IGRH model: a mechanistic model Integrating the relationship between average Glucose levels (Cg,avg), RBCs & HbA1c in a mixed population of healthy volunteers and diabetic subjects

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Background

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HbA1c ?

- Chronic glycemia biomarker (2-3 months)

Standard biomarker for:

- Diagnosis (ADA 2010)
- Adequacy of glycemic management

Background

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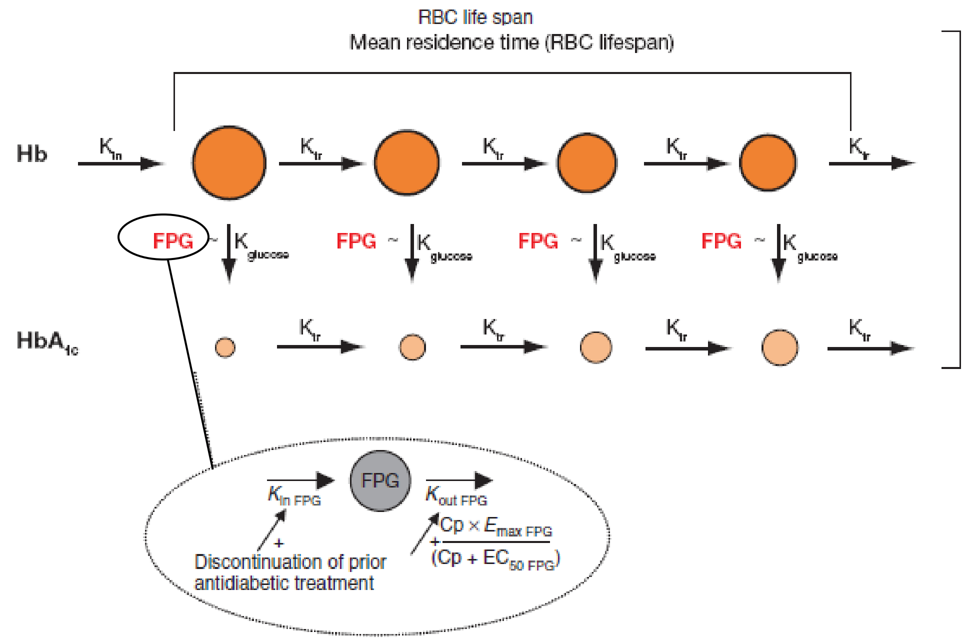
FPG – HbA1c Model Hamrén et al. 2008



- Mechanistic PKPD model:

RBC ageing and glycosilation to HbA1c

- Gaps:

  FPG ~ chronic glycemia → to relate to HbA1c

  HbA1c depends on RBC LS → the LS model from a small group of Tesaglitazar therapy

Hamren B, Bjork E, Sunzel M and Karlsson M. Models for plasma glucose, HbA1c, and hemoglobin interrelationships in patients with type 2 diabetes following tesaglitazar treatment. *Clin Pharmacol Ther. 2008; 84(2): 228-235.*

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Rationale - Why?

- We wanted to explore more and fill up these gaps!
- To use average glucose concentration (Cg,avg) better descriptor of chronic glycemia
- Better RBC LS description
- Empirical models exist that relate:

Cg,avg ~ HbA1c

↓

Lacking mechanism-based model

Aims

To derive a dynamic mechanism-based model for describing the underlying relationship between Cg,avg- HbA1c using information from literature. Including sources of variability (i.e: IIV RBC life-span,...)

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How to build the model when you have different sources of data?

Integrating the data formal analysis Nonmem

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Overview – Integrating different sources

Digitized data Nathan et al. 2008 : Cg,avg ~ HbA1c at steady state

Mechanistic re-inforcement by **literature priors** in structural & variability components (i.e.LS, IIV-LS, KG,...)

Digitized data & clinical data as external validation : hypothesis testing of specific mechanisms with high impact

Mechanistic model in NONMEM: IGRH model

Methods – Integrating literature data

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Main analysis: ADAG study - Nathan et al. 2008

Cg,avg ~ HbA1c relationship

(N=507 ; Diabetic & Non-diab.)

