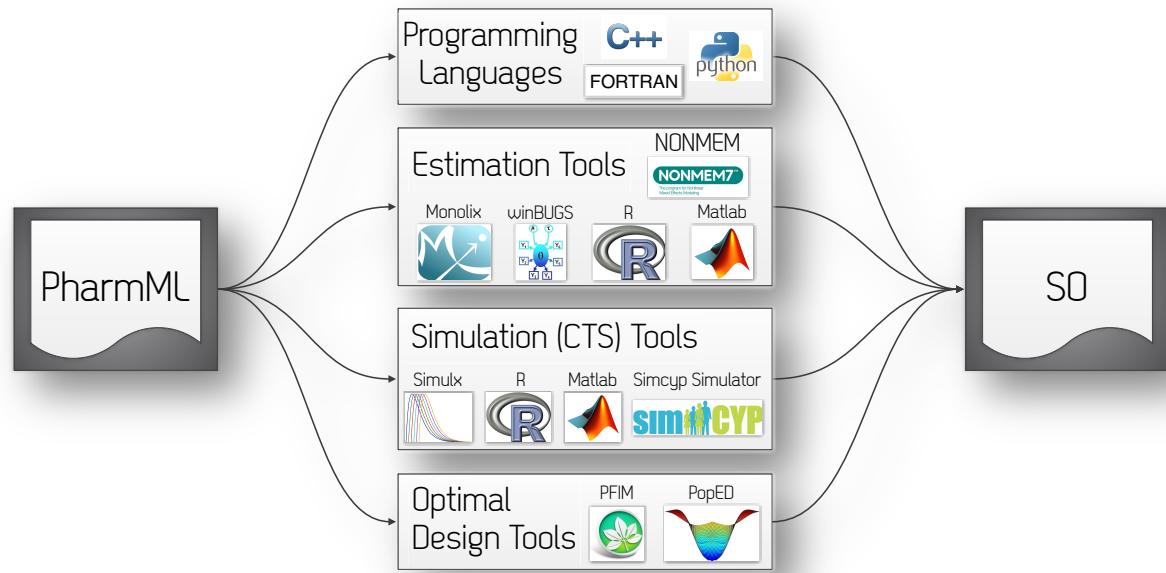




PharmML & SO – exchange formats for models used in QSP and PMx



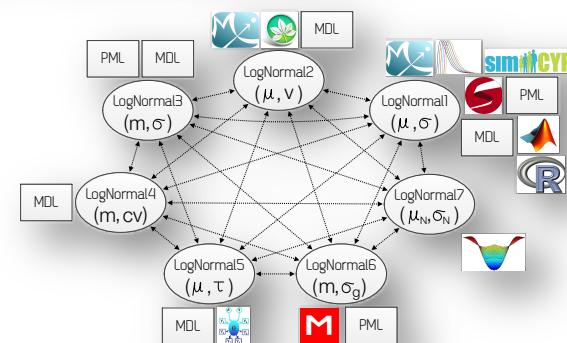
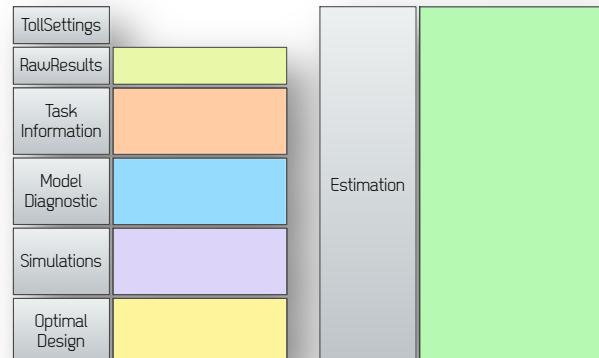
Maciej J Swat (mjswat@ebi.ac.uk)

EMBL-EBI

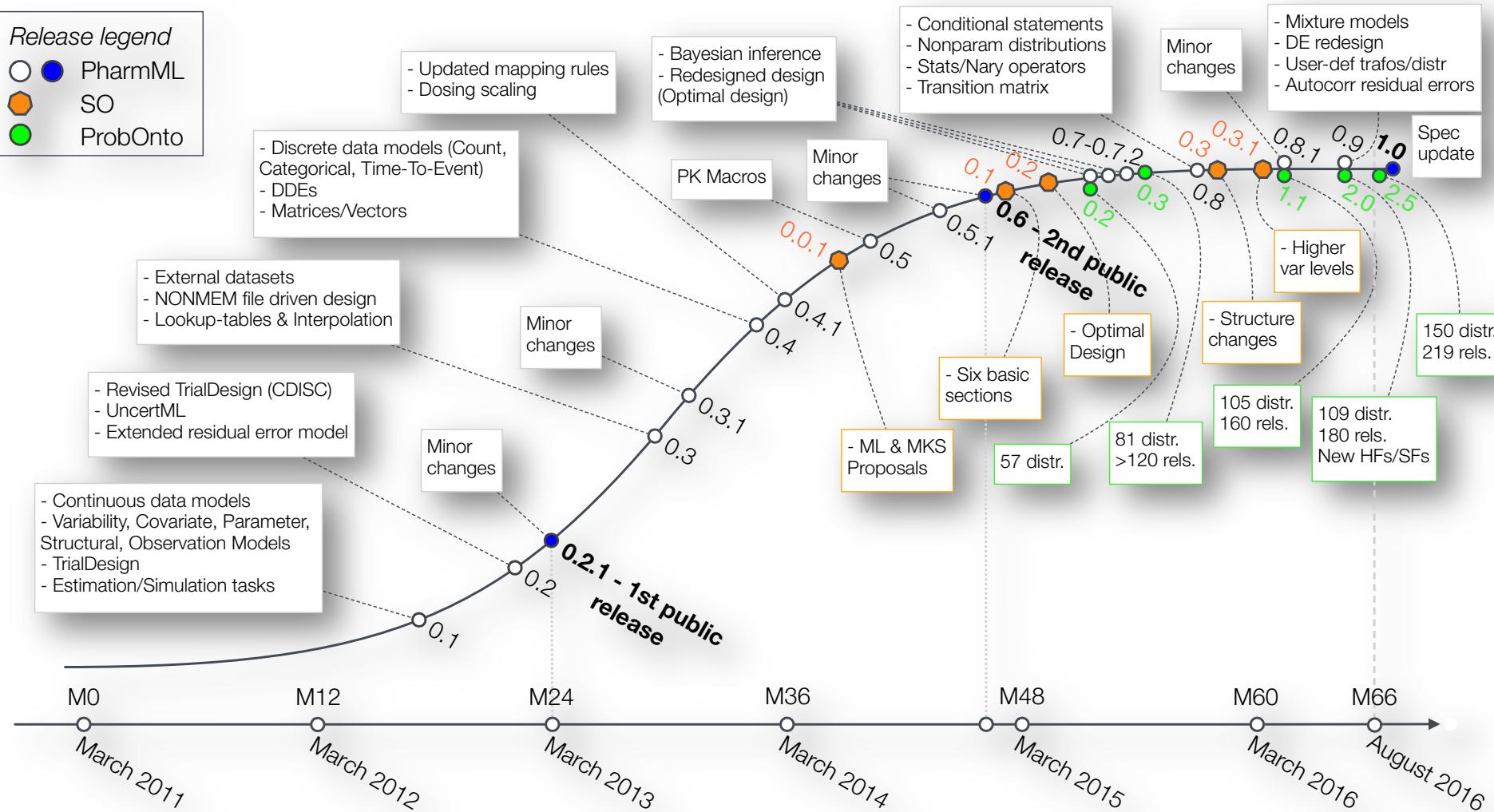
On behalf of the DDMoRe consortium

Outline

- IMI/DDMoRe – brief introduction
- Exchange standards & databases
 - PharmML
 - connection to SBML
 - SO
 - ProbOnto
- Conclusions



Timeline



Changes and extensions in recent 2 years

– only PharmML related



PharmML 0.6 - 28th Jan 2015

- Discrete data models
- PK macros
- Delay Differential Equations, DDE

PharmML 0.7 - 2nd July 2015

- ProbOnto - ontology and knowledge base of parametric probability distributions - first introduction of the
- Hierarchical models & Bayesian inference support
- Complete redesign of the trial design and optimal design support

PharmML 0.7.2 - 4th Sept 2015

Design optimization and evaluation tasks support.

PharmML 0.8 - 11th January 2016

- Assignment statements
- Conditional statements
- Nested piecewise statements
- Probability functions support (PDF, CDF, HZ and SF)
- Empirical distributions support
- Random realisations
- Transition matrix for Markov models
- N-ary operators
- Statistical operators
- Conditional ignorance

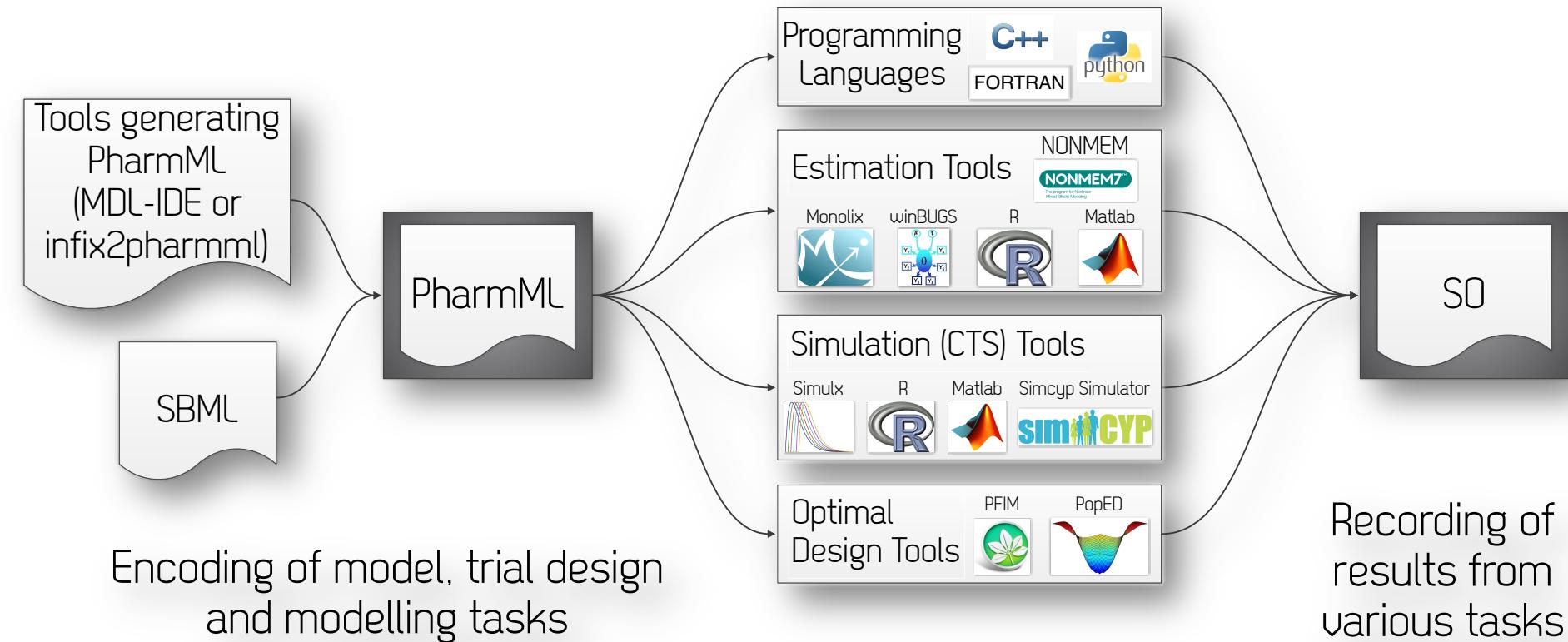
PharmML 0.8.1 - 16th March 2016

- ParametersToEstimate added to optimal design (OD)
- Stage definition added in OD
- ODEs allowed in conditional statements
- Support for software settings in external files and specification of output files
- New values added to 'columnType', removed redundant ones

