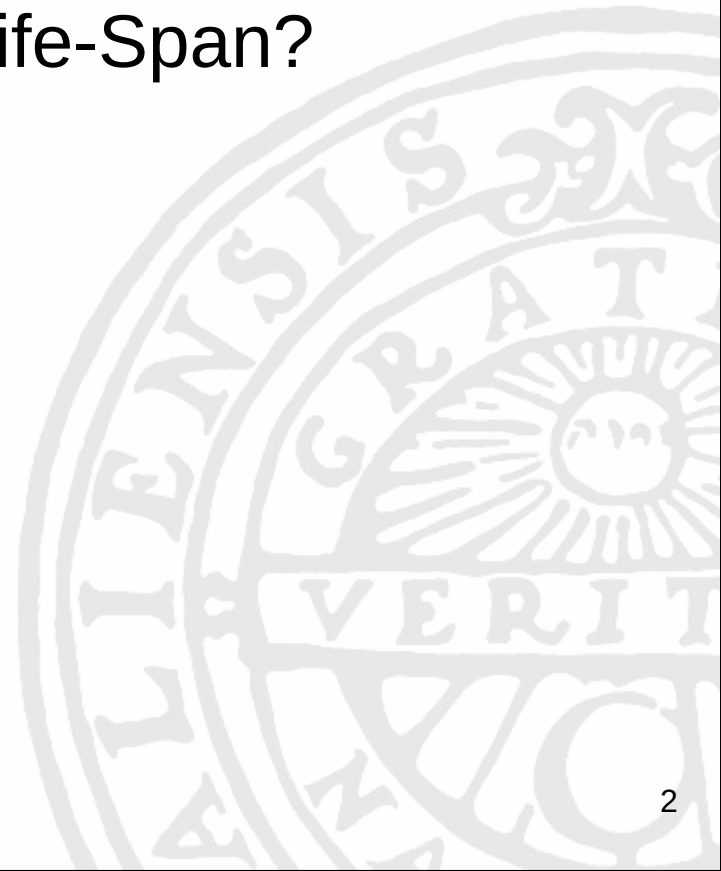
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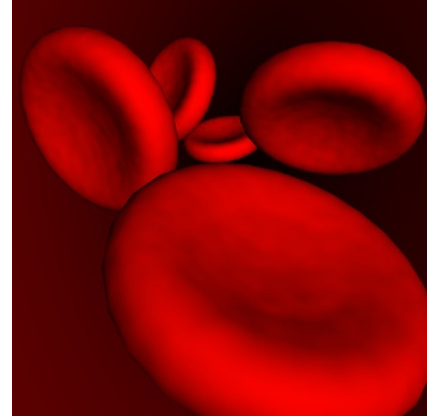
• Outline

- Introduction
- Why interest in RBC lifespan characteristics?
- How?
 - How to measure Life-Span?
 - Previous models
 - Data
- Aim
- Results
- Conclusions





• Introduction: RBC



Red blood cells (RBC)

-Erythropoiesis:

hematopoietic stem cells → mature erythrocytes

-Normal homeostasis of erythropoietic system:

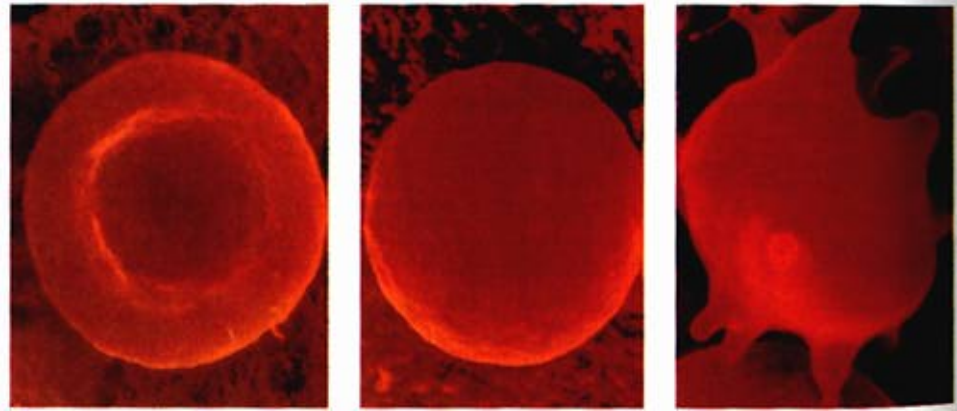
Production ~ destruction

└→ Stimulus: hypoxia → synthesis of erythropoietin (EPO)

Destruction

-After a life-span → senescence (morphological changes, loss of membrane) & removal (macrophages)

- Other possible causes: bleeding, clots, ...



Why are we interested in RBC destruction patterns?

- Treatment decisions in individual patients
- Analyses and predictions in drug development

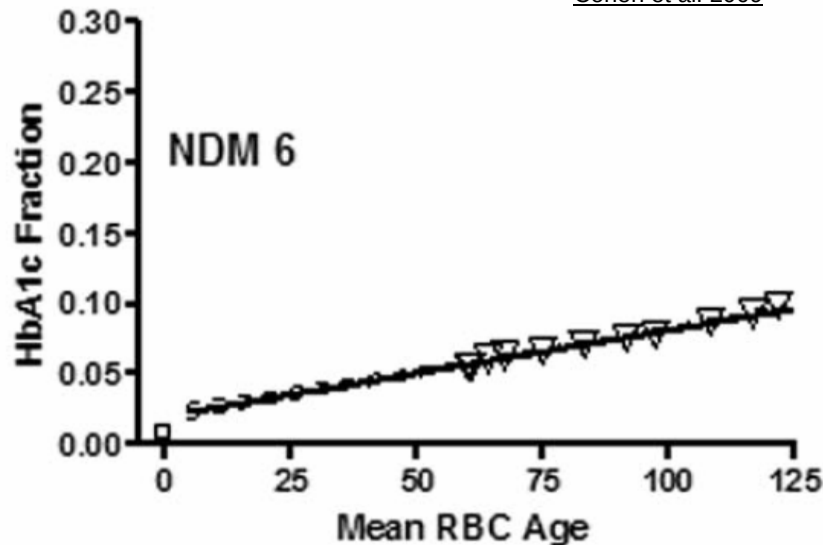


• Why?: Aging and destruction patterns

Diabetes: HbA1c (hemoglobin glycosylated)

-Diagnosis → change of state “how long will it take for a change in HbA1c when you change the food habits or drug treatment?”

