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Blood Supply

Quantitative methods in Donor Management

Blood and Beyond

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Sanquin Blood Supply Foundation

- The only organisation in the NL authorised to supply blood (products)
- Not-for-profit organisation
- Employing approximately 3,000 people working in 5 divisions:
  - Blood Bank
  - Plasma Products
  - Diagnostic Services
  - Research – Sanquin staff working with / partly employed at academic centers
  - Reagents

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Sanquin Blood Bank - numbers

- ± 380,000 Donors
  - 2.3% of the total Dutch population (16.8 million)
- Approximately 800,000 donations per year
  - Mostly whole blood (60%, 2wk walk-in)
  - Plasmapheresis (by appointment)
- Donation interval
  - Minimum 8 weeks (3/yr women, 5/yr men)
  - Average 11-12 weeks

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Research

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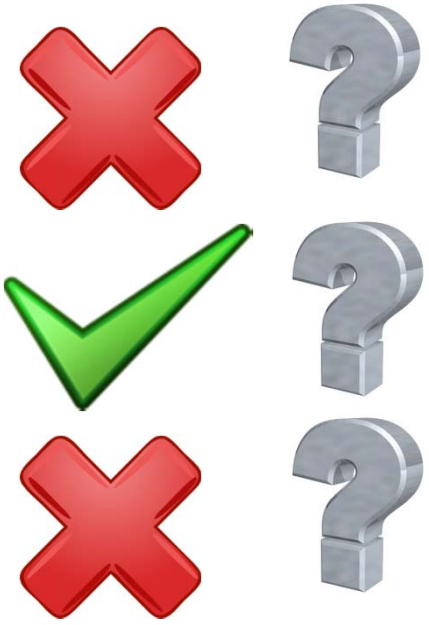
How about simple calculus?

1	+	1	=	1
1	+	1	=	2
1	+	1	=	3



How about simple calculus?

~~0.6~~	1	+	~~0.7~~	1	=	~~1.3~~	1
~~0.9~~	1	+	~~1.2~~	1	=	~~2.1~~	2
~~1.3~~	1	+	~~1.4~~	1	=	~~2.7~~	3



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Research Topics

- Risk Based Selection
  - Donor Risk vs. Patient Risk
  - Cost-Effectiveness
- Adverse Events and Reactions in Donors
  - Vasovagal Reactions
  - Iron Status and Metabolism
  - Genetic Variation
- Donor Base Management
  - Recruitment and Retention
  - Involvement of Minorities

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Platelet Inventory Management

Theory meets Practice

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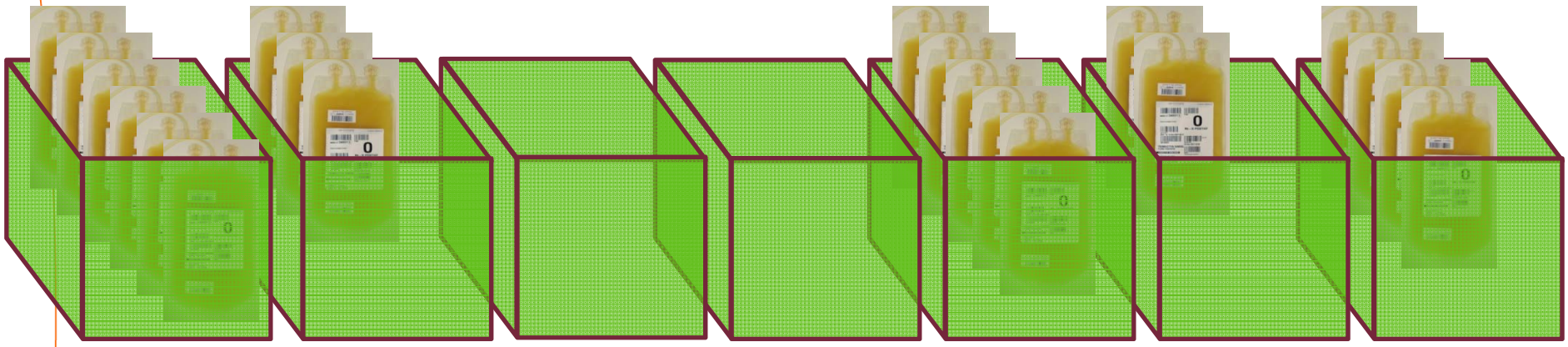


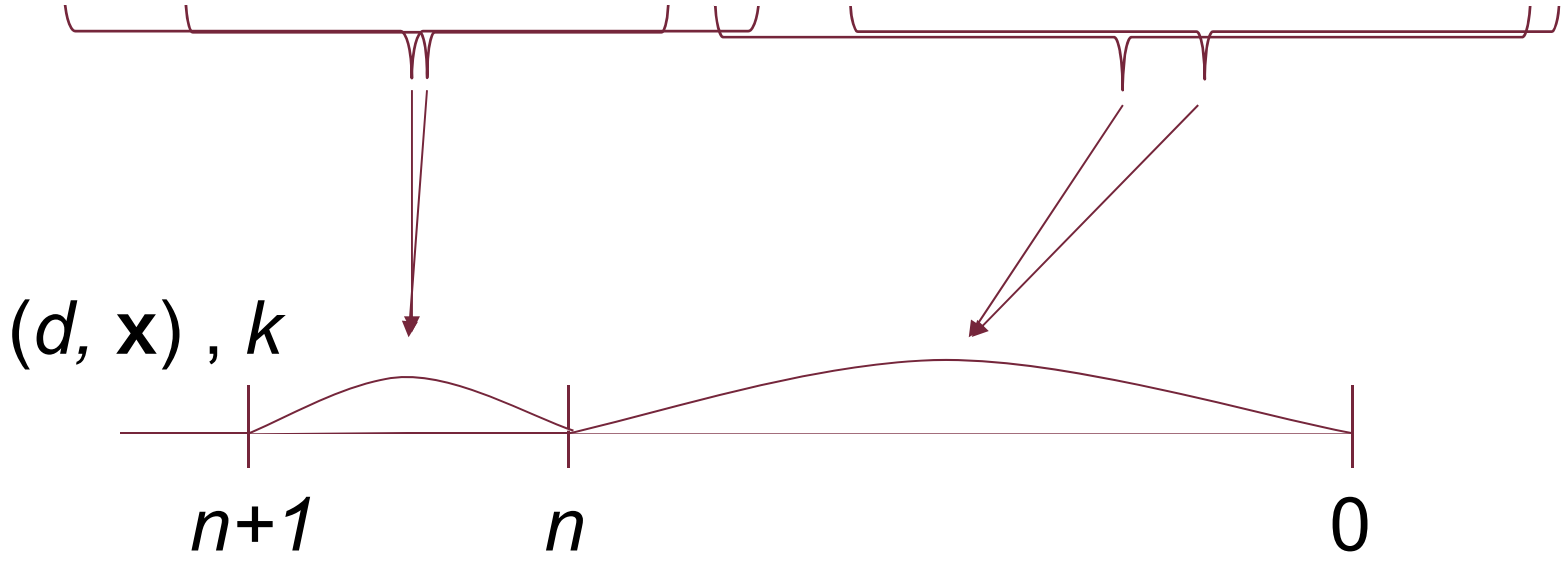
TTO = | 7 days | 6 days | 5 days | 4 days | 3 days | 2 days | 1 day

NB: on Sundays and Mondays no production!