PharmML 0.9 - 20th July 2016

- Mixture models
 - * mixtures of distributions
 - * mixtures of structural models (wsmm, bsmm)
- New DE notation - encodable are ODEs, DDEs & PDEs with boundary and initial conditions
- Autocorrelation models of residual errors
- BoxCox2 & user-defined transformations
- User-defined distributions
- Updated covariates, occasions/design spaces handling in TD
- Exclusion and inclusion criteria for covariates
- Categorical covariates building (clustering)
- Observation model extensions - multiple models and models in conditionals permitted
- Tool-specific settings support

PharmML & SO – Big Picture



Typical NLME model with trial design

Structural model

$$k = \frac{CL}{V}$$

$$C(t) = \begin{cases} 0 & \text{if } t - t_D < T_{lag} \\ \frac{D}{V} \frac{k_a}{k_a - k} [e^{-k(t-t_D-T_{lag})} - e^{-k_a(t-t_D-T_{lag})}] & \text{otherwise} \end{cases}$$

Parameter model

$$\log(ka_i) = \log(ka_{pop}) + \beta_{ka,TreatSeq} 1_{TreatSeq_i=AB} + \eta_{ka,i}$$

$$\begin{aligned} \log(V_{ik}) = & \log(V_{pop}) + \beta_V 1_{S_i=F} + \beta_{V,occ} 1_{OCC_{ik}=1} \\ & + \beta_{V,Treat} 1_{Treat_{ik}=A} + \beta_{V,TreatSeq} 1_{TreatSeq_i=AB} \\ & + \eta_{V,i}^{(0)} + \eta_{V,ik}^{(+1)} \end{aligned}$$

$$\begin{aligned} \log(CL_{ik}) = & \log(CL_{pop}) + \beta_{CL} 1_{S_i=F} + \beta_{CL,occ} 1_{OCC_{ik}=1} \\ & + \eta_{CL,i}^{(0)} + \eta_{CL,ik}^{(+1)} \end{aligned}$$

$$\begin{aligned} \eta_{ka,i}^{(0)} &\sim \mathcal{N}(0, \omega_{ka}), \quad \eta_{V,i}^{(0)} \sim \mathcal{N}(0, \omega_V), \quad \eta_{CL,i}^{(0)} \sim \mathcal{N}(0, \omega_{CL}), \\ \eta_{V,ik}^{(+1)} &\sim \mathcal{N}(0, \gamma_V), \quad \eta_{CL,ik}^{(+1)} \sim \mathcal{N}(0, \gamma_{CL}) \end{aligned}$$

Variability model

$$\Omega^{(0)} = \begin{pmatrix} \omega_{ka}^2 & 0 & 0 \\ 0 & \omega_V^2 & 0 \\ 0 & 0 & \omega_{CL}^2 \end{pmatrix}$$

$$\Omega^{(+1)} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & \gamma_V^2 & 0 \\ 0 & 0 & \gamma_{CL}^2 \end{pmatrix}$$

Covariate model

	Weight
Type	Continues
Transformation	$\log(W/70)$

Other covariates

	Sex	Treat	TreatSeq	Occasion
Type	Categorical	Categorical	Categorical	Categorical
Category Count	2	2	2	2
Categories	F, M	A, B	AB,BA	1, 2
Reference	F	A	AB	1

Trial design

Segment	Activity	Treatment	DoseTime	DoseSize	Target Variable
TA	OR1	OR bolus	0 : 12 : 72	150	D
TA	OR2	OR bolus	0 : 24 : 72	100	D

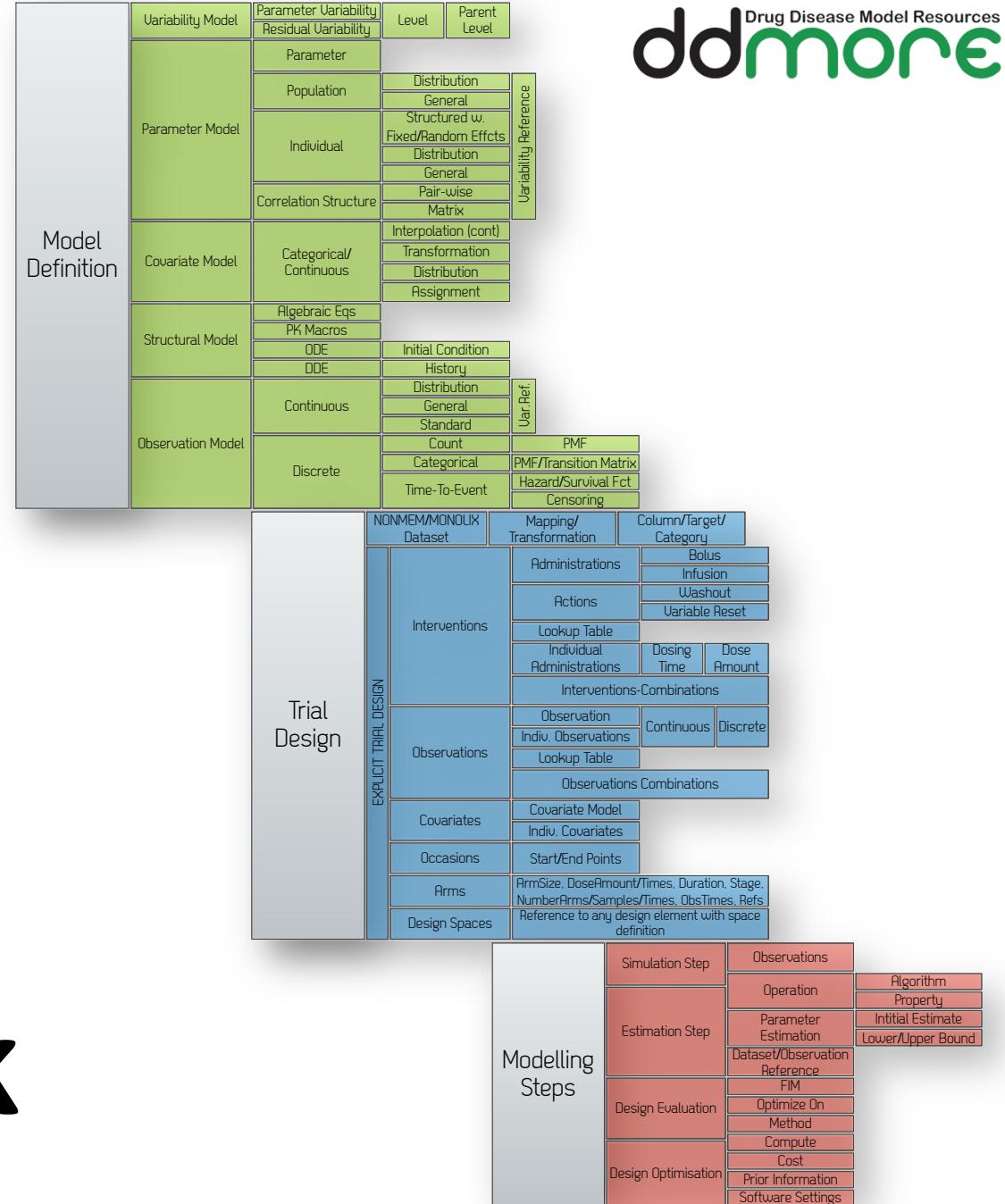
Epoch	Occasion	Start time	End time
Treatment Epoch	OCC1	0	180
Washout	-	0	10
Treatment Epoch	OCC2	0	180

PharmML is about ...

Model

Design

Task



Mathematical formalism 1

– standard continuous/discrete models

ObservationModel

y_{ij}

ContinuousData

Distribution Type $u(y_{ij}) \sim N(u(f(x_{ij}, \psi_i)), \sigma)$

Structured Type $u(y_{ij}) = u(f(x_{ij}, \psi_i)) + g(x_{ij}, \psi_i, \xi_i) \epsilon_{ij}$

Equation Type $u(y_{ij}) = U(f(x_{ij}, \psi_i), \xi_i, \epsilon_{1,ij}, \epsilon_{2,ij}, \dots)$

$$\log(y_{ij}) \sim N(\log(f(x_{ij}, \psi_i)), a^2)$$

$$\log(y_{ij}) = \log(f(x_{ij}, \psi_i)) + a^2 \epsilon_{ij}, \quad \epsilon_{ij} \sim N(0, 1)$$

$$y_{ij} = f(x_{ij}, \psi_i) \exp(a \epsilon_{ij}), \quad \epsilon_{ij} \sim N(0, 1)$$

Usually

$$f(x_{ij}, \psi_i) \equiv Cc(t, \psi)$$

i.e. drug concentration as predicted by the structural model

CountData

$$y_{ij} \sim Poisson(\lambda(t_{ij}, \psi_i))$$

$$\lambda(t_{ij}, \psi_i) = \lambda_i$$

$$\lambda(t_{ij}, \psi_i) = \lambda_{0,i} \left(1 - I_{max_i} \frac{f_i(x_{ij}, \psi_i)}{IC50_i + f_i(x_{ij}, \psi_i)} \right)$$

CategoricalData

$$y_{ij} \sim Cat(\pi_1, \pi_2, \dots, \pi_K)$$

$$\text{logit}(P(y_{ij} \leq cat1)) = \theta_1 + \theta_2 f(x_{ij}, \psi_i)$$

TimeToEventData

$$P(y_i > t; \psi_i) = S(t, \psi_i) = \exp(-H(\tau_0, t; \psi_i))$$

$$H(a, b; \psi_i) = \int_a^b h(t, \psi_i) dt, \quad \text{e.g. } h(t, \beta) = \beta \times f(x_{ij}, \psi_i)$$

Mathematical formalism 2

– structural/parameter/covariate/variability models

StructuralModel f

ODE $dAd/dt = -k_a Ad$

$$dAc/dt = k_a Ad - k Ac, \quad C = Ac/V$$

Algebraic Eq. $C = \frac{D}{V} \frac{k}{k_a - k} (e^{-k t} - e^{-k_a t})$

PK macros compartment(amount= Ac , volume= V)
 oral(k_a)
 elimination(k)