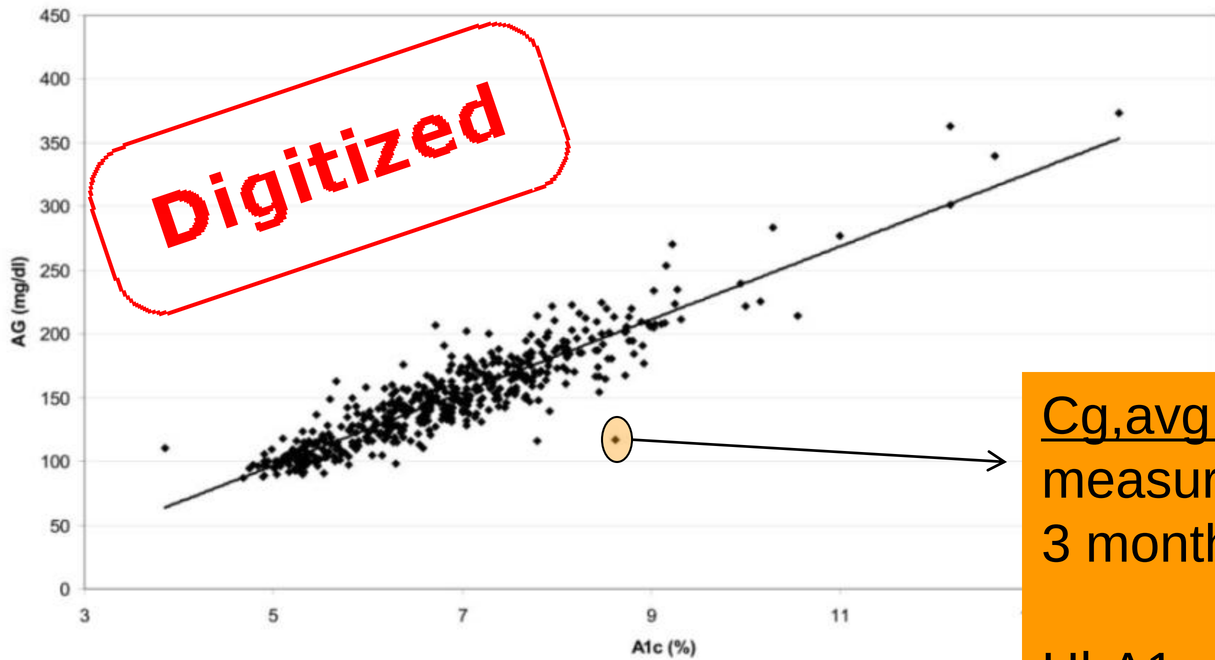


Figure 1—*Linear regression of A1C at the end of month 3 and calculated AG during the preceding 3 months. Calculate* *46.7 (AG_{mmol} = 1.59 × A1C − 2.59) (R^2 = 0.84, $P < 0.0001$).*

Cg,avg (CGM ~2500 measurements / subject in a 3 month period)

HbA1c (monthly measured)

Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D and Heine RJ. Translating the A1C assay into estimated average glucose values. *Diabetes Care. 2008; 31(8): 1473-1478.*

Methods - Structural model

HbA1c formation:

i) RBC life-span and life-span distribution

ii) Synthesis rate of HbA1c: f(Cg,avg)

iii) HbA1c contribution in RBC precursors

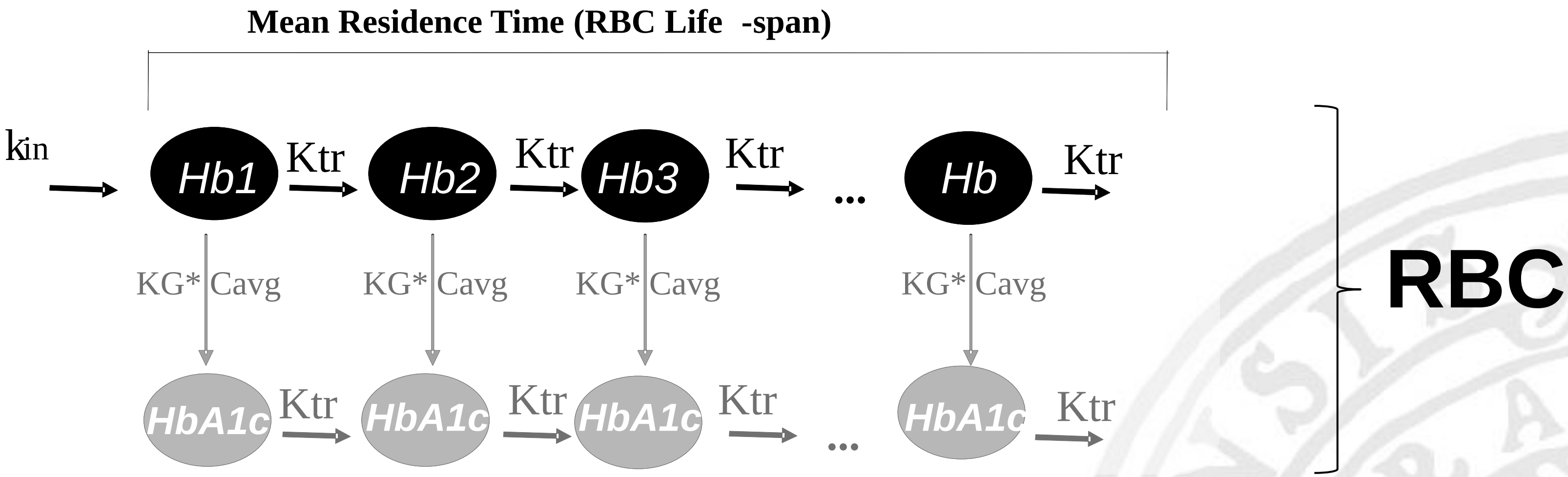
iv) Impact of HbA1c and Cg,avg measurement imprecision

