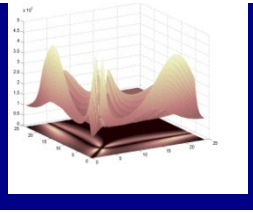

Design of survival studies for red blood cells

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Motivating Context

- Despite more than 90 years of research the lifespan of the red blood cells remains elusive.
- Knowledge of the turn-over of red blood cells is essential in understanding the disease process and progress in a variety of conditions such as:
  - Diabetes - HbA_{1c} is a glycation product of haemoglobin which provides a prognostic indicator in diabetic care and is dependent on RBC lifespan.
  - Other examples: chronic kidney failure, sickle cell disease, anaemia of chronic diseases.

GOLDSTEIN, D. *et al.* (2004) Diabetes Care 27(7):1761-1773

FRANCO, R. (2009) American Journal of Hematology 84(2):109-114

Introduction – Labelling methods

- Cohort labelling:
  - Labelling a cohort of RBCs of similar age
  - E.g.: Glycine tagged with heavy nitrogen (^{15}N)
- Random labelling:
  - Labelling RBCs of all ages present at one point in time
  - E.g.: Radioactive chromium (^{51}Cr)

BUT: All labelling methods are flawed!

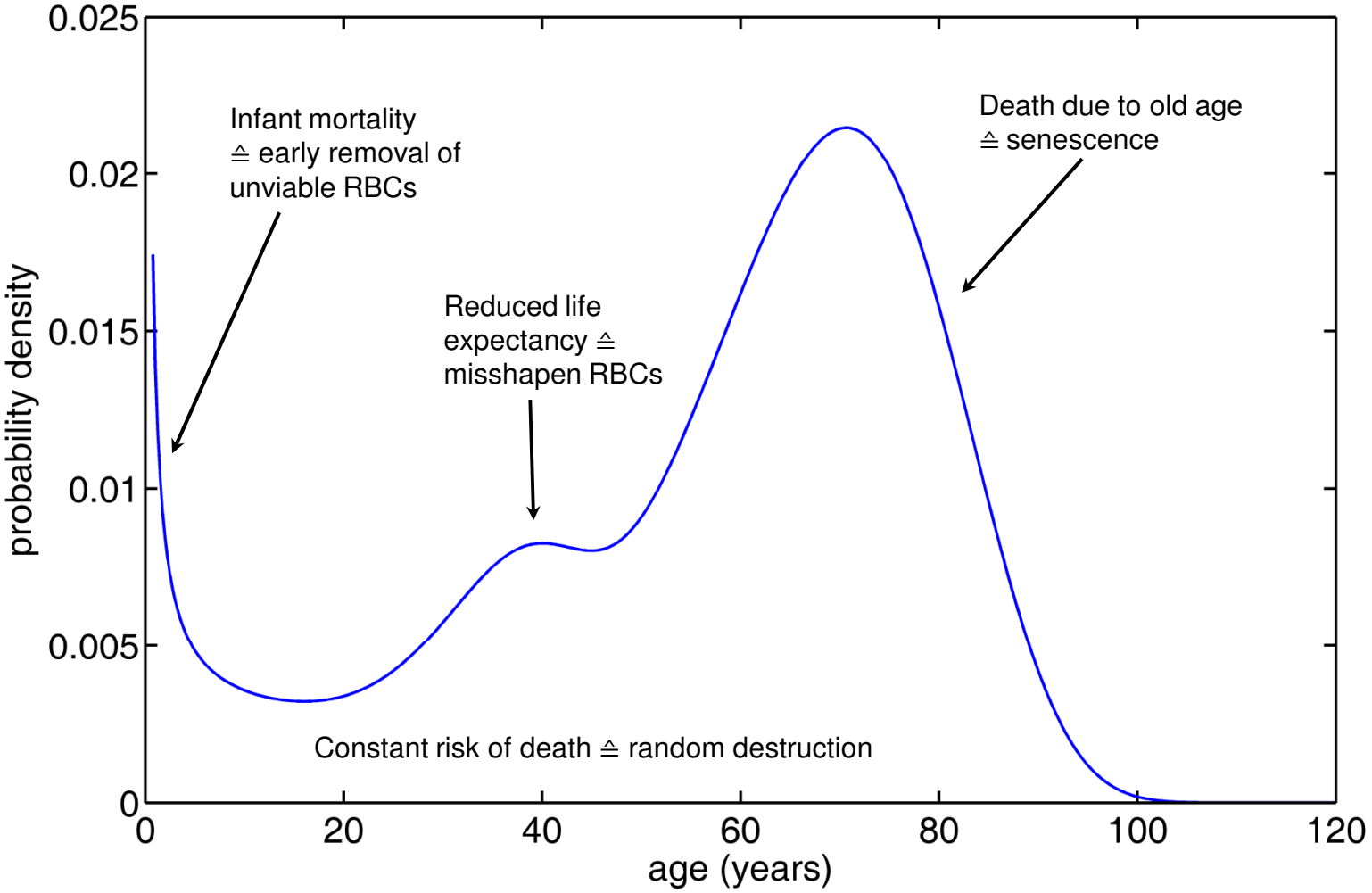
⇨Inaccurate estimation of RBC lifespan

Aims

1. To develop a model for RBC survival based on statistical theory that incorporates known physiological mechanisms of RBC destruction.
2. To assess the local identifiability of the parameters of the lifespan model under ideal cohort and random labelling method.
3. To evaluate the precision to which the parameter values can be estimated from an *in vivo* RBC survival study using a random labelling method with loss of the label and a cohort labelling method with reuse of the label.