ParameterModel ψ_i

Structured Type $h(\psi_i) = h(\psi_{pop}) + \beta c_i + \eta$

Distribution Type $h(\psi_i) \sim N(h(\psi_{pop}) + \beta c_i, \omega^2)$

Equation Type $h(\psi_i) = H(\beta, c, \psi_{pop}, \eta)$

$$\log(V_i) = \log(V_{pop}) + \beta \log WT70 + \eta_V$$

$$\log(V_i) \sim N(\log(V_{pop}) + \beta \log WT70, \omega_V^2)$$

$$V_i = V_{pop} (WT/70)^\beta \exp(\eta_V) \quad \eta_V \sim N(0, \omega_V^2)$$

CovariateModel C_i

Distribution $WT \sim LN(\mu_{WT}, \sigma_{WT}^2)$

$$\log WT70 = \log(WT/70)$$

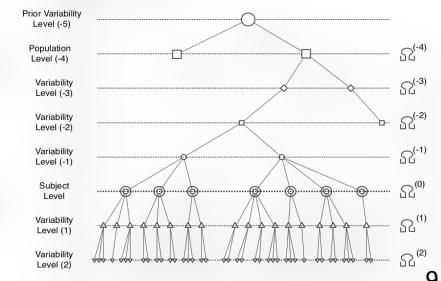
Transformation $linear : WT$ versus $Age/Time$

New covariate $CL = \frac{(180 - Age) \times W \times 0.85}{72 \times Scr}$

VariabilityModel η, ϵ

Hierarchical structures for

- Parameter related variability
- Residual error related variability



Selected models 1

Count data models

- Conway-Maxwell-Poisson (λ, ν)
- Double Poisson (μ, ϕ)
- Generalized Negative Binomial (θ, β, m)
- Generalized Poisson
 - Generalized Poisson 1 (θ, δ)
 - Generalized Poisson 2 (μ, δ)
 - Generalized Poisson 3 (μ, α)
- Inverse Binomial (k, p)
- Negative Binomial
 - Negative Binomial 1(r, p)
 - Negative Binomial 2 (λ, τ)
 - Negative Binomial 3 (μ, k)
 - Negative Binomial 4 (r, p)
 - Negative Binomial 5 (α, β)
- Poisson (λ)
- Zero-Inflated Negative Binomial (λ, τ, p_0)
- Zero-Inflated Generalized Poisson (μ, α, p_0)
- Zero-Inflated Poisson (λ, π)

Drug-drug interaction models – ‘open’ form models

$$\frac{d_1}{\mu_1 \left[\frac{E}{E_c - E} \right]^{1/m_1}} + \frac{d_2}{\mu_2 \left[\frac{E}{E_c - E} \right]^{1/m_2}} + \frac{\alpha d_1 d_2}{\mu_1 \mu_2 \left[\frac{E}{E_c - E} \right]^{(1/2m_1+1/2m_2)}} = 1$$

A pharmacodynamic model for a combined effect, E, a function of two drug doses, d_1 and d_2 , which does not have a closed form.

Indian J Pharm Sci. 2014 Mar-Apr; 76(2): 107–115.

PMCID: PMC4023279

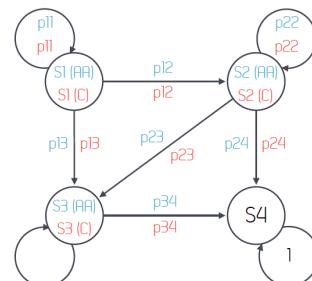
Markov models

- S1 – vulnerable
- S2 – HIV infective
- S3 – clinical AIDS persons
- S4 – death

Markov Chain Modelling Analysis of HIV/AIDS Progression: A Race-based Forecast in the United States

S. Lee, J. Ko,¹ Xi Tan,² Isha Patel,² R. Balkrishnan,² and J. Chang^{3,*}

model and the according transition matrix which is *Race* dependent.

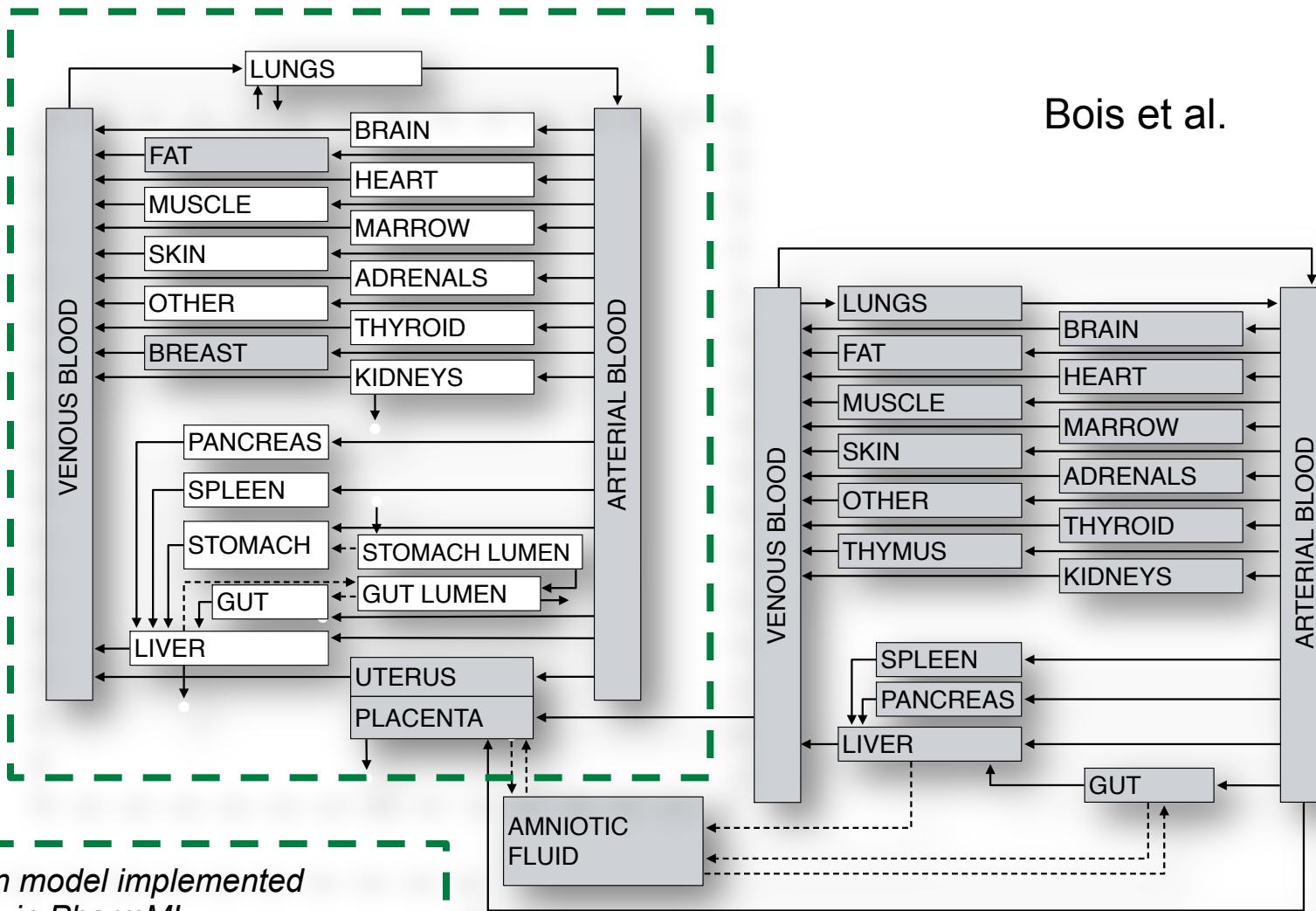


	S1	S2	S3	S4	P(row)
S1	0.99893 0.9998787	0.00066 0.000073	0.00041 0.000048	0	=1
S2	0 0.97033	0.00005 0.000015	0.02962 0.0227725	0 0.04224	=1
S3	0 0	0 0.95776	0.9693415 0.0306585	0 1	=1
S4	0 0	0 0	0 0	1	=1

Figure 3.2: Markov model of HIV/AIDS progression.

Selected models 2 – (pregnant) woman PBPK model

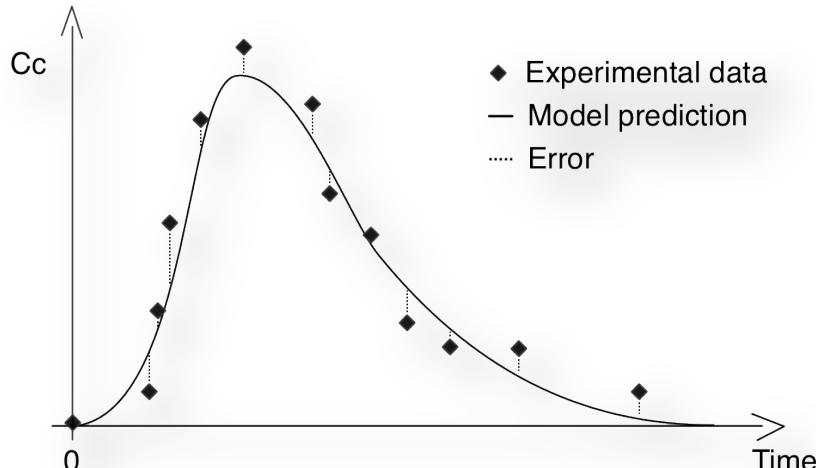
Bois et al.



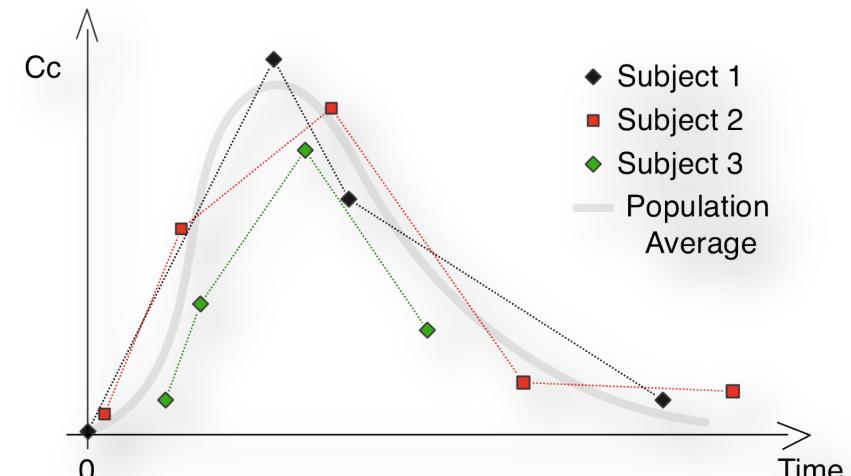
Woman model implemented
already in PharmML