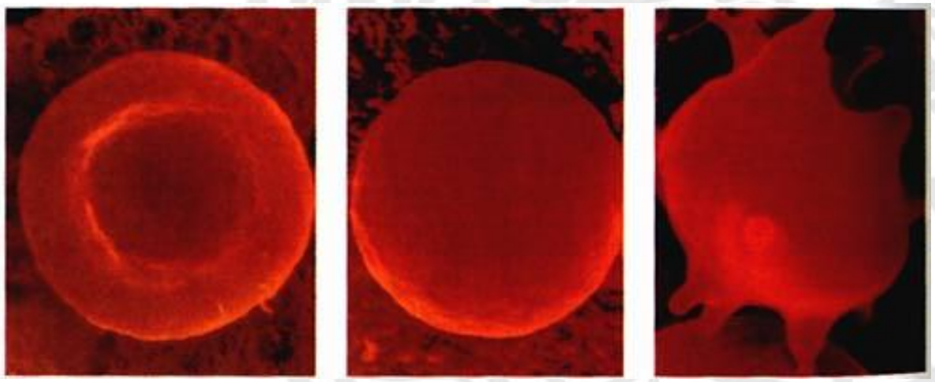
v) The fractional nature of HbA1c

Methods: Structural model

i) RBC life-span and life-span distribution

Prior: Kalicki et al. (PAGE meeting 2009)





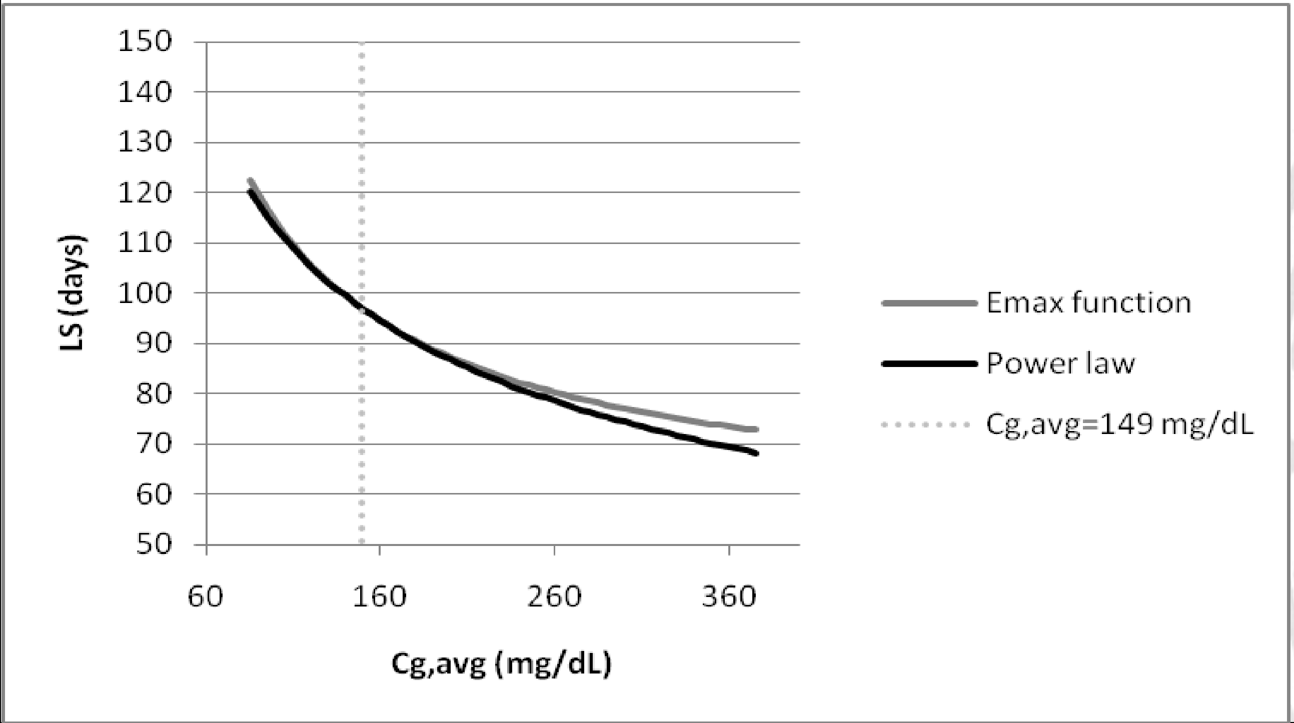
Methods: Structural model

i) RBC life-span and life-span distribution

Influence of Cg,avg on RBC life-span

Power

$$LS = TVLS \cdot \left(\frac{149}{Cg, avg} \right)^{\delta} \cdot \exp^{\eta}$$



Methods: Structural model

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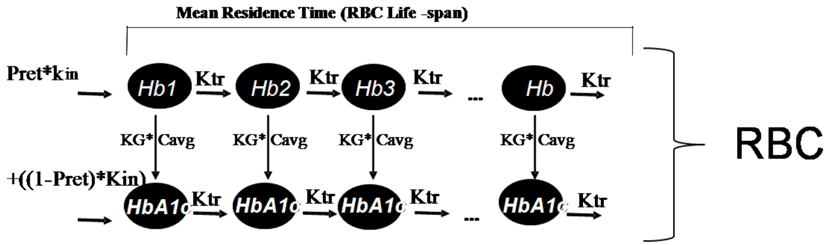
ii) Synthesis rate of HbA1c