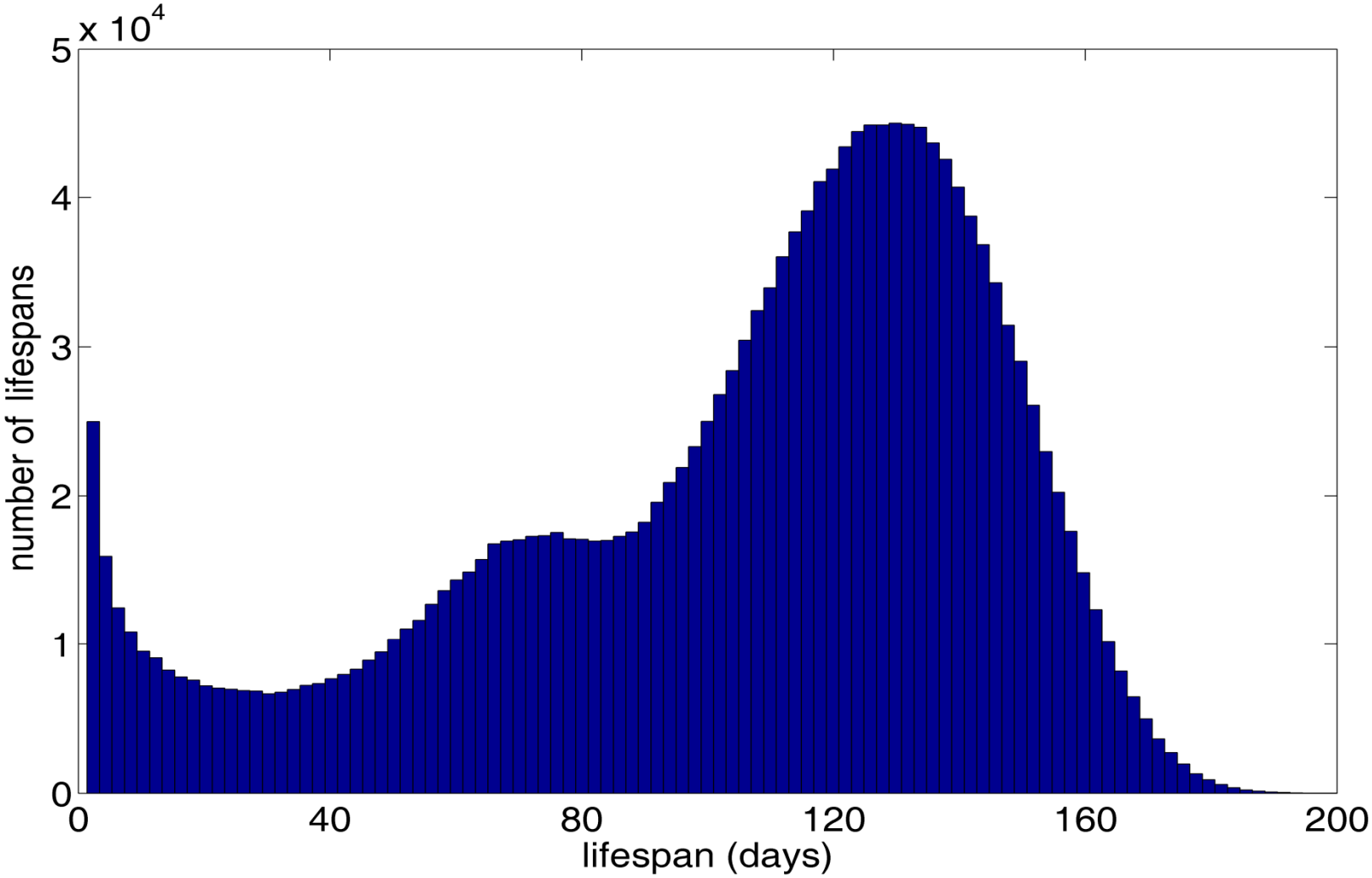
1. RBC survival model

Theory – Human mortality

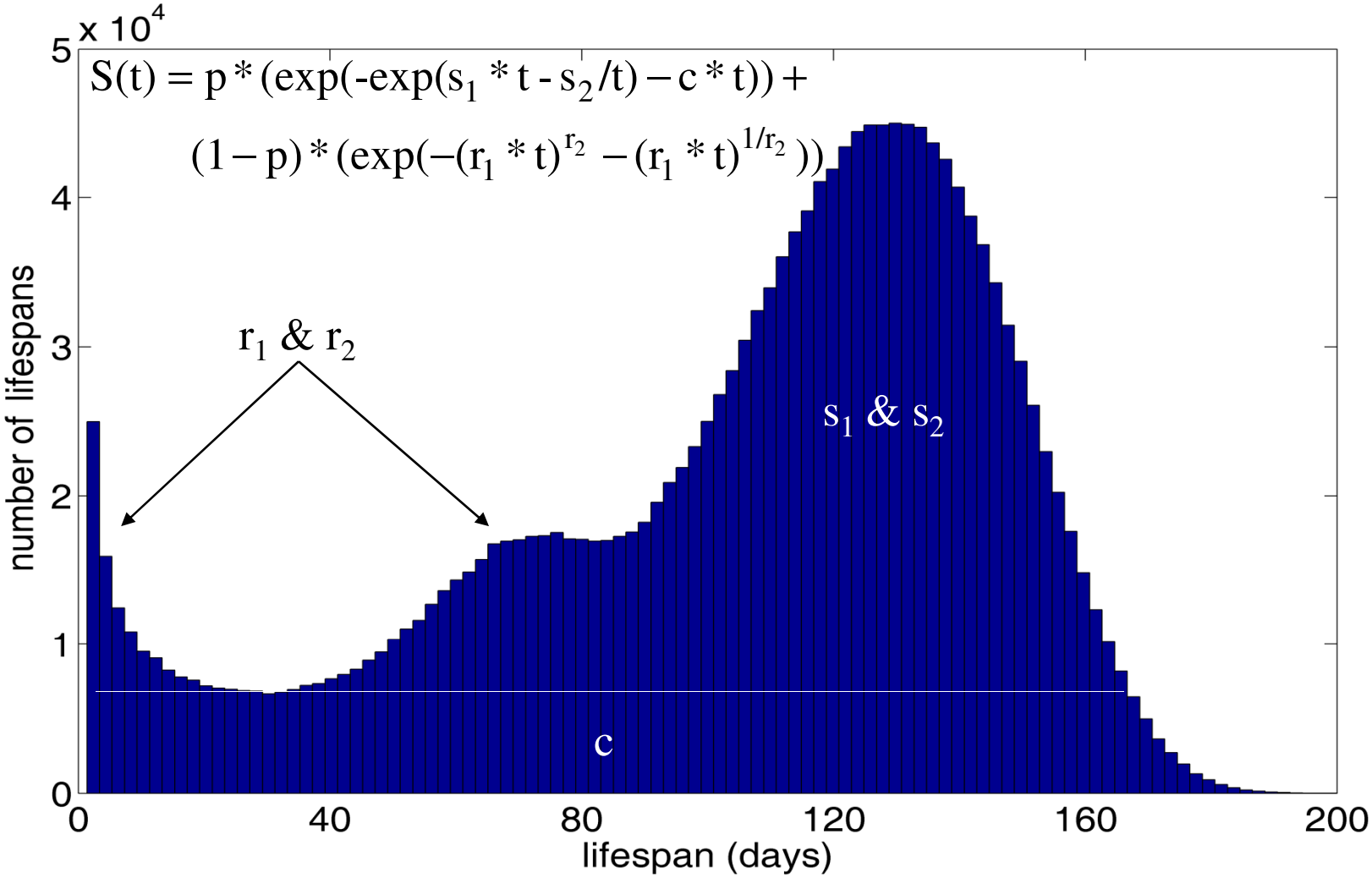


BEBBINGTON, M. *et al.* (2007) Journal of Theoretical Biology 245(3):528-538