Cohen et al. 2009



Nathan et al. 2008

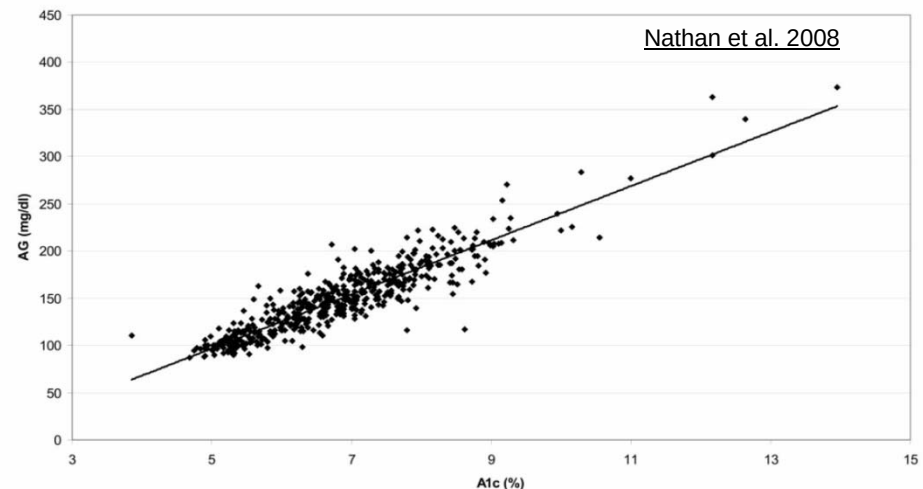


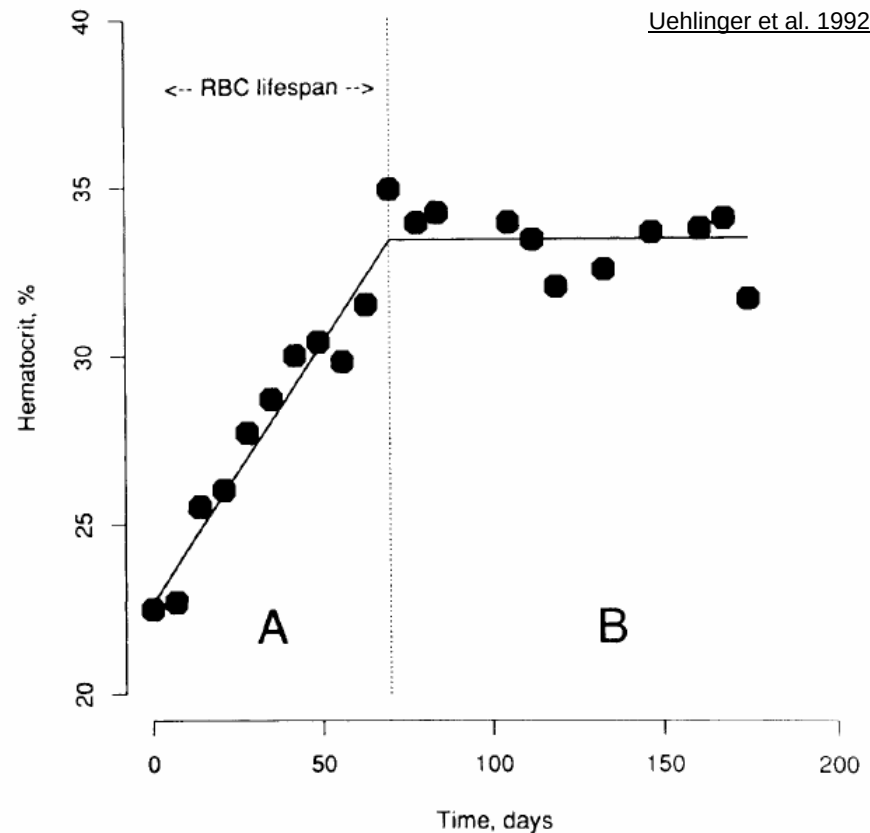
Figure 1—Linear regression of A1C at the end of month 3 and calculated AG during the preceding 3 months. Calculated $AG_{mg/dl} = 28.7 \times A1C - 46.7$ ($AG_{mmol} = 1.59 \times A1C - 2.59$) ($R^2 = 0.84$, $P < 0.0001$).



• Why?: Aging and destruction patterns

Anemia in patients with hemodialysis: EPO

- How often & how much the doses should be changed? → function of the life-span (LS)
- Early prediction of long term therapy

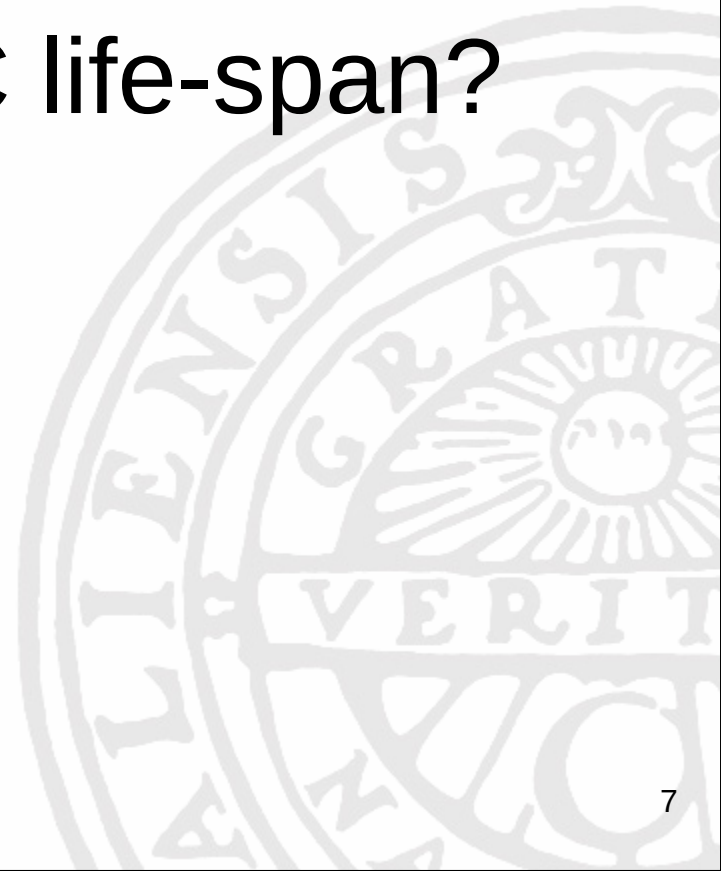




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How to measure RBC life-span?





• How?: Measurement of RBC life-span

INDIRECT METHODS

* By modeling!

- If we make changes in production (EPO) or glycosylation (glucose levels) of RBC, the change of state will allow us to get an estimate of the lifespan.



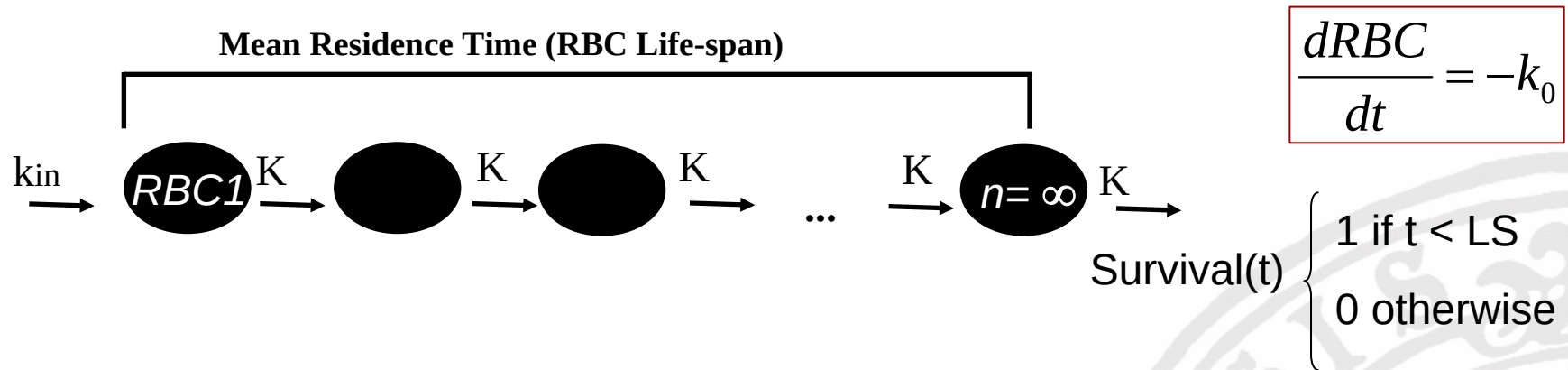
In literature, we find that this has
previously been done



