BUGS/WBDiff software: Bayesian inference for dynamical systems

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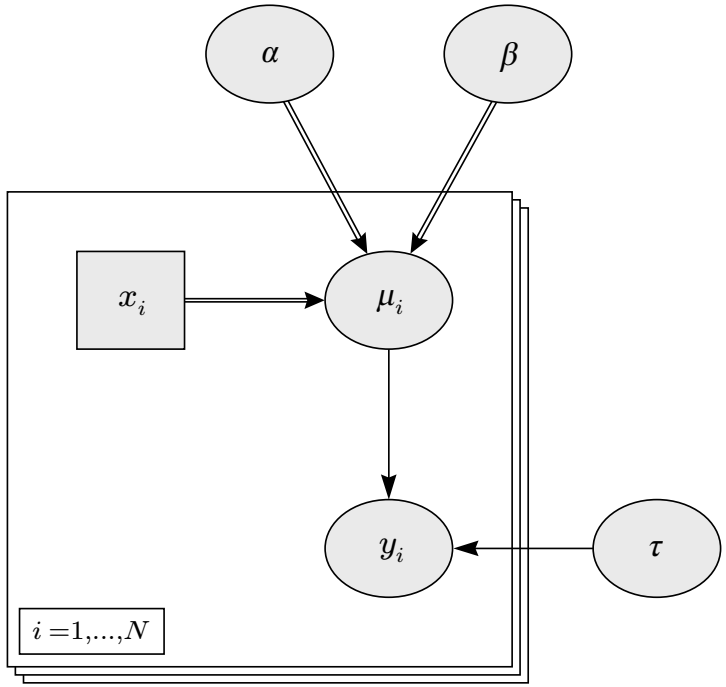
Outline

- The BUGS project
  - mathematical framework – graphical models/Gibbs sampling
  - underlying philosophy
- WinBUGS Differential Interface (WBDiff)
  - illustration with pharmacokinetic models
- Applied examples
  - insulin/glucose/acipimox data
  - interstitial-/plasma-glucose data
  - experimental epidemiology – host-parasite system
- Conclusions + future work...

Graphical models: linear regression example



$$y_i \sim \mathrm{N}(\mu_i, \tau^{-1}) \qquad \mu_i = \alpha + \beta x_i \qquad i = 1, ..., N$$

$$\alpha \sim p(\alpha) \quad \text{eg } \mathrm{N}(0, 100^2) \qquad \beta \sim p(\beta) \quad \text{eg } \mathrm{N}(0, 100^2) \qquad \tau \sim p(\tau) \quad \text{eg } \mathrm{Ga}(\epsilon, \epsilon)$$

Why?

- Can describe (pictorially) very wide class of models with *Directed Acyclic Graphs* (DAGs) – links are *directed* and there are no *cycles*
- Obvious benefit when models become complicated
- Convey essential structure of problem without recourse to large set of equations
- Achieved through abstraction – hiding of detail
- Graph encodes series of conditional independence assumptions

$$v \perp\!\!\!\perp \text{non-descendants}[v] | \text{parents}[v]$$

which allow properties of model to be derived abstractly – more later...

Linear regression example

- Bayes' Theorem:

$$p(\theta|y) \propto p(\theta)p(y|\theta)$$

$$p(\alpha,\beta,\tau|y) \propto p(\alpha)p(\beta)p(\tau)\prod_{i=1}^{N}\mathrm{N}(\alpha+\beta x_i,\tau^{-1})$$

- Full conditional distributions (for Gibbs sampling):

$$p(\alpha|\beta,\tau,y) \propto p(\alpha)\prod_{i=1}^{N}\mathrm{N}(\alpha+\beta x_i,\tau^{-1})$$

$$p(\beta|\alpha,\tau,y) \propto p(\beta)\prod_{i=1}^{N}\mathrm{N}(\alpha+\beta x_i,\tau^{-1})$$

$$p(\tau|\alpha,\beta,y) \propto p(\tau)\prod_{i=1}^{N}\mathrm{N}(\alpha+\beta x_i,\tau^{-1})$$

More generally...

- For *any* DAG:

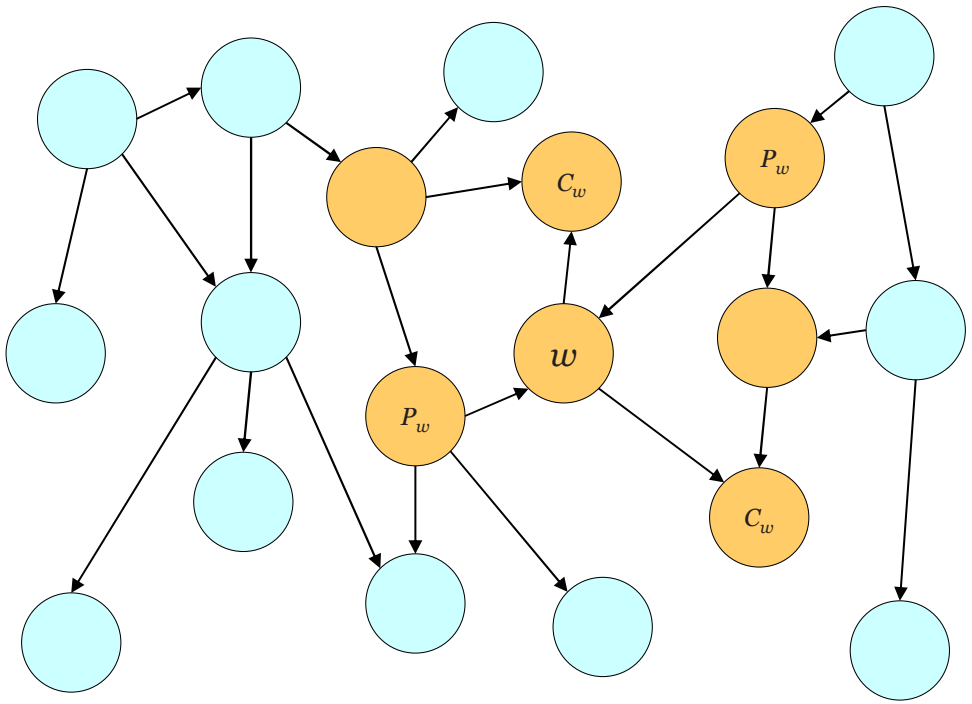
$$p(V) = \prod_{v \in V} p(v|\text{parents}[v]) \qquad [\textit{factorization theorem}]$$

  where V is the set of all nodes
- Note that $p(\theta|y) \propto p(\theta, y) = p(V)$
- Also $\text{FCD}(w) = p(w|V \backslash w) \propto p(V)$

$$\Rightarrow \text{FCD}(w) \propto p(w|\text{parents}[w]) \times \prod_{v \in \text{children}[w]} p(v|\text{parents}[v])$$

