Execution of complex Bayesian workflows with the DDMoRe Interoperability Framework: a case study in the diabetes area

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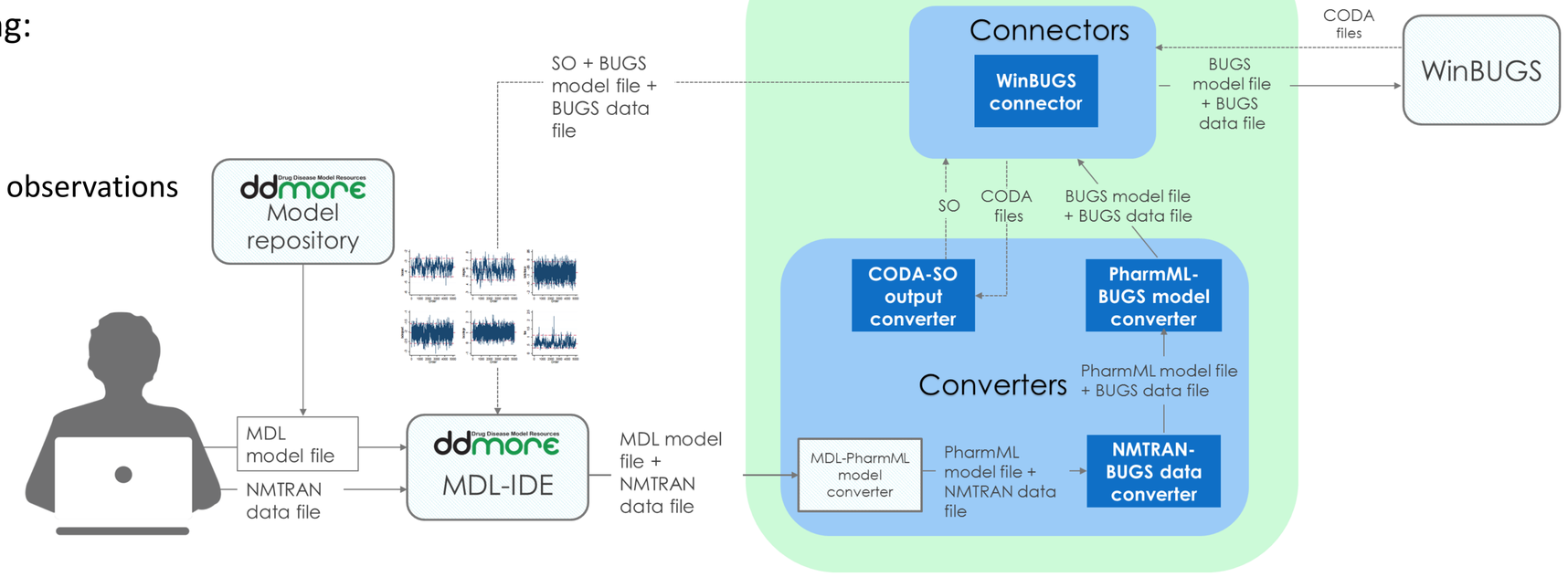
BACKGROUND. The DDMoRe Interoperability Framework (IOF) [1] can execute a desired model using different target tools, requiring a single model encoding effort, through Modelling Description Language (MDL) and the R *ddmore* package. The interoperability is based on two system-to-system interchange standards: the Pharmacometrics Markup Language (PharmML) [2] and the Standard Output (SO) [3].

OBJECTIVE. We integrated WinBUGS, a popular Bayesian estimation tool, in the IOF (downloadable at [4]) and we demonstrated its use to design and execute a complex interoperable modelling workflow, based on two diabetes-related models.

MATERIALS AND METHODS.