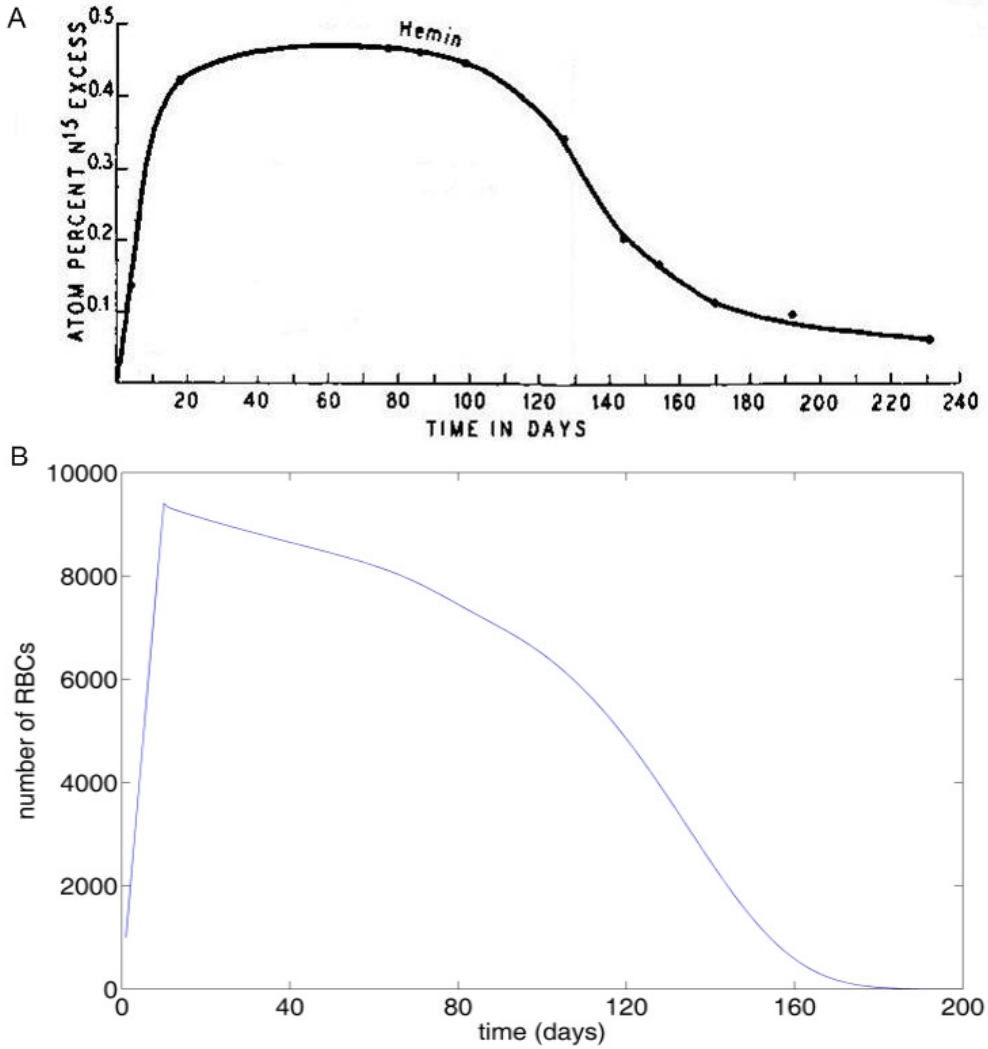
RBC lifespan distribution



RBC lifespan distribution



Simulation 1 – Cohort labelling



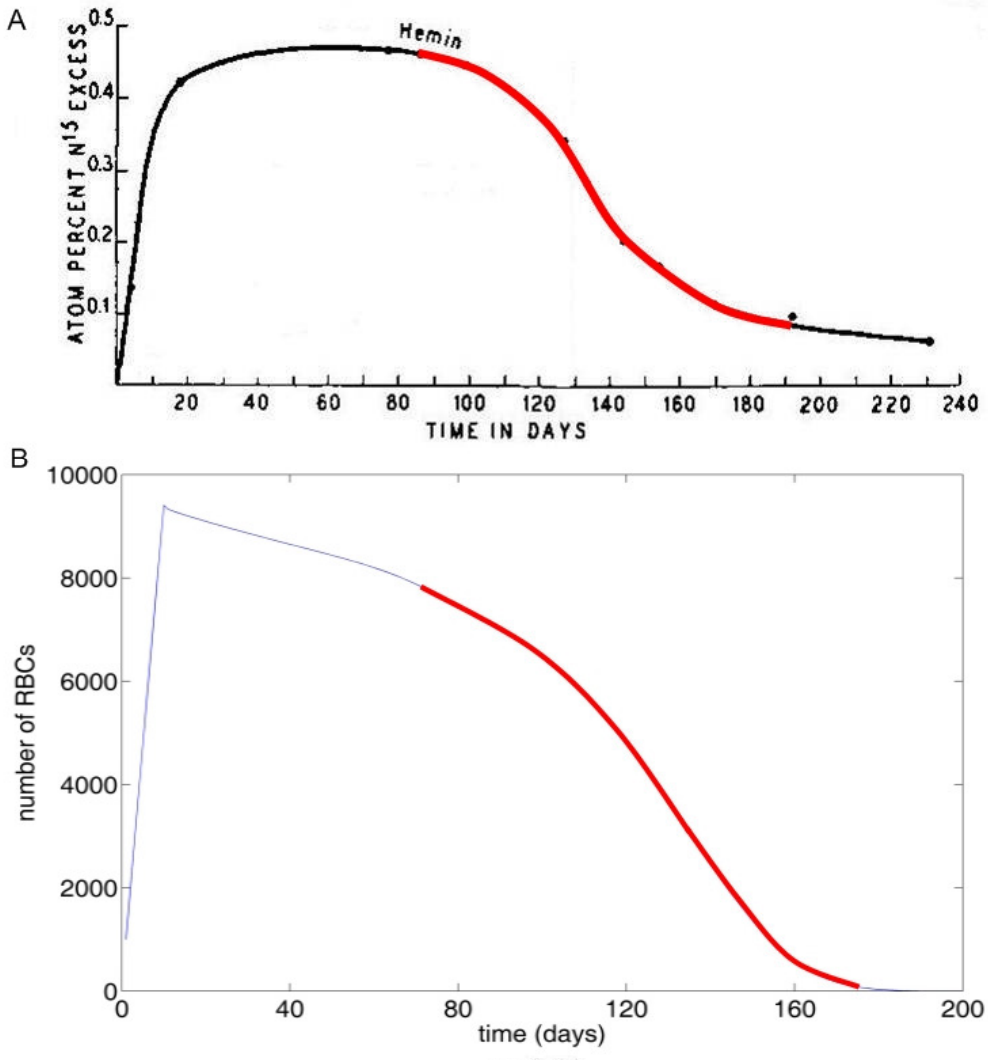
Real data (1946)