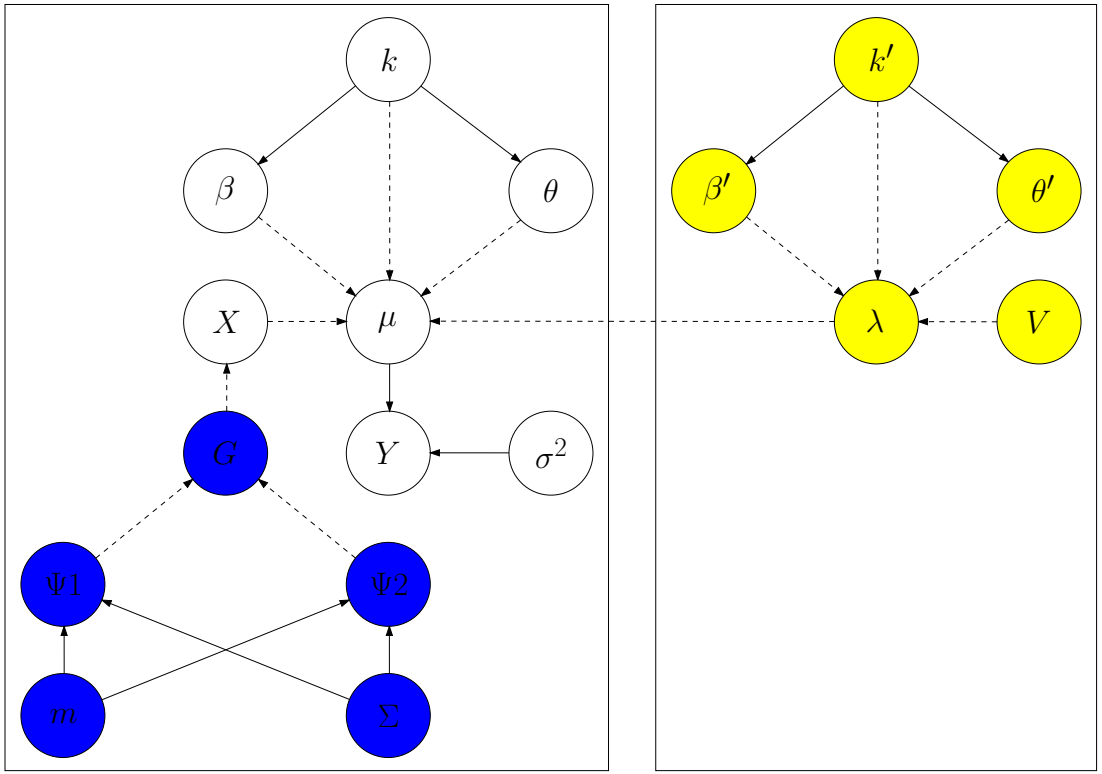
Factorization theorem

- Beauty of FT is two-fold:
  - (i) can write down joint posterior for any DAG simply by knowing relationship between each node and its parents
  - (ii) full conditional is *local computation* on the graph, involving only the node-parent dependencies for node of interest and its children



Combining models

- Only need to consider small part of model at any given time; no need to take account of bigger picture...
- Can construct arbitrarily complex structures by combining submodels together – mechanism of inference remains the same



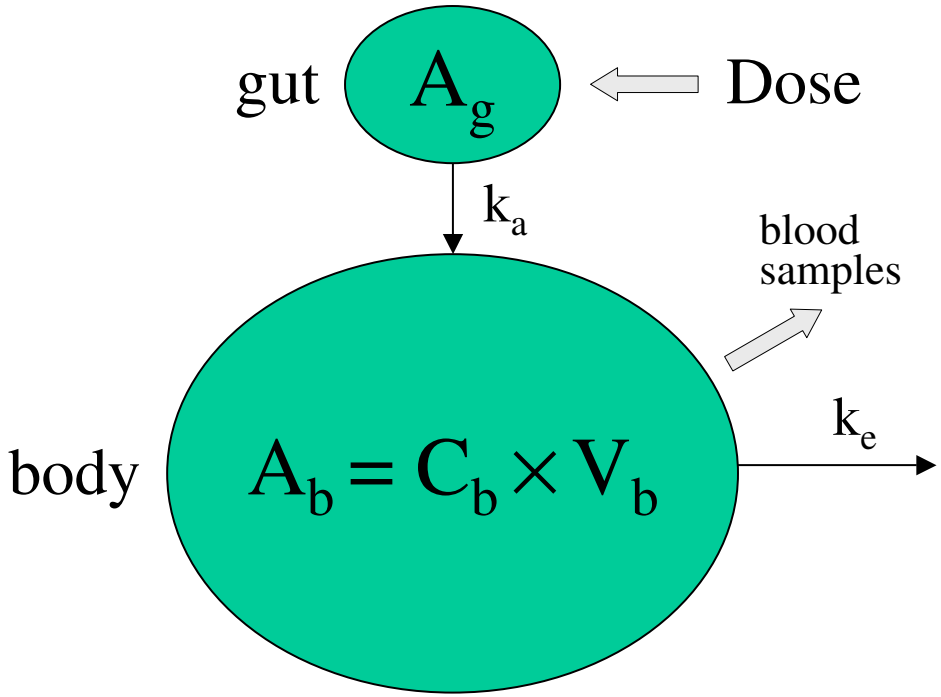
BUGS

- BUGS: **B**ayesian inference **U**sing **G**ibbs **S**ampling
- Provides language for specifying parent-child relationships
- Uses (inverts) these to calculate full conditional distributions

```
model {
    for (i in 1:N) {
        y[i] ~ dnorm(mu[i], tau)
        mu[i] <- alpha + beta * x[i]
    }
    alpha ~ dnorm(0, prec)
    beta ~ dnorm(0, prec)
    tau ~ dgamma(a, b)
}
```

```
list(
    N = 20,
    prec = 0.0001,
    a = 0.001, b = 0.001,
    y = c(1.3, 2.4, ...),
    x = c(9.7, 5.9, ...)
)
```