PharmML can handle single subject and population data

Individual data



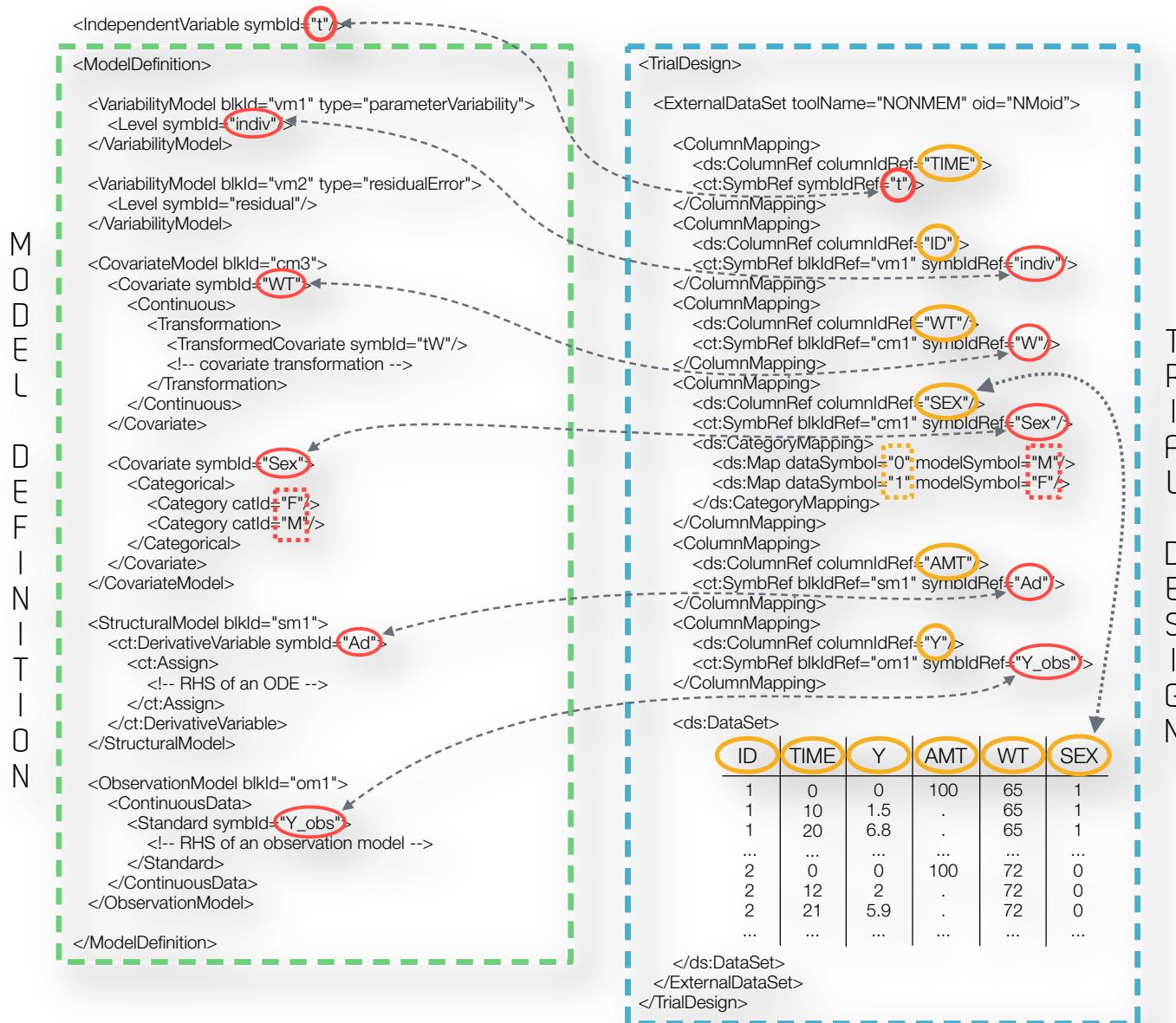
Multiple subject data



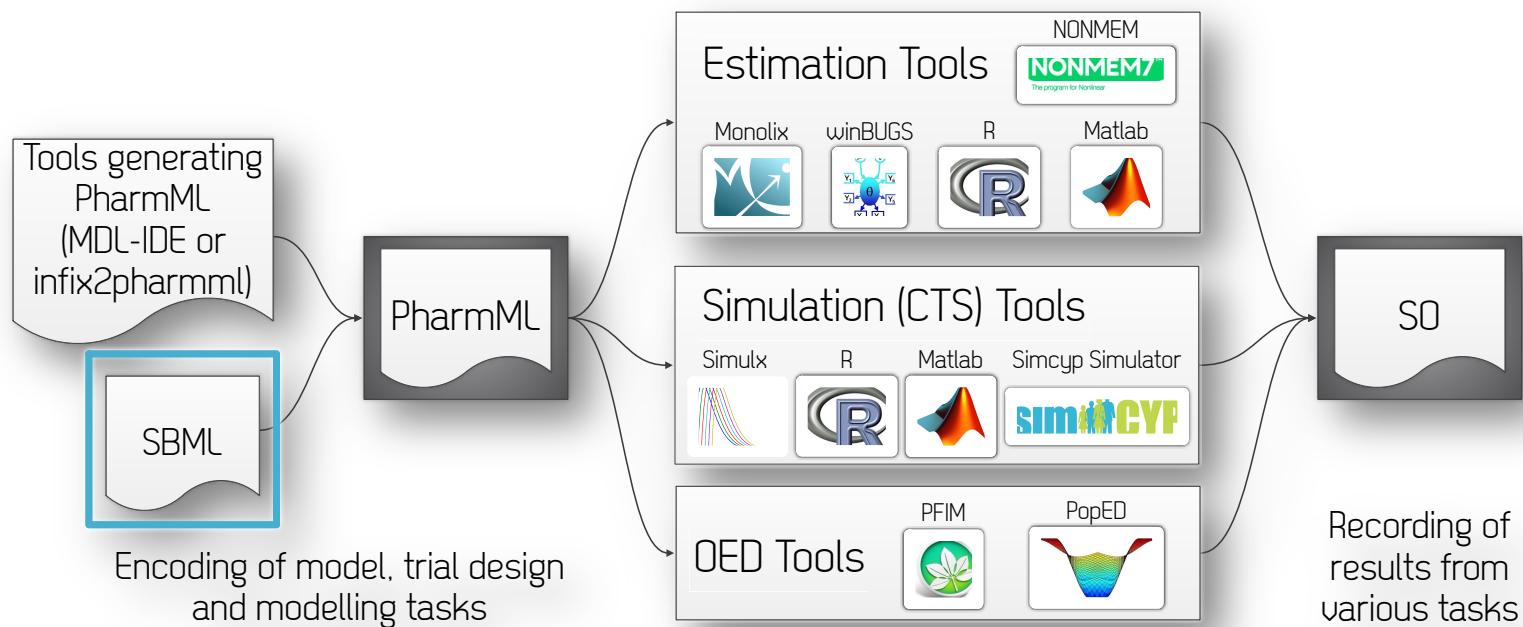
$$\underbrace{y_j}_{\text{Experimental data}} = \underbrace{f(t_j, \phi)}_{\text{Model prediction}} + \underbrace{g(t_j; \phi, \xi) \epsilon_j}_{\text{Error}} \quad 1 \leq j \leq n$$

$$\underbrace{y_{ij}}_{\text{Experimental data}} = \underbrace{f(x_{ij}, \psi_i)}_{\text{Model prediction}} + \underbrace{g(x_{ij}; \psi_i, \xi) \epsilon_{ij}}_{\text{Error}} \quad 1 \leq i \leq N, \quad 1 \leq j \leq n_i$$

Model – data mapping

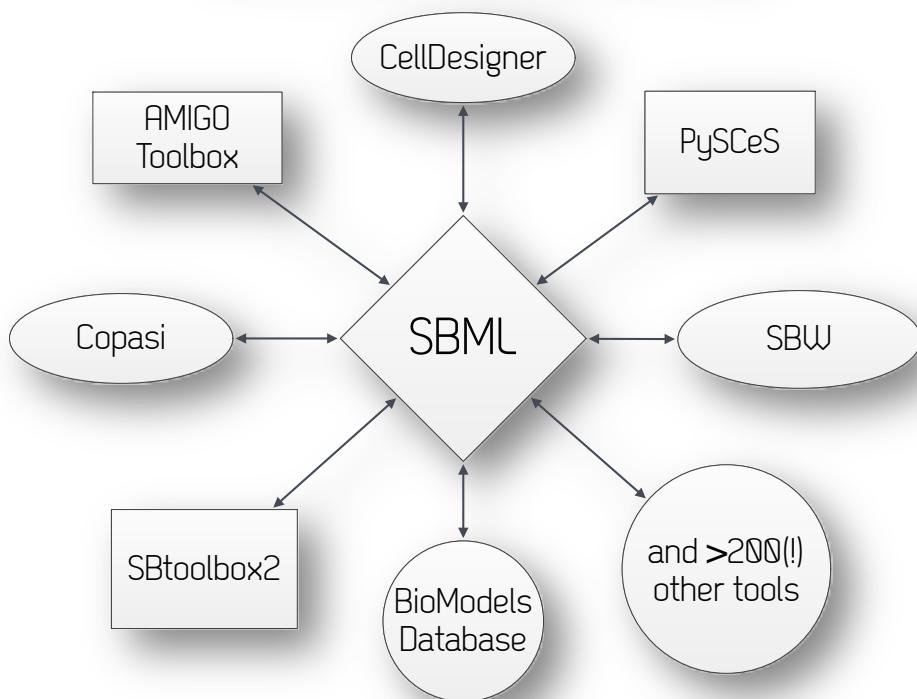


SBML in DDMoRe environment



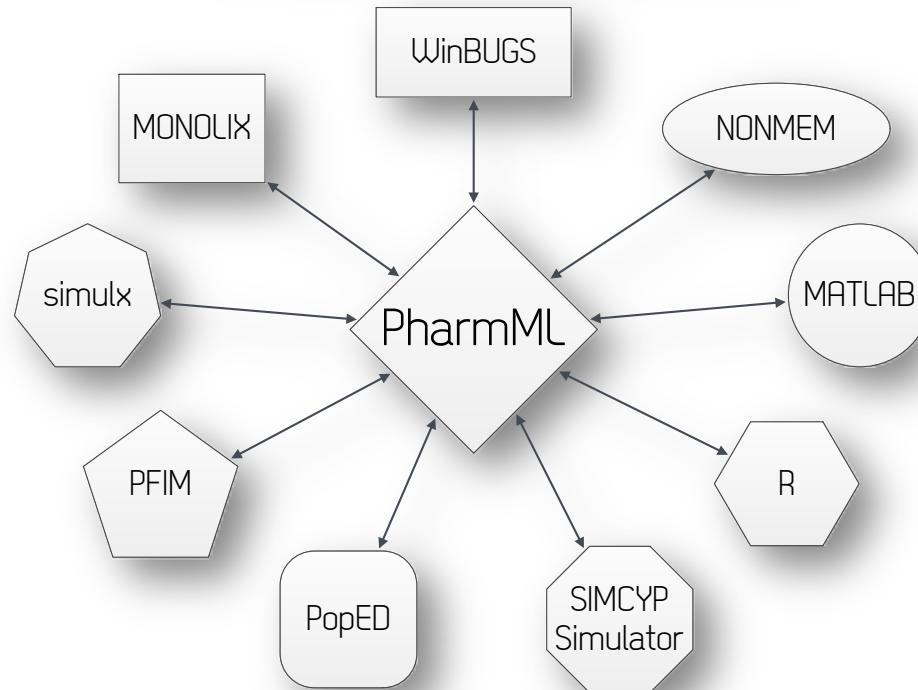
Interoperability in SB/QSP and PMX ca. 1 year ago

