A novel mechanistic model for CD4 lymphocyte reconstitution following paediatric haematopoietic stem cell transplantation

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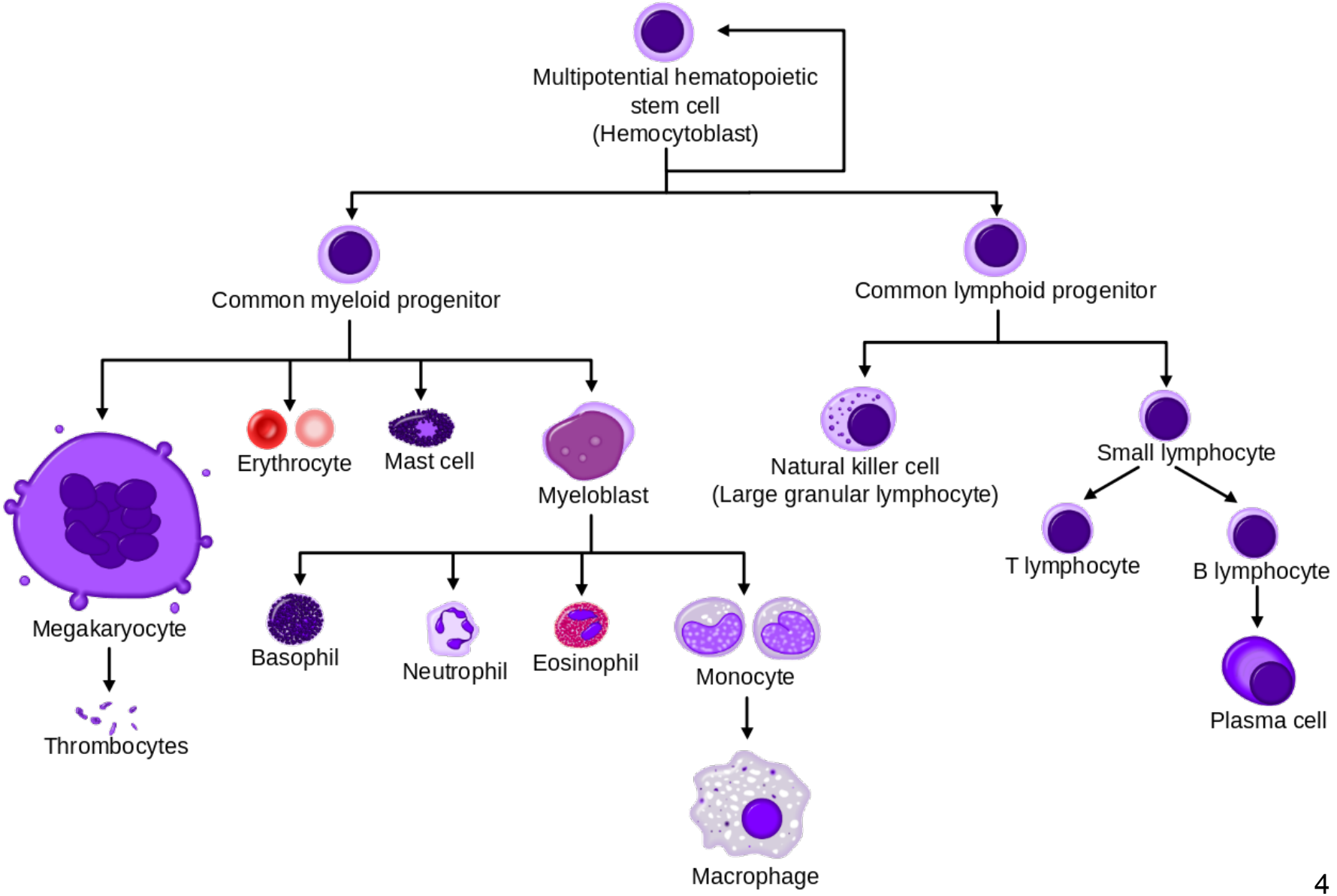
Contents

Haematopoietic stem cell transplants (HSCT)

- Treatment for disorders including immunodeficiencies, leukaemias and lymphomas
- Before HSCT patient given conditioning for immune system ablation
  - Prevent graft rejection
  - Lower chances of graft-versus-host disease
  - Lower chances of relapse
- This leaves the patient severely immunocompromised.

Introduction



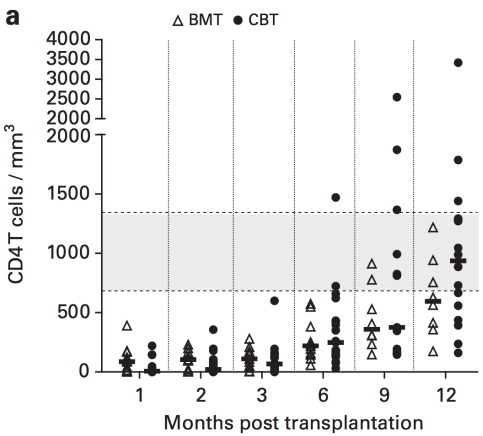
Adapted by Mikael Häggström from original by A. Rad

Why build a new model for CD4 T cells?

Table III. Median times to lymphocyte subset recoveries in patients after UCBT or UBMT (non parametric test of Mann-Whitney) (bold value: $P < 0{\cdot}05$).

	Total n = 226			UCBT n = 112			UBMT n = 114			
	Number of patients at risk	Median time (months)	Range (months)	Number of patients at risk	Median time (months)	Range (months)	Number of patients at risk	Median time (months)	Range (months)	P value
CD3 > 0·5 × 10^9/l	**161**	**5·6**	**0·5–62·3**	**72**	**6·3**	**1·5–55·3**	**89**	**3·2**	**0·5–62·3**	**0·008**
CD3 > 1·5 × 10^9/l	118	9·9	1·1–66·2	55	10·0	1·7–55·3	63	9·3	1·1–66·2	0·940
CD4 > 0·2 × 10^9/l	161	5·1	0·5–51·4	72	5·0	1·5–23·6	89	6·0	0·5–51·4	0·636
CD4 > 0·5 × 10^9/l	**135**	**10·0**	**1·1–55·3**	**61**	**9·3**	**2·6–55·3**	**74**	**12·3**	**1·1–37·2**	**0·003**
CD8 > 0·25 × 10^9/l	**161**	**4·4**	**0·5–74·7**	**70**	**7·7**	**0·9–55·3**	**91**	**2·8**	**0·5–74·7**	**<0·001**
CD19 > 0·2 × 10^9/l	**164**	**4·2**	**0·7–51·4**	**78**	**3·2**	**0·7–19·1**	**86**	**6·4**	**1·6–51·4**	**<0·001**
NK > 0·1 × 10^9/l	185	1·3	0·6–62·3	86	1·0	0·9–4·3	99	1·4	0·6–62·3	0·167