Differential equation models: e.g. 'one-compartment' pharmacokinetic model

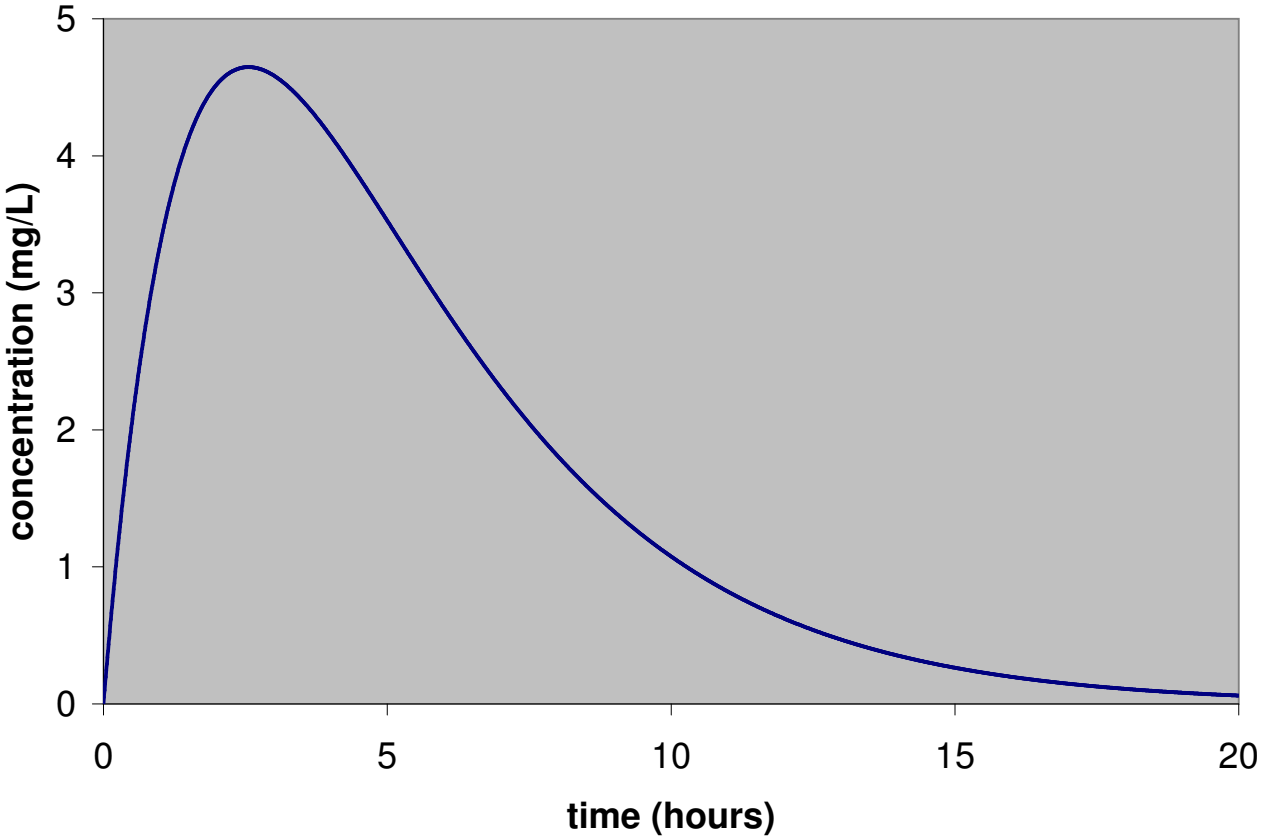


$$\frac{dA_g}{dt} = -k_a A_g \qquad \frac{dA_b}{dt} = k_a A_g - k_e A_b$$

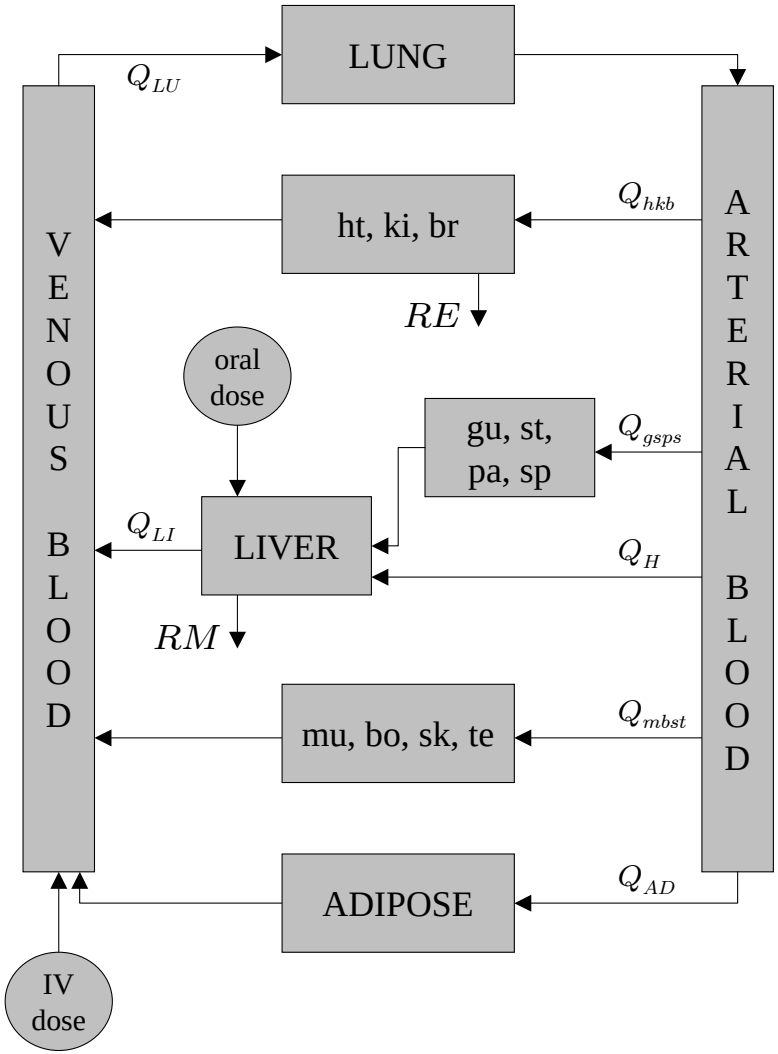
$$A_g(0) = Dose \qquad A_b(0) = 0$$

One-compartment model, solution

$$C_b(t) = \frac{Dose}{V_b} \times \frac{k_a}{k_e - k_a} \{\exp(-k_a t) - \exp(-k_e t)\}$$



Physiologically based PK model



$$\frac{dA_{LU}}{dt} = Q_{LU} \times (C_{VEN} - C_{LU}/Kp_{LU})$$

$$\frac{dA_{hkb}}{dt} = Q_{hkb} \times (C_{ART} - C_{hkb}/Kp_{hkb}) - RE(t)$$

$$\frac{dA_{gsps}}{dt} = Q_{gsps} \times (C_{ART} - C_{gsps}/Kp_{gsps})$$

$$\frac{dA_{LI}}{dt} = Q_H.C_{ART} + Q_{gsps}.C_{gsps}/Kp_{gsps} + RA(t) - Q_{LI}.C_{LI}/Kp_{LI} - RM(t)$$

$$\frac{dA_{mbst}}{dt} = Q_{mbst} \times (C_{ART} - C_{mbst}/Kp_{mbst})$$

$$\frac{dA_{AD}}{dt} = Q_{AD} \times (C_{ART} - C_{AD}/Kp_{AD})$$

$$\frac{dA_{ART}}{dt} = Q_{LU}.C_{LU}/Kp_{LU} - CO.C_{ART}$$

$$\frac{dA_{VEN}}{dt} = Q_{hkb}.C_{hkb}/Kp_{hkb} + Q_{LI}.C_{LI}/Kp_{LI} + Q_{mbst}.C_{mbst}/Kp_{mbst} + Q_{AD}.C_{AD}/Kp_{AD} + RI(t) - Q_{LU}.C_{VEN}$$

BUGS language specification

$$\frac{dA_g}{dt} = -k_a A_g \qquad \frac{dA_b}{dt} = k_a A_g - k_e A_b \qquad [A_g(0) = Dose, \quad A_b(0) = 0]$$

```
model {
  for (i in 1:N) {
    y[i] ~ dnorm(Cb[i], tau)
    Cb[i] <- solution[i, 2] / Vb
  }
  solution[1:N, 1:2] <- ode(init[], grid[], D(A[1:2], t), origin, tol)
  D(A[1], t) <- -ka * A[1]
  D(A[2], t) <-  ka * A[1] - ke * A[2]
#  solution[1:N, 1:2] <- one.comp(init[], grid[], theta[], origin, tol)
#  theta[1] <- ka; theta[2] <- ke
  init[1] <- dose; init[2] <- 0
  ke ~ dunif(0, 10)
  ka ~ dunif(0, 10)
  Vb ~ dunif(0, 1000)
  sd ~ dunif(0, 10)
  tau <- 1 / pow(sd, 2)
}
```

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  ke ~ dunif(0, 10)
  ka ~ dunif(0, 10)
  Vb ~ dunif(0, 1000)
  sd ~ dunif(0, 10)
  tau <- 1 / pow(sd, 2)
}
```

Source code (template)

```
MODULE WBDiffOneComp;

  IMPORT
    WBDiffODEMath, Math;

  TYPE
    Equations = POINTER TO RECORD (WBDiffODEMath.Equations) END;
    Factory = POINTER TO RECORD (WBDiffODEMath.Factory) END;

  CONST
    nEq = 2;