SOFTWARE MODULES DEVELOPED

1. PharmML-to-BUGS converter, supporting:
   - Algebraic/ODE/PKMacro models
   - Multiple variability levels (with pairwise covariance/correlation)
   - Single/multiple (indipendent/correlated) observations
   - Univariate/multivariate parametric/ non-parametric/empirical distributions
   - (Transformed) continuous/categorical covariates
   - IF-THEN-ELSE statements
   - Matrices/vectors
2. NMTRAN-to-BUGS data converter
3. BUGS output-to-SO converter
4. WinBUGS connector



DIABETES-RELATED MODELS

- Population regression model to estimate CP kinetic parameters [5]

M0

$$\boldsymbol{\theta}_i = \begin{pmatrix} ts \\ F \\ V \\ tl \end{pmatrix} = f(\tilde{\boldsymbol{\theta}}, \mathbf{U}_i)$$

$$\text{with } \mathbf{U}_i = \begin{pmatrix} Hstatus \\ BSA \\ Sex \\ Age \end{pmatrix}$$

$$\boldsymbol{\phi}_i = \boldsymbol{\theta}_i + \boldsymbol{\eta}_i$$

$$\boldsymbol{\eta}_i \sim N(0, \boldsymbol{\Sigma})$$

$$+$$

$$\tilde{\boldsymbol{\theta}} \sim N\left(\tilde{\boldsymbol{\theta}}_0, \boldsymbol{\Sigma}_0^{-1}\right)$$

$$\boldsymbol{\Sigma}^{-1} \sim W(\rho, \mathbf{R})$$

M4

$$k_{12} = \ln(2)\left(\frac{F}{tl} + \frac{1-F}{ts}\right)$$

$$k_{01} = \left(\frac{\ln(2)}{ts}\right)\left(\frac{\ln(2)}{tl}\right)\left(\frac{1}{k_{12}}\right)$$

$$k_{21} = \left(\frac{\ln(2)}{ts}\right) + \left(\frac{\ln(2)}{tl}\right) - k_{12} - k_{01}$$

- Glucose-insulin minimal model (MM)[6] to estimate physiologically-relevant insulin secretion indexes

$$\begin{cases} \frac{dCP_1(t)}{dt} = -(k_{01} + k_{21})CP_1(t) + k_{12}CP_2(t) + mX(t) \\ \frac{dCP_2(t)}{dt} = -k_{12}CP_2(t) + k_{21}CP_1(t) \end{cases}$$

$$CP_1(0) = CP_2(0) = 0$$

$$\begin{cases} \frac{dX(t)}{dt} = -mX(t) + Y(t) \\ \frac{dY(t)}{dt} = \begin{cases} -\alpha\left(Y(t) - \beta(G(t) - h)\right) \text{ if } G(t) > h \\ -\alpha Y(t) \quad \text{otherwise} \end{cases} \end{cases}$$

$$X(0) = x_0, Y(0) = 0$$

Insulin secretion indexes

$$\phi_1 = \frac{x_0}{\Delta G}$$

$$\phi_2 = \beta$$

$$ISR = mX(t)$$

IMPLEMENTED COMPLEX WORKFLOW

MLE approach

01 **M0 identification** — M0 parameters are estimated via a MLE approach in NONMEM

02 **M0 simulation** — CP kinetic parameters for a new subject are simulated in PsN using the identified M0 model at step 1

03 **MM identification** — MM parameters are estimated in NONMEM, fixing the values of CP kinetic parameters to the values simulated at step 2

→ Point estimates of ISR and physiological indexes

Bayesian approach

01 **M4 identification** — M4 parameters are estimated via a Bayesian approach in WinBUGS

02 **M4 simulation** — The joint probability distribution of CP kinetic parameters for a new subject is simulated in WinBUGS using the identified M4 model at step 1

03 **MM identification** — MM parameters are estimated in WinBUGS using as empirical prior distribution the joint probability distribution of CP kinetic parameters simulated at step 2

→ Probability distributions of ISR and physiological indexes

Mixed approach

01 **M0 identification** — M0 parameters are estimated via a MLE approach in NONMEM

02 **M0 simulation** — CP kinetic parameters for a new subject are simulated in PsN using the identified M0 model at step 1

03 **MM identification** — MM parameters are estimated in WinBUGS, fixing the values of CP kinetic parameters to the values simulated at step 2

→ Probability distributions of ISR and physiological indexes

RESULTS. Parameters estimates obtained at points 1) and 3) were consistent with the published values, which were originally obtained via Matlab.