Stochastic Dynamic Programming

V_n = Minimal expected Costs as of tomorrow

V_{n+1} = (Today's Production Costs) + (Minimal Costs after today)



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Risk Based Selection

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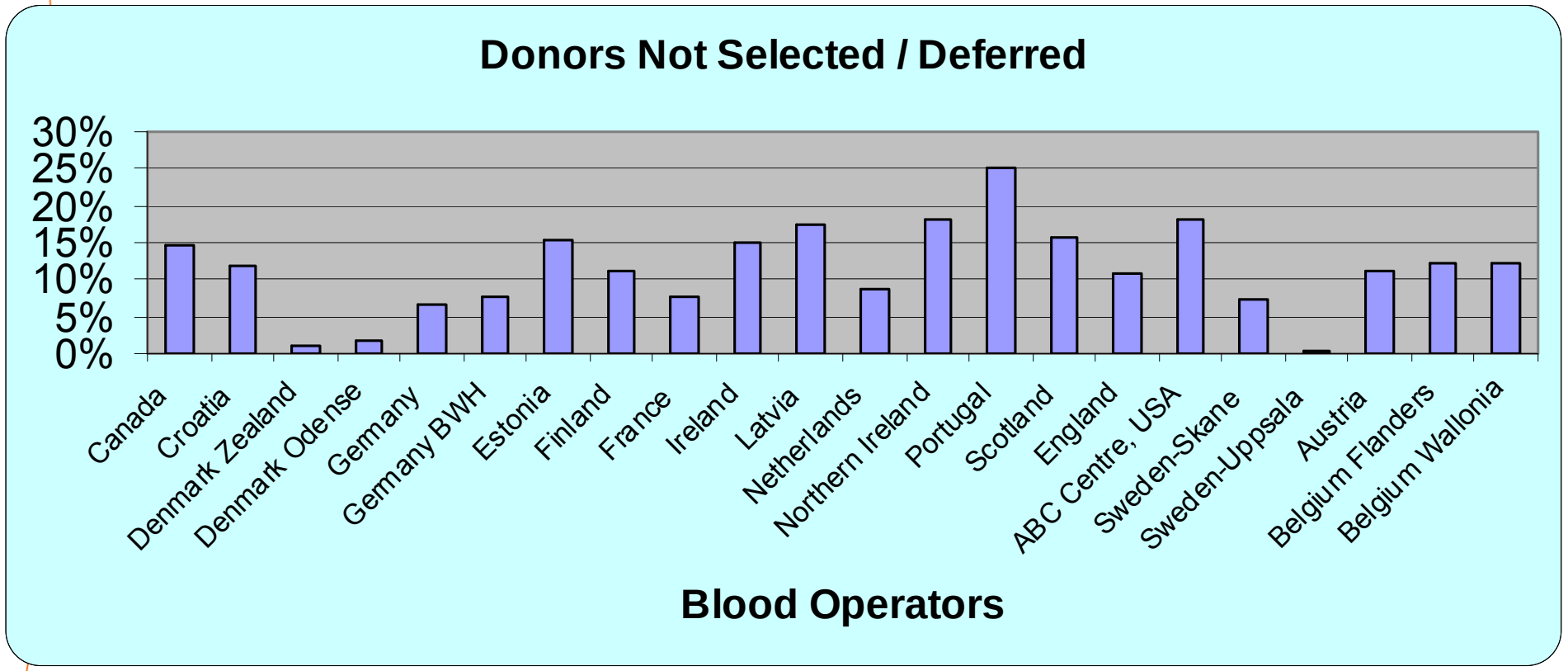
Donor deferral

- Every new donor: screening visit
- Donor screening at every donation
- About 10% of all visits lead to deferral, new donors >20%
  - For donor health
  - For recipient health
- Very disappointing for donor
- Very expensive for blood bank

Donor Deferral Workshop (Amsterdam, 2012): Donations Not Selected / Deferred



Screening

		Condition	
		Yes	No
Test	Pos		
	Neg		

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Number of deferrals to prevent one case of a Transfusion Transmitted Disease*

Disease	# Deferrals
Hepatitis B	39,760
Hepatitis C	564,600
HIV	352,875
Syfilis	42,772

* De Kort et al., 2014

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Donor Base Management

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Databases used for research

- Donor Database (ePrognosa, n ±380,000, ±900,000 donations per year): monthly extractions of:
  - Donors (sex, age, blood group, stopping reasons, height, weight, donation count)
  - Donations (type, date, amount donated)
  - Donor screening data (hemoglobin, blood pressure, reasons for deferral)
  - Etc...

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Databases used for research

Separate studies

- Donor InSight Study (n>30,000)
- Kinetics of IroN in Donors
- CARDON
- Donor Stress – homeostasis – blood products
- Donor Lapse questionnaires
- Consultancy research (internal evaluations of Mobile Blood Drive, donor satisfaction, waiting times, etc.)

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Donor InSight (DIS)

- 50,000 donors randomly selected, 31,338 (63%) participated
- Questionnaires completed from April 2007-April 2009
  - Socio-Economical Status
  - Ethnicity
  - Nutrition
  - Medical History (health, disease)
  - Physical activity
  - Donor motivation
  - Donation process
  - Adverse reactions
- Linkage with blood bank data
- Linkage with medical and disease registries
- Consent to recontact

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Donor InSight 2

In the past years, again 50,000 donors were asked to complete questionnaires:

- All surviving respondents DIS 1 (n=29,532)
- New random samples of donors (n=20,468)

Data collection has just been completed...

34,823 (69.7%) participated, data are being cleaned

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Donor Health

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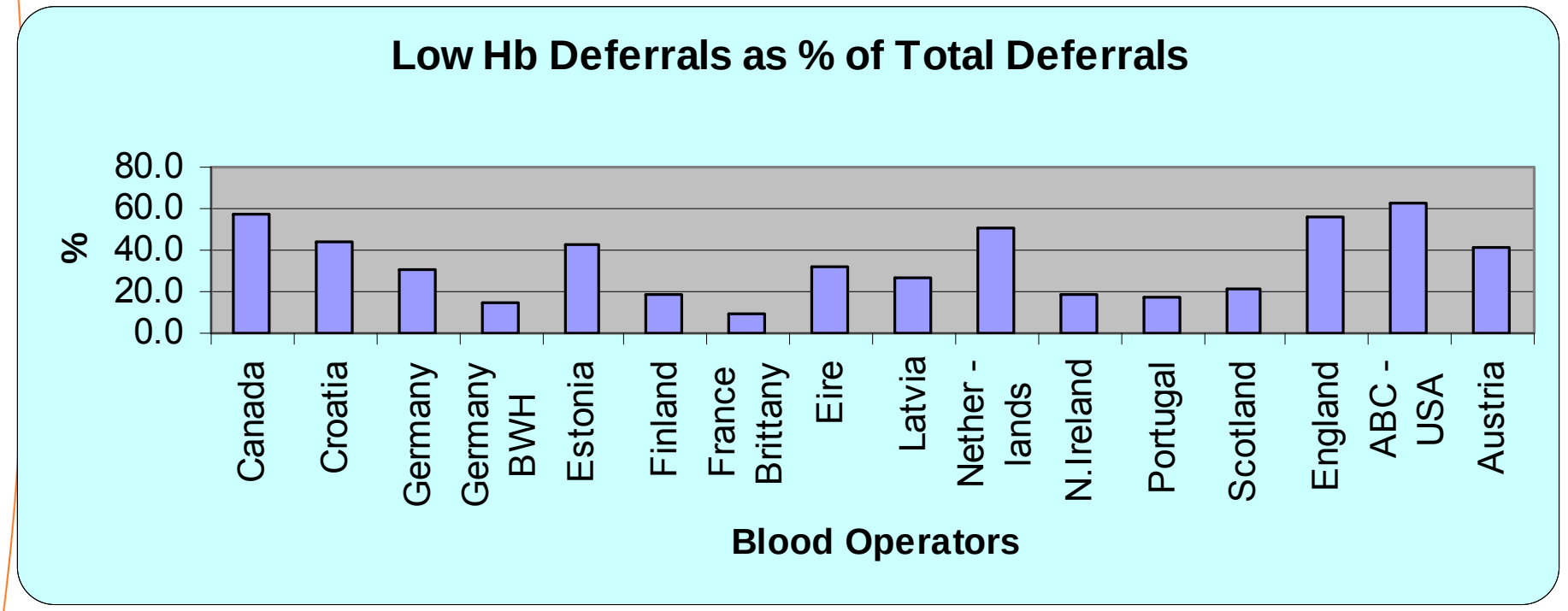
Deferral Rates