Linear $$Glycosilationrate = KG \cdot Cg,avg \cdot Hb$$

Non-Linear $$Glycosilationrate = KG \cdot \left(\frac{149}{Cg,avg}\right)^{\delta} \cdot Hb$$

PRIORS from literature

- Beach et al. 1979
- Higgins et al. 1981
- Mortensen-Volund et al. 1984
- Ladyzynski et al.2008

Non-Linear due to Glut1 saturation $$Glycosilationrate = KG \cdot \left(\frac{Cg,avg \cdot Km}{Cg,avg + Km}\right) \cdot Hb$$

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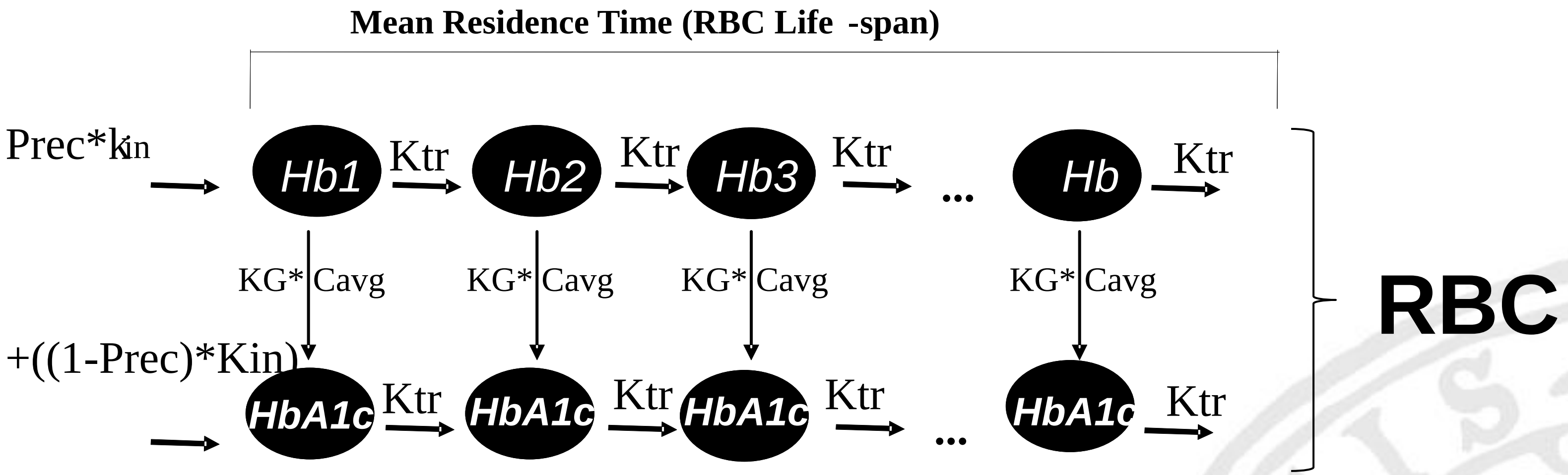
Methods: Structural model

iii) HbA1c contribution in RBC precursors



$$Prec = exp(-KGP*Cg,avg*LSP)$$

PRIORS from literature

Woo S, Krzyzanski W, Duliege AM, Stead RB and Jusko WJ. Population pharmacokinetics and pharmacodynamics of peptidic erythropoiesis receptor agonist (ERA) in healthy volunteers. *J Clin Pharmacol*. 2008; 48(1): 43-52.

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Methods – External validation

Hypothesis testing:

digitized data and clinical data as external validation for mechanisms

Hypothesis testing

Digitized literature data:

- Virtue et al. 2004 data (LS vs GHb – T2D N=23)

Clinical data (shared by the authors)

- Nuttall et al. 2004 data (LS & GHb vs FPG - Non-diab. N=37)
- Ribbing et al. 2010 data (HbA1c vs FPG – T2D N=1460)