Renard *et al*. **2010** Brit J Haematol 152 322-30



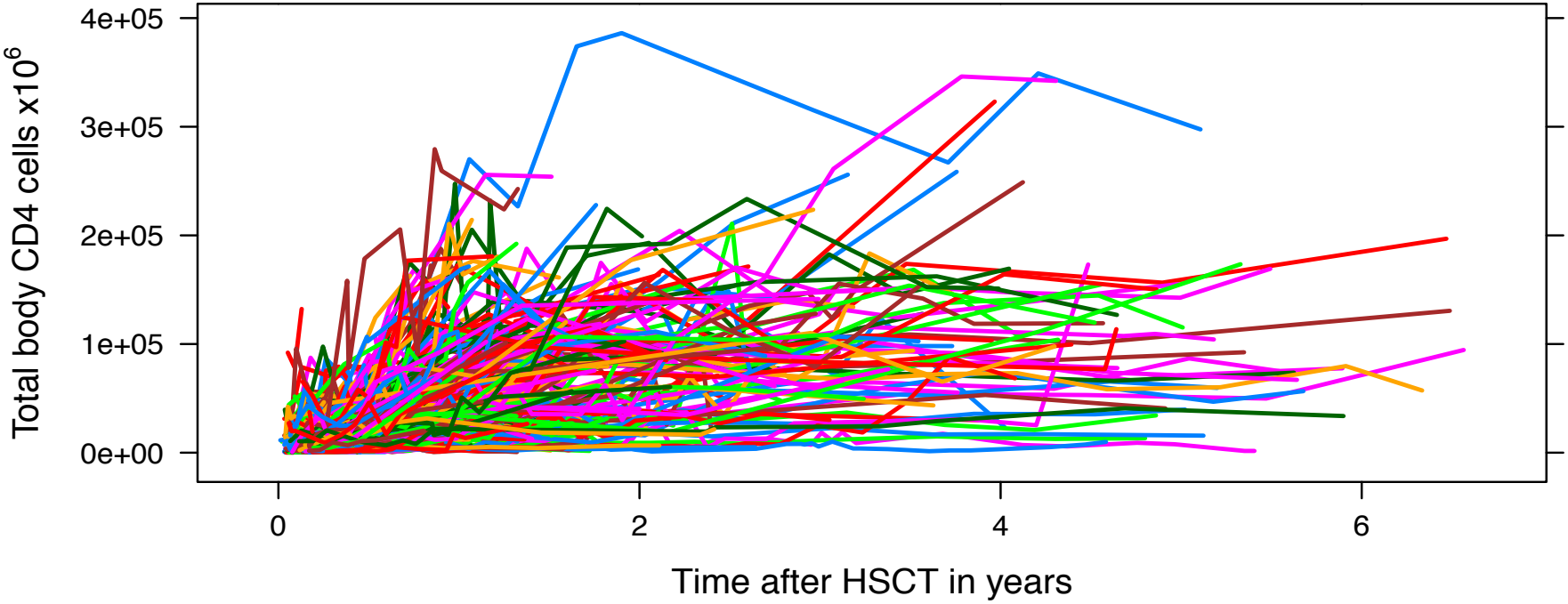
Charrier *et al*. **2013**
Bone Marrow Transplant 48 376-82

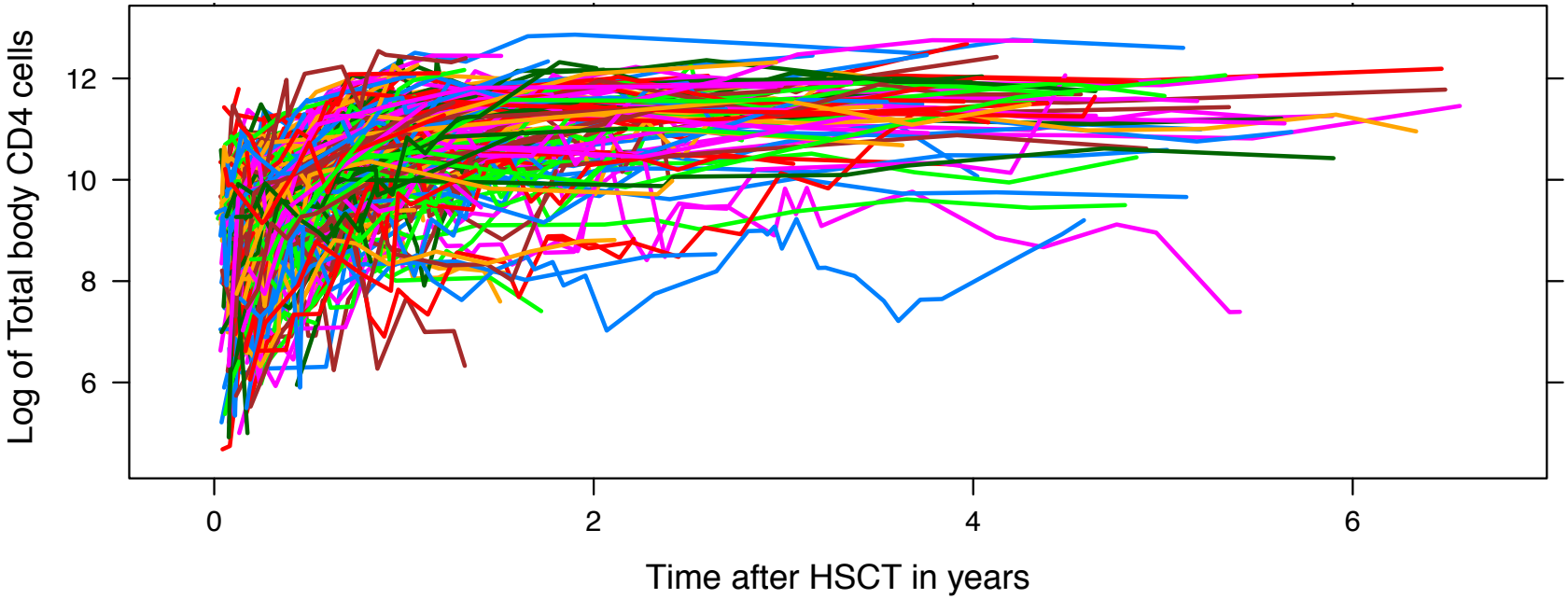
- Standard methods to assess immune reconstitution are simplistic
- Mechanistic modelling can improve our understanding of reconstitution
  - ➢ It allows a more meaningful covariate analysis
  - ➢ Possible to analyse noisy and uneven data
- CD4 reconstitution over time-scale of months and years
  - ➢ Present models of reconstitution cannot be applied to CD4 cells

The data

- Routine clinical data from children having HSCTs at Great Ormond Street Hospital for Children
- CD4 T cell concentrations for up to 7 years post HSCT
- Converted to total body CD4 cell counts
- 288 patients, 3019 measurements.
- Median age at HSCT 37 months, (16 days to 16 years)
- Highly heterogeneous data