using ^{15}N

Prediction from our model

SHEMIN, D. & RITTENBERG, D. (1946) Journal of Biological Chemistry 166:627-636

Simulation 1 – Cohort labelling



Real data (1946)

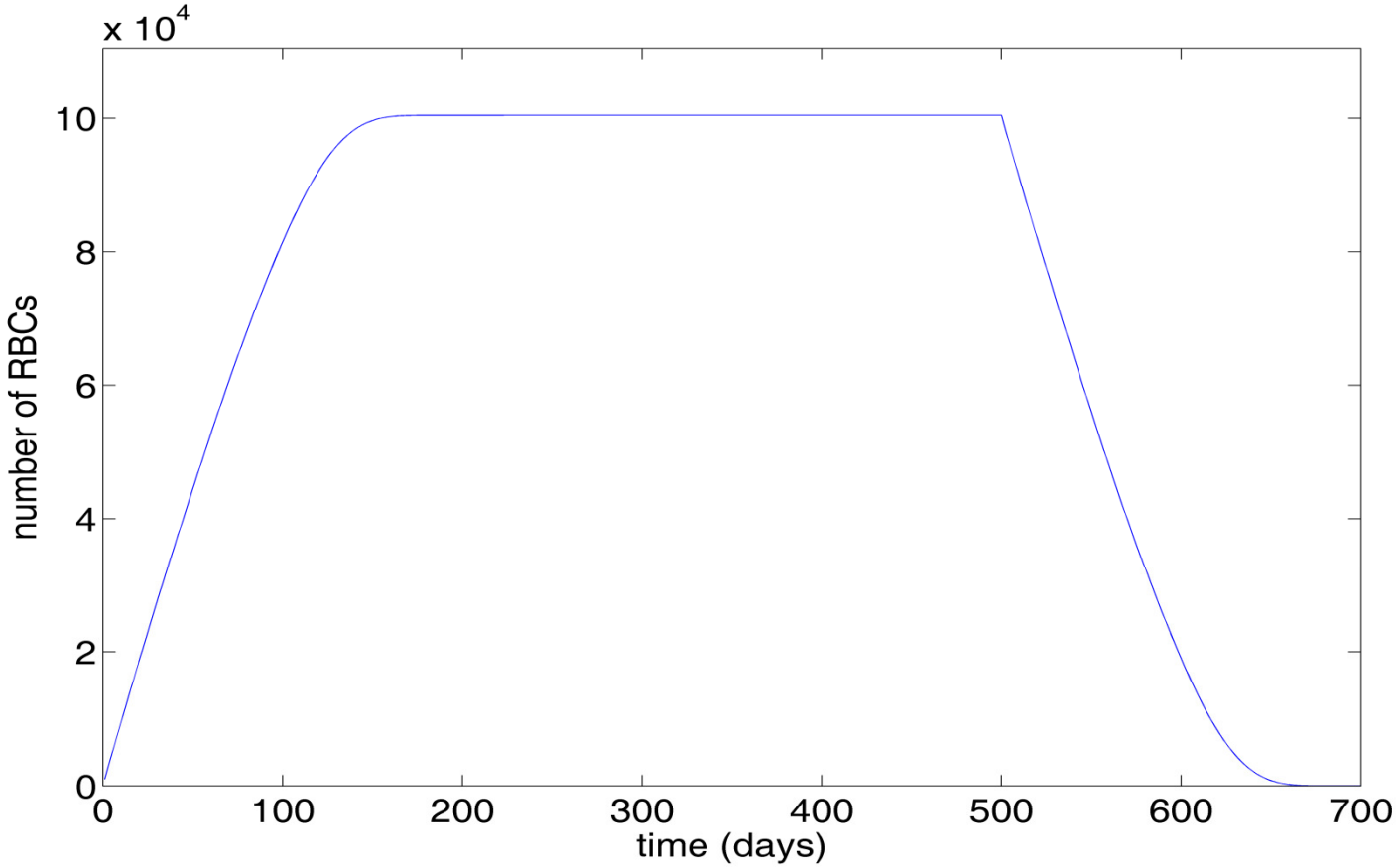
using ^{15}N

Prediction from our model

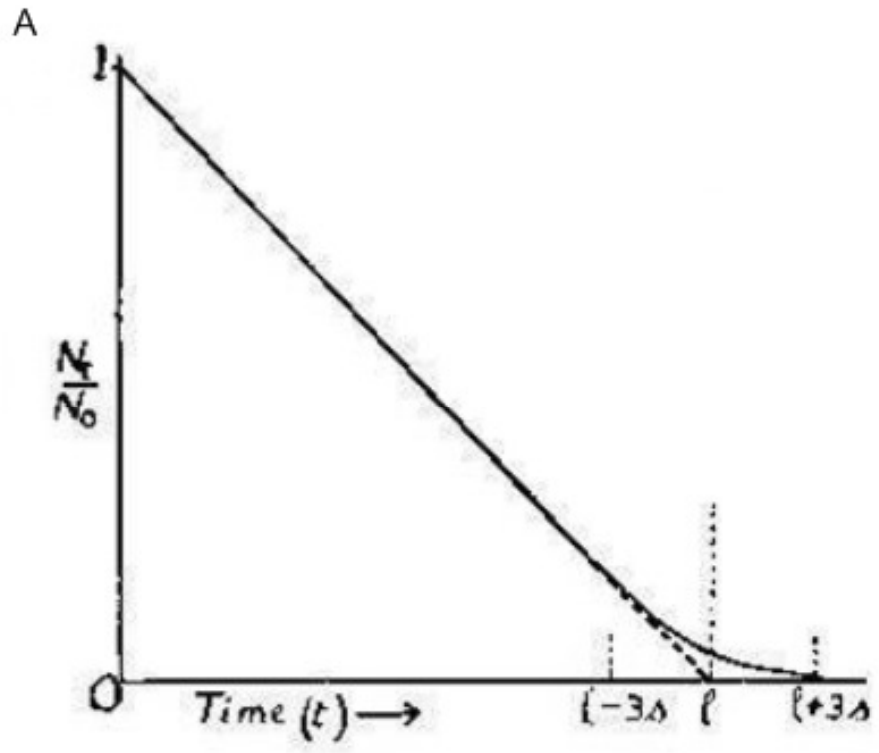