• How?: Previous models

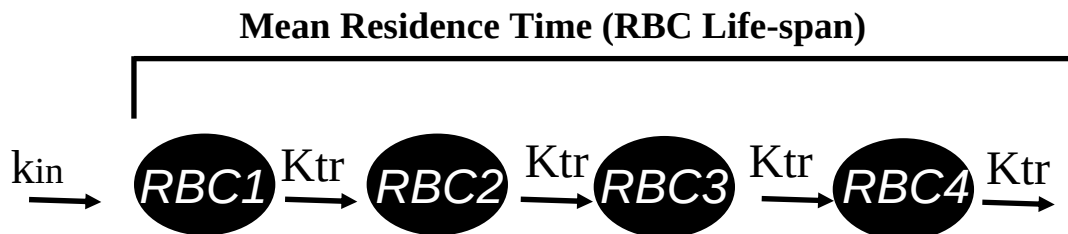
Homogeneous life-span model (Uehlinger et al. 1992; Uremic patients)

- Assumes that each of the patients' erythrocytes has the same LS



Transit 4-compartment model (Hamrén et al. 2006; Ribbing 2007, Diabetic patients)

- Considers a distribution on RBC lifespan



$$\frac{dRBC_1}{dt} = (k_{in}) - k_{tr} \cdot RBC_1$$

$$\frac{dRBC_2}{dt} = k_{tr} \cdot RBC_1 - k_{tr} \cdot RBC_2$$

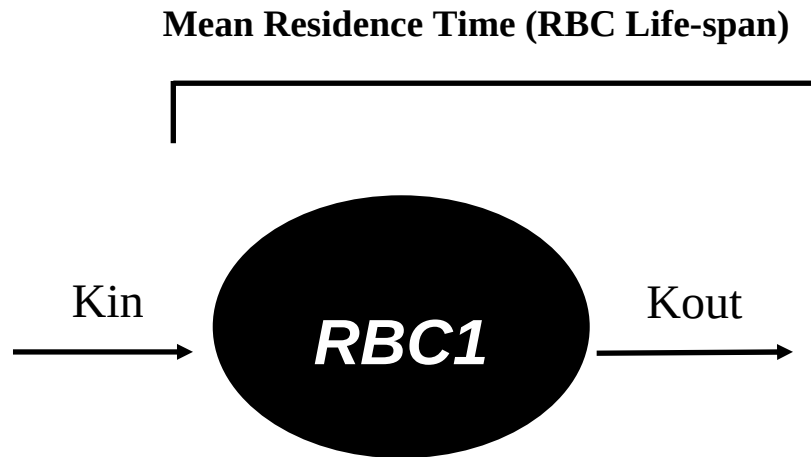
$$\frac{dRBC_3}{dt} = \dots$$



• How?: Previous models

Indirect model (de Winter et al. 2006; Diabetic patients)

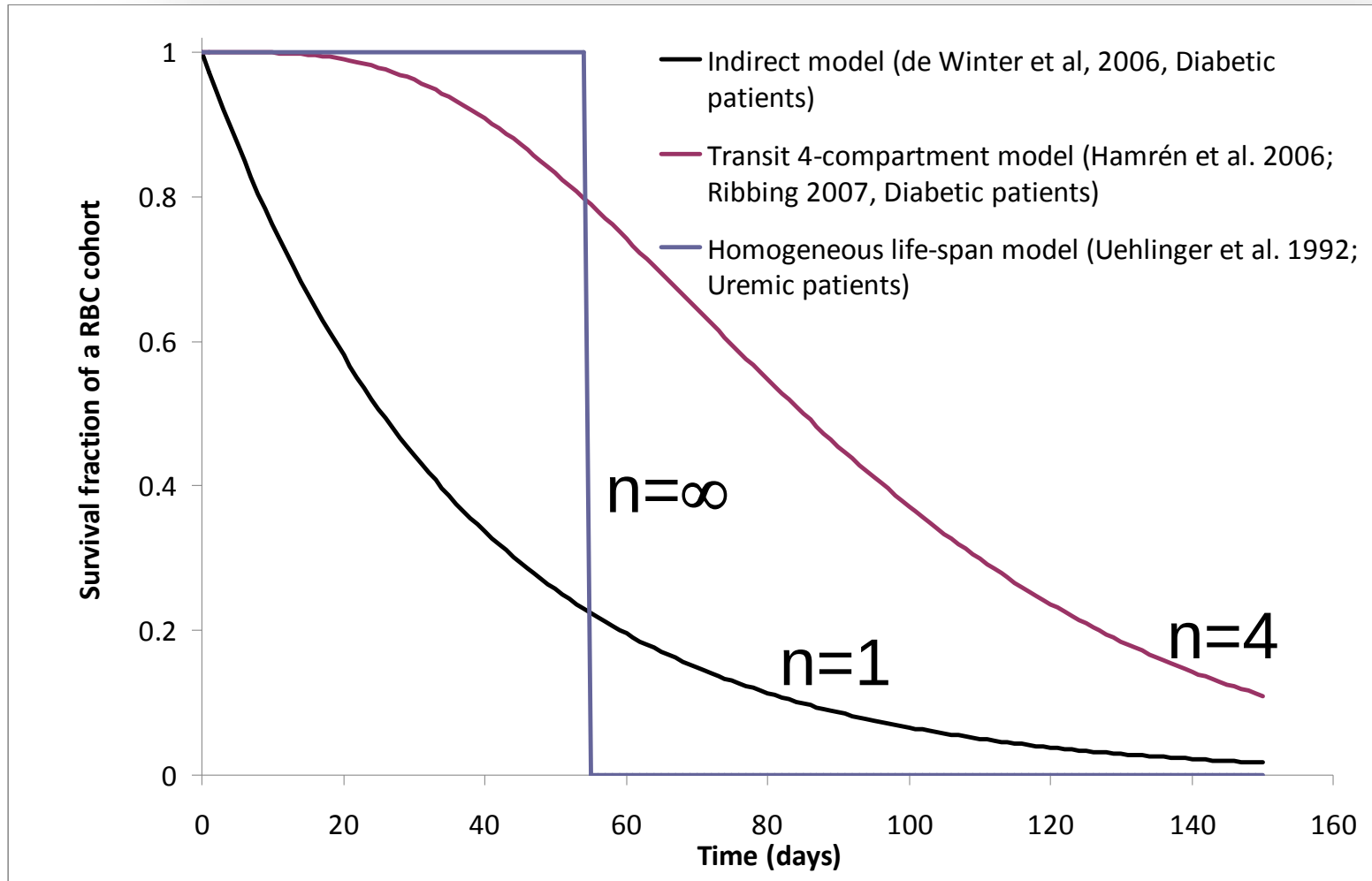
- Considers a distribution on RBC lifespan