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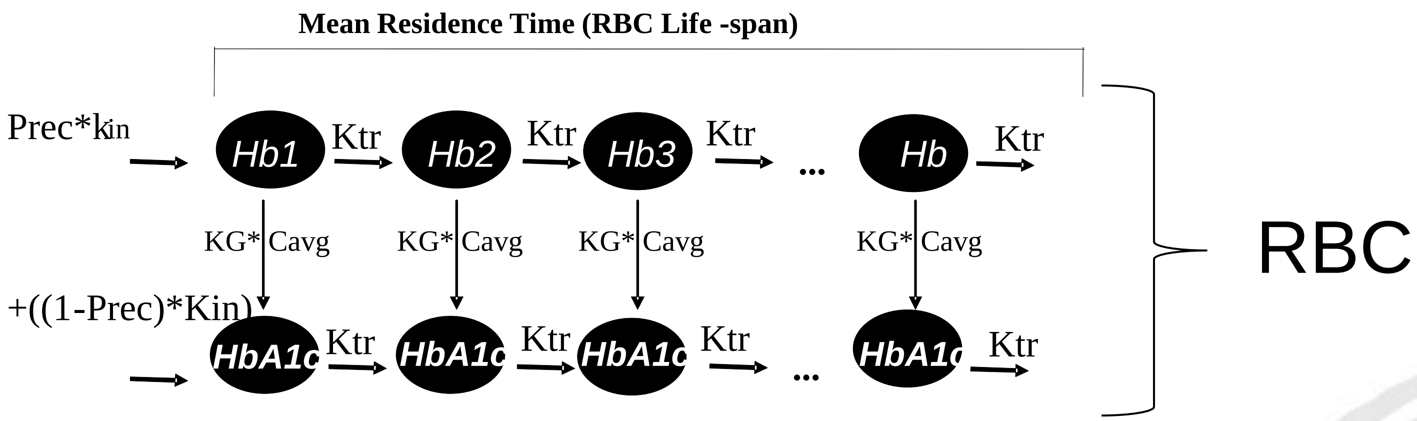
The integration of the data allowed to derived the I$_{ntegrated}$G$_{lucose}$R$_{BC}$H$_{bA1c}$ model

Results – Final I$_{ntegrated}$G$_{lucose}$R$_{BC}$H$_{bA1c}$ model



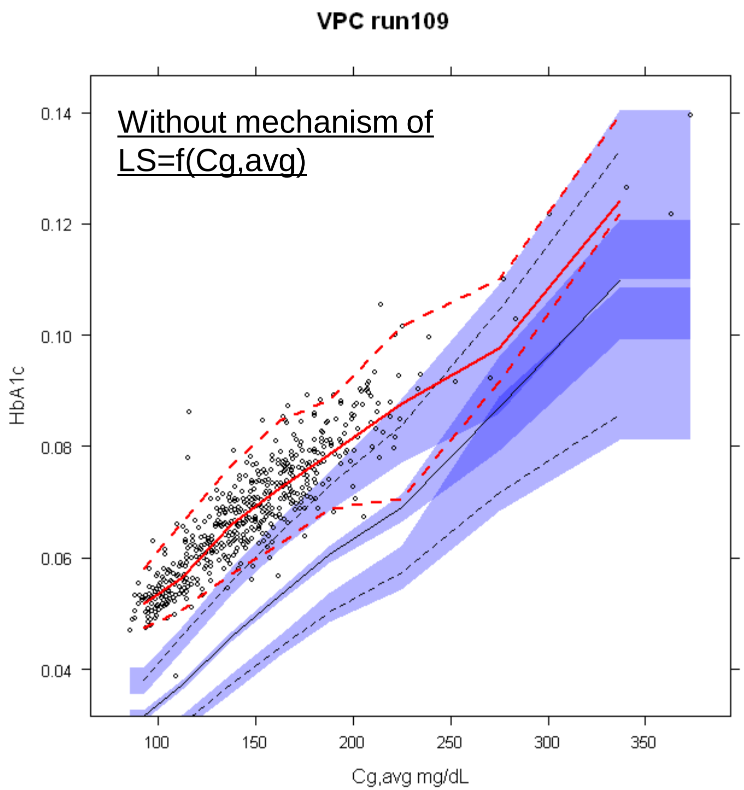
Prec = exp(-KGP*Cg,avg*LSP)

Power $$LS = TVLS \cdot \left(\frac{149}{Cg, avg} \right)^{\delta} \cdot \exp^{\eta}$$

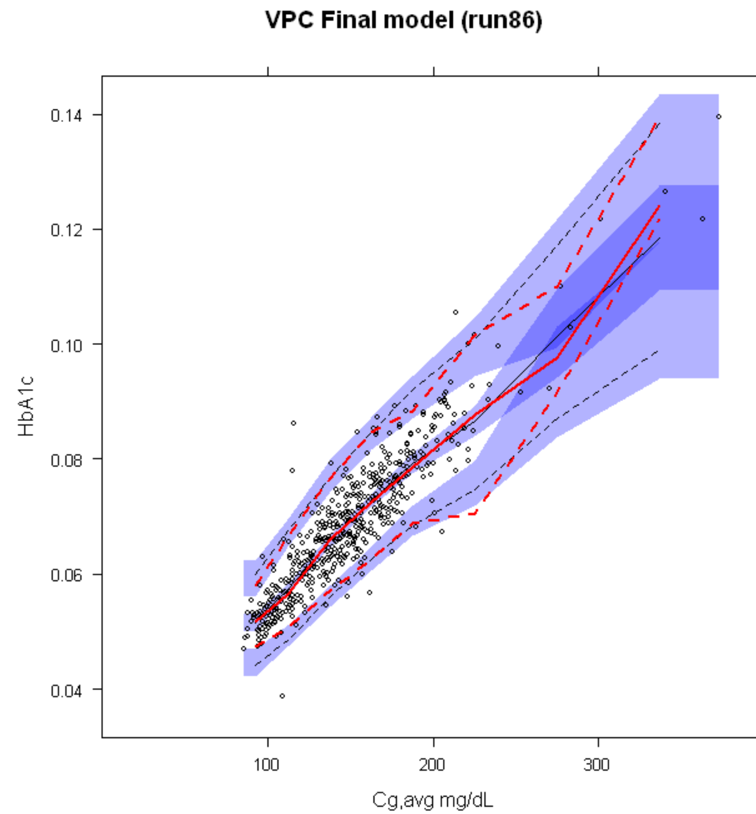
Linear $$Glycosilationrate = KG \cdot Cg, avg \cdot Hb$$