  VAR
    fact-: WBDiffODEMath.Factory;

  PROCEDURE (e: Equations) Derivatives (IN theta, A: ARRAY OF REAL;
                                        n: INTEGER; t: REAL;
                                        OUT dAdt: ARRAY OF REAL);
  VAR
    ka, ke: REAL;
  BEGIN
    ka := theta[0]; ke := theta[1];
    dAdt[0] := -ka * A[0];
    dAdt[1] :=  ka * A[0] - ke * A[1];
  END Derivatives;
  .....
```

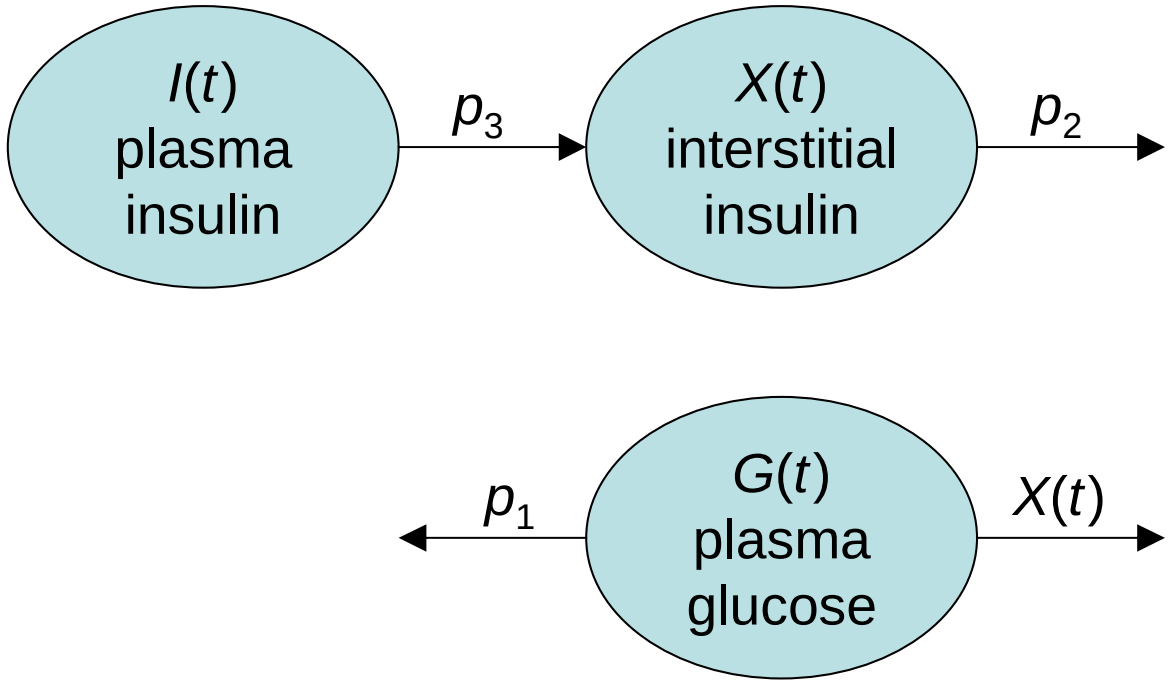
Source code continued

```
PROCEDURE (e: Equations) Derivatives (IN theta, A: ARRAY OF REAL;
                                      n: INTEGER; t: REAL;
                                      OUT dAdt: ARRAY OF REAL);
VAR
  ka, ke: REAL;
BEGIN
  ka := theta[0]; ke := theta[1];
  dAdt[0] := -ka * A[0];
  dAdt[1] :=  ka * A[0] - ke * A[1];
END Derivatives;
```

Another example: insulin/glucose kinetics

- Insulin produced by pancreas to stimulate glucose transport into and utilisation by cells
- Intravenous glucose tolerance test (IVGTT) used to measure sensitivity of glucose disappearance to insulin
- Administer bolus dose of glucose and monitor blood-glucose and blood-insulin concentrations
- Fit minimal model...

Minimal model for glucose kinetics



$$\frac{dG}{dt} = -p_1(G(t) - G_b) - X(t)G(t) \qquad \frac{dX}{dt} = p_3(I(t) - I_b) - p_2X(t)$$

$$G(0) = G_0 + \frac{Dose}{V} \qquad X(0) = 0$$

Minimal model continued

- Reparameterize slightly...
- Define insulin sensitivity $S_I = p_3/p_2$ and glucose effectiveness $S_G = p_1$
- Also let $Z = X/S_I$

$$\frac{dG}{dt} = -S_G(G(t) - G_b) - S_I Z(t) G(t) \quad \frac{dZ}{dt} = p_2 \{(I(t) - I_b) - Z(t)\}$$

- S_G: combined effect of glucose to enhance glucose uptake and suppress endogenous glucose production at basal insulin levels
- S_I: insulin's action to accelerate glucose uptake and suppress glucose production

Implementation

- We have observed values of G and I at various times + G_b, I_b and G_0
- Solve equations for G and Z
- $I(t)$ is a *forcing function*, need to evaluate at arbitrary times
  $\longrightarrow$ interpolate between observed values? Fit spline?
- Currently no way to define 'functions' in BUGS language (except for derivatives)
  $\longrightarrow$ have to 'hard-wire' equations...

Implementation

```
PROCEDURE Interpolate (IN time, insulin: ARRAY OF REAL; t: REAL;
                       OUT x: REAL);
...
END Interpolate;

PROCEDURE (e: Equations) Derivatives (IN theta, A: ARRAY OF REAL;
                                      n: INTEGER; t: REAL;
                                      OUT dAdt: ARRAY OF REAL);
VAR
  time, insulin: ARRAY 22 OF REAL;
  Gb, Ib, SI, SG, p2, It: REAL; i: INTEGER;
BEGIN
  i := 0;
  WHILE i < 22 DO
    time[i] := theta[i]; insulin[i] := theta[22 + i];
    INC(i)
  END;
  Gb := theta[44]; Ib := theta[45];
  SI := theta[46]; SG := theta[47]; p2 := theta[48];
  Interpolate(time, insulin, t, It);
  dAdt[0] := -SG*(A[0] - Gb) - SI*A[1]*A[0];
  dAdt[1] := p2*((It - Ib) - A[1]);
END Derivatives;
```

$$\frac{dG}{dt} = -S_G(G(t) - G_b) - S_I Z(t) G(t) \qquad \frac{dZ}{dt} = p_2 \{(I(t) - I_b) - Z(t)\}$$

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```
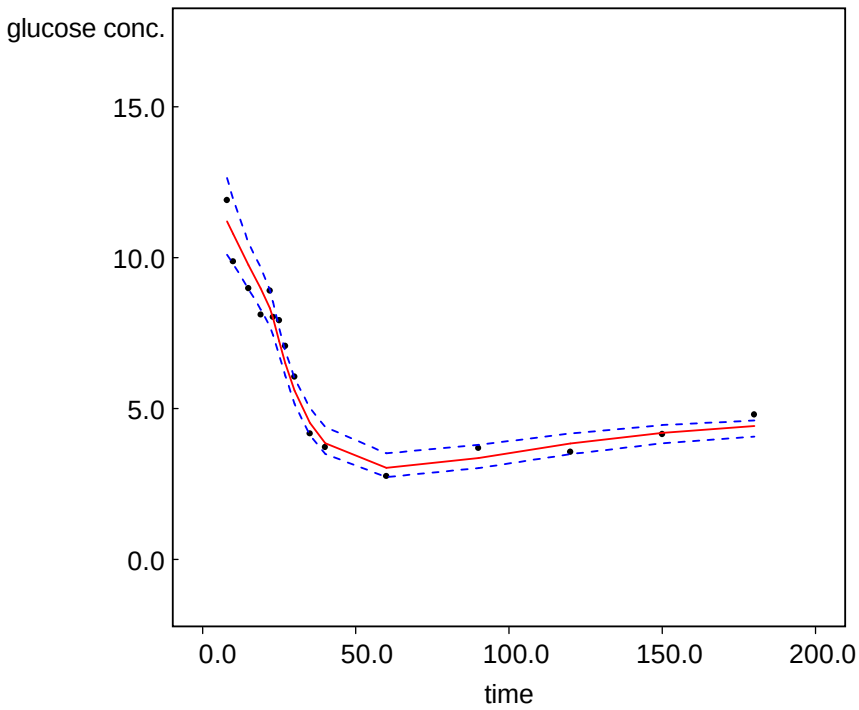

$$\frac{dG}{dt} = -S_G(G(t) - G_b) - S_I Z(t) G(t) \qquad \frac{dZ}{dt} = p_2 \{(I(t) - I_b) - Z(t)\}$$

BUGS code