Introduction





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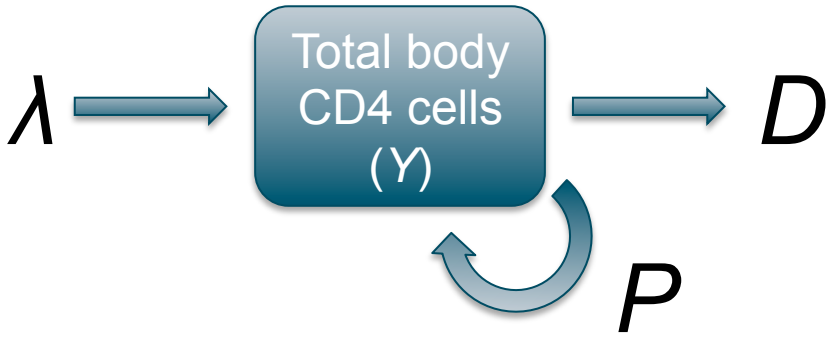
The Model



λ = Thymic output
P = Rate of proliferation
D = Rate of loss
Y = Total body CD4 cells
$\delta = D - P$

- Giving the following differential equation:

$$\frac{dY}{dt} = \lambda - D \cdot Y + P \cdot Y$$

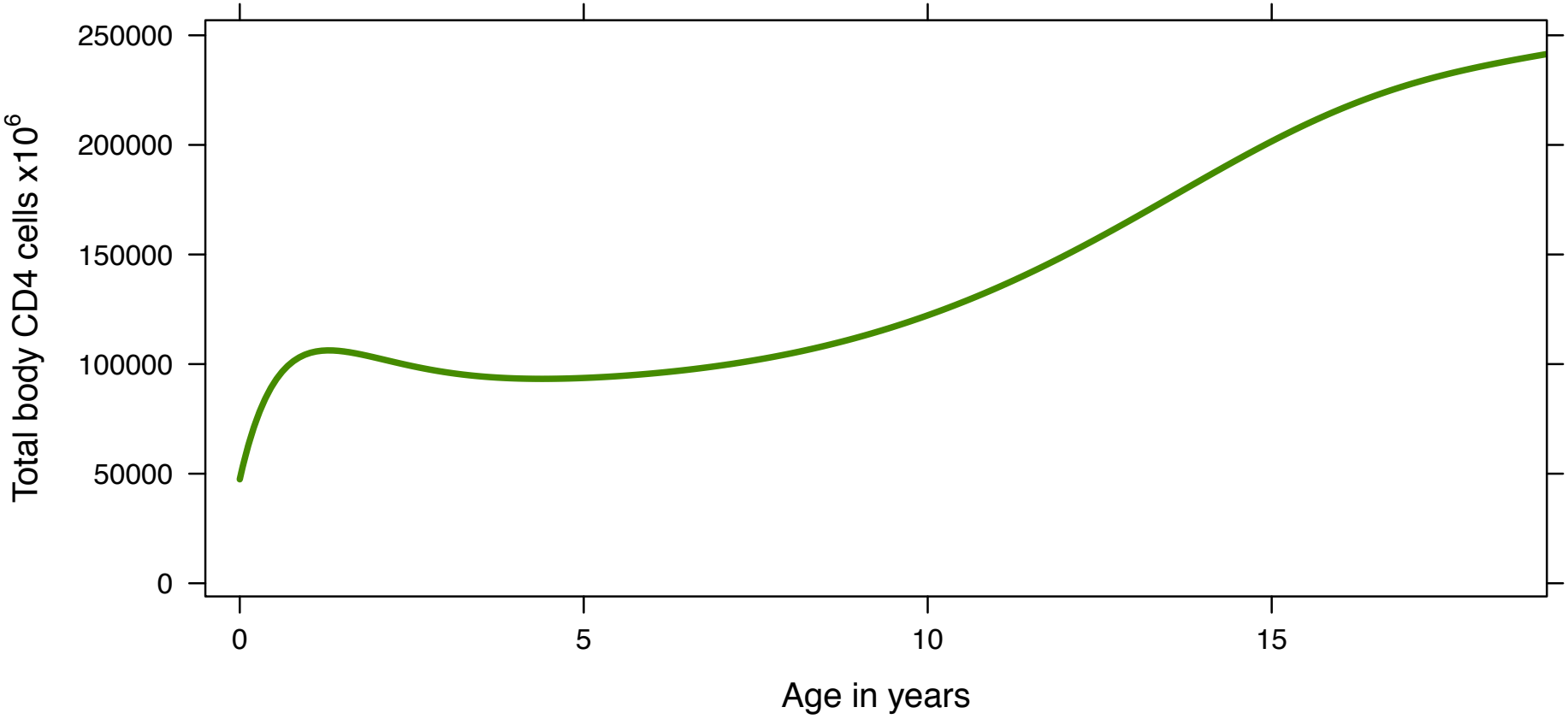
$$\frac{dY}{dt} = \lambda - \delta \cdot Y$$

Model has 3 parameters:
λ, thymic output (cells per day)
δ, net loss of cells (per day)
Y_0, initial number of cells in the body

- Functional forms for the parameters are chosen to represent the underlying biology

CD4 T cell numbers and age

- Total body CD4 T cell numbers change across childhood[1,2]



[1]Huenecke *et al.* **2008** Eur J Haematol 80 532-9
[2]Bains *et al.* **2009** Blood 113 5480-7

Accounting for age changes

- A functional form for thymic output[3] with age in days, τ:

$$\lambda(\tau) = \theta_\lambda \times \frac{y(\tau)v(\tau)V(\tau)\gamma}{0.02\eta(c-\gamma)}$$

where:

$$y(\tau) = 0.02e^{-0.00027\tau}$$
$$v(\tau) = 924 + 2354e^{-0.001012\tau}$$

  - $y(\tau)$ the proportion of cells expressing Ki67 with age
  - $v(\tau)$ the CD4 concentration with age
  - $V(\tau)$ the standard blood volume with age
  - η = 0.52 the duration of Ki67 expression
  - c = 0.25 and γ = 0.08 constants related to CD4 cell TREC content

- The corresponding functional form for net loss with age:

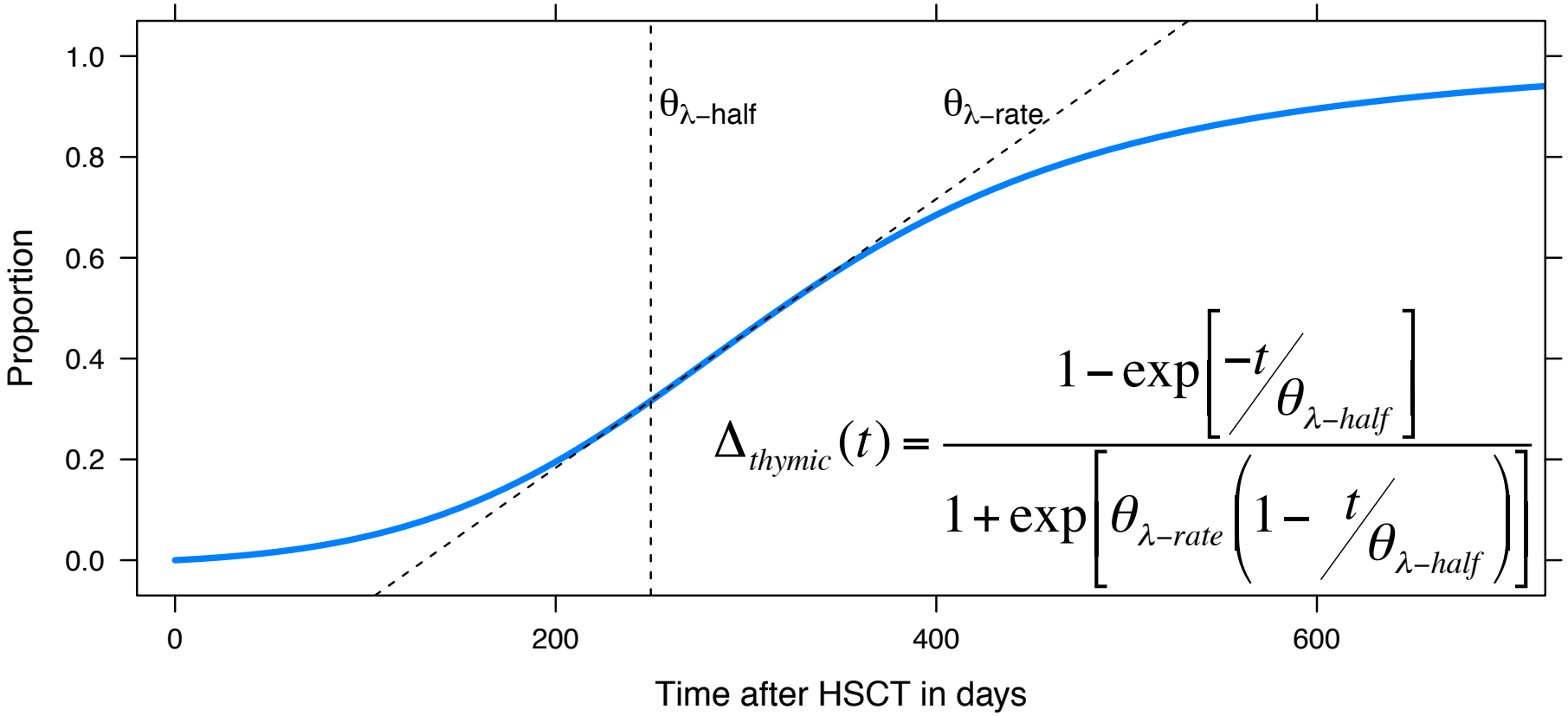
$$\delta(\tau) = \theta_\delta \times 0.9y(\tau)$$

- θ_λ and θ_δ are parameters to be estimated.

[3]Bains *et al.* **2009** J Immunol 183(7) 4329–36.

Thymic effects

- TREC analysis suggests thymic production is impaired post HSCT[4].

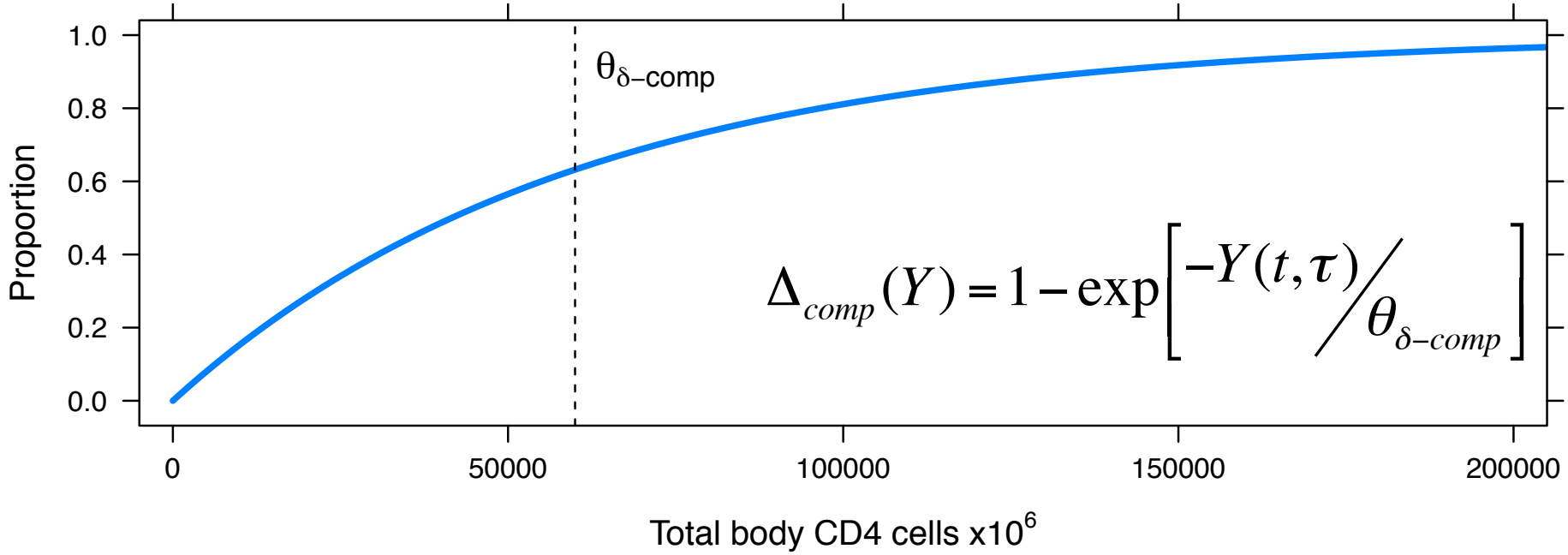


- $\theta_{\lambda\text{-}half}$ and $\theta_{\lambda\text{-}rate}$ are new parameters to be estimated

[4]Fallen *et al*. **2003** Bone Marrow Transplant 32(10) 1001-14

Competition effects

- Competition for homeostatic signals may affect proliferation and loss rates for CD4 cells[4]:



- $\theta_{\delta\text{-}comp}$ is a new parameter to be estimated and gives the number of cells at which Δ_{comp} will reach 0.63.

[4]Surh, Sprent. **2008** Immunity 29(6) 848–62

Full model and parameter values

Time = t
Age = τ

$$\frac{dY(t,\tau)}{dt} = \lambda(t,\tau) - \delta(\tau,Y)\cdot Y(t,\tau)$$

$$\lambda(t,\tau) = \theta_\lambda \times \frac{y(\tau)v(\tau)V(\tau))}{0.0221} \times \frac{1-\exp\left[-t/\theta_{\lambda-half}\right]}{1+\exp\left[\theta_{\lambda-rate}\left(1-t/\theta_{\lambda-half}\right)\right]}$$

$$\delta(\tau,X) = \theta_\delta \times 0.9 \times y(\tau) \times \left(1-\exp\left[-Y(t,\tau)/\theta_{\delta-comp}\right]\right)$$

Where: $y(\tau) = 0.02e^{-0.00027\tau}$

$v(\tau) = 924 + 2354e^{-0.001012\tau}$

The patient-specific random effects are defined as:

$$I\theta_\lambda = \theta_\lambda \times \exp(\eta_\delta)$$
$$I\theta_\delta = \theta_\delta \times \exp(\eta_\lambda)$$
$$IY_0 = Y_0 \times \exp(\eta_{Yo})$$

with:

$$\text{variance}(\eta_\lambda) = \Omega_\lambda$$
$$\text{variance}(\eta_\delta) = \Omega_\delta$$
$$\text{variance}(\eta_{Yo}) = \Omega_{Yo}$$

And proportional residual variability with variance σ.