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Prediction of Hb deferral

- Prediction models were developed for men and women separately
- Predictors:
  - Age
  - Season
  - Hb previous visit
  - ΔHb at 2 last visits
  - (Hb)-deferral at last visit
  - Time since last visit
  - Number of donations in the last 2 years
  - ZPP (Zinc ProtoPorphyrin)

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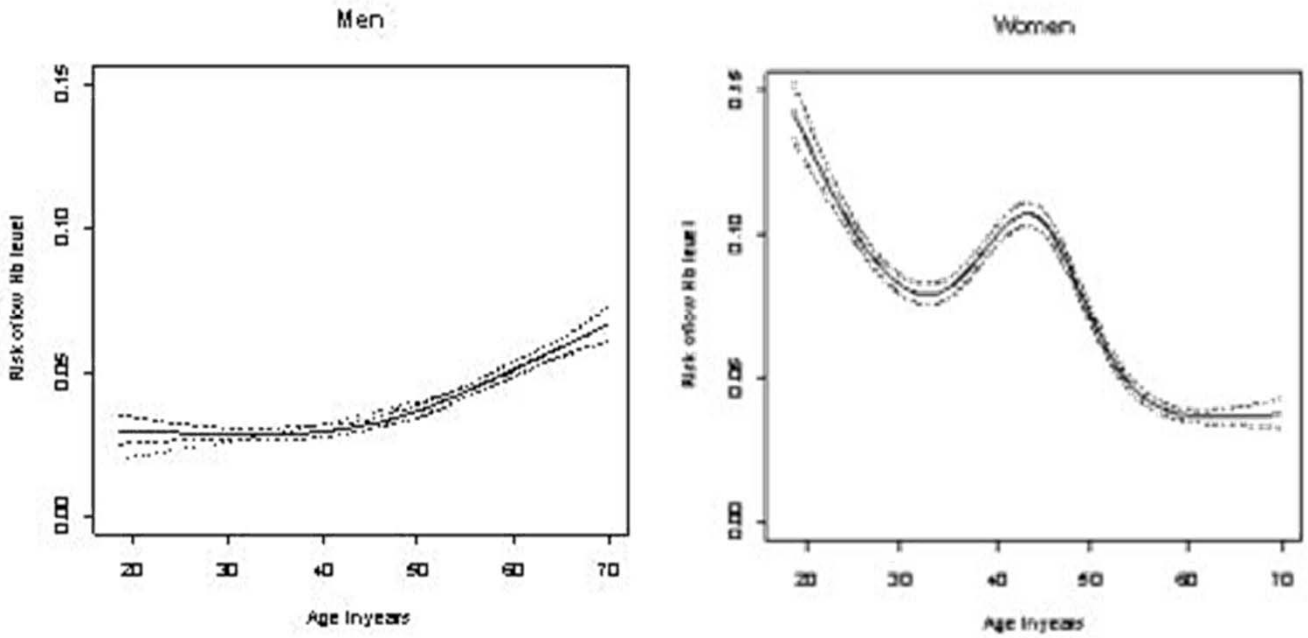

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Impact study

- Evaluate effectiveness of prediction models by selective invitation of donors
- Randomized controlled trial

All Dutch Donors, four regions/groups:

Group 1 Invited as usual. i.e. without using prediction model

Groups 2-4 Interventions for donors in high risk groups:

Group 2 Prolongation of donation interval

Group 3 Dietary advice

Group 4 Both prolongation of donation interval and dietary advice

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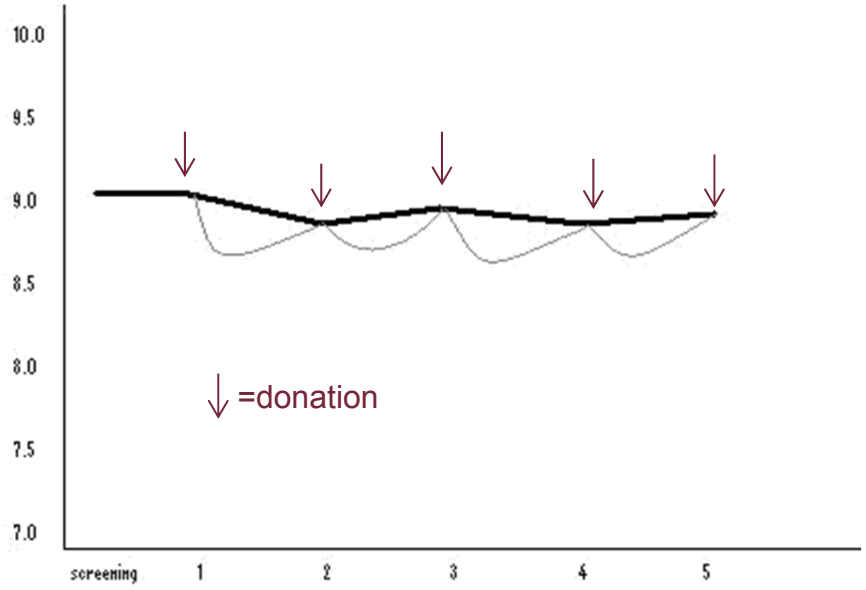
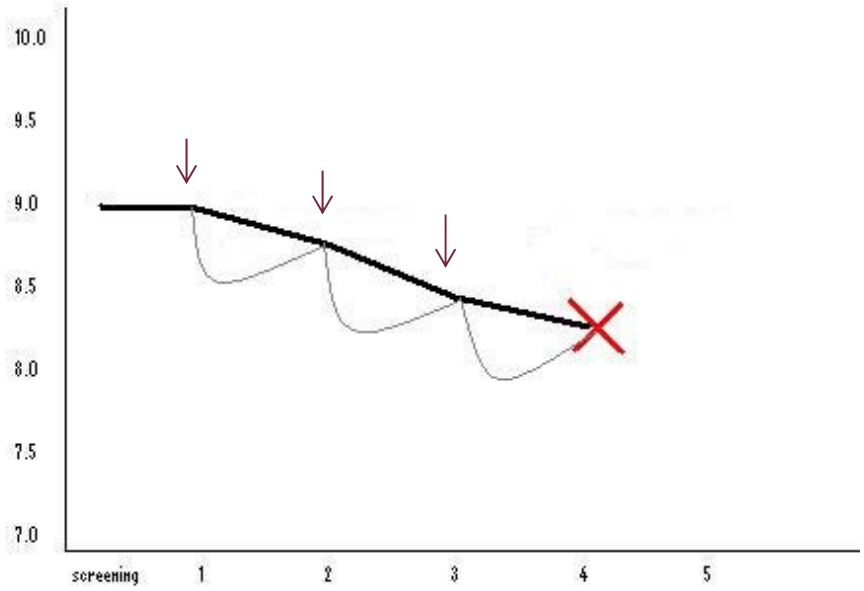
Patterns of hemoglobin levels

- Hemoglobin is measured at every visit
- Hypothesis: different people cope differently with repeated donations:





- Faster hemoglobin recovery > genetic basis?