```
model {
  for (i in 7:N) {
    glucose[i] ~ dnorm(solution[i, 1], p[i])
    p[i] <- tau / pow(solution[i, 1], 2)
  }
  solution[1:N, 1:2] <- ivgtt(init[], grid[], theta[],
                                origin, tol)
  init[1] <- G0 + dose / V
  init[2] <- 0
  for (i in 1:22) {
    theta[i] <- grid[i]
    theta[22 + i] <- insulin[i]
  }
  theta[45] <- Gb; theta[46] <- Ib
  theta[47] <- SI
  theta[48] <- SG
  theta[49] <- p2
  ...
}
```



Insulin/glucose/acipimox data

- 13 individuals each given IVGTT on 3 occasions (randomized)
  - A: overnight fast (control)
  - B: 24hr fast + placebo
  - C: 24hr fast + acipimox
- Elevate NEFA (non-esterified fatty acid) levels via 24 hour fast – effect on insulin sensitivity and/or secretion?
- Are effects reversed by anti-lipolytic agent acipimox?
- Four parameters per IVGTT profile: S_I, S_G, V, p_2
  $\longrightarrow$ 3×4 parameters for each individual
- Are there any systematic differences in four basic parameters between 'treatments'?

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Statistical model

- Let y_{ijk} denote kth glucose concentration (taken at time t_{ijk}) from individual i on occasion j...

$$y_{ijk} \sim \text{Normal}\left(\mu_{ijk}, \frac{\mu_{ijk}^2}{\tau}\right)$$

$$\mu_{ijk} = \text{IVGTT}(\theta_{ij}, t_{ijk}, I_{ij}(t)), \quad \theta_{ij} = (S_{I_{ij}}, S_{G_{ij}}, V_{ij}, p2_{ij})'$$

- Let $\phi_i = \begin{pmatrix} \theta_{i1} \\ \theta_{i2} \\ \theta_{i3} \end{pmatrix}$... $\quad \mu_{ijk} = \psi(\phi_i, t_{ijk}, I_{ij}(t))$

$$\phi_i \sim \text{MVN}_{12}(m, \Sigma)$$

$$m \sim \text{MVN}_{12}(m_0, \mathbf{I}), \quad \Sigma^{-1} \sim \text{Wishart}(12\Sigma_0, 12)$$

Bayes vs. likelihood

- MCMC unhindered by non-linearity – can fit desired model: $\mu_{ijk} = \psi(\phi_i, t_{ijk}, I_{ij}(t))$
- For likelihood based approach have to linearize:

$$\psi \approx \psi(\hat{\phi}_i, t_{ijk}, I_{ij}(t)) + (\phi_i - \hat{\phi}_i) \left.\frac{\partial \psi}{\partial \phi_i}\right|_{\phi_i = \hat{\phi}_i}$$

- Disadvantages:
  - don't know $\psi \Rightarrow$ don't know $\frac{\partial \psi}{\partial \phi_i}$ – have to evaluate numerically
  - no idea how good/adequate approximation is
  - difficulties with non-continuous derivatives $\frac{\partial \psi}{\partial \phi_i}$, e.g. unknown change-points
- But, much quicker?

Bayes vs. likelihood

- Bayesian methods allow incorporation of external evidence:
  - often desirable to incorporate prior knowledge, e.g. from other studies