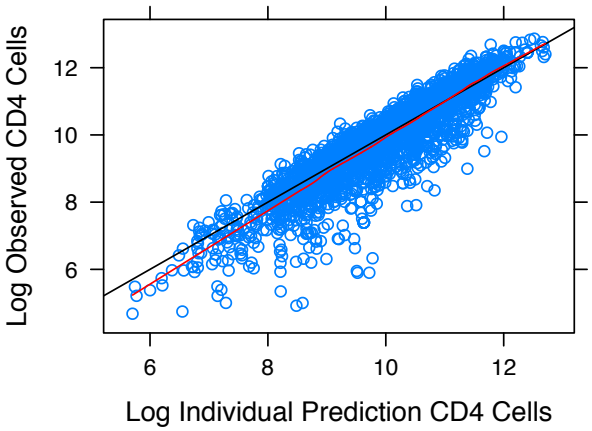
Parameter Values:

θ_λ *(10^6 cells/day)*	0.518
θ_δ *(per day)*	0.659
Y_0 *(x10^6 cells)*	6983
$\theta_{\lambda\text{-half}}$	225
$\theta_{\lambda\text{-rate}}$	2.78
$\theta_{\delta\text{-comp}}$ *(Fixed)*	60000
Ω_λ	4.72
Ω_δ	5.76
$\Omega_{\lambda,\delta}$	7.97
Ω_{Yo}	2.46
σ	0.201