Results – Final I$_{\text{ntegrated}}$G$_{\text{lucose}}$R$_{\text{BC}}$H$_{\text{bA1c}}$ model

OFV=-4499.935



OFV=- 4888.172



Dots: Observations

Red lines: 5th, 50th & 95th percentiles of the observations

Black lines: 5th, 50th & 95th percentiles of the predictions (1000 simulations)

Blue area: 90% CI of prediction intervals

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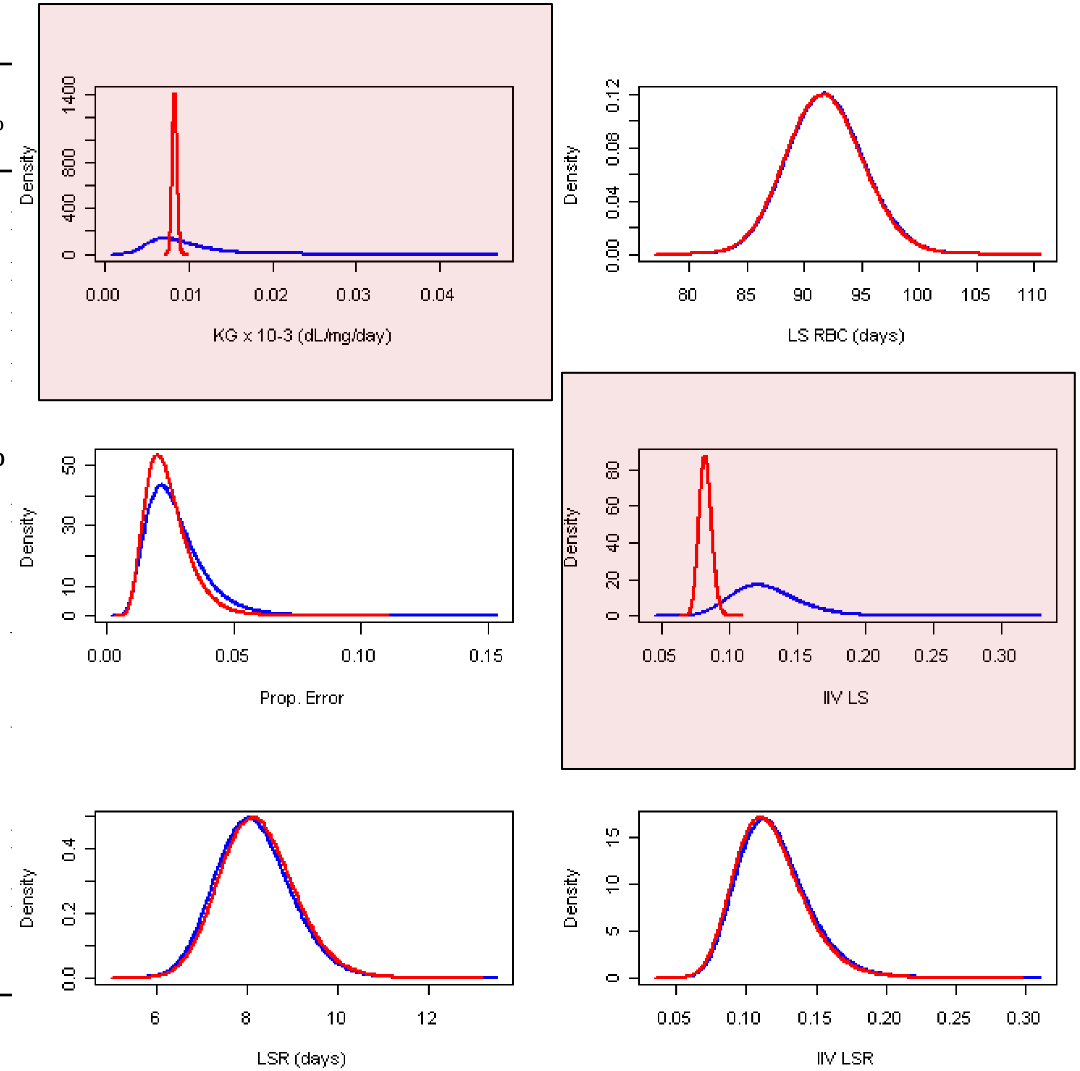
Results – Final I$_{ntegrated}$G$_{lucose}$R$_{BC}$H$_{bA1c}$ model