$$\frac{dRBC_1}{dt} = (k_{in}) - k_{out} \cdot RBC_1$$



• How?: Previous models





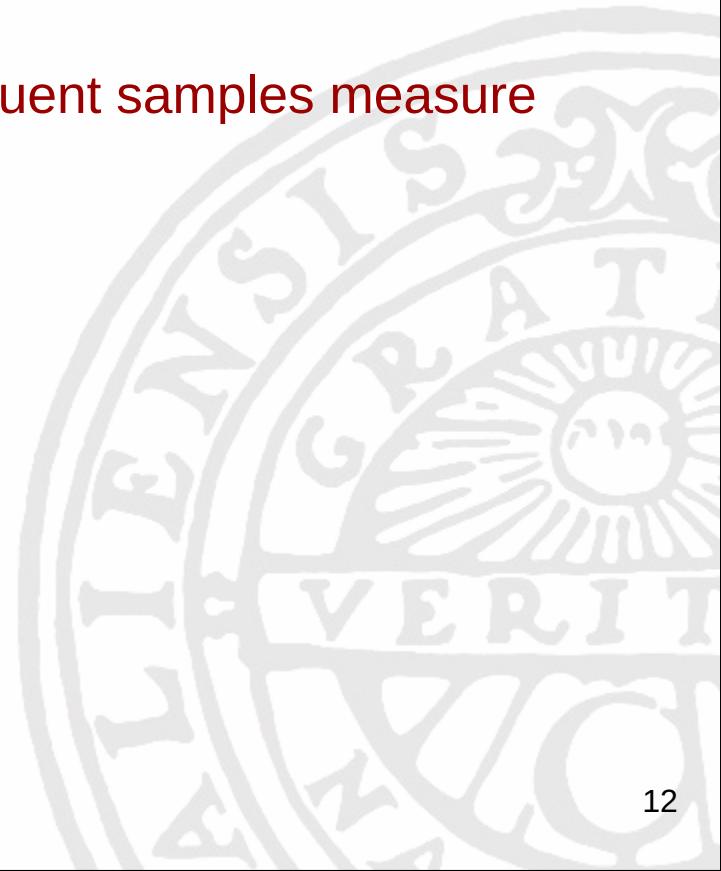
• How?: Measurement of RBC life-span

Several methods exist

One commonly used is borrowed from catch-and-release studies of wild animals

Blood is collected, marked, reinfused. Subsequent samples measure recapture of marked RBCs

Markers used are ^{51}Cr or biotin





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LOOK

Our study ...



• How?: “Our” Data

Cohen et al. 2008:

- “Red cell life-span heterogeneity in hematologically normal people is sufficient to alter HbA1c”

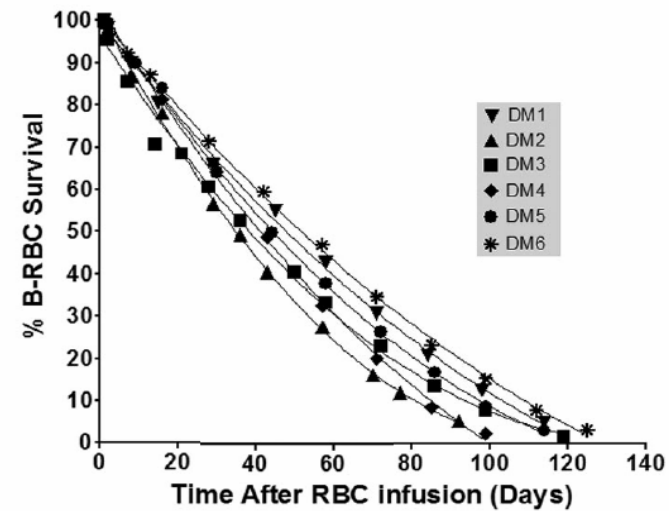
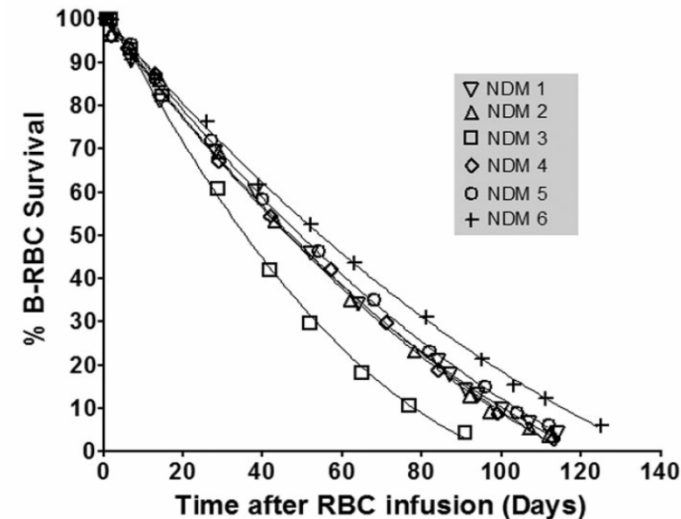
-Biotin-labelled RBC survival- time profiles

- 6 non-diabetic and 6 diabetic patients
(Type I and II)

Data digitalization:

-3 repeated measurements with two different softwares (xy-Extract and TechDig)

Mean SD of 0.4% units → satisfactory precision





• How?: “Our” Data

Hamrén et al. 2006; Ribbing et al., 2007

- FPG and HbA1c data (n=1083)

Uehlinger et al., 1992

- Hb data following EPO therapy (n=54)





- Aim

To re-visit the question of:

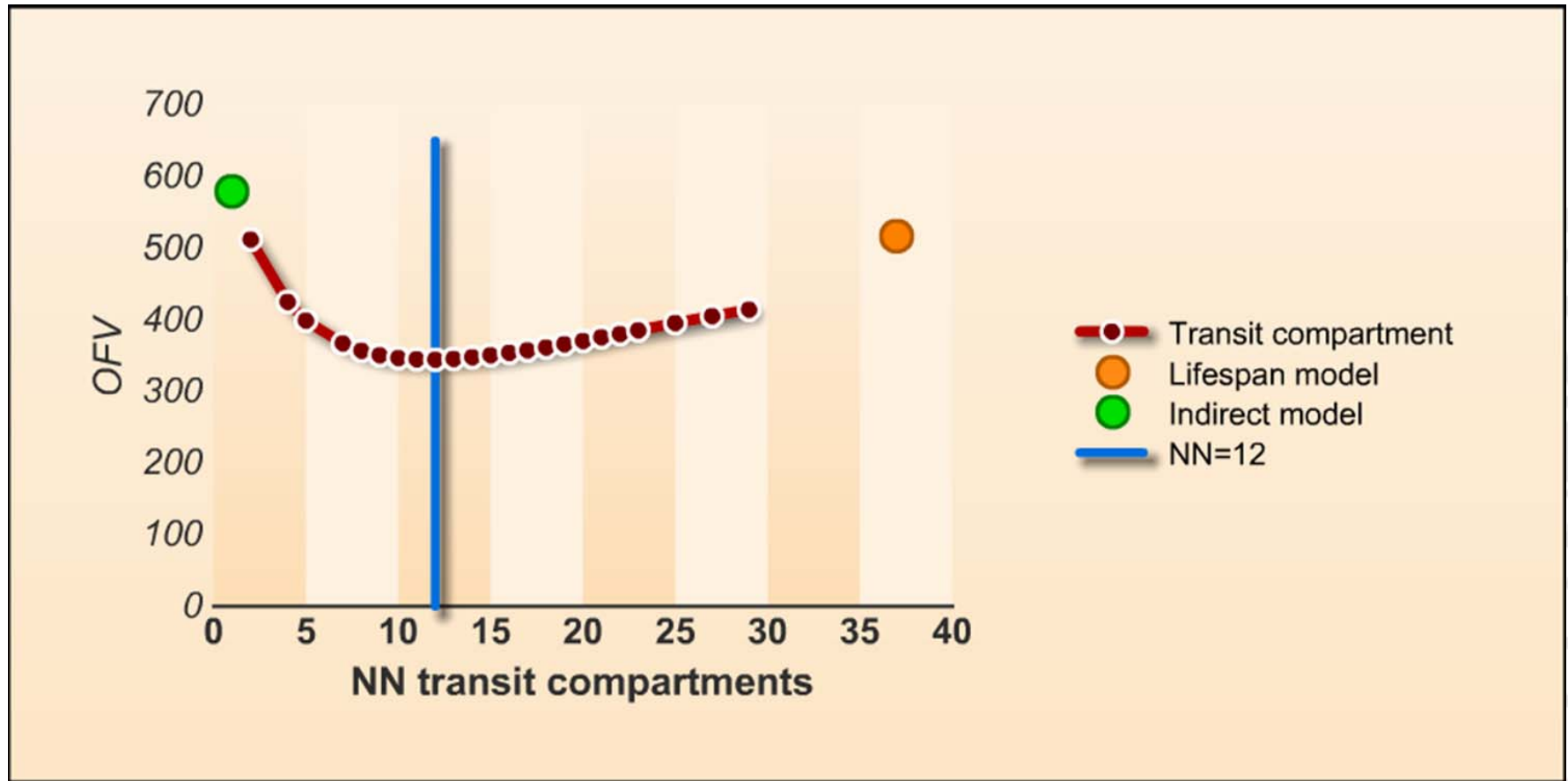
Which life-span model better describes the RBC survival data in a more physiologically meaningful way?