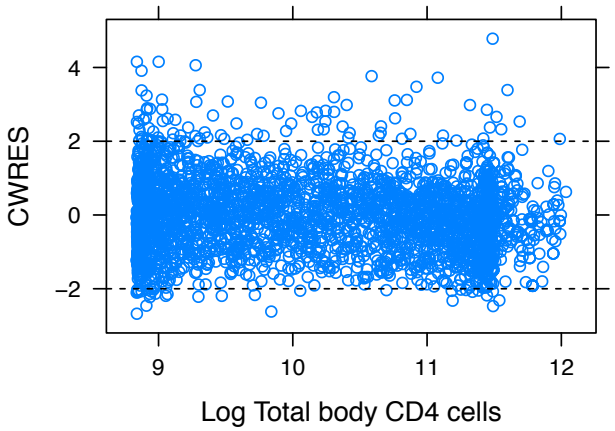
Contents

Goodness of fit plots

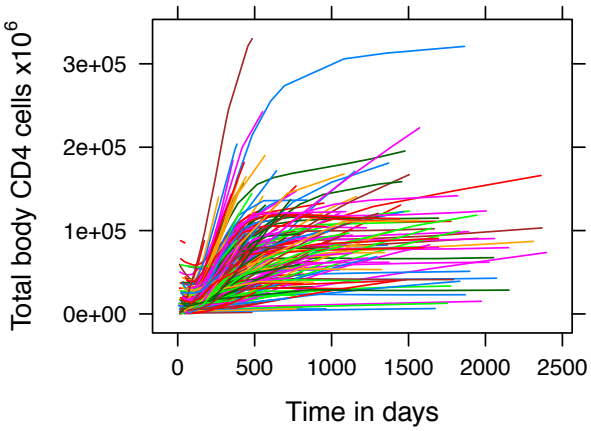
Observed Vs Individual Prediction



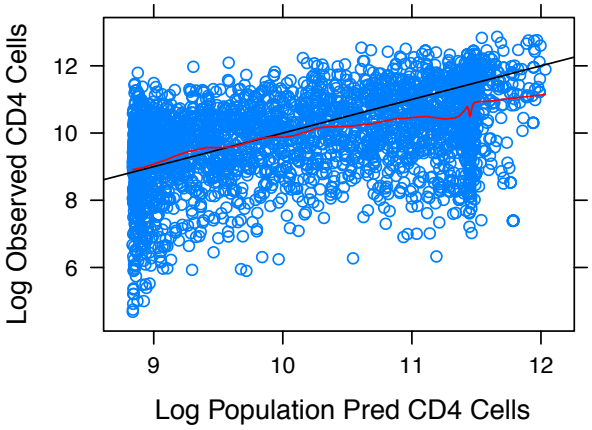
CWRES Vs Population Prediction



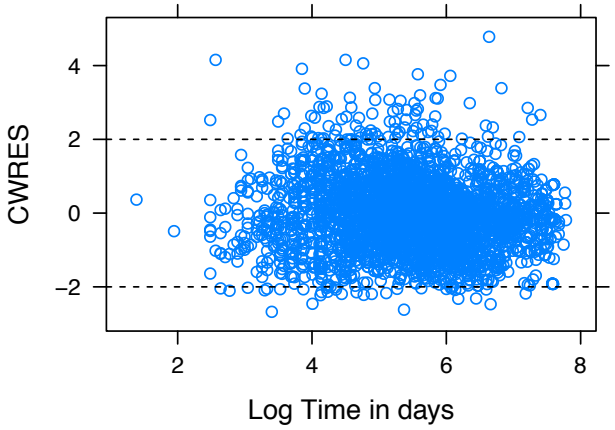
Individual Prediction Vs Time



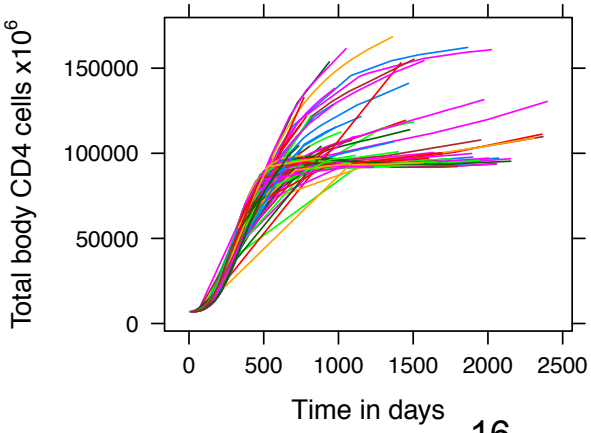
Observed Vs Population Prediction



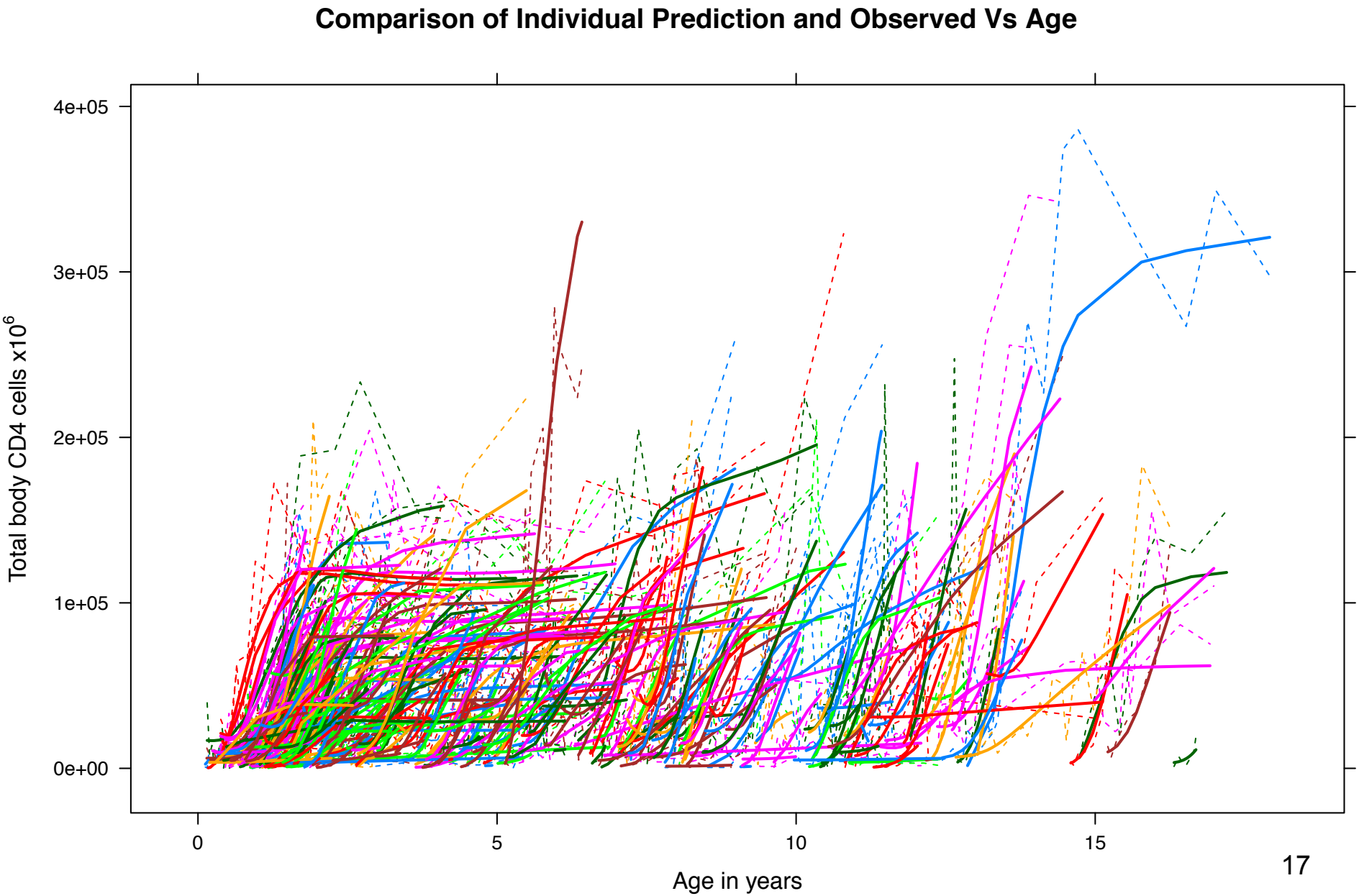
CWRES Vs Time



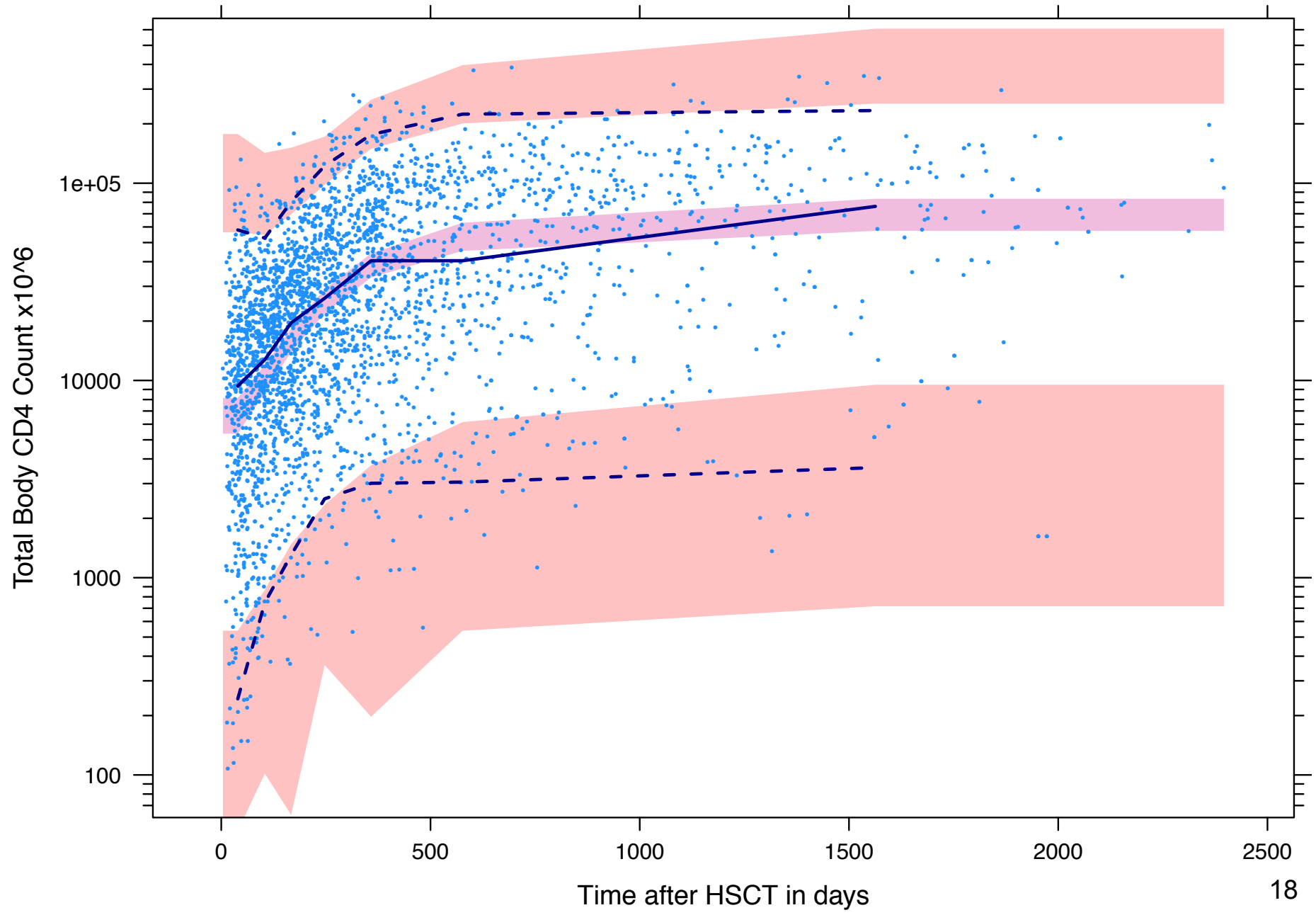
Population Prediction Vs Time