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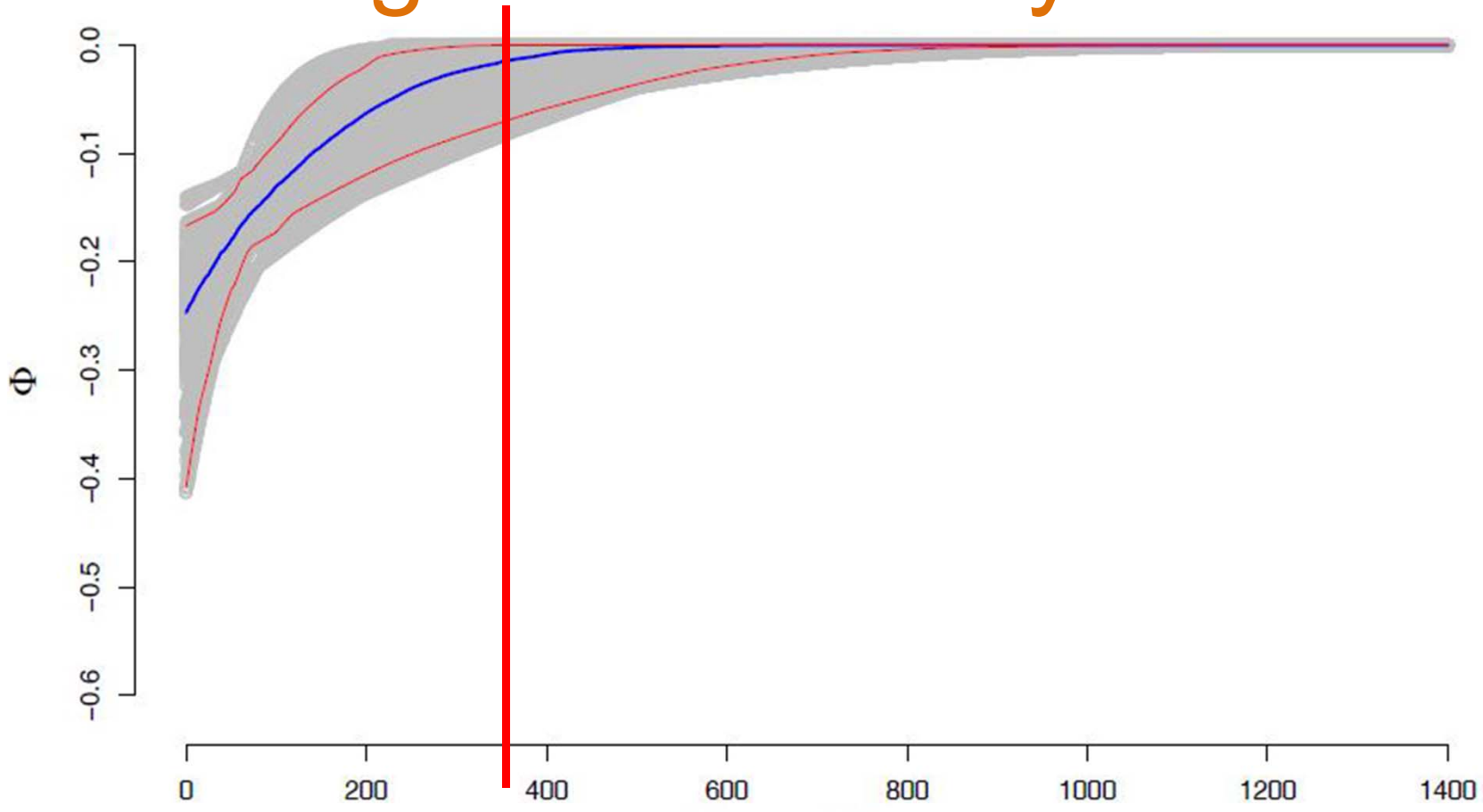
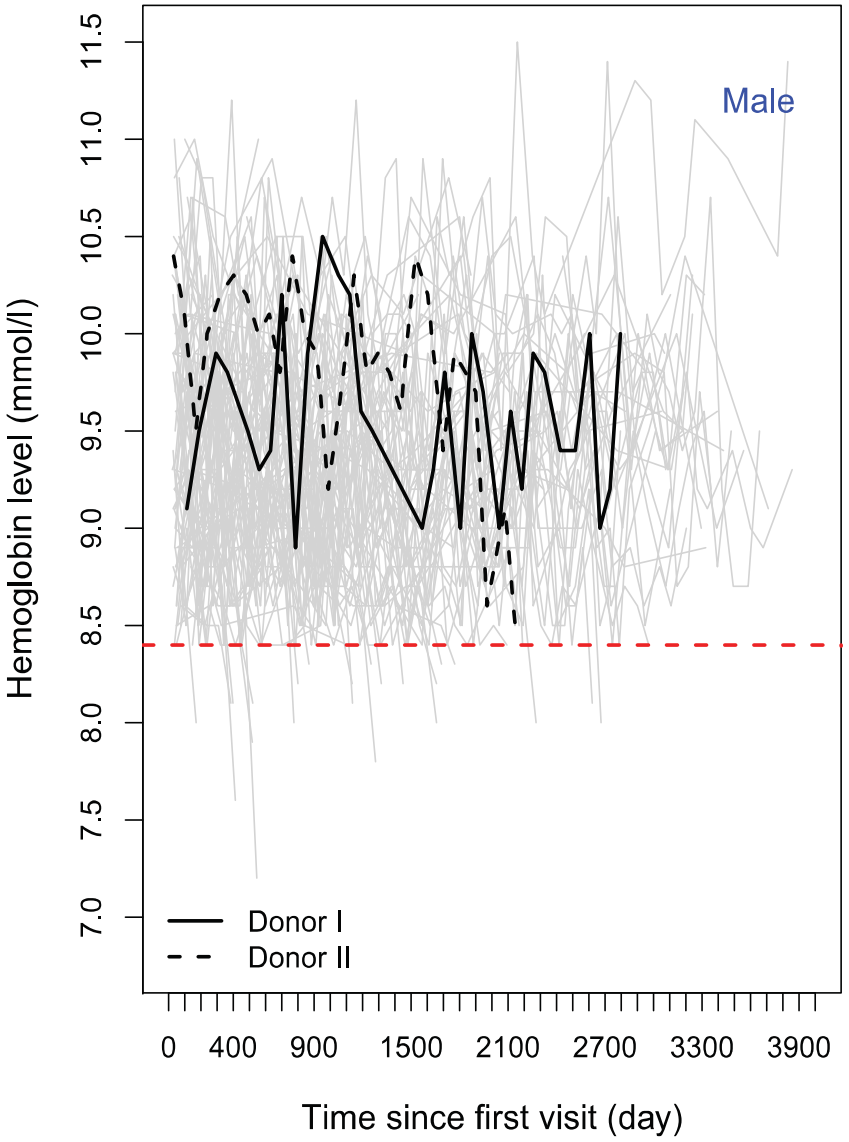
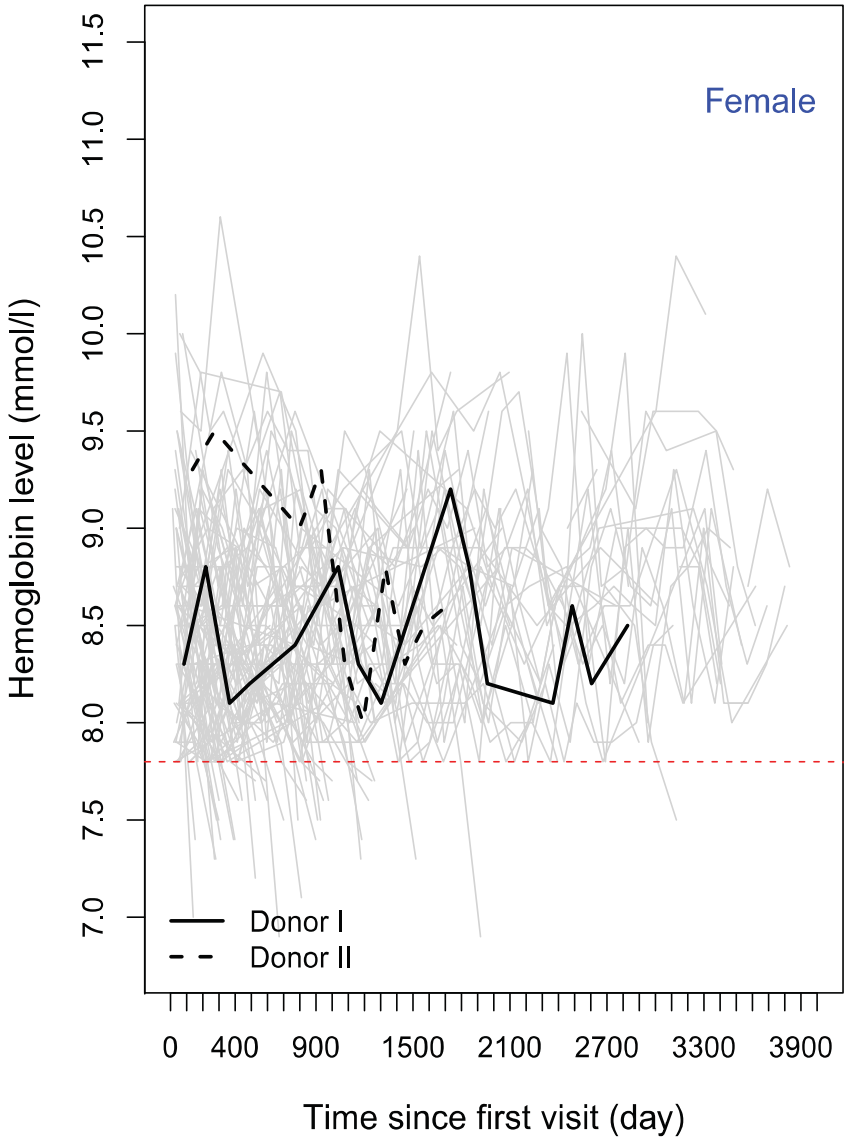
Hemoglobin recovery