Interoperability in Systems Biology



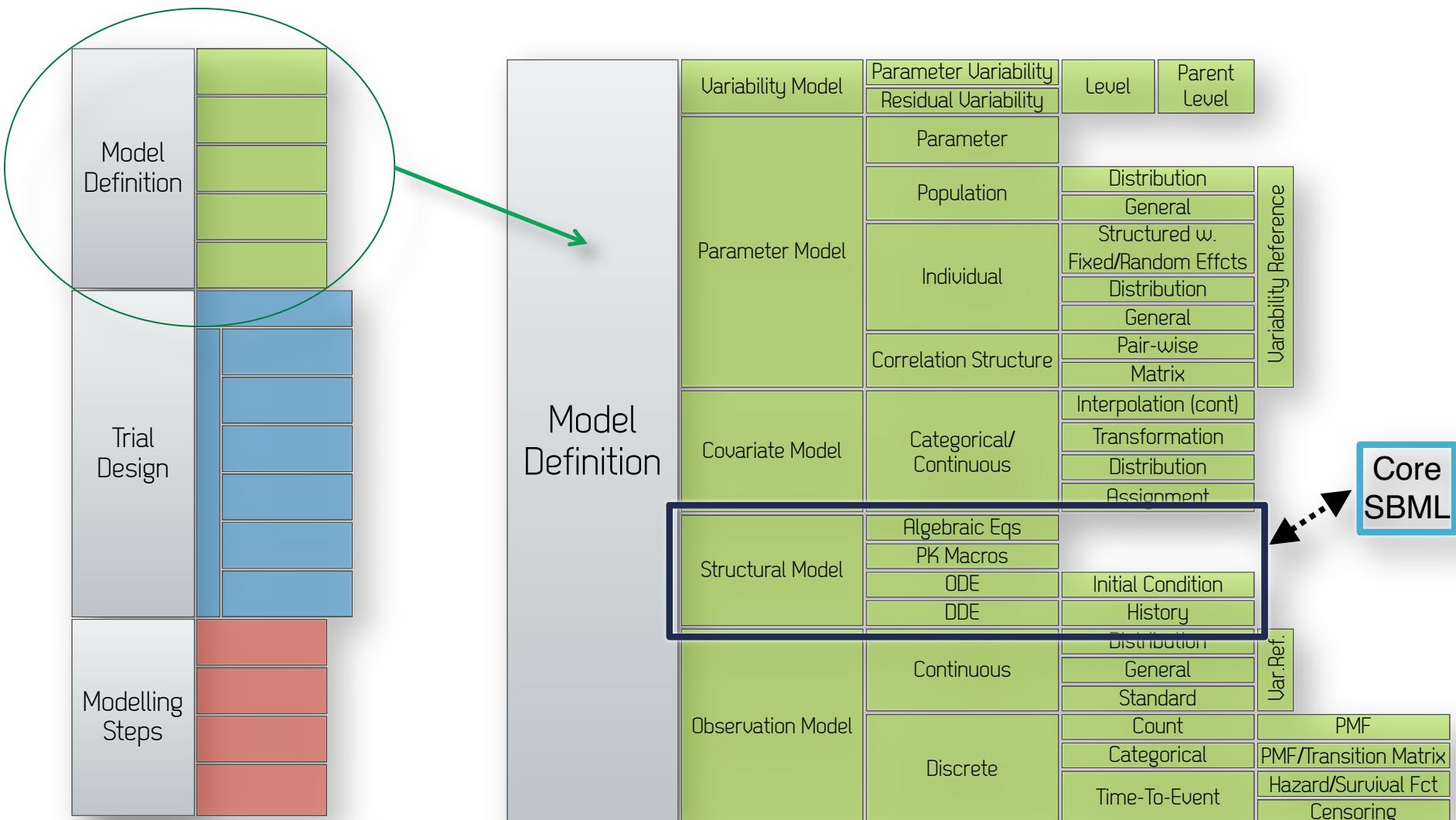
Selected SBML compatible software tools

Interoperability in Pharmacometrics



Current DDMoRe target tools

Where PharmML and core SBML overlap



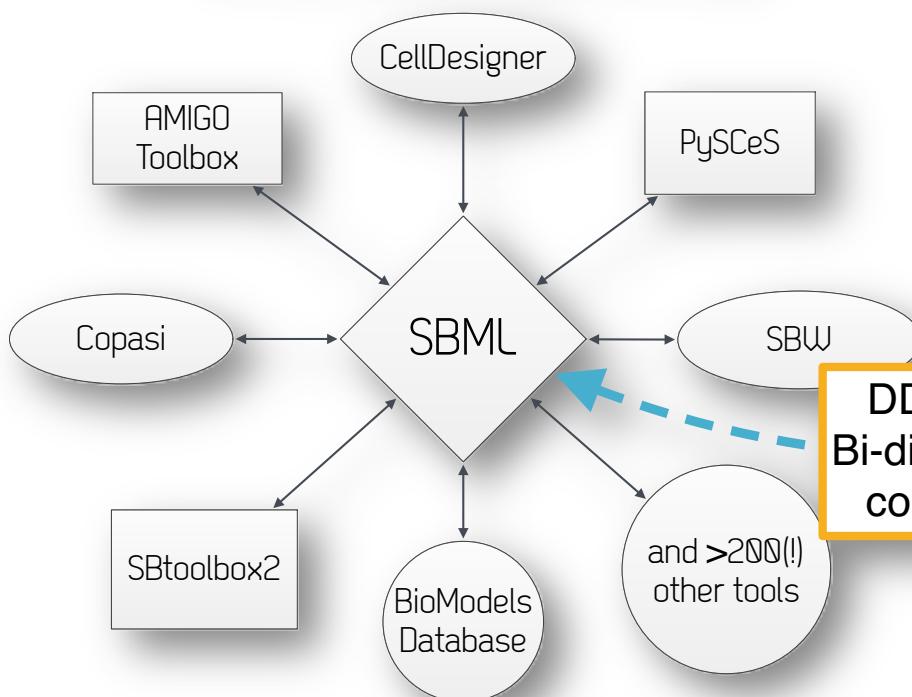
Structure of PharmML:
model definition, trial design
and modelling steps

DDMoRe (Cyprotex & SBML) provides bi-directional
translator between PharmML and SBML

Interoperability in SB/QSP and PMX today

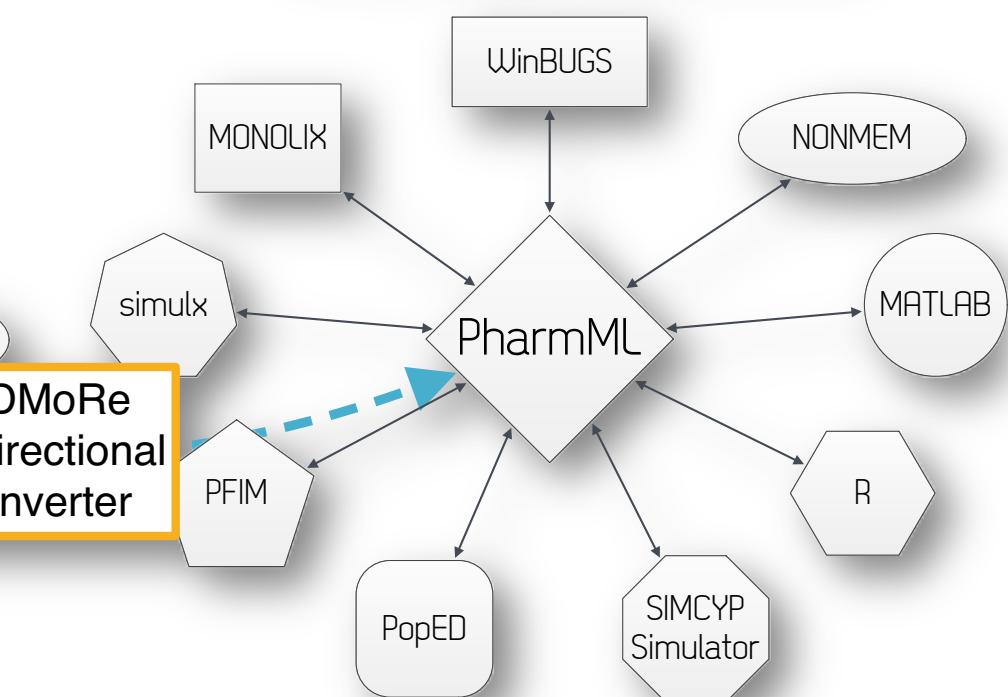


Interoperability in Systems Biology



Selected SBML compatible software tools

Interoperability in Pharmacometrics

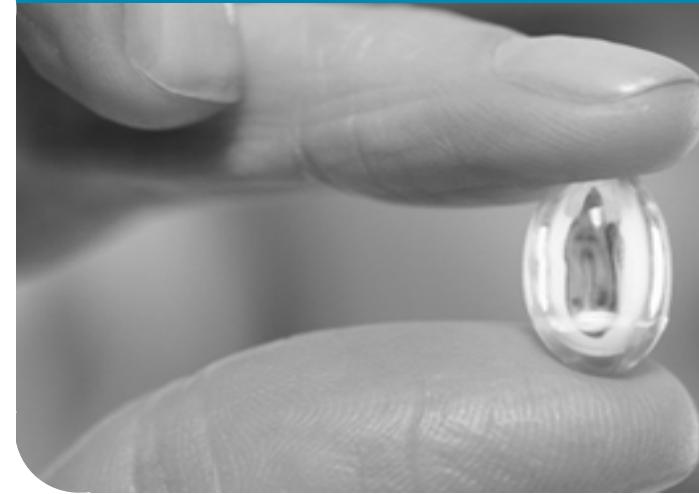


Current DDMoRe target tools

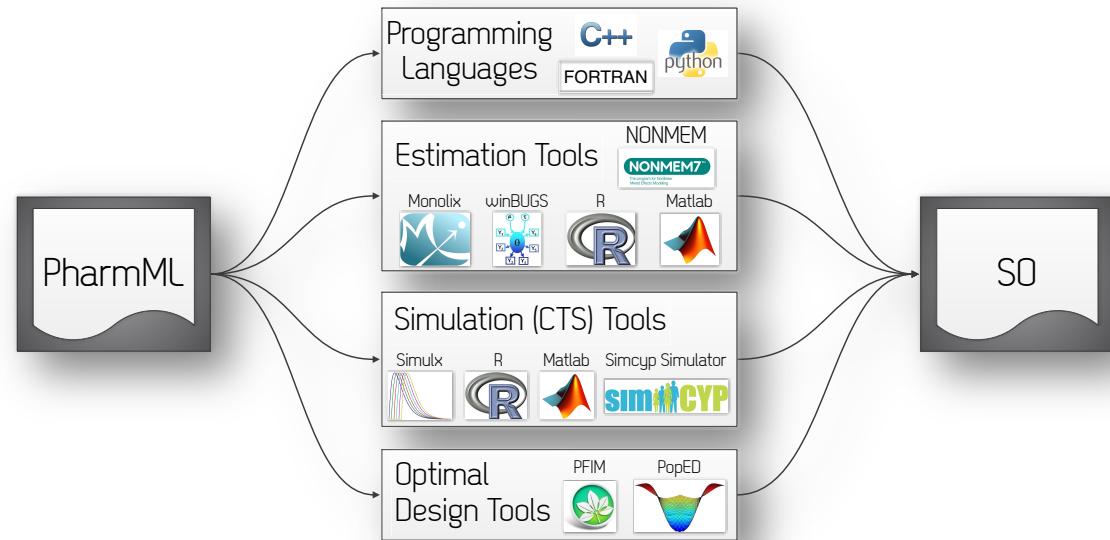
SB – QSP – PMX: data types and objectives

Clinical phase	<i>Preclinical</i>	<i>Early Clinical</i>	<i>Late Clinical</i>
Discipline	Systems Biology	Quantitative Systems Pharmacology	Translational PKPD
Data type		Frequently sampled single subject data	(Sparse) Population data
Main objective	Drug - Target	Drug - Pathway/Tissue	Drug/PBPK - Organism
Model exchange formats	SBML		PharmML

Thanks to the available **converters between SBML and PharmML**, these two exchange formats have the potential to cover the entire spectrum of M&S in Systems Biology, Quantitative Systems Pharmacology and Pharmacometrics.