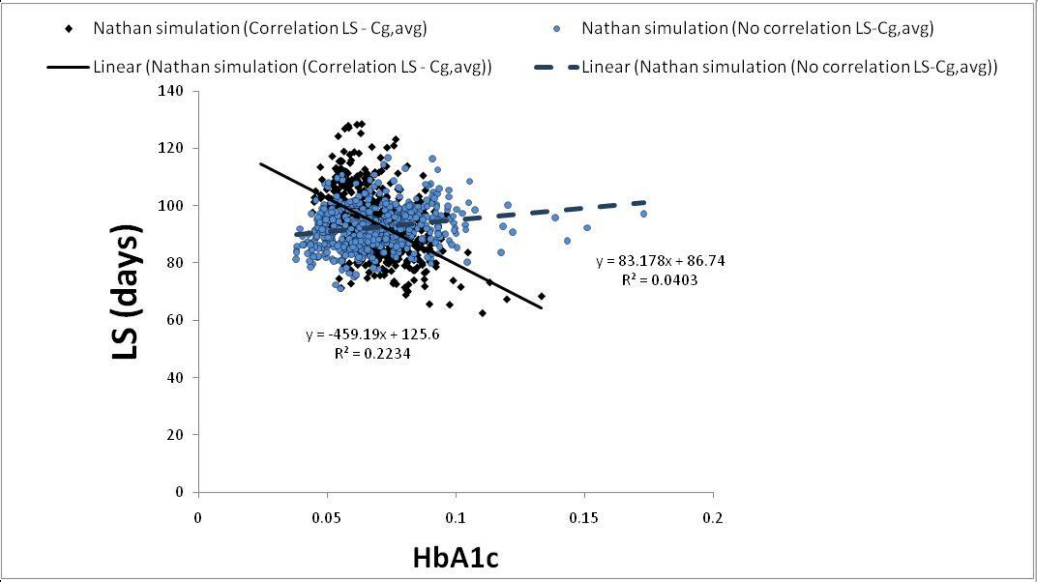
Parameter	Estimated value	RSE%	Prior	RSE%
KG (dL/mg/day)	8.37×10^{-6}	3.4%	8.23×10^{-6}	27%
LS RBC (days)	91.7	3.6%	91.8	3.6%
IIV LS RBC (CV%)	8.22 %	5.5%	12.4%	19%
LS Prec. (days)	8.20	9.8%	8.11	10%
IIV LS Prec. (CV%)	11.5%	20%	12%	19%
Prop. RE	2.27 %	35%	2.5%	40%
δ (LS - Cg,avg)	0.381	4.5%		
OFV	-4888.172			