Hemoglobin profiles for male and female donors





Statistical model to capture heterogeneity across donors

Some statistical models for longitudinal (repeated measures) data.

- Mixed-effects model
- Transition (autoregressive) model
- Latent class model

Mixed-effects model

Capture the unobserved heterogeneity by random effects.

Mixed-effects model

$$Hb_{it} = \theta_1 + b_{i0} + \beta_1 Age_{i1} + \beta_2 Season_{it} + \beta_3 TSPD_{it}$$
$$+\beta_4 TSPD_{it}^2 + \beta_5 BFD_{it} + (\theta_2 + b_{i1}) NODY2_{it} + \epsilon_{it}$$

Transition model

Capture the state dependence by lag effect.

Transition model

$$Hb_{it} = \theta_1 + \beta_1 Age_{i1} + \beta_2 Season_{it} + \beta_3 TSPD_{it}$$
$$+\beta_4 TSPD_{it}^2 + \beta_5 BFD_{it} + \gamma Hb_{it-1} + \theta_2 NODY2_{it} + \epsilon_{it}$$

Latent class model

Latent class model

This model assumes that each donor belongs to one of several unobserved groups (latent classes in statistical terminology).

The model assigns each donor to one of several groups, in such a way that donors with similar Hb trajectories are in the same group.

For examples: are those who are vegetarians and those who aren't, those who regularly exercise and those who don't (assuming those data were not collected).

Latent class model

A latent class model with two classes.

If person i belongs to class 1:

$$Hb_{it} = \theta_{11} + \beta_1 Age_{i1} + \beta_2 Season_{it} + \beta_3 TSPD_{it}$$

$$+\beta_4 TSPD_{it}^2 + \beta_5 BFD_{it} + \theta_{12} NODY2_{it} + \epsilon_{1it}$$

If person i belongs to class 2:

$$Hb_{it} = \theta_{21} + \beta_1 Age_{i1} + \beta_2 Season_{it} + \beta_3 TSPD_{it}$$

$$+\beta_4 TSPD_{it}^2 + \beta_5 BFD_{it} + \theta_{22} NODY2_{it} + \epsilon_{2it}$$

θ_{11}, θ_{12}, θ_{21}, θ_{22} are class specific parameters and the rest are shared parameters.

Latent class mixed-effects model

Latent class models typically do not capture the entire variation in the Hb trajectories. To capture the remaining heterogeneity between donors in the same class, the Hb trajectory follows a linear mixed model.