How important is it to use the right model?



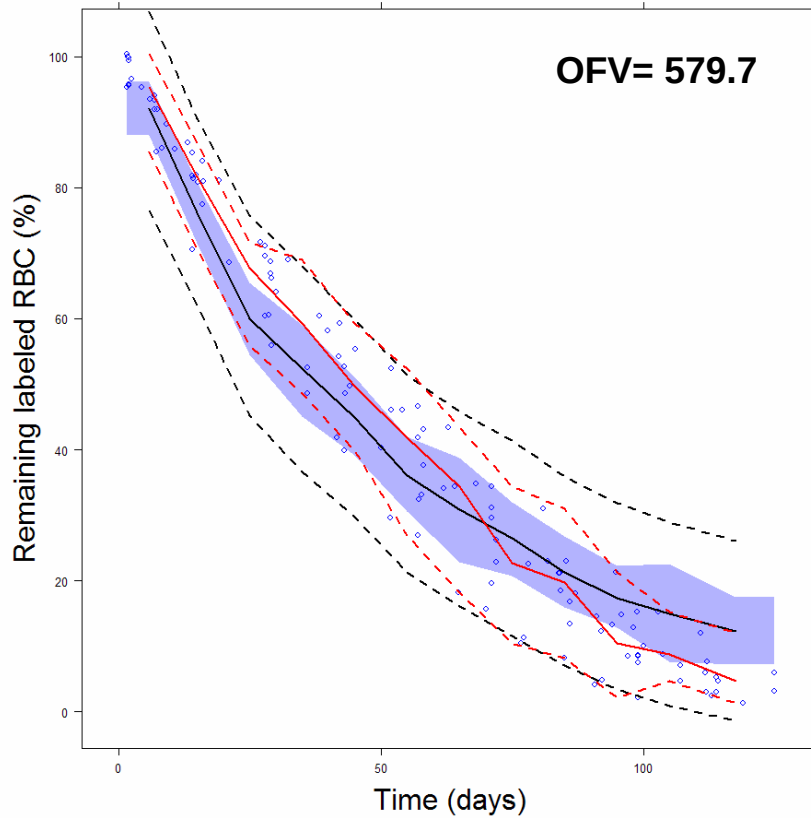
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Results – ...