SHEMIN, D. & RITTENBERG, D. (1946) Journal of Biological Chemistry 166:627-636

Simulation 2 – Random labelling

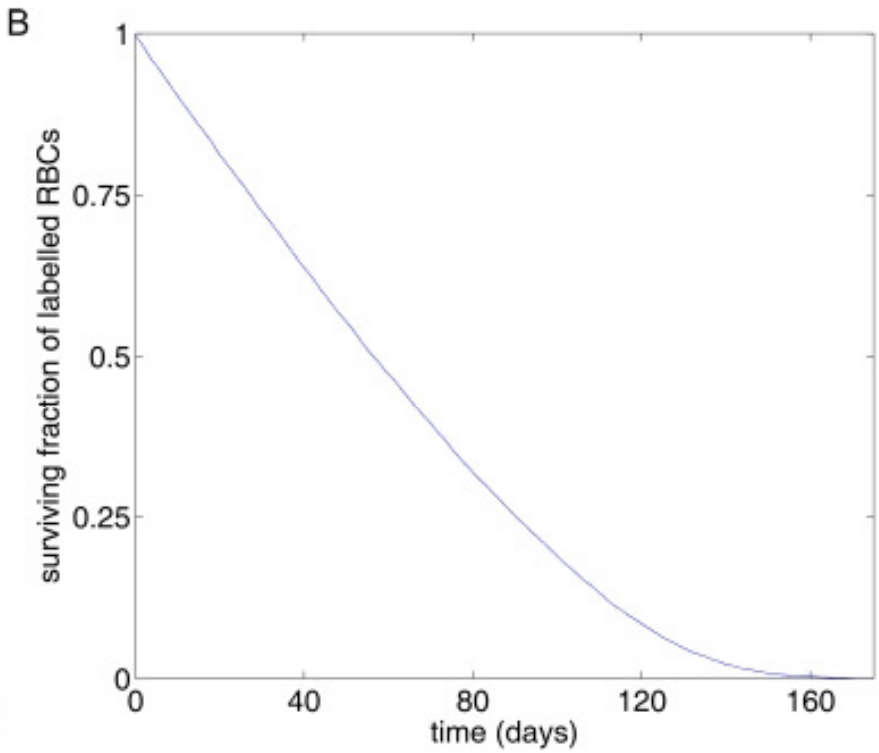
- 1000 RBCs produced daily over 500 days



Simulation 2 – Random labelling



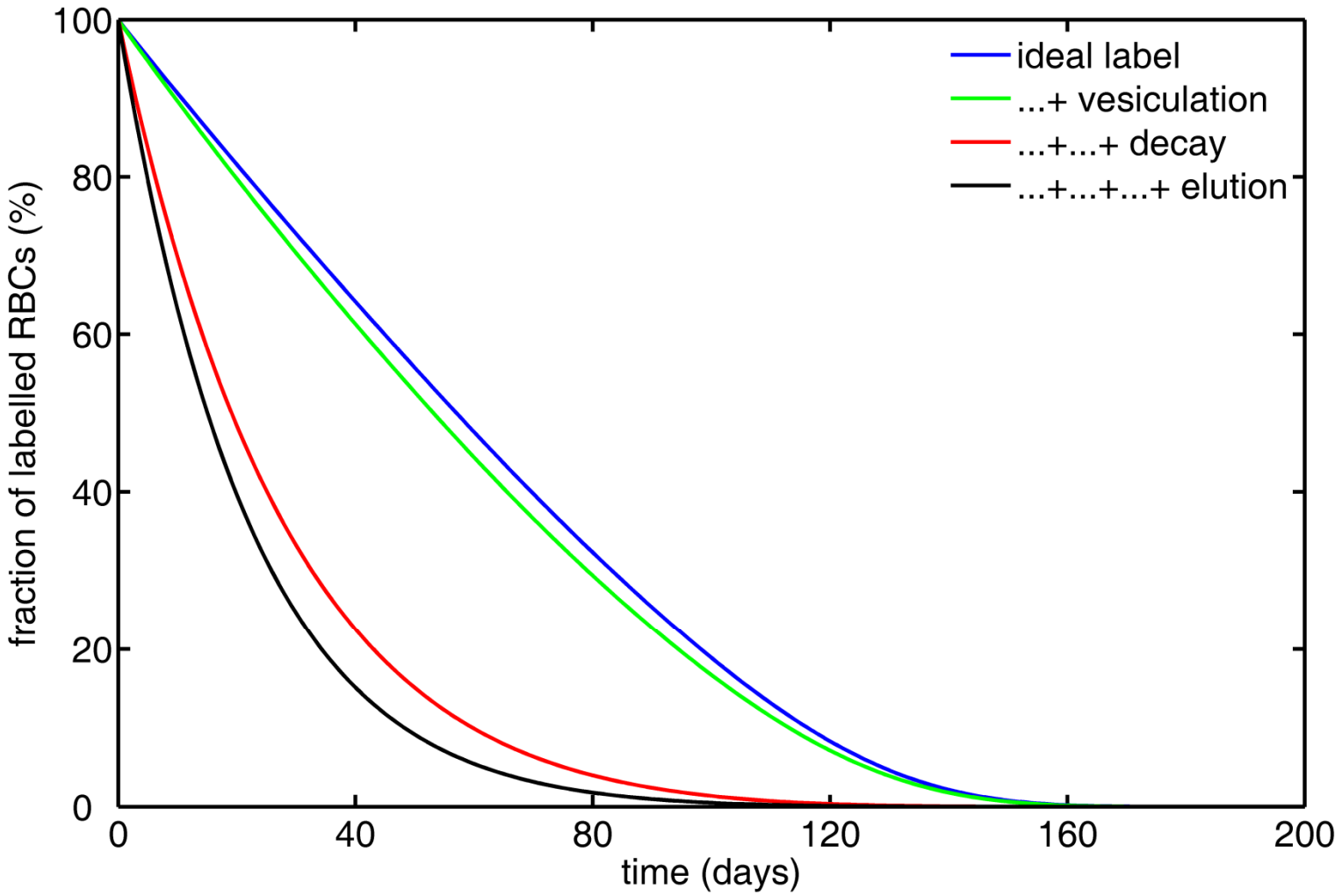
Prediction assuming a normal distribution of RBC lifespans (1951)