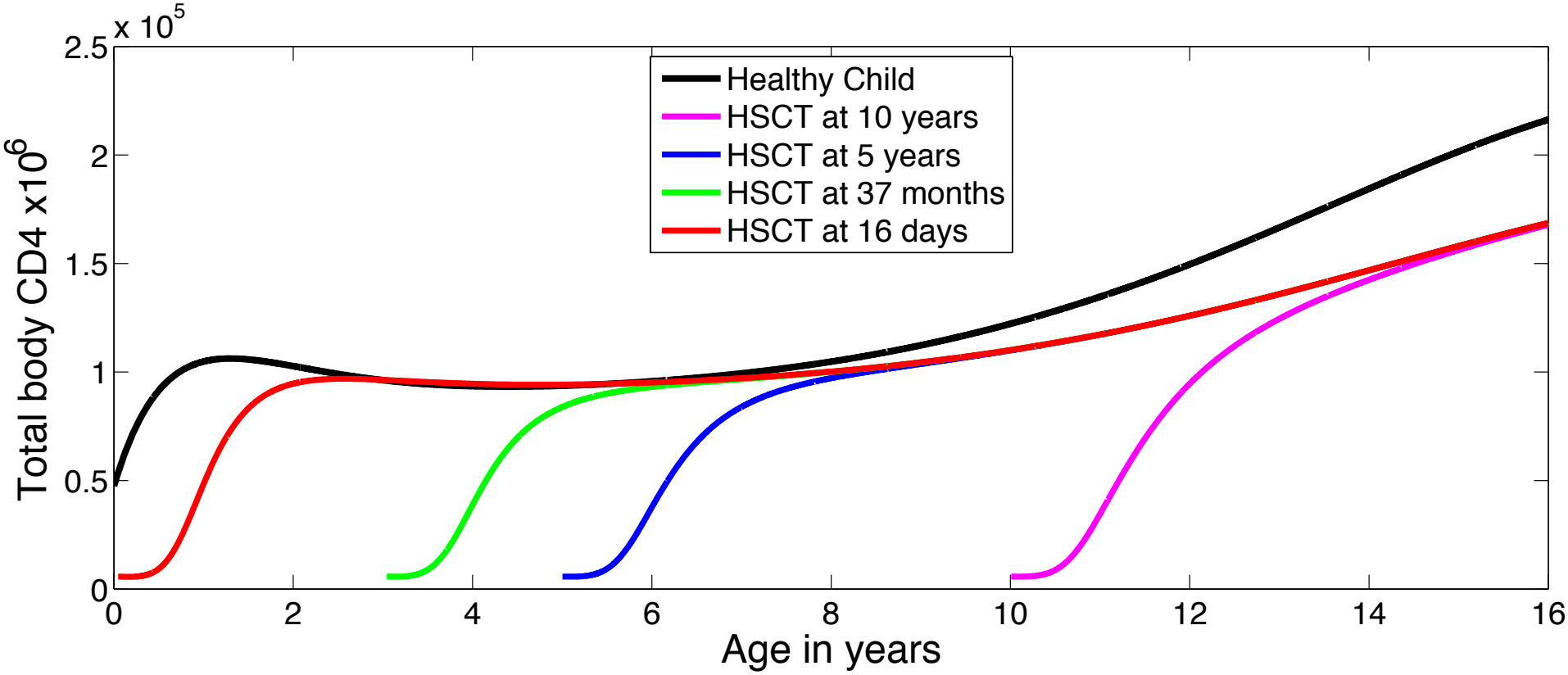
Results


Comparison of Individual Prediction and Observed Vs Age
Total body CD4 cells x10^6
4e+05
3e+05
2e+05
1e+05
0e+00
0
5
10
15
Age in years

Results


Total Body CD4 Count x10^6
1e+05
10000
1000
100
0
500
1000
1500
2000
2500
Time after HSCT in days

Model compared with healthy child



- The modelled population average reconstitution of a child with age having an HSCT at various ages against the expected progression of a health child.