SO – Standard Output

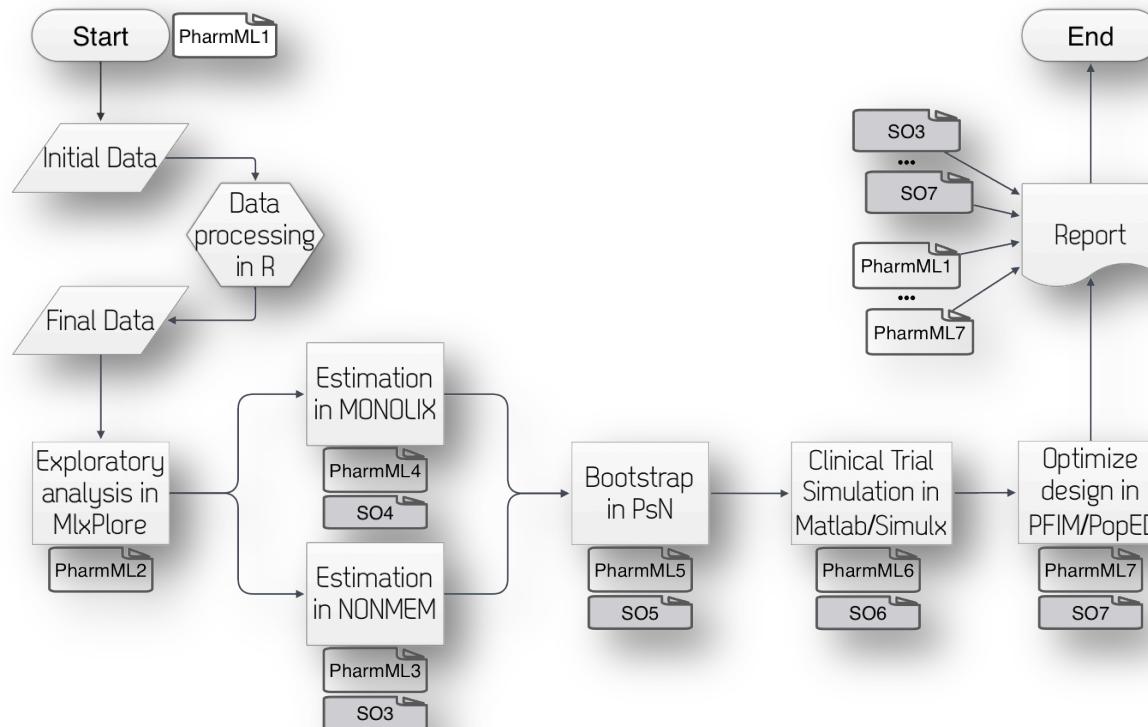


On behalf of the DDMoRe consortium

SO - storing and retrieving typical M&S results

The Standard Output (SO) represents a **tool-independent format** for storing typical output produced in a PMx/QSP workflow. It aims at:

- providing a **flexible storage structure** for typical results of M&S analyses performed in any DDMoRe target tool;
- enabling **effective data flow across tasks** to ensure optimal interactions among software tools and, then, extend the modeling capabilities of the workflow;
- facilitating **information retrieval for post-processing and reporting**, by allowing immediate access to M&S results.



SO structure (latest spec...)



INTERNAL RELEASE

Standard Output (SO)

Format Specification for Version 0.3.1

Nadia TERRANOVA¹, Marc LAVIELLE², Mike K SMITH³, Emmanuelle COMETS⁴, Kajsa HARLING⁵, Rikard NORDGREN⁵, Duncan EDWARDS⁶, Andrew HOOKER⁵, Celine SARR⁷, France MENTRÉ⁴, Florent YVON⁸, Maciej J SWAT⁸

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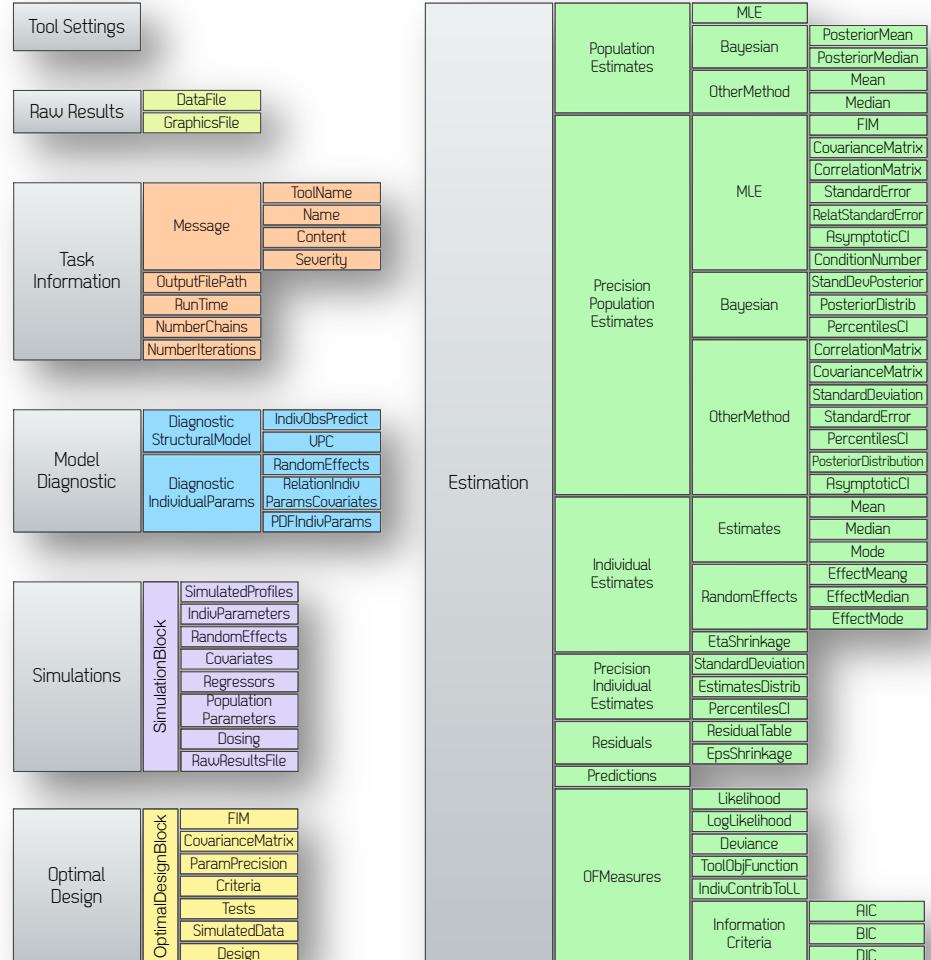
⁶Simecyp (a Certara company), Sheffield, UK

⁷SGS Exprim NV, Mechelen, Belgium

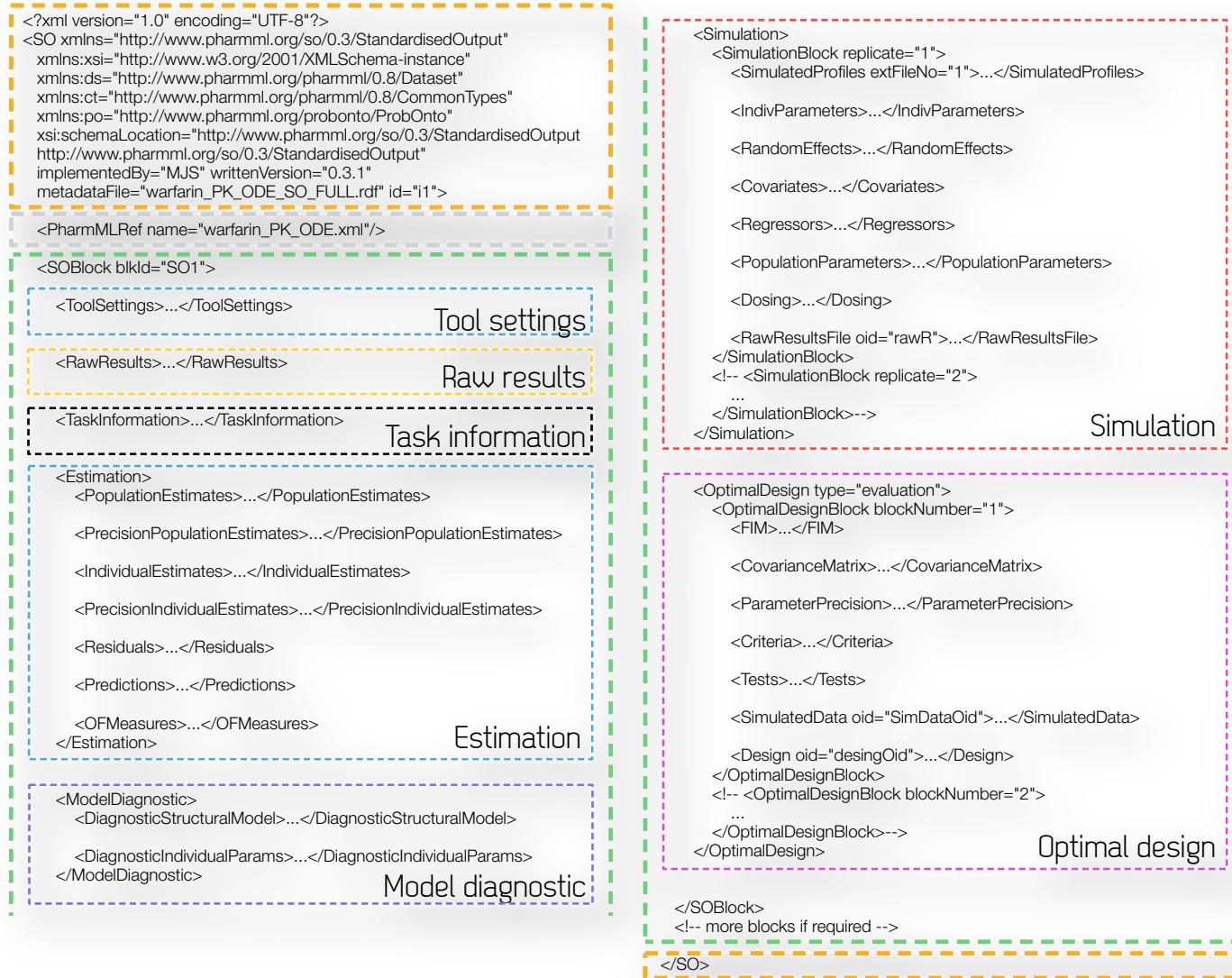
⁸EMBL - European Bioinformatics Institute, Cambridge, UK,