Prediction from our model

DORNHORST, A. (1951) Blood 6:1284-1292

Model application – Random labelling with radioactive chromium (^{51}Cr)



2. Local identifiability

Optimal design - Theory

- Sensitivity of a function f to changes in a certain parameter θ_1:

$$\frac{\partial f}{\partial \theta_1} = f'(\theta_1) = \lim_{h \to 0} \frac{f(\boldsymbol{\theta}, \theta_1 + h) - f(\boldsymbol{\theta}, \theta_1 - h)}{2h}; \ \boldsymbol{\theta} = (\theta_2 \ldots \theta_p)^T$$

- Sensitivity matrix = Jacobian matrix $\mathbf{J}$:

$$\mathbf{J} = \begin{bmatrix} \frac{\partial f(t_1)}{\partial \theta_1} & \cdots & \frac{\partial f(t_n)}{\partial \theta_1} \\ \vdots & \ddots & \vdots \\ \frac{\partial f(t_1)}{\partial \theta_p} & \cdots & \frac{\partial f(t_n)}{\partial \theta_p} \end{bmatrix}$$

Optimal design - Theory

- Fisher Information matrix (M_F) weighted by residual unexplained variability (RUV) Σ:

$$M_F = \mathbf{J}^T \Sigma^{-1} \mathbf{J}$$

- D-optimality used as criterion to maximize M_F:

$$\Psi_D = \underset{t}{arg\,max}(det(M_F(\boldsymbol{\theta}, t)))$$

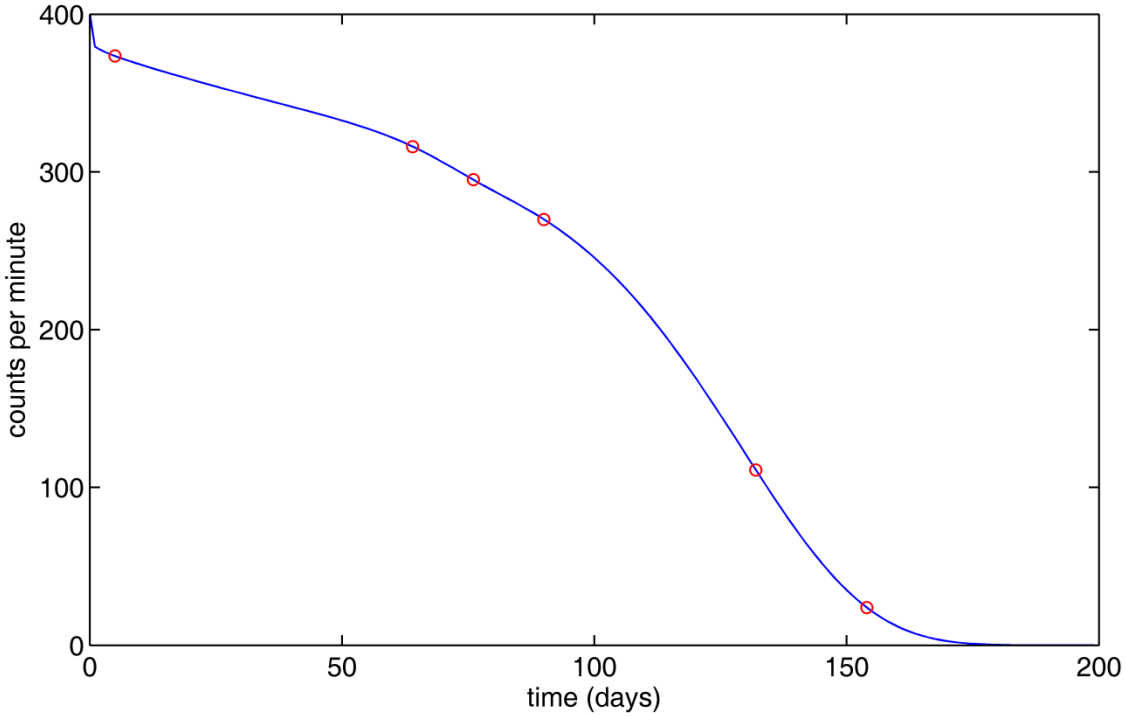
- Square root of inverse diagonal entries of M_F = standard error of parameter estimates $\boldsymbol{\theta}$

Local identifiability

- For both ideal random and ideal cohort labelling the Fisher Information matrix is positive definite.

⇨ Informally, all parameter values are locally identifiable under ideal labelling conditions.