A latent class mixed-effects model with two classes:

If person i belongs to class 1:

$$Hb_{it} = \theta_{11} + \mathbf{b_{i11}} + \beta_1 Age_{i1} + \beta_2 Season_{it} + \beta_3 TSPD_{it}$$

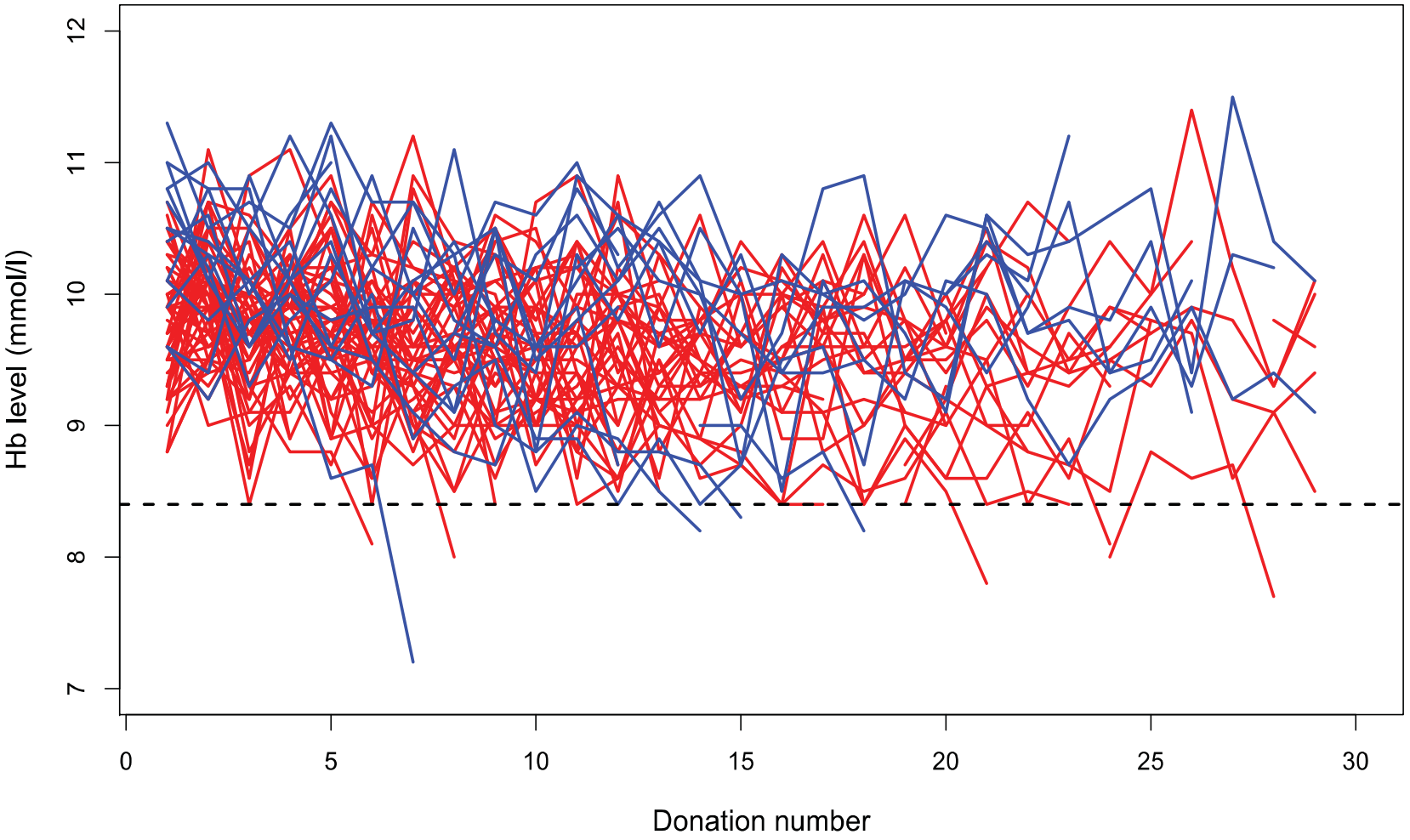
$$+\beta_4 TSPD_{it}^2 + \beta_5 BFD_{it} + (\theta_{12} + \mathbf{b_{i12}}) NODY2_{it} + \epsilon_{1it}$$

If person i belongs to class 2:

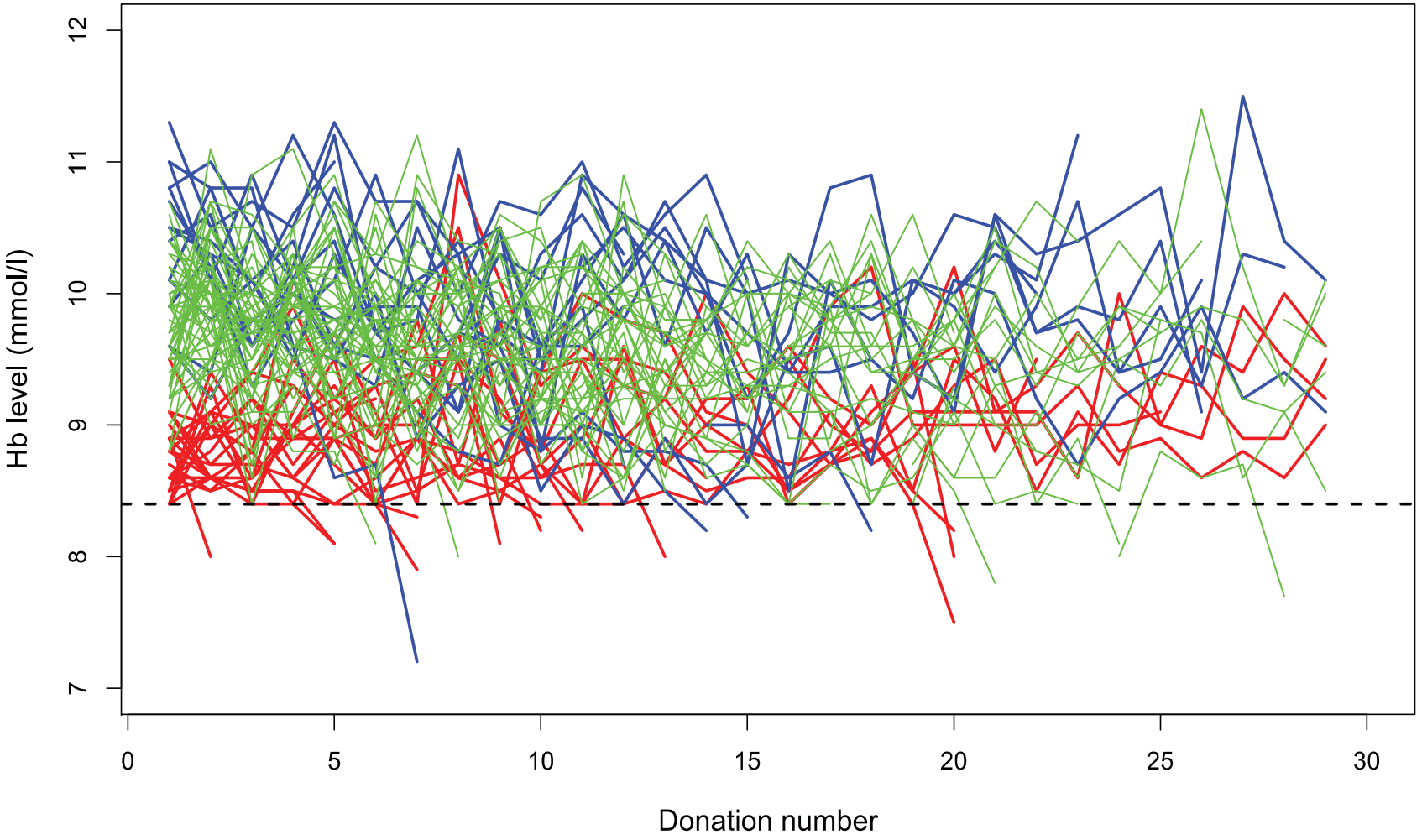
$$Hb_{it} = \theta_{21} + \mathbf{b_{i21}} + \beta_1 Age_{i1} + \beta_2 Season_{it} + \beta_3 TSPD_{it}$$

$$+\beta_4 TSPD_{it}^2 + \beta_5 BFD_{it} + (\theta_{22} + \mathbf{b_{i22}}) NODY2_{it} + \epsilon_{2it}$$