- Population regression model (M4)

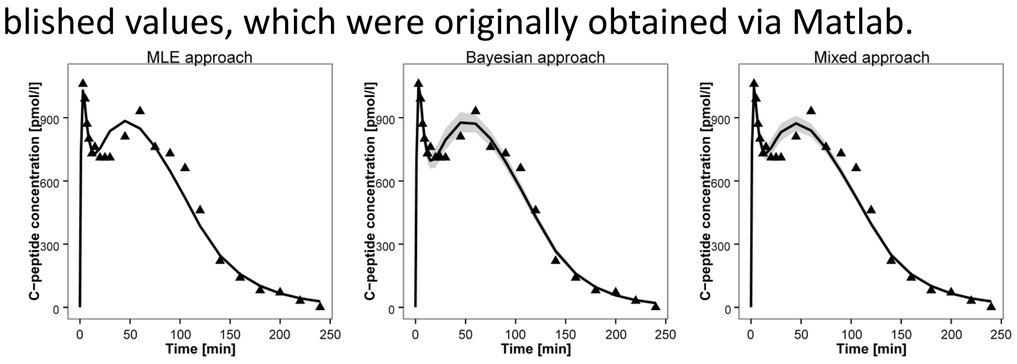
	mtsn (min)	mtso (min)	mtsd (min)	mFn (-)	mFo (-)	mFd (-)	atl (min)	btl (min/yr)	aVm (L)	aVf (L)	bVm (L/m²)	bVf (L/m²)
Matlab	4.99	4.50	4.70	0.767	0.781	0.778	26.70	0.209	0.417	0.89	2.04	1.77
BUGS	4.99	4.50	4.69	0.765	0.781	0.778	26.71	0.209	0.341	0.83	2.06	1.80

	VAR_ts (min²)	VAR_F (-)	VAR_tl (min²)	VAR_V (L²)	COV_ts_F (min)	COV_ts_tl (min²)	COV_ts_V (min L)	COV_F_tl (min)	COV_F_V (L)	COV_tl_V (min L)
Matlab	1.30	0.0022	32.94	0.71	0.0062	3.24	0.59	0.071	-0.0055	1.89
BUGS	1.30	0.0022	33.04	0.71	0.0062	3.24	0.59	0.071	-0.0057	1.91

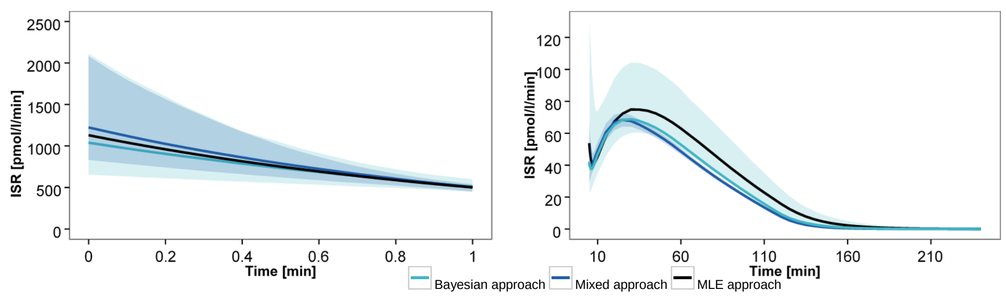
- Glucose-insulin minimal model (MM)

	h (pmol/L)	ϕ_1 (-)	ϕ_2 (1/min)	m (1/min)	α (1/min)
Matlab	88.83	85.6	10.07	0.73	0.044
BUGS	89.16	88.5	10.93	0.79	0. 050

The insulin secretion indexes indicate the β-cell sensitivity to glucose in the first fast release (ϕ_1) and in the second slower release (ϕ_2) after an IVGTT, and the time course of insulin secretion rate (ISR).



Residual variability is not reported.



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[3] PAGE 25 (2016) Abstr 5954 [www.page-meeting.org/?abstract=5954]
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