Optimal design – Ideal cohort labelling



Parameter estimation

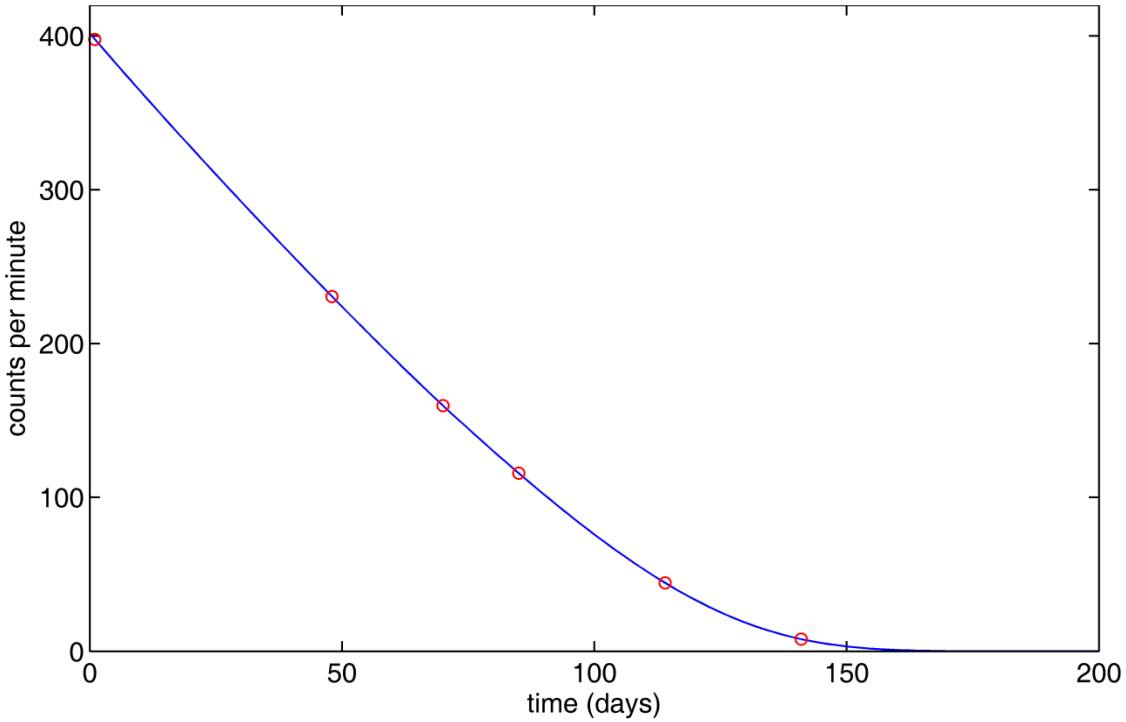
100 subjects

θ	%SE
r_1	2.2
r_2	18.0
s_1	0.6
s_2	0.8
c	4.6
p	0.8

Optimal blood sampling times

days	5	64	76	90	132	154

Optimal design – Ideal random labelling



Parameter estimation

100 subjects

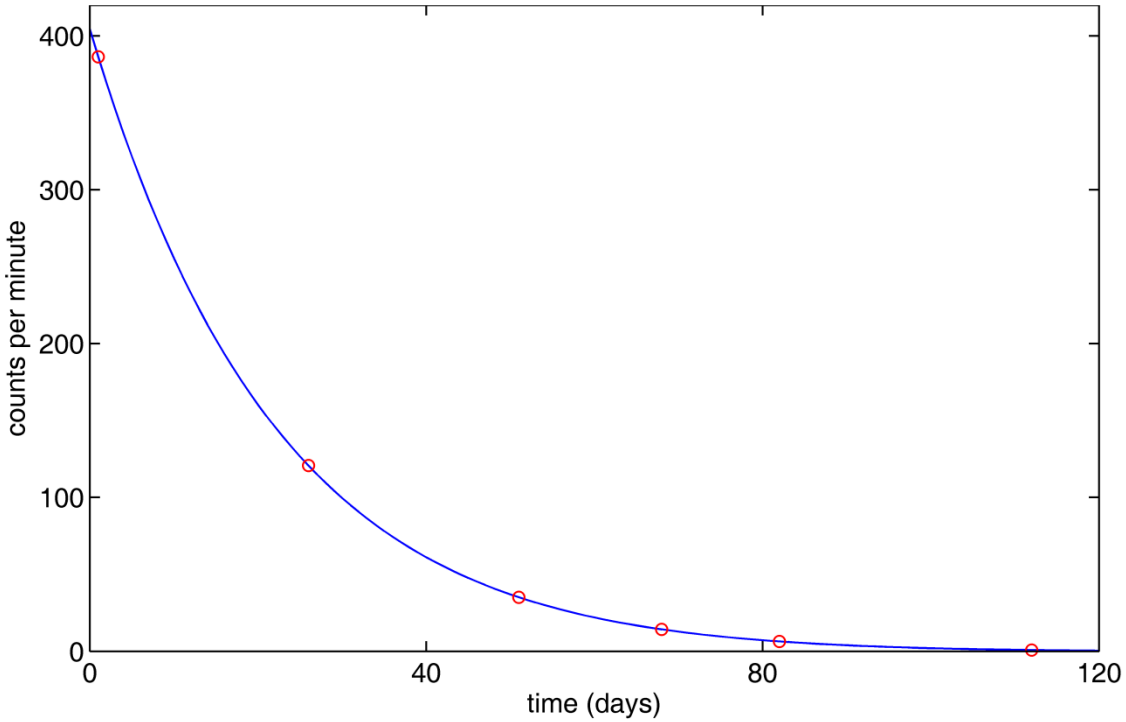
θ	%SE
r_1	12.0
r_2	120.0
s_1	2.8
s_2	4.0
c	21.0
p	3.7