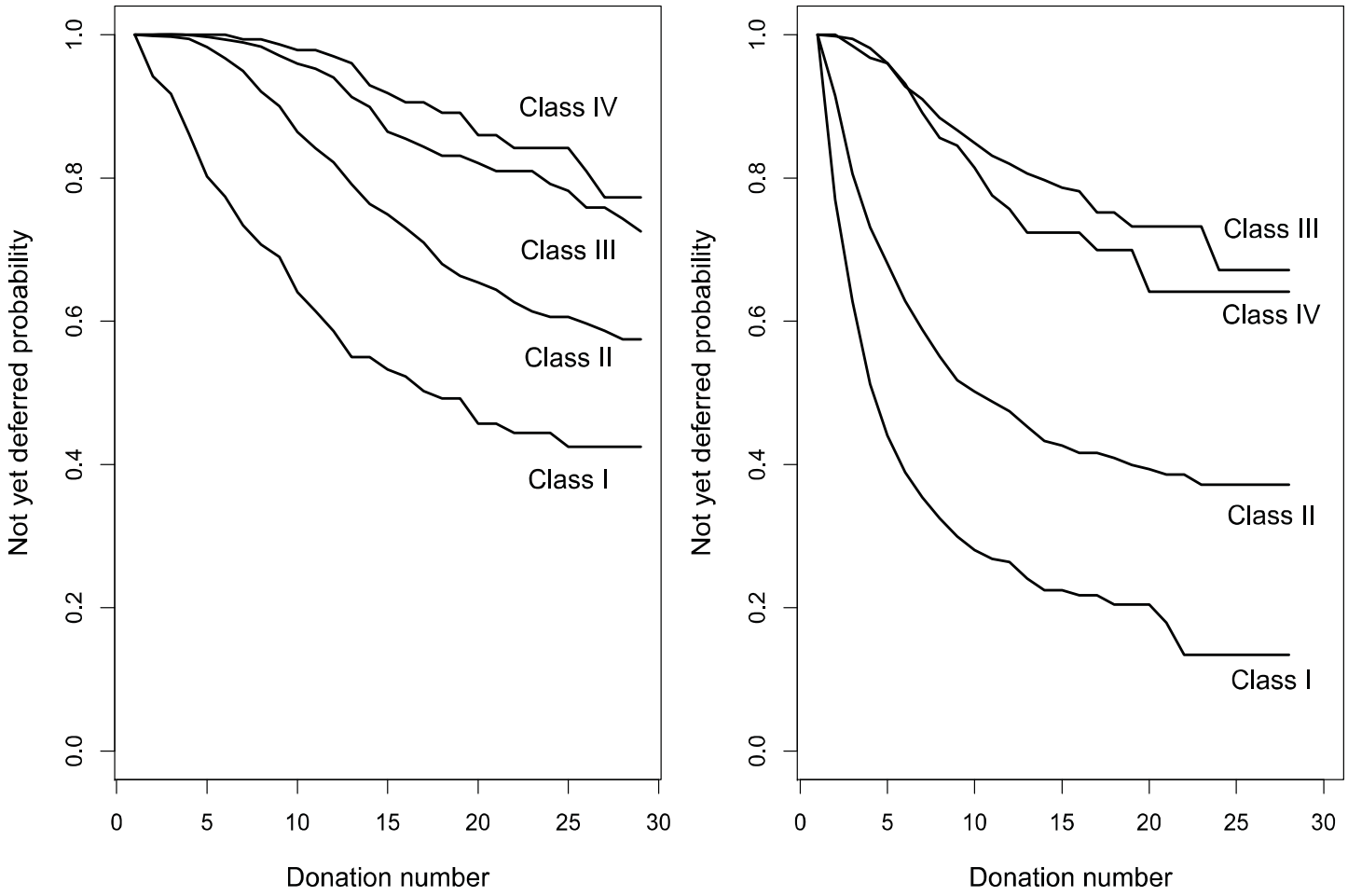
Male Hb profiles (two groups)



Male Hb profiles (three groups)



Donors deferred proportion Kaplan-Meier curves of the latent classes



Conclusion and future research

- We classified donors in 4 different classes based on their Hb trajectories.
- This model gives some insight in the donation process and is a start to better predict for which donors care needs to be exercised not to produce a too low Hb level.
- We aim to explain these classifications based on gene expression of donors.

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Kinetics of IroN after Donation (KIND)

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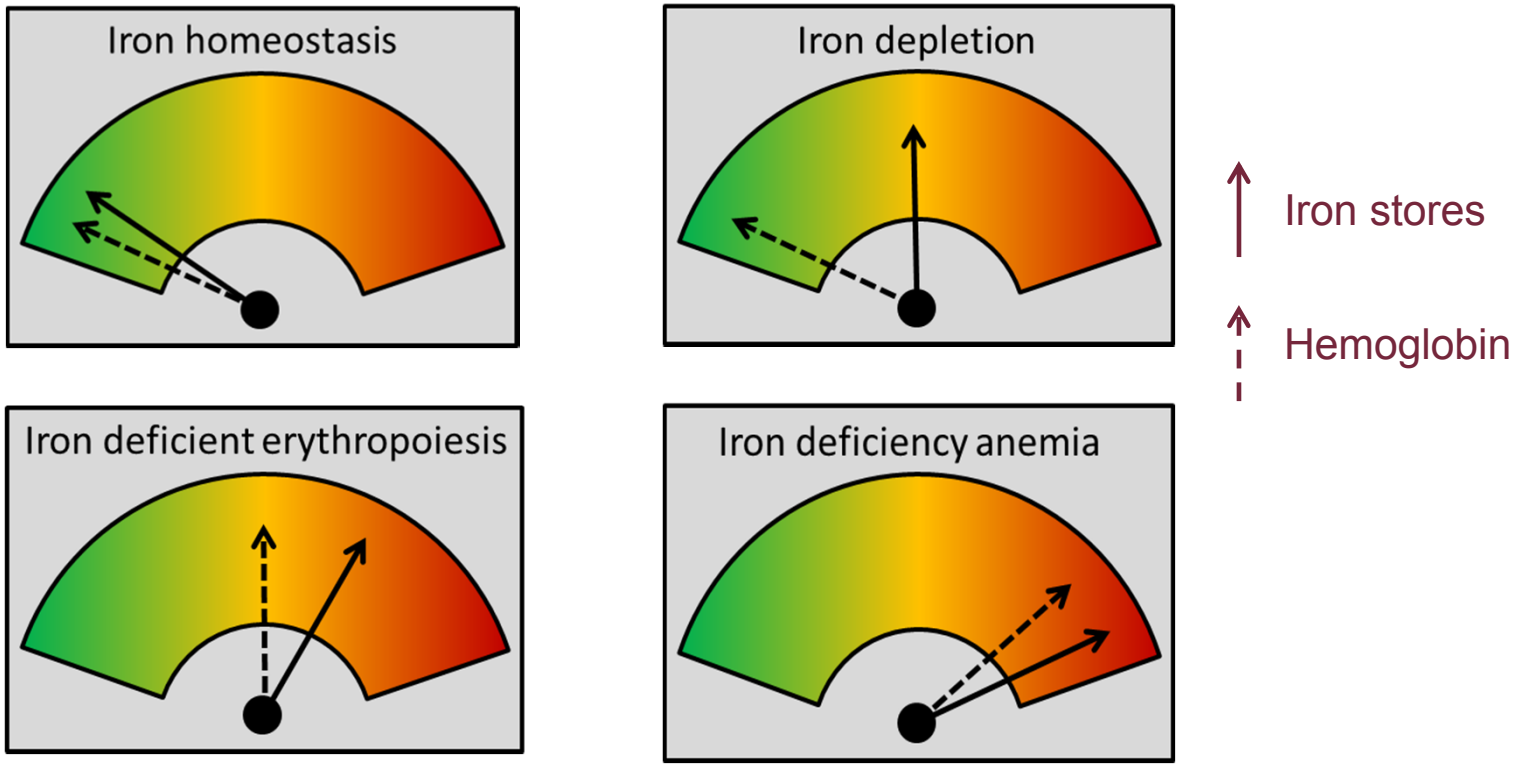
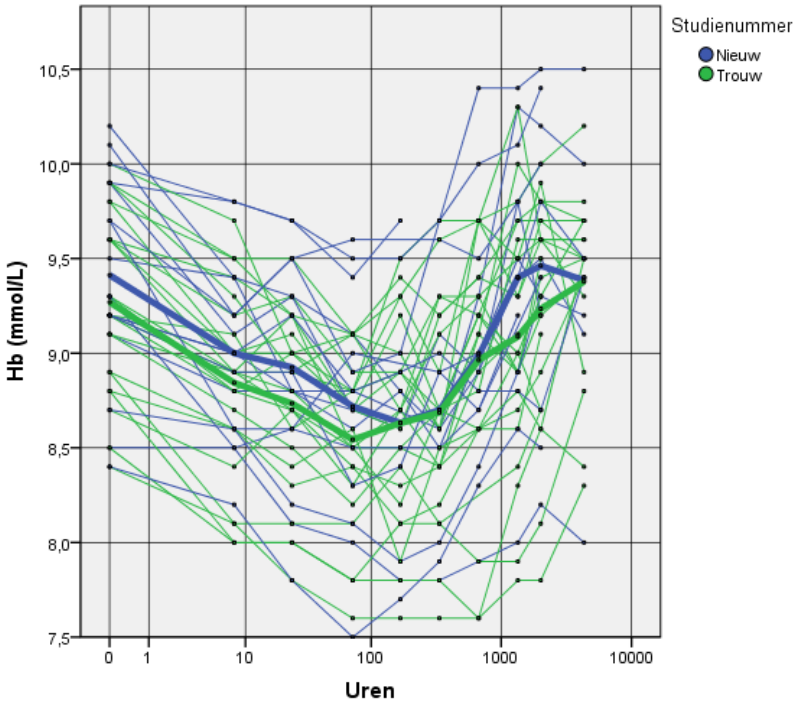
Depleting iron stores