April 14, 2016



Standard Output (SO) – Structure



Bioinformatics

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Oxford Journals, Science & Mathematics, Bioinformatics, Advance Access, 10.1093/bioinformatics/btw170

ProbOnto: ontology and knowledge base of probability distributions

Maciej J. Swat^{1,*}, Pierre Grenon² and Sarala Wimalaratne¹

+ Author Affiliations

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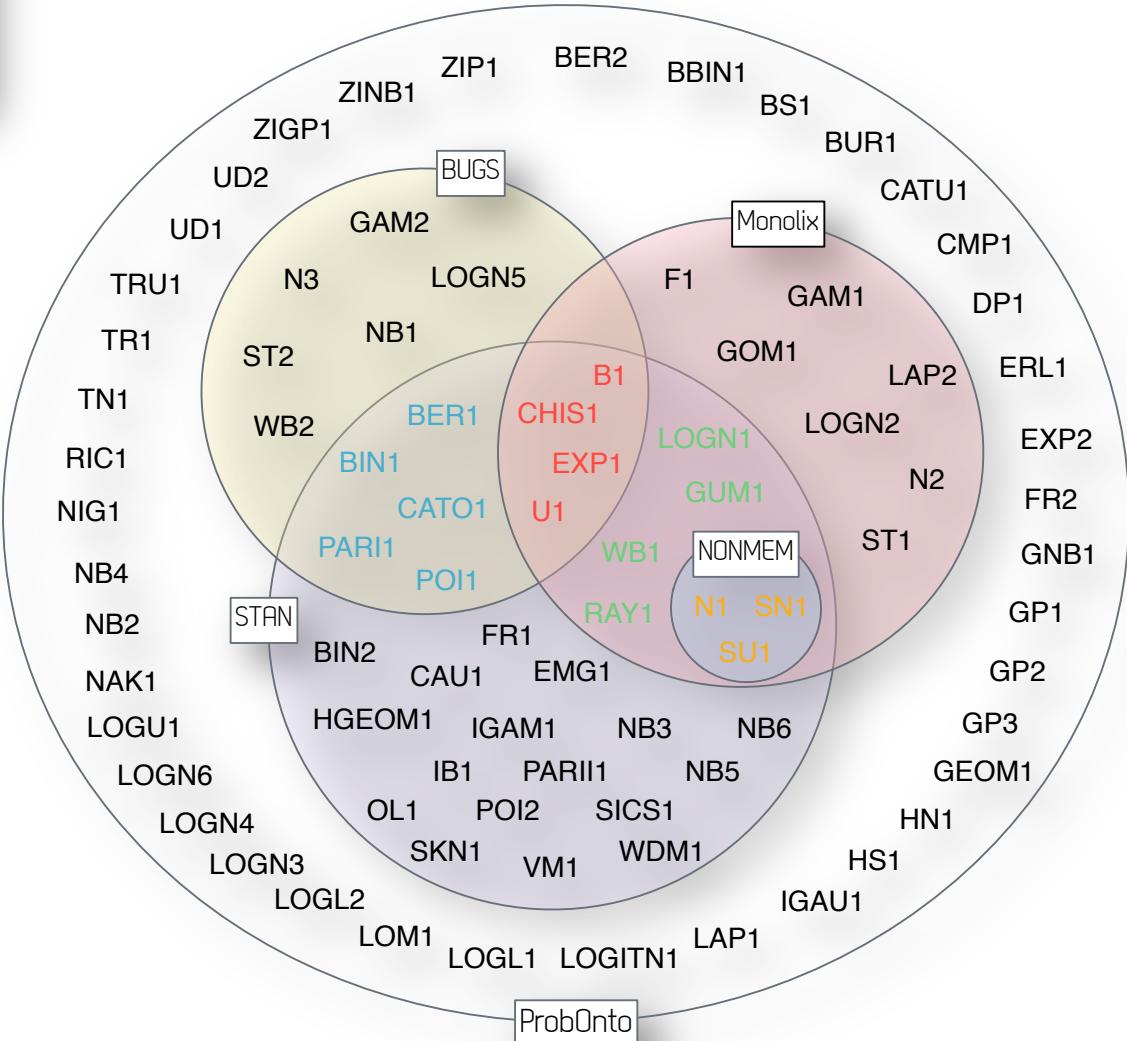
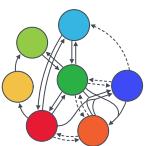
CORRECTED PROOF

This Article

Bioinformatics (2016)
 10.1093/bioinformatics/btw170
 First published online: April 3, 2016

ProbOnto

Ontology and Knowledge Base of Probability Distributions



URL: probonto.org

Re-parameterization relationships

- Interoperability background: various tools support different parameterisations, e.g. *log-normal distribution*
- When moving model from tool to tool
→ re-parameterisation is needed
- ProbOnto stores the formulas

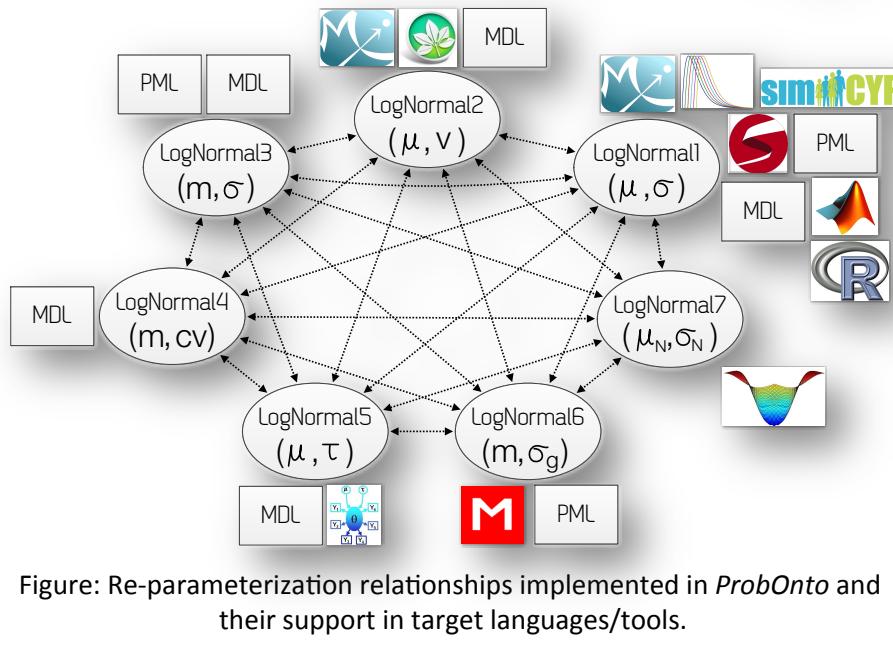
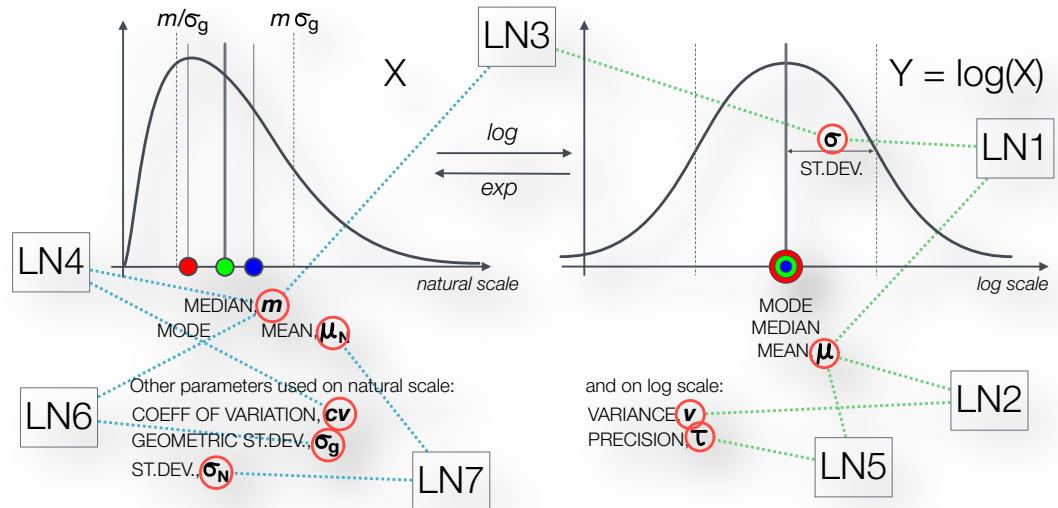


Figure: Re-parameterization relationships implemented in *ProbOnto* and their support in target languages/tools.

Available parameterisations are

- LogNormal1(μ, σ) with *mean*, μ , and *standard deviation*, σ , both on the log-scale,

$$P(x; \mu, \sigma) = \frac{1}{x\sigma\sqrt{2\pi}} \exp\left[-\frac{-(\log x - \mu)^2}{2\sigma^2}\right]$$
- LogNormal2(μ, v) with *mean*, μ , and *variance*, v , both on the log-scale,

$$P(x; \mu, v) = \frac{1}{x\sqrt{v}\sqrt{2\pi}} \exp\left[-\frac{-(\log x - \mu)^2}{2v}\right]$$
- LogNormal3(m, σ) with *median*, m , on the natural scale and *standard deviation*, σ , on the log-scale,

$$P(x; m, \sigma) = \frac{1}{x\sigma\sqrt{2\pi}} \exp\left[-\frac{-[\log(x/m)]^2}{2\sigma^2}\right]$$
- LogNormal4(m, cv) with *median*, m , and *coefficient of variation*, cv , both on the natural scale,

$$P(x; m, cv) = \frac{1}{x\sqrt{\log(cv^2 + 1)}\sqrt{2\pi}} \exp\left[-\frac{-[\log(x/m)]^2}{2\log(cv^2 + 1)}\right]$$
- LogNormal5(μ, τ) with *mean*, μ , and *precision*, τ , both on the log-scale,

$$P(x; \mu, \tau) = \sqrt{\frac{\tau}{2\pi}} \frac{1}{x} \exp\left[-\frac{\tau}{2}(\log x - \mu)^2\right]$$
- LogNormal6(m, σ_g) with *median*, m , and *geometric st. deviation*, σ_g , both on the natural scale,

$$P(x; m, \sigma_g) = \frac{1}{x \log(\sigma_g)\sqrt{2\pi}} \exp\left[-\frac{-[\log(x/m)]^2}{2\log^2(\sigma_g)}\right]$$
- NEW LogNormal7(μ_N, σ_N) with *mean*, μ_N , and *st. deviation*, σ_N , both on the natural scale,

$$P(x; \mu_N, \sigma_N) = \frac{1}{x\sqrt{2\pi \log(1 + \sigma_N^2/\mu_N^2)}} \exp\left(-\frac{[\log(x) - \log\left(\frac{\mu_N}{\sqrt{1 + \sigma_N^2/\mu_N^2}}\right)]^2}{2\log(1 + \sigma_N^2/\mu_N^2)}\right).$$