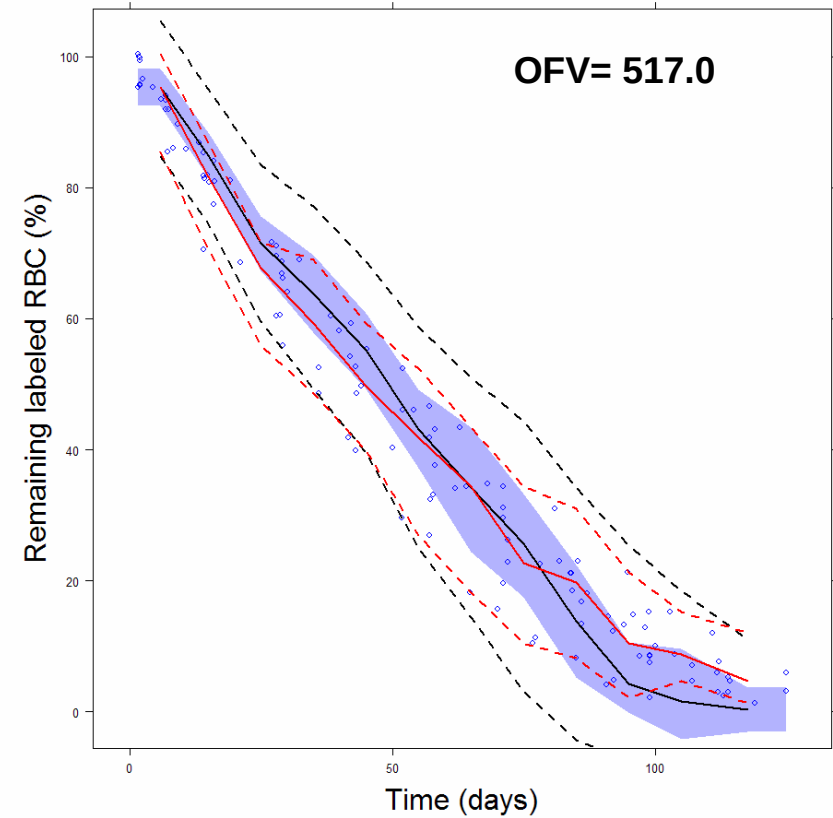




Indirect effect model

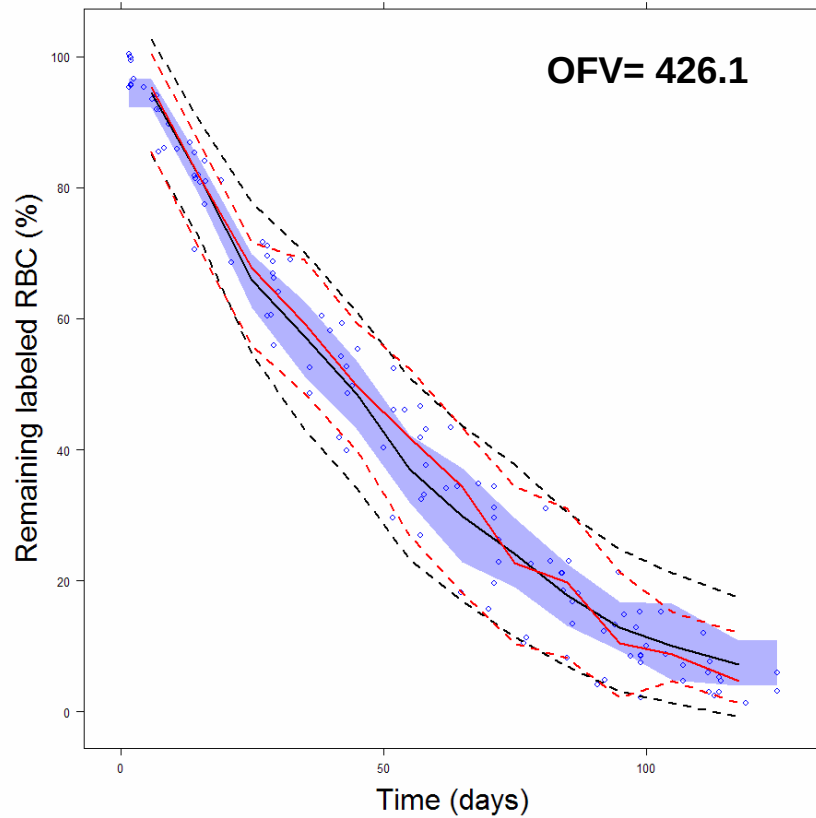


Homogeneous life-span model

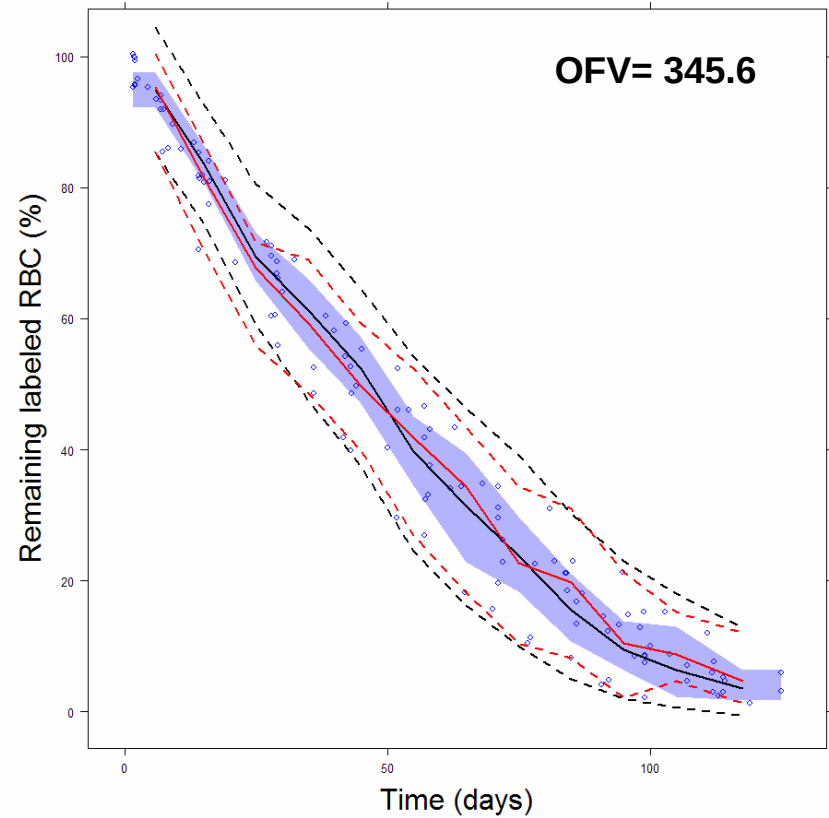




Transit 4-compartment model

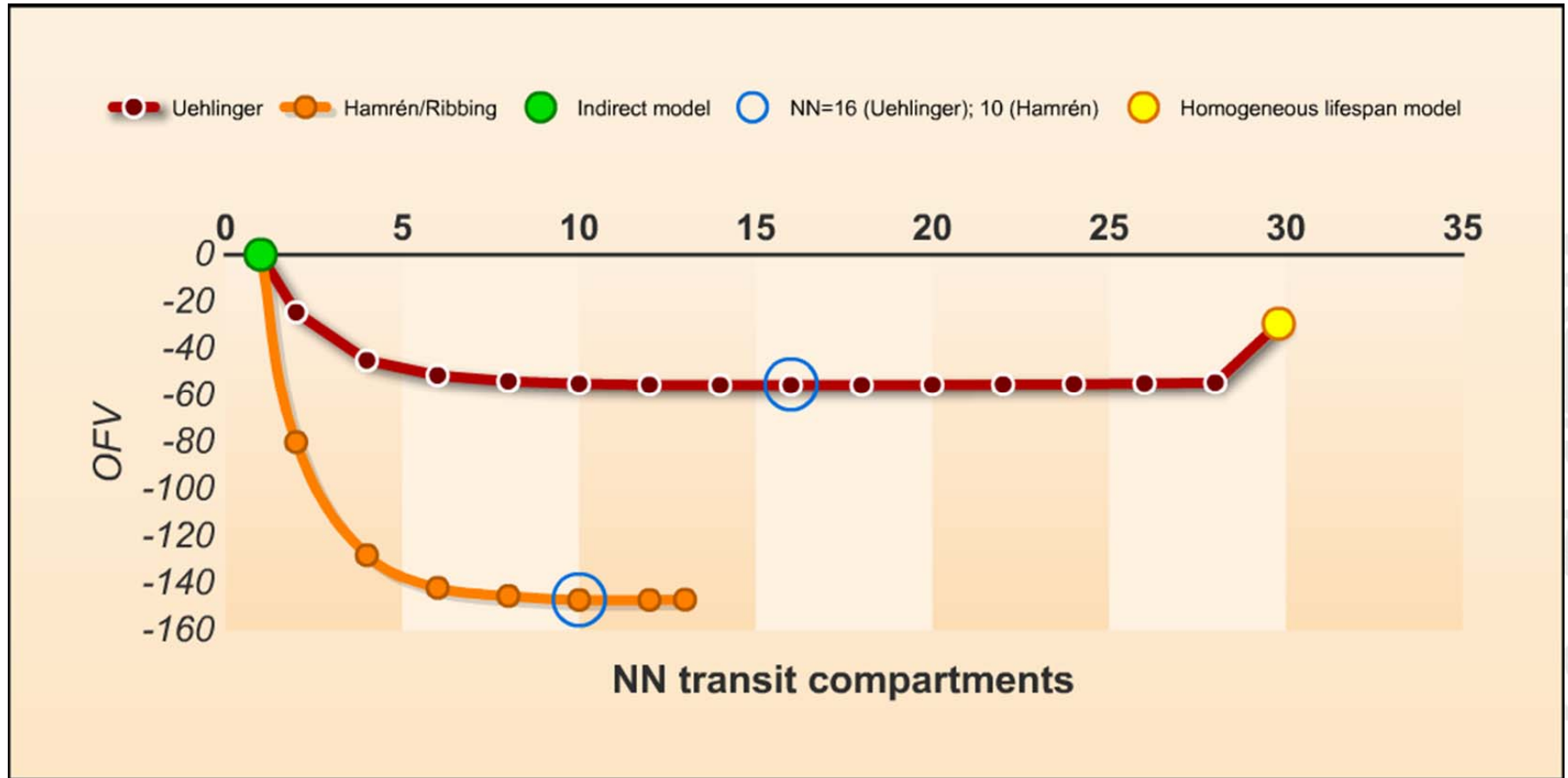