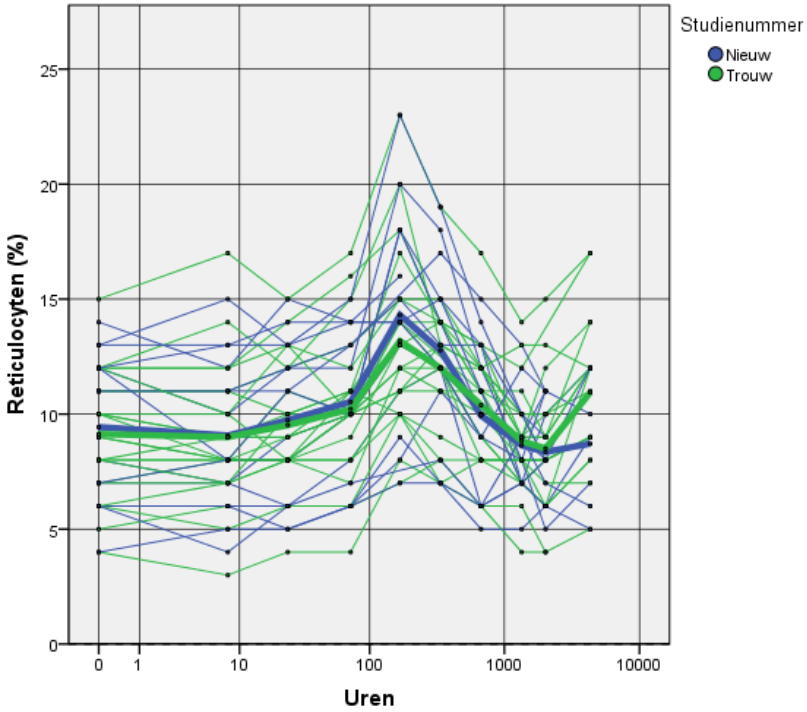


Kinetics of IroN after Donation, KIND

Preliminary results

Hours	Days
0	
8	
24	Day 2
72	Day 4
168	Day 8
336	Day 15
672	Day 29
1344	Day 57
2016	Day 85
4320	Day 180





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CARdiovascular risk and DONation (CARDON)

- Active WB donors (n=633) & new WB donors (n=112) with 2yr follow-up
- Questionnaire, metabolic factors
- Sex-specific donation tertiles of:
  - Lifetime # donations
  - # donations last 2 years
  - # donations last 4 years
  - Donation frequency

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Does stress influence blood product quality?

- Measuring stress during donations
  - Questions
  - Saliva cortisol
  - Continuous blood pressure, heart rate (variability)
- Participants (189 per group):
  - New donors
  - Regular never deferred donors
  - Recently deferred donors
- Outcomes:
  - Effects on platelet and coagulation activity in the donor and the blood products

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Recruitment and Retention of Donors

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MI MI

Missing Minorities

- Ethnic minorities are underrepresented in the donor base
- Different ethnic groups:
  - different diseases
  - different blood types
- The more diverse the donor population, the more patients can be helped
- General recruitment methods: not successful in reaching minority populations

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Follow-up on MIMI

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Return behaviour

- ± 2,000 donors completed questionnaire
  - Theory of Planned Behaviour
  - Self-identity: "blood donation is part of who I am"
  - Organizational factors
    - Feeling pressure to donate
    - Perceived satisfaction with the blood bank
- Whole blood donors
  - 2-10 donations
  - >10 donations

Positive feeling about giving blood

Yes I can!

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Retention results

Most strongly associated with donor lapse:

- Vasovagal reactions
- Anxiety
- Fatigue, particularly in men
- Subjective distress

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Donation Process Management

Waiting Times; Operational Staffing

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Product Form (also Markov Model)

This System's Steady State Chances:

$$\pi(\boldsymbol{n}) = \pi(\boldsymbol{0}) * \prod_{i=1}^{3} \left[\left(\frac{\lambda}{\mu_i} \right)^{\min\{n_i, s_i\}} * \frac{1}{\min\{n_i, s_i\}!} * \left(\frac{\lambda}{s_i \mu_i} \right)^{[n_i - s_i]^+} \right]$$

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Conclusion

Virtually all Research in Donor Management is Quantitative

However:

- In Epidemiological Trend Analyses and Prediction Statistical Modelling is an important Tool
- Operations Research applies Different Mathematical Techniques, e.g. Stochastic Dynamic Programming
- Cooperation with other Research Groups is mandatory

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$$P\{\Sigma\Delta\Pi/S(V_n)\}?$$

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No Questions?