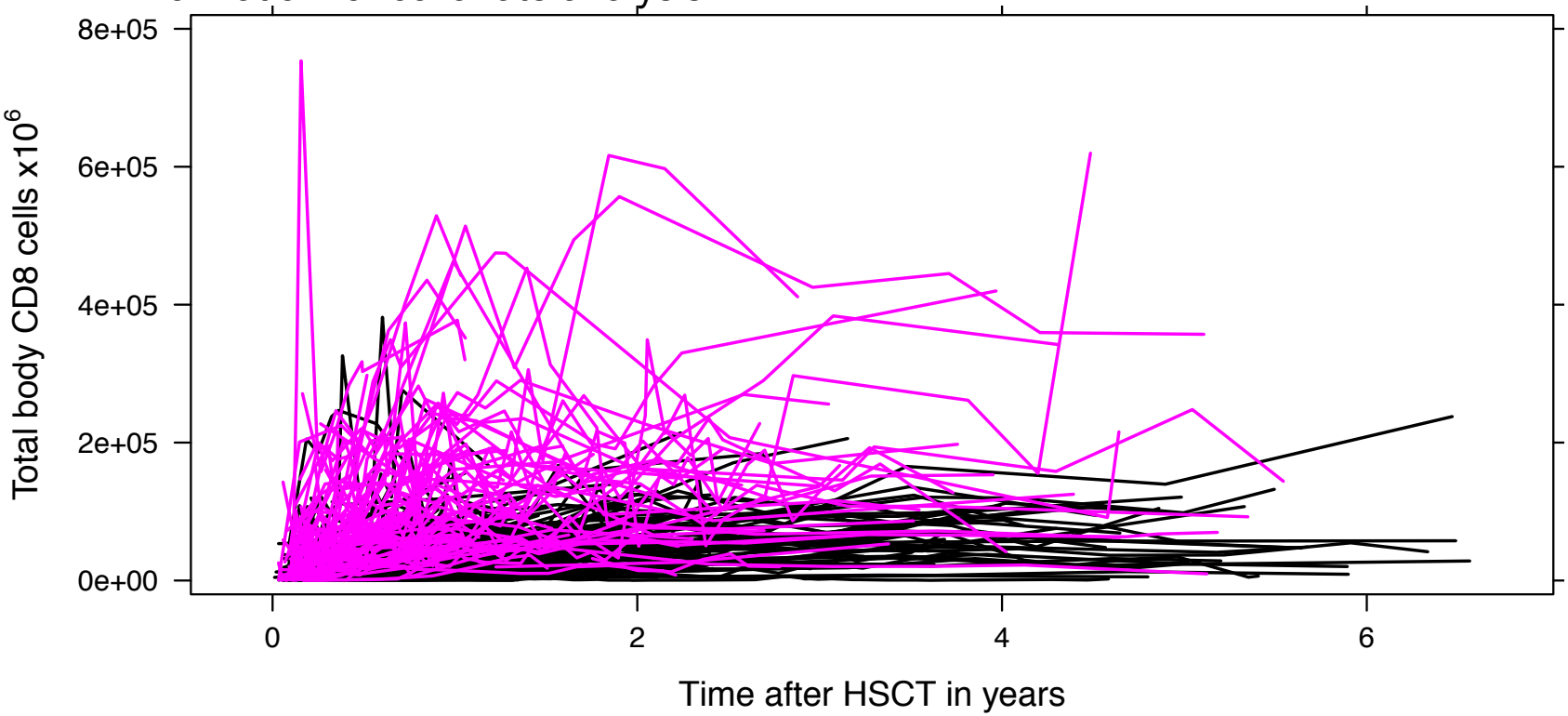
Contents

Conclusions

- A novel mechanistic model for the immune reconstitution of CD4 cells following HSCTs in children has been developed.
- The model fundamentally represents homeostatic mechanisms for CD4 cells in the immune system
- It brings together multiple ideas about reconstitution in children:
  - The changes in the thymus with age,
  - Reduced thymic function in the period after an HSCT,
  - Competition for homeostatic signals by CD4 cells in the body.
- Early covariate analysis implies:
  - Alemtuzumab and anti-thymocyte globulin both reduce the number of CD4 T cells immediately after the HSCT
  - Having no conditioning implied decreased thymic output after HSCT.

Further Work

- We would like to apply the model to CD8 reconstitution.
  - The differences and similarities between CD4 and CD8 reconstitution will give more information for covariate analysis.



- Once we have a final model with covariates included, we hope to be able to predict immune reconstitution given early data.

Acknowledgements

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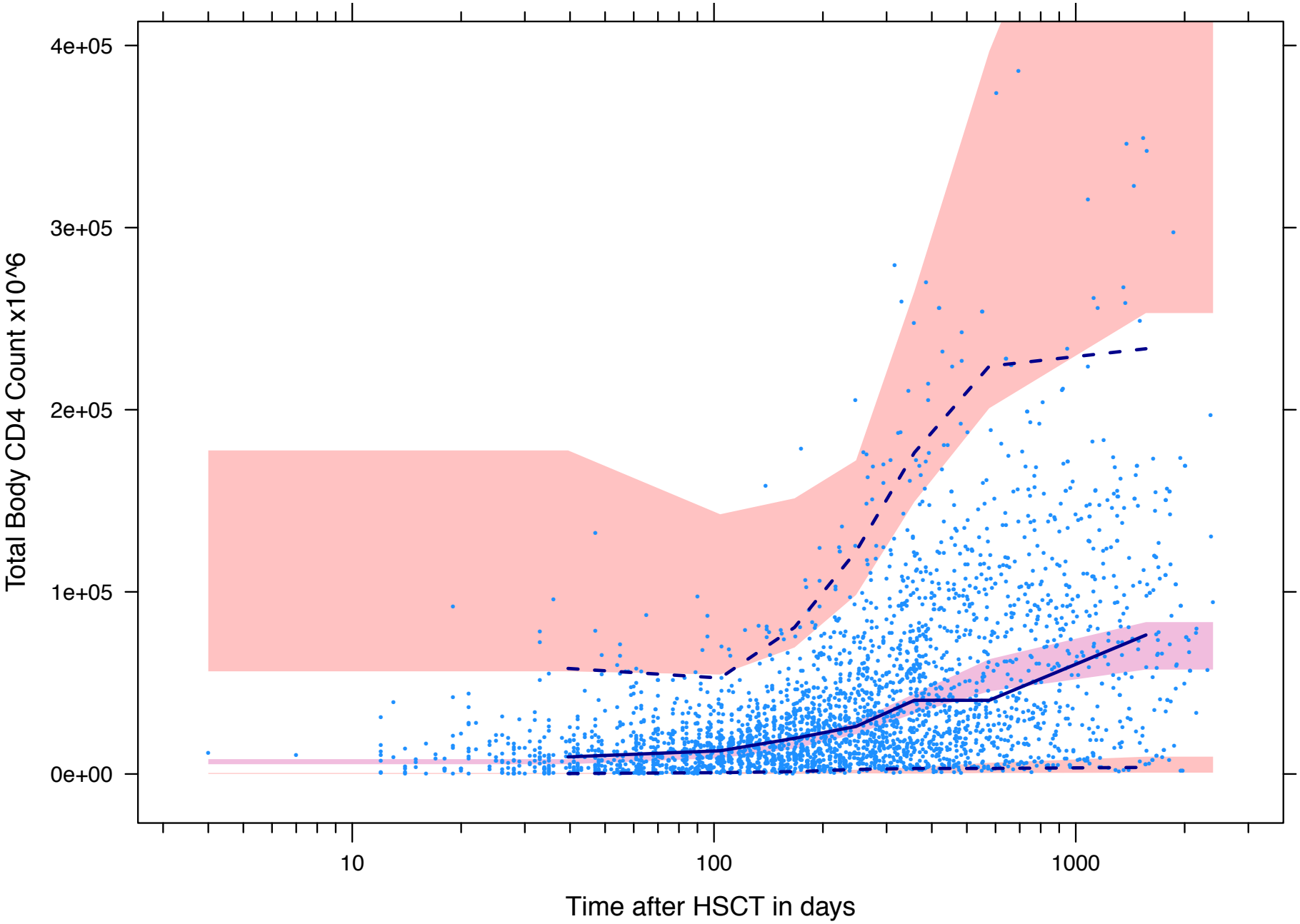
Standard Errors on Parameters (Bootstrap)

Parameter	Parameter Estimate	Bootstrap Median	Bootstrap 95% Confidence Interval
θ_{λ} *(10^6 cells/day)*	0.518	0.518	0.356 - 0.685
θ_{δ} *(per day)*	0.659	0.659	0.450 - 0.902
Y_0 *(x10^6 cells)*	6983	6941	4683 - 7368
$\theta_{\lambda\text{-half}}$	225	225	185 - 267
$\theta_{\lambda\text{-rate}}$	2.78	2.78	2.20 - 3.36
$\theta_{\delta\text{-comp}}$ *(Fixed)*	60000	60000	60000 - 60000
Ω_{λ}	4.72	4.69	2.99 - 5.05
Ω_{δ}	5.76	5.63	2.96 - 5.99
$\Omega_{\lambda,\delta}$	7.97	7.88	3.43 - 8.73
Ω_{Yo}	2.46	2.46	1.84 - 3.23
σ	0.201	0.201	0.179 - 0.223


4e+05
3e+05
2e+05
1e+05
0e+00
Total Body CD4 Count x10^6
10
100
1000
Time after HSCT in days