Transit 12-compartment model



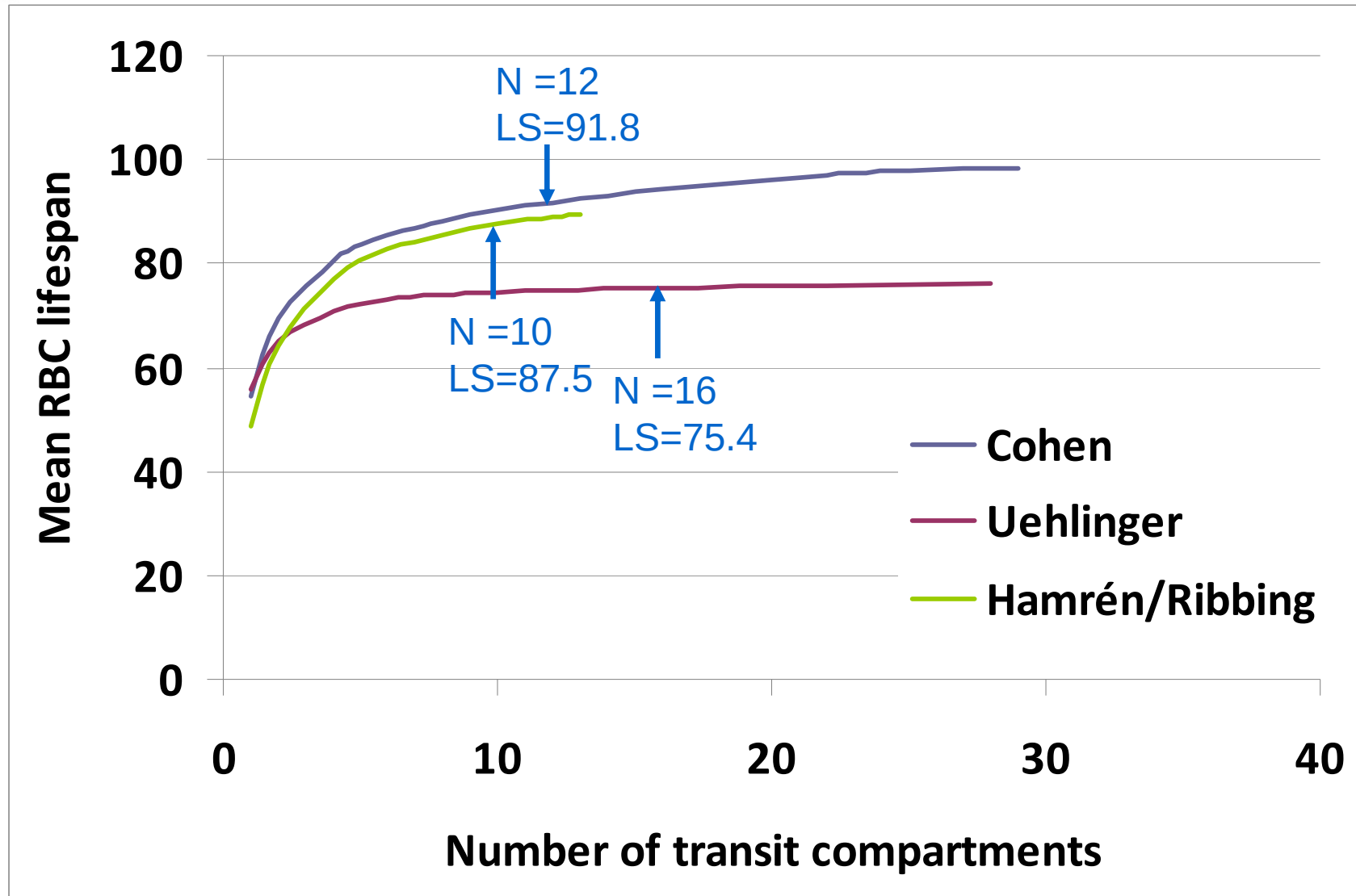


• Results – Other data sets





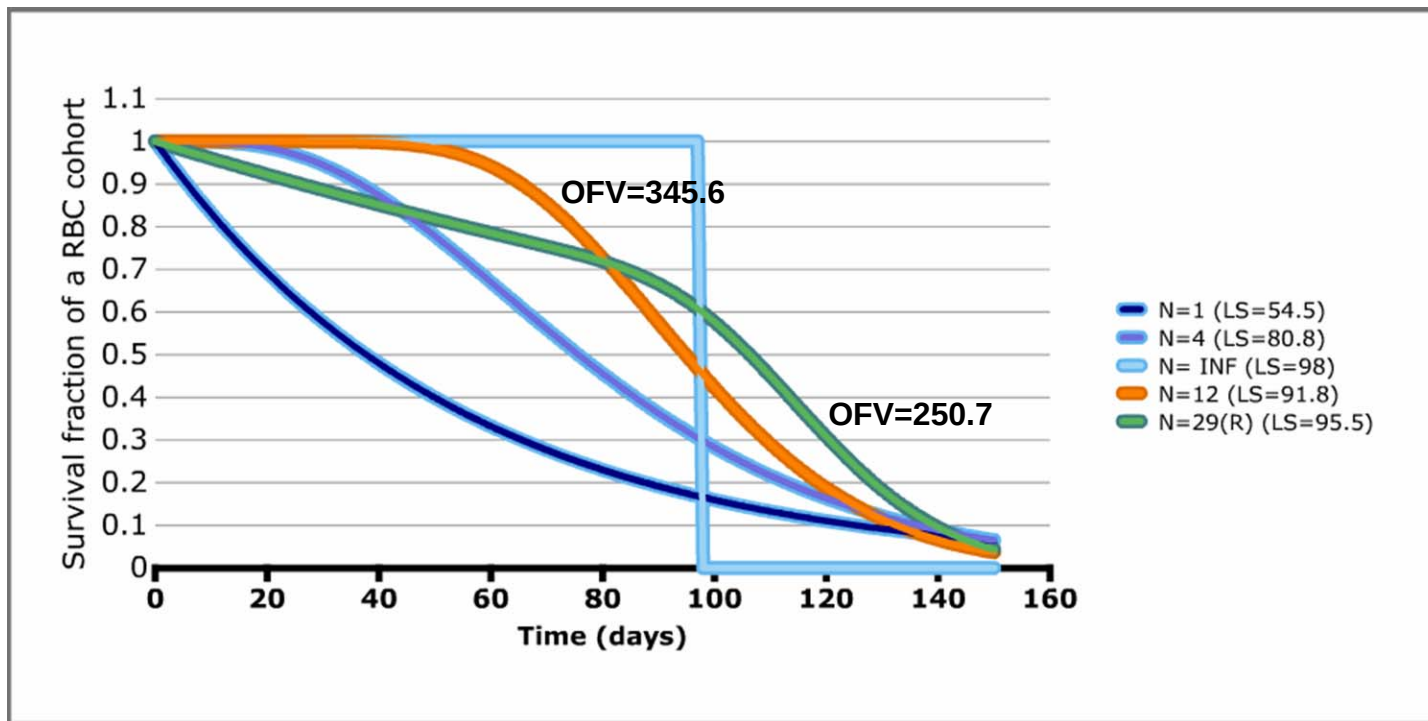
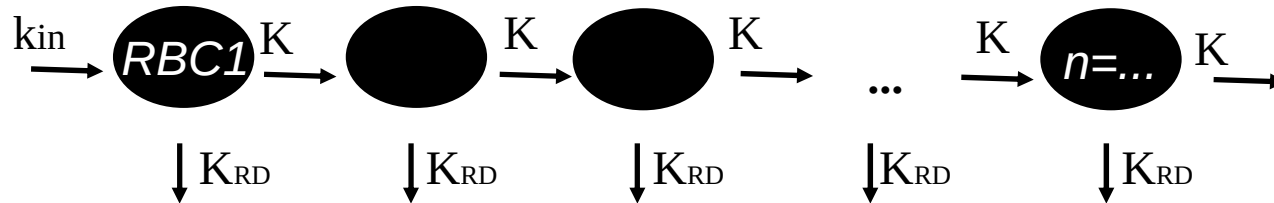
• Results- Life-span estimates