  - in complex models, may be essential for parameter identifiability
  - may also be essential for reliability of numerical solvers
- Graphical modelling approach allows easy adaptation to complexities of 'real data', e.g.
  - unknown change-points
  - different error distributions
  - measurement error
  - arbitrary hierarchical structures

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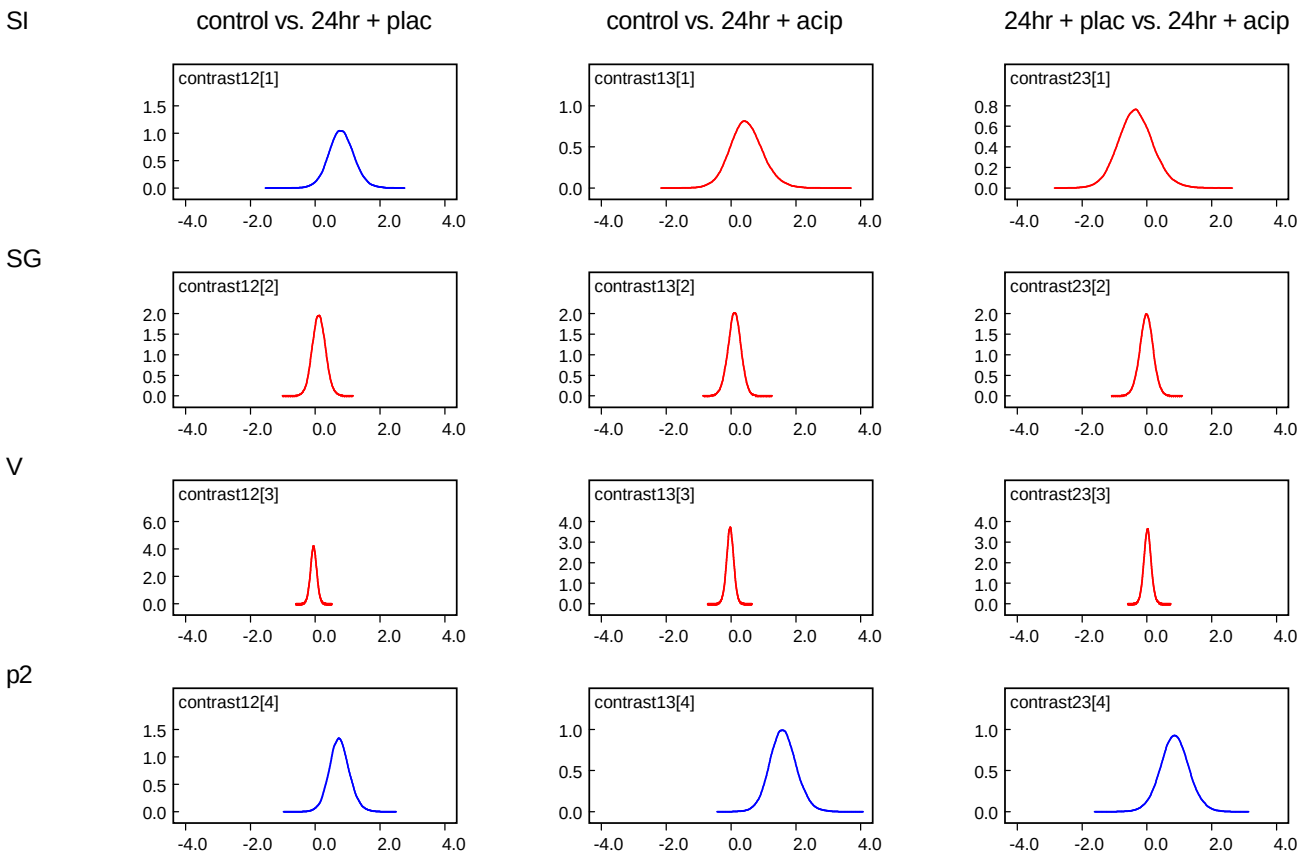
Results

- Interested in

$$m_1 - m_5, \ldots, m_4 - m_8 \text{ (contrast12, control vs. 24hr + plac)}$$

$$m_1 - m_9, \ldots, m_4 - m_{12} \text{ (contrast13, control vs. 24hr + acip)}$$

$$m_5 - m_9, \ldots, m_8 - m_{12} \text{ (contrast23, 24hr + plac vs. 24hr + acip)}$$



Results

- Elevated NEFA levels associated with decrease in insulin sensitivity S_I
- Other analyses show decrease in *first phase insulin secretion* also
- These effects partially reversed by acipimox, suggesting lipid-driven mechanisms important
- Decreases in p_2 (takes longer for insulin to work) linked to increases in max overnight growth-hormone levels (independent of changes in NEFA and insulin)

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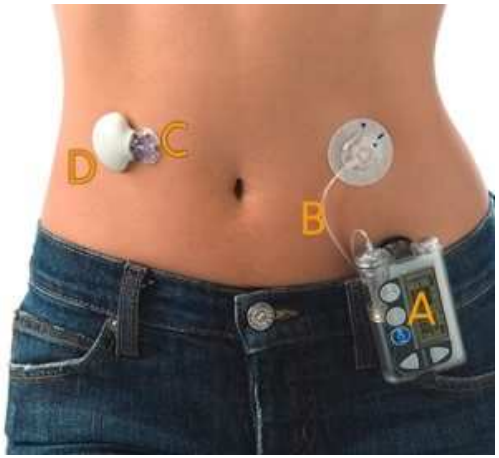
Interstitial-/plasma-glucose data

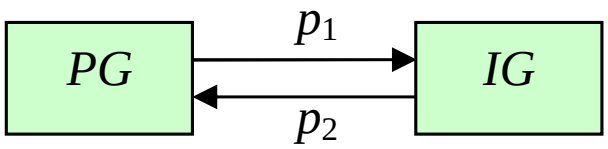
- Artificial pancreas measures interstitial glucose via current and converts to plasma glucose to determine appropriate insulin input
- Current can be measured continually via subcutaneous sensor $\longrightarrow$ provides great scope for better management of glucose levels



A. Insulin pump
B. Cannula
C. Glucose sensor
D. Transmitter

Interstitial-/plasma-glucose model

- First aim is to characterise relationship between interstitial- and plasma-glucose



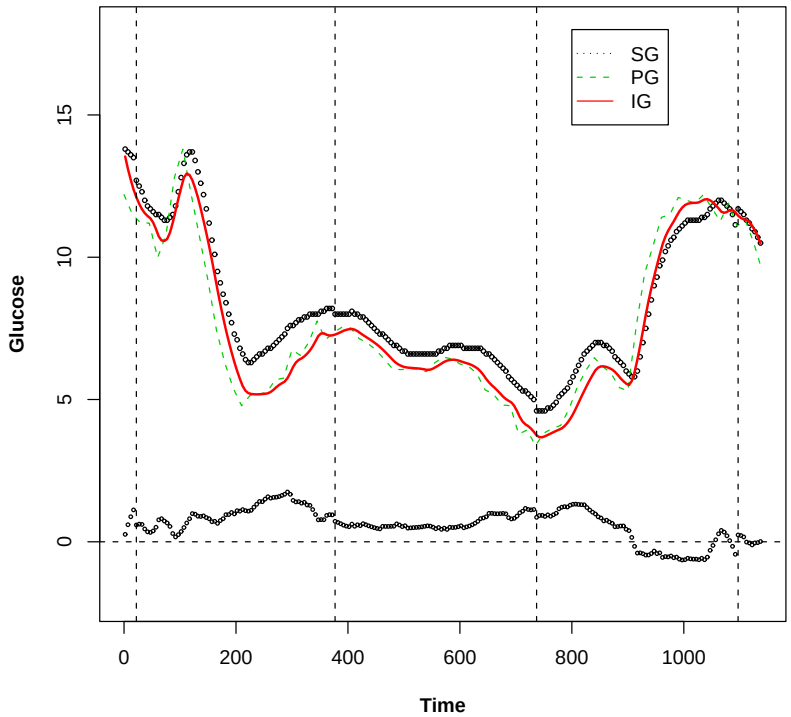
$$\frac{dIG}{dt} = -p_1 IG + p_2 PG$$

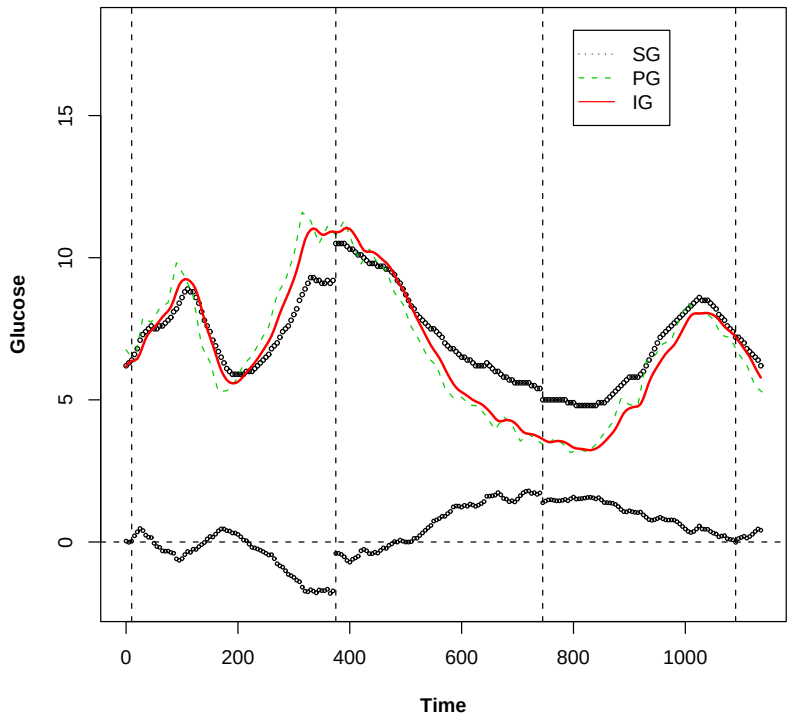
- Scale/normalize IG so that it is on the same scale as PG: $NIG = \nu IG$, where $\nu = p_1/p_2$

$$\frac{dNIG}{dt} = -p_1 NIG + p_1 PG$$

($NIG = PG$ at steady state)

Fits – individuals 2 & 6 / 12





Sensor calibration

- $IG = (C - C_B)/S \qquad (S = \textit{sensitivity},\ C_B = \textit{basal current})$
- Assume sensor measures current with error

$$C^m = C + \delta = NIG.S/\nu + C_B + \delta$$

- Sensor is calibrated every several hours: given current PG value, calculate appropriate scaling factor for mapping $C^m \rightarrow NIG^m$, i.e. $NIG^m = A.C^m \Rightarrow$

$$NIG^m = F.NIG + B + \eta$$