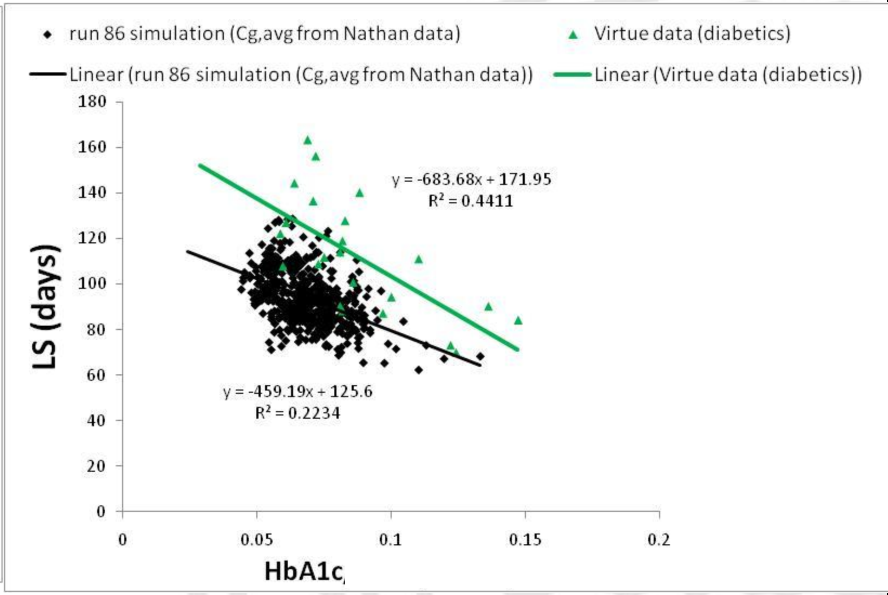


Results – Final I$_{ntegrated}$G$_{lucose}$R$_{BC}$H$_{bA1c}$ model

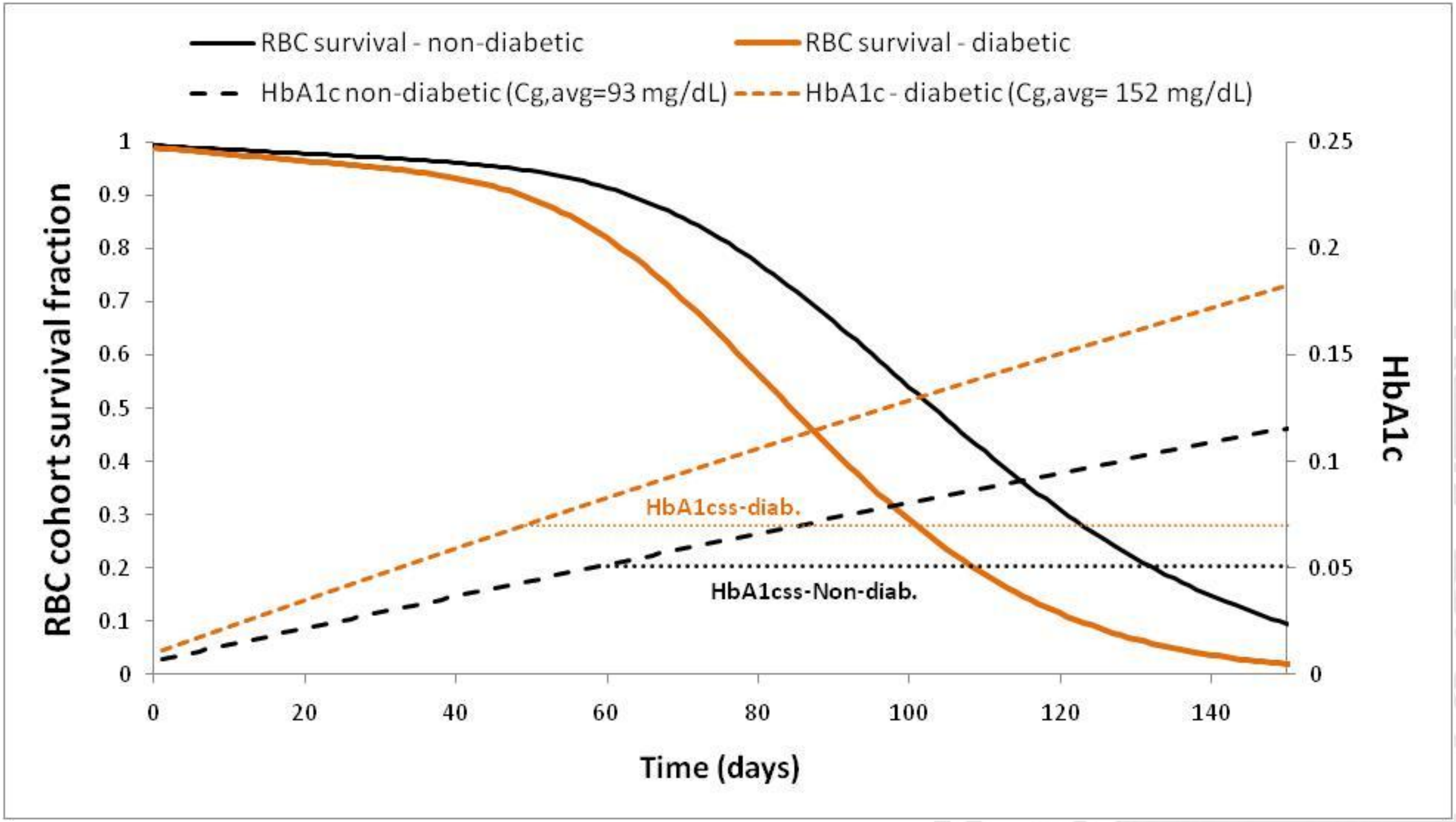
Data supporting this relationship between LS- Cg,avg:

Ribbing et al. (HbA1c vs FPG) δ=0.48 vs δ IGRH model=0.38
Nuttall et al. (LS vs FPG) δ=0.49 vs δ IGRH model=0.38
Virtue et al. (GHb vs LS)





Results – Final I$_{ntegrated}$G$_{lucose}$R$_{BC}$H$_{bA1c}$ model



Conclusions - I_{ntegrated}G_{lucose}R_{BC}H_{bA1c} model

- 1st quantitative description of the Cg,avg-HbA1c relationship on mechanistic basis.

- The model describes well the relationship in both diabetic and non-diabetic patients

Conclusions - $I_{ntegrated}G_{lucose}R_{BC}H_{bA1c}$ model

- To predict the impact of changes in Cg,avg (due to diet or therapeutic interventions) on the time-course of HbA1c levels.

Conclusions - I_{ntegrated}G_{lucose}R_{BC}H_{bA1c} model

- If any of the processes involved are subjected to change in an individual patient, the expected temporal and steady state change of HbA1c can also be predicted

(e.g.uremic patients (LS decreased))

Conclusions - I_{ntegrated}G_{lucose}R_{BC}H_{bA1c} model

- Literature data can be used not only to support parameter estimates, but combined from different sources to test hypothesis and build structurally novel models!

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