Optimal blood sampling times

days	1	48	70	85	114	141

3. Precision of parameter estimation for labelling methods including flaws

Optimal design – ^{51}Cr labelling



Optimal blood sampling times

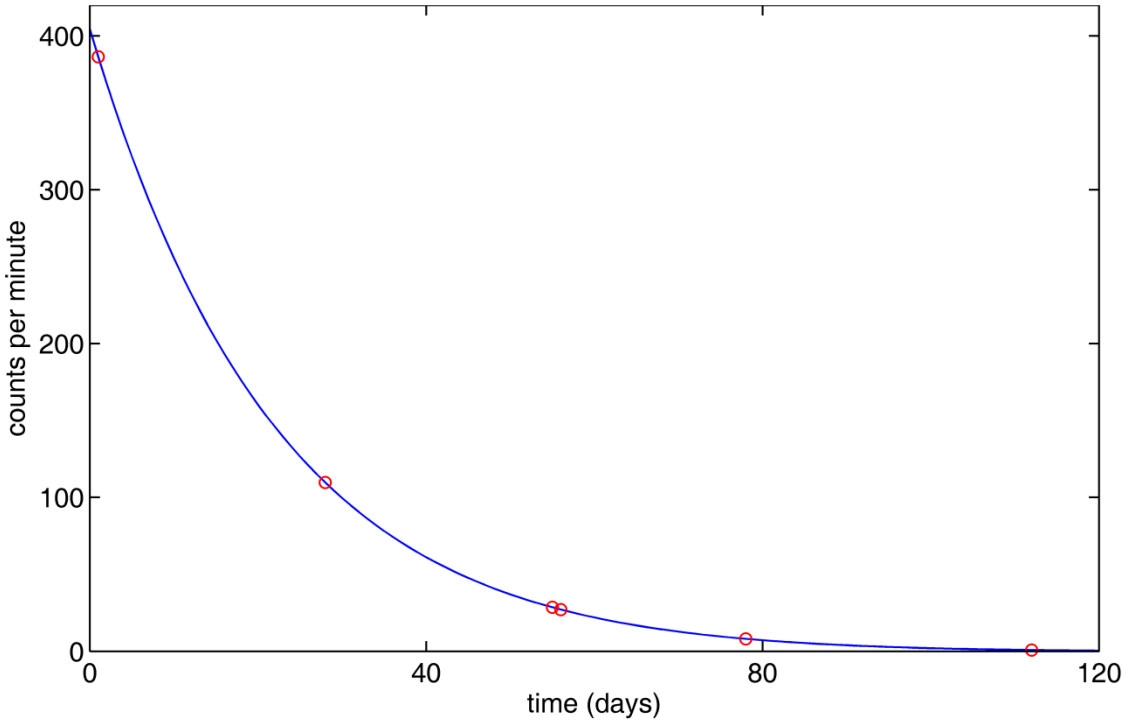
days	1	26	51	68	82	112

Parameter estimation

100 subjects

θ	%SE
r_1	54.0
r_2	670.0
s_1	63.0
s_2	62.0
c	120.0
p	19.0

Optimal design – ^{51}Cr labelling



Optimal blood sampling times

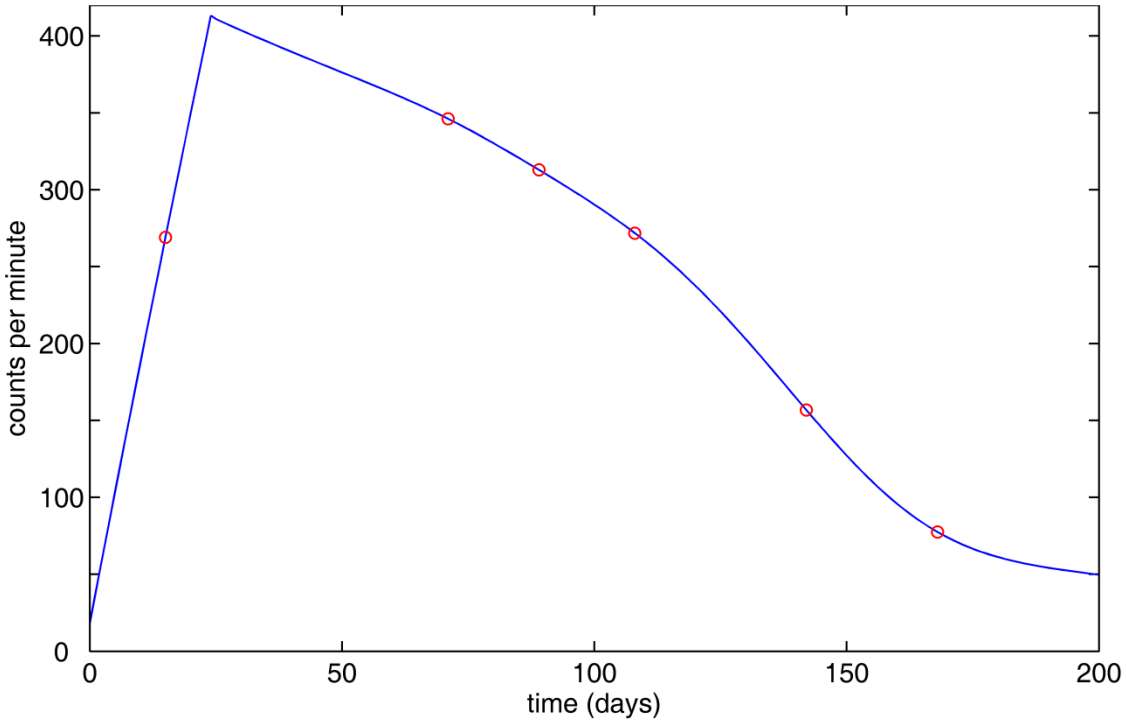
days	1	28	55	56	78	112

Parameter estimation

100 subjects

θ	%SE
r_1	43.0
r_2	fixed
s_1	54.0
s_2	49.0
c	36.0
p	4.0

Optimal design – ^{15}N labelling



Parameter estimation

100 subjects

θ	%SE
r_1	5.0
r_2	50.0
s_1	1.3
s_2	1.8
c	9.3
p	1.6

Optimal blood sampling times

days	15	71	89	108	142	168

Conclusion

- The RBC survival model accounts for the plausible physiological processes of RBC destruction.
- The model can be used to simulate cohort labelling as well as random labelling methods.
- Flaws associated with certain labelling methods can be incorporated into the model.

Conclusion

- The model shows local identifiability for all parameter values under ideal labelling conditions.
- Precision of parameter estimation using labelling methods with flaws:
  - Using random labelling with loss (^{51}Cr):

    Only 5 of the 6 parameter values can be estimated.
  - Using a cohort label with reuse (^{15}N):

    All parameters can be estimated with high precision.

⇨Cohort labelling is superior to random labelling.

Acknowledgements

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- Friends from the Modelling & Simulation Lab
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- School of Pharmacy
- PAGE
- Pharsight – Student Sponsorship

Thank you!