where $F = A.S/\nu$, $B = A.C_B$ and $\eta = A.\delta$

Sensor calibration continued

- In general there are K calibration times, each giving a different value of A
- If we index time points by j and let $P(j)$ denote the calibration period to which observation j belongs:

$$NIG_j^m = F_{P(j)} NIG_j + B_{P(j)} + \eta_j, \quad \eta_j \sim \mathrm{N}\left(0, \sigma^2_{P(j)}\right)$$

where NIG_j is the solution to $\frac{dNIG}{dt} = p_1(PG(t) - NIG)$ at time t_j (with $PG(t)$ as a forcing function)

Population model

- Index individuals by i:

$$NIG_{ij}^{m} = F_{iP(j)} NIG_{ij} + B_{iP(j)} + \eta_{ij}, \quad \eta_{ij} \sim \mathrm{N}\left(0, \sigma^2_{iP(j)}\right)$$

- Exchangeability assumptions:

$$\log p_{1_i} \sim \mathrm{N}(\mu_{p1}, \tau_{p1}^{-1}), \quad i = 1, ..., N$$
$$\log \sigma_{ik} \sim \mathrm{N}(\mu_{\sigma}, \tau_{\sigma}^{-1}), \quad k = 1, ..., K$$
$$\begin{pmatrix} \log F_{ik} \\ B_{ik} \end{pmatrix} \sim \mathrm{MVN}_2(\theta_i, \Sigma_{intra}), \quad \theta_i \sim \mathrm{MVN}_2(\mu_{\theta}, \Sigma_{inter})$$

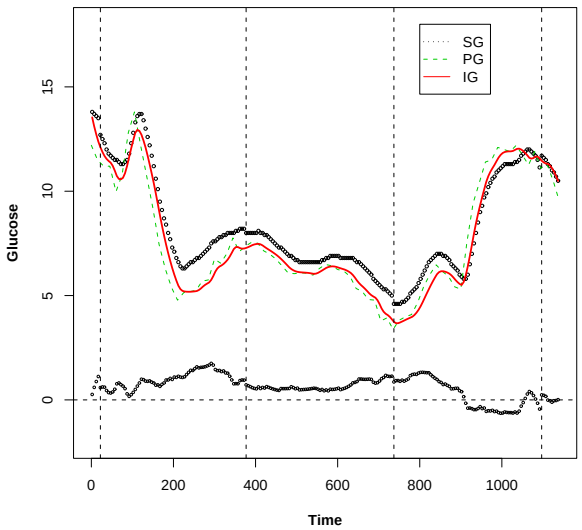
- $+$ appropriate priors on hyperparameters....

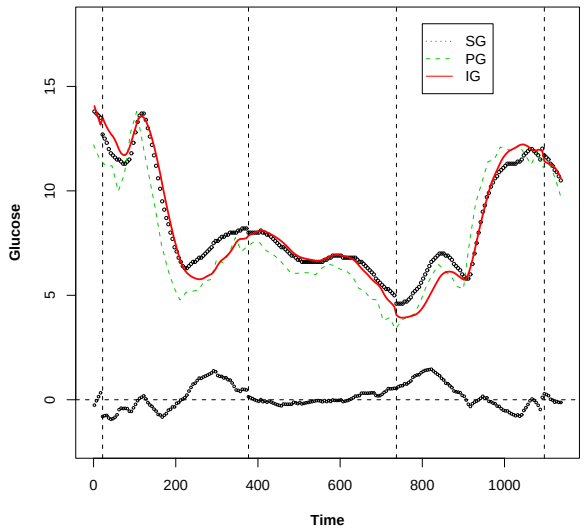
Exchangeability assumptions: BUGS code

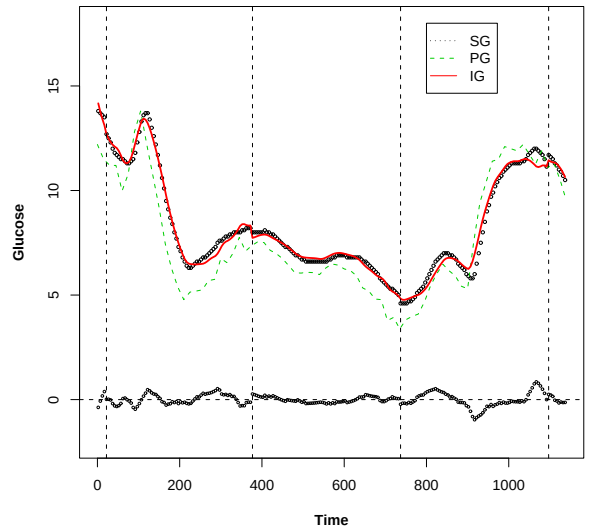
```
for (i in 1:N) {
  for (k in 1:K) {
    log(sigma[i, k]) <- log.sigma[i, k]
    log.sigma[i, k] ~ dnorm(mu.sigma, tau.sigma)
    F[i, k] <- exp(calib[i, k, 1])
    B[i, k] <- calib[i, k, 2]
    calib[i, k, 1:2] ~ dmnorm(theta[i, ], T.intra[, ])
  }
  theta[i, 1:2] ~ dmnorm(mu.theta[], T.inter[, ])
  log(p1[i]) <- log.p1[i]
  log.p1[i] ~ dnorm(mu.p1, tau.p1)
}
```

Fits – individual 2/12

- uncalibrated; scaled; scaled + shifted.....

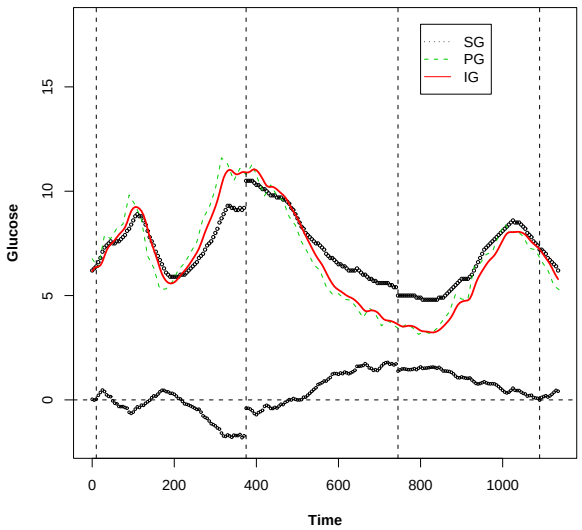


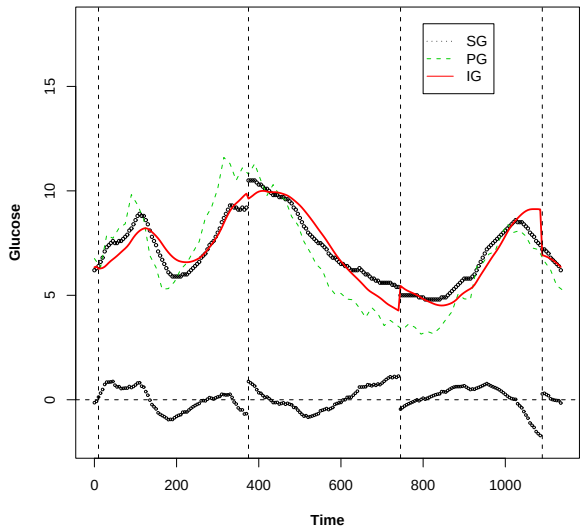


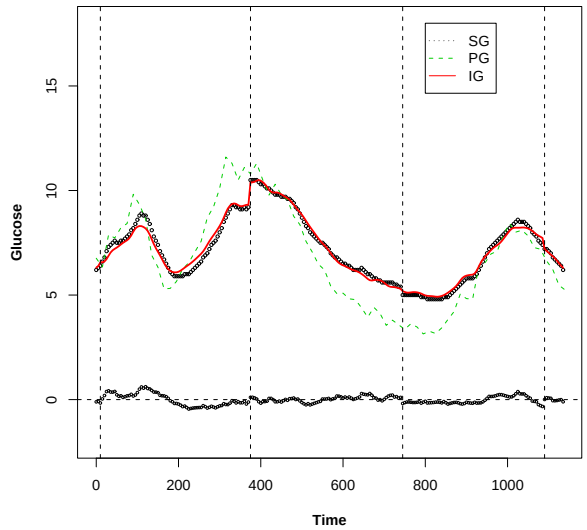


Fits – individual 6/12

- uncalibrated; scaled; scaled + shifted.....







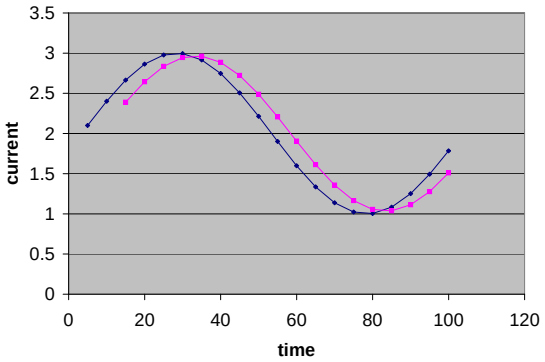
Estimates for lag-time $\tau = p_1^{-1}$

τ (mins)	Median	25%Q	75%Q
1	17.84	17.09	18.54
2	15.07	14.61	15.53
3	15.88	14.63	17.11
4	10.33	9.38	11.27
5	19.48	19.06	19.94
6	16.06	15.31	16.87
7	16.47	16.03	16.95
8	15.60	14.93	16.35
9	20.53	19.30	21.76
10	11.06	10.42	11.72
11	13.96	13.62	14.25
12	13.78	13.01	14.51
Population	15.23	14.51	15.94

- Accepted value, based on physiology, is around 10 minutes...
- Results show that ∼15 minutes more appropriate

Explanation

- Additional lag could be due to:
  - time-delay induced by data processing?