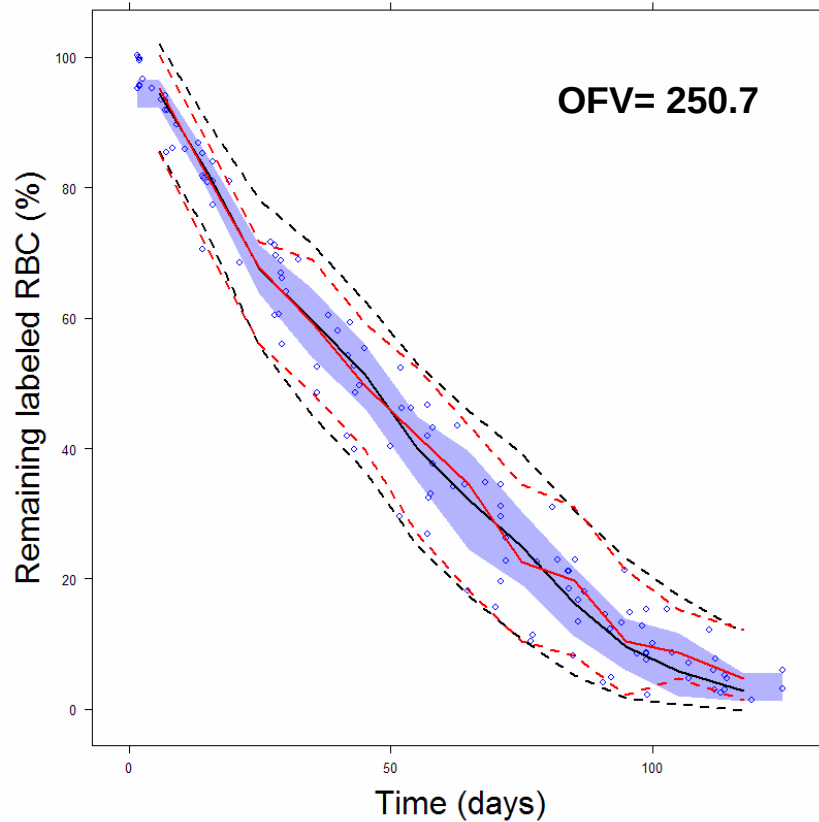
• Results

Cohen data

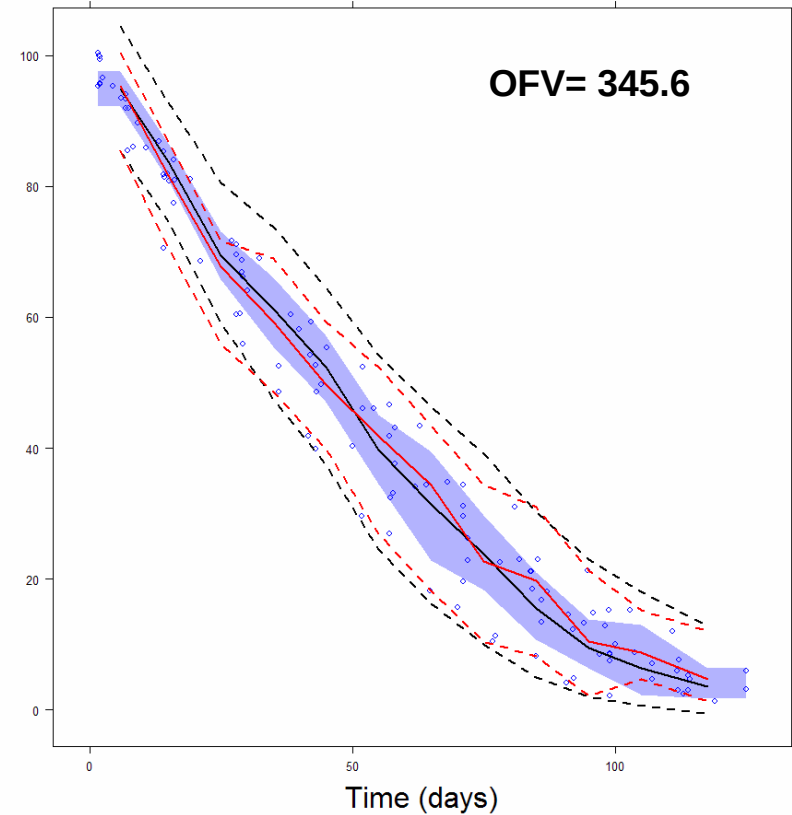




Transit model with random destruction

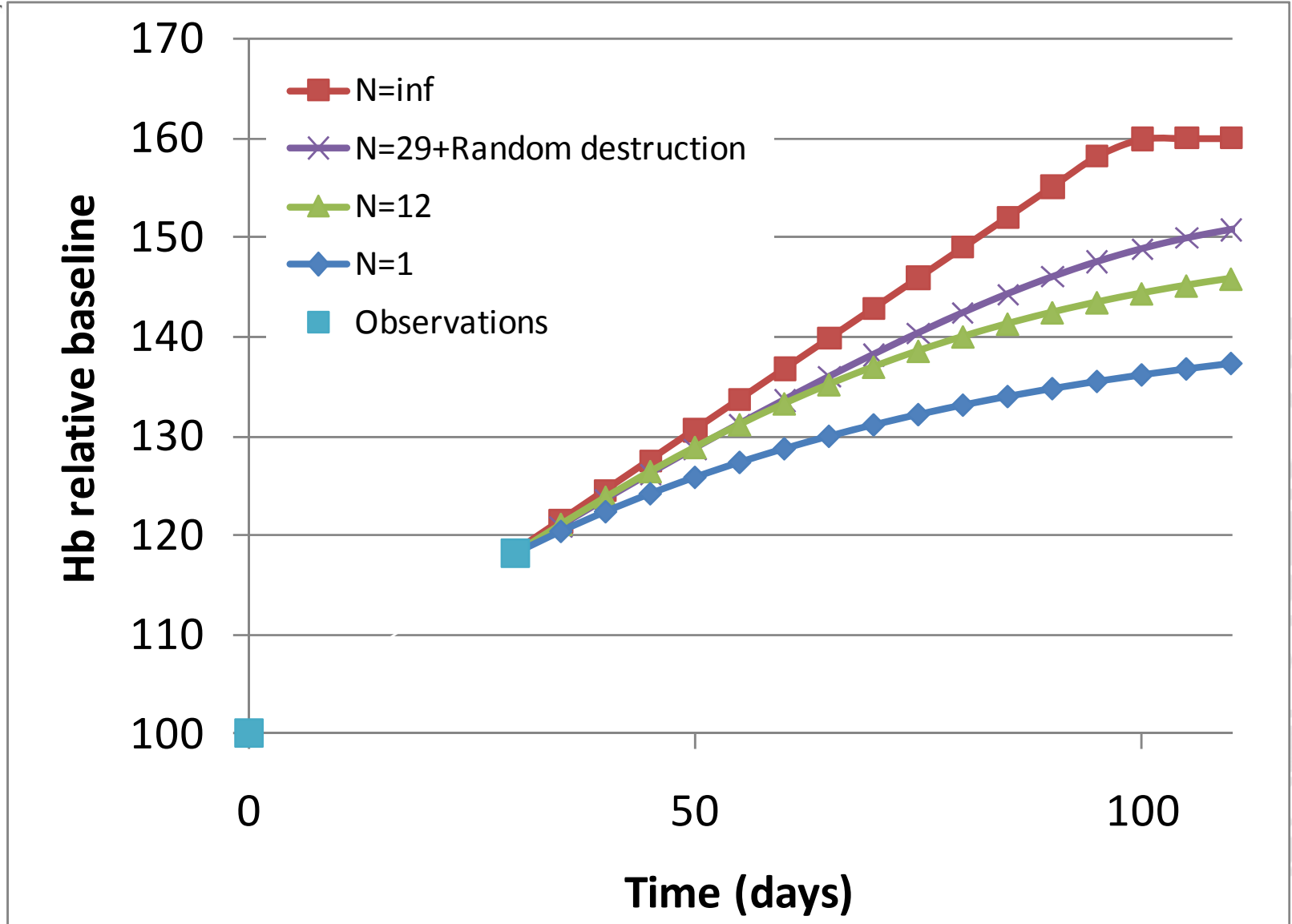


Transit 12-compartment model





• Choice of models for prediction





• Conclusions

- Predictions from non-steady state data depend on RBC model chosen.
- The transit compartment model, which considers variation in LS, better describes RBC survival data and in a more physiological way than the indirect or homogenous life-span models.
- The incorporation of random destruction patterns improved the fit.
- Information about RBC lifespan characteristics vary with type of data:
mark&recapture > Hb > HbA1c



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Dominik Uehlinger for sharing his data





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Thank you!