  - incorrect model?

- Results backed up by correlating unlagged-NIG^m with PG at various lags:
  $\rho = 0.911$ 0.932 0.937 0.935

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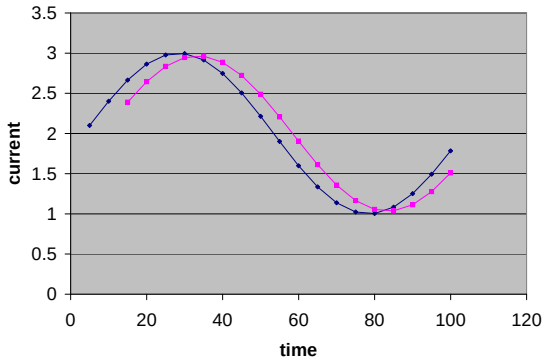

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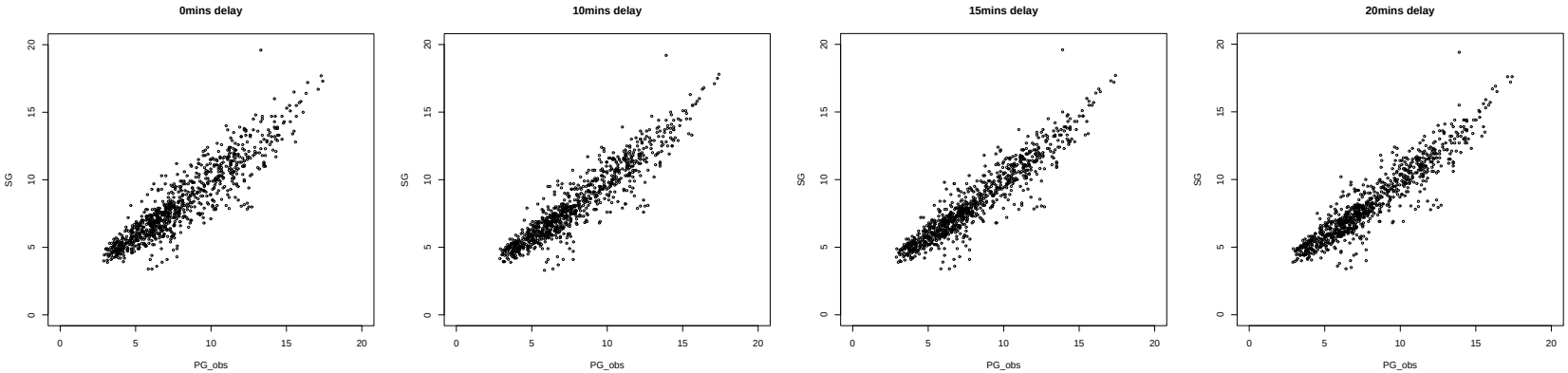

Extensions/future work

- Long-term goal of current work: simulation of *in silico* population of pseudo-data for fully testing insulin-delivery algorithm (with Roman Hovorka @ Cambridge-Paediatrics and Chen Wei/Michael Lawton @ MRC-BSU)
  - Acknowledge uncertainty in forcing functions
  - Acknowledge uncertainty in calibration times?
  - Modelling autocorrelated residuals
  - Adjust for other biases
  - Extend to modelling of other sensors
  - ...
- Other applied work:
  - Explore use for modelling infectious disease dynamics (with Dani de Angelis, Anne Presanis and Chen Wei @ MRC-BSU + Olivier Restif @ Cam-Vet-Med + Christl Donnelly @ Imperial)
  - Use in systems biology (with Lorenz Wernisch @ MRC-BSU)
  - ...

Extensions/future work

- Methodological
  - Currently can allow for discrete changes in system, e.g. piecewise constant parameters $\longrightarrow$ extend to continuously changing parameters?
  - Facilitate specification of stochastic processes
  - Allow for system noise via SDEs
  - Allow for lagged/asynchronous systems
  - Specification of 'functions' (of dummy variables rather than specific nodes) in BUGS language
  - Migration to OpenBUGS
  - ...

Conclusions

- WBDiff allows specification of (Bayesian) models defined in terms of ODEs
- BUGS/graphical modelling framework provides great scope for dealing with complexities of 'real data', e.g. error distributions, arbitrary model structures, ...
- System currently limited by lack of flexibility re specification of DEs, e.g. forcing functions, lagged systems, ...
- Bayesian approach has several advantages over likelihood-based approach: no approximations, non-continuous derivatives, prior knowledge
- But slower + informative priors may be essential

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- Interstitial-/plasma-glucose data: joint work with Chen Wei (MRC-BSU) and Roman Hovorka[1]
- Experimental host-parasite system: joint work with Olivier Restif (Cambridge Veterinary Medicine)
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[1]University Department of Paediatrics, University of Cambridge, UK

[2]Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, UK