LN1...LN7 re-parameterisations

- LN1 relationships

- $\text{LN1}(\mu, \sigma) \rightarrow \text{LN2}(\mu, v) : \sigma \rightarrow v = \sigma^2$
 $\text{LN2}(\mu, v) \rightarrow \text{LN1}(\mu, \sigma) : \sigma = \sqrt{v}$
- $\text{LN1}(\mu, \sigma) \rightarrow \text{LN3}(m, \sigma) : m = \exp(\mu)$
 $\text{LN3}(m, \sigma) \rightarrow \text{LN1}(\mu, \sigma) : \mu = \log(m)$
- $\text{LN1}(\mu, \sigma) \rightarrow \text{LN4}(m, cv) : m = \exp(\mu); \quad cv = \sqrt{\exp(\sigma^2) - 1}$
 $\text{LN4}(m, cv) \rightarrow \text{LN1}(\mu, \sigma) : \mu = \log(m); \quad \sigma = \sqrt{\log(cv^2 + 1)}$
- $\text{LN1}(\mu, \sigma) \rightarrow \text{LN5}(\mu, \tau) : \tau = 1/\sigma^2$
 $\text{LN5}(\mu, \tau) \rightarrow \text{LN1}(\mu, \sigma) : \sigma = 1/\sqrt{\tau}$
- $\text{LN1}(\mu, \sigma) \rightarrow \text{LN6}(m, \sigma_g) : m = \exp(\mu); \quad \sigma_g = \exp(\sigma)$
 $\text{LN6}(m, \sigma_g) \rightarrow \text{LN1}(\mu, \sigma) : \mu = \log(m); \quad \sigma = \log(\sigma_g)$
- $\text{LN1}(\mu, \sigma) \rightarrow \text{LN7}(\mu_N, \sigma_N) : \mu_N = \exp\left(\mu + \frac{1}{2}\sigma^2\right); \quad \sigma_N = \exp\left(\mu + \frac{1}{2}\sigma^2\right)\sqrt{\exp(\sigma^2) - 1}$
 $\text{LN7}(\mu_N, \sigma_N) \rightarrow \text{LN1}(\mu, \sigma) : \mu = \log\left(\mu_N/\sqrt{1 + \sigma_N^2/\mu_N^2}\right); \quad \sigma = \sqrt{\log(1 + \sigma_N^2/\mu_N^2)}$

- remaining LN2 relationships

- $\text{LN2}(\mu, v) \rightarrow \text{LN3}(m, \sigma) : m = \exp(\mu); \quad \sigma = \sqrt{v}$
 $\text{LN3}(m, \sigma) \rightarrow \text{LN2}(\mu, v) : \mu = \log(m); \quad v = \sigma^2$
- $\text{LN2}(\mu, v) \rightarrow \text{LN4}(m, cv) : m = \exp(\mu); \quad cv = \sqrt{\exp(v) - 1}$
 $\text{LN4}(m, cv) \rightarrow \text{LN2}(\mu, v) : \mu = \log(m); \quad cv \rightarrow v = \log(cv^2 + 1)$
- $\text{LN2}(\mu, v) \rightarrow \text{LN5}(\mu, \tau) : \tau = 1/v$
 $\text{LN5}(\mu, \tau) \rightarrow \text{LN2}(\mu, v) : v = 1/\tau$

- $\text{LN2}(\mu, v) \rightarrow \text{LN6}(m, \sigma_g) : \mu \rightarrow m = \exp(\mu); \quad v \rightarrow \sigma_g = \exp(\sqrt{v})$
 $\text{LN6}(m, \sigma_g) \rightarrow \text{LN2}(\mu, v) : m \rightarrow \mu = \log(m); \quad \sigma_g \rightarrow v = \log(\sigma_g^2)$
- $\text{LN2}(\mu, v) \rightarrow \text{LN7}(\mu_N, \sigma_N) : \mu_N = \exp(\mu + v/2); \quad \sigma_N = \exp(\mu + v/2)\sqrt{\exp(v) - 1}$
 $\text{LN7}(\mu_N, \sigma_N) \rightarrow \text{LN2}(\mu, v) : \mu = \log\left(\mu_N/\sqrt{1 + \sigma_N^2/\mu_N^2}\right); \quad v = \log(1 + \sigma_N^2/\mu_N^2)$

- remaining LN3 relationships

- $\text{LN3}(m, \sigma) \rightarrow \text{LN4}(m, cv) : cv = \sqrt{\exp(\sigma^2) - 1}$
 $\text{LN4}(m, cv) \rightarrow \text{LN3}(m, \sigma) : \sigma = \sqrt{\log(cv^2 + 1)}$
- $\text{LN3}(m, \sigma) \rightarrow \text{LN5}(\mu, \tau) : \mu = \log(m); \quad \tau = 1/\sigma^2$
 $\text{LN5}(\mu, \tau) \rightarrow \text{LN3}(m, \sigma) : m = \exp(\mu); \quad \sigma = 1/\sqrt{\tau}$
- $\text{LN3}(m, \sigma) \rightarrow \text{LN6}(m, \sigma_g) : \sigma_g = \exp(\sigma)$
 $\text{LN6}(m, \sigma_g) \rightarrow \text{LN3}(m, \sigma) : \sigma = \log(\sigma_g)$
- $\text{LN3}(m, \sigma) \rightarrow \text{LN7}(\mu_N, \sigma_N) : \mu_N = m \exp(\sigma^2/2); \quad \sigma_N = m \exp(\sigma^2/2)\sqrt{\exp(\sigma^2) - 1}$
 $\text{LN7}(\mu_N, \sigma_N) \rightarrow \text{LN3}(m, \sigma) : m = \mu_N/\sqrt{1 + \sigma_N^2/\mu_N^2}; \quad \sigma = \sqrt{\log(1 + \sigma_N^2/\mu_N^2)}$

- remaining LN4 relationships

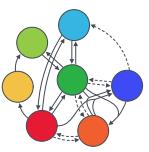
- $\text{LN4}(m, cv) \rightarrow \text{LN5}(\mu, \tau) : \mu = \log(m); \quad \tau = 1/\log(cv^2 + 1)$
 $\text{LN5}(\mu, \tau) \rightarrow \text{LN4}(m, cv) : m = \exp(\mu); \quad cv = \sqrt{\exp(1/\tau) - 1}$
- $\text{LN4}(m, cv) \rightarrow \text{LN6}(m, \sigma_g) : \sigma_g = \exp(\sqrt{\log(cv^2 + 1)})$
 $\text{LN6}(m, \sigma_g) \rightarrow \text{LN4}(m, cv) : cv = \sqrt{\exp(\log^2(\sigma_g)) - 1}$
- $\text{LN4}(m, cv) \rightarrow \text{LN7}(\mu_N, \sigma_N) : \mu_N = m\sqrt{cv^2 + 1}; \quad \sigma_N = m cv \sqrt{cv^2 + 1}$
 $\text{LN7}(\mu_N, \sigma_N) \rightarrow \text{LN4}(m, cv) : m = \mu_N/\sqrt{1 + \sigma_N^2/\mu_N^2}; \quad cv = \sigma_N/\mu_N$

- remaining LN5 relationships

- $\text{LN5}(\mu, \tau) \rightarrow \text{LN6}(m, \sigma_g) : m = \exp(\mu); \quad \sigma_g = \exp(1/\sqrt{\tau})$
 $\text{LN6}(m, \sigma_g) \rightarrow \text{LN5}(\mu, \tau) : \mu = \log(m); \quad \tau = 1/\log^2(\sigma_g)$
- $\text{LN5}(\mu, \tau) \rightarrow \text{LN7}(\mu_N, \sigma_N) : \mu_N = \exp(\mu + 1/(2\tau)); \quad \sigma_N = \exp(\mu + 1/(2\tau))\sqrt{\exp(1/\tau) - 1}$
 $\text{LN7}(\mu_N, \sigma_N) \rightarrow \text{LN5}(\mu, \tau) : m = \log\left(\mu_N/\sqrt{1 + \sigma_N^2/\mu_N^2}\right); \quad \tau = 1/\log(1 + \sigma_N^2/\mu_N^2)$

- remaining LN6 relationships

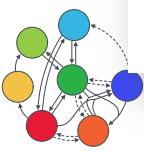
- $\text{LN6}(m, \sigma_g) \rightarrow \text{LN7}(\mu_N, \sigma_N) : \mu_N = m \exp\left(\frac{1}{2}\log^2(\sigma_g)\right); \quad \sigma_N = m \exp\left(\frac{1}{2}\log^2(\sigma_g)\right)\sqrt{\exp[\log^2(\sigma_g)] - 1}$
 $\text{LN7}(\mu_N, \sigma_N) \rightarrow \text{LN6}(m, \sigma_g) : m = \mu_N/\sqrt{1 + \sigma_N^2/\mu_N^2}; \quad \sigma_g = \exp\left(\sqrt{\log(1 + \sigma_N^2/\mu_N^2)}\right)$



ProbOnto – coverage of univariates

Distribution		Parameters		
Code name	Symbol	Code name	Symbol	Code name
<i>Discrete Univariate</i>				
Bernoulli11	p	probability	—	—
Bernoulli12	α	logitProbability	—	—
BetaBinomial1	n	numberOfTrials	α	alpha
			β	beta
Binomial1	n	numberOfTrials	p	probability
Binomial2	n	numberOfTrials	α	logitProbability
CategoricalOrdered1	p_1, \dots, p_k	categoryProb	—	—
CategoricalNonordered1	p_1, \dots, p_k	categoryProb	—	—
ConwayMaxwellPoisson1	λ	rate	ν	rateOfDecay
DoublePoisson1	μ	rate	ϕ	dispersion
GeneralizedNegativeBinomial1	θ	theta	β	beta
			m	m
GeneralizedPoisson1	θ	rate	δ	dispersion
GeneralizedPoisson2	μ	mean	δ	dispersion
GeneralizedPoisson3	μ	mean	α	dispersion
Geometric1	p	probability	—	—
Hypergeometric1	N	populationSize	K	numberOfSuccesses
			n	numberOfTrials
InverseBinomial1	k	index	p	probability
NegativeBinomial1	r	numberOfSuccesses	p	probability
NegativeBinomial2	λ	rate	τ	overdispersion
NegativeBinomial3	μ	mean	ϕ	index
NegativeBinomial4	r	numberOfFailures	p	probability
NegativeBinomial5	α	shape	β	inverseScale
NegativeBinomial6	η	logMean	ϕ	dispersion
OrderedLogistic1	c_1, \dots, c_{K-1}	cutpoints	η	predictor
Poisson1	λ	rate	—	—
Poisson2	α	logRate	—	—
UniformDiscrete1	a	minimum	b	maximum
			n	numberOfValues
UniformDiscrete2	$a = 0$	minimum	n	numberOfValues
ZeroInflatedNegativeBinomial1	λ	rate	τ	overdispersion
			p_0	probabilityOfZero
ZeroInflatedGeneralizedPoisson1	μ	mean	α	dispersion
			p_0	probabilityOfZero
ZeroInflatedPoisson1	λ	rate	π	probabilityOfZero
<i>Continuous Univariate</i>				
Beta1	α	alpha	β	beta
BirnbaumSaunders1	α	scale	γ	shape
Burr1	α	scale	c	shape1
			k	shape2
Cauchy1	x_0	location	γ	scale
ChiSquared1	k	degreesOfFreedom	—	—
Erlang1	b	scale	c	shape
Exponential1	λ	rate	—	—
Exponential2	β	mean	—	—
ExponentiallyModifiedGaussian1	μ	mean	σ	stdev
			λ	rate
F1	n_1	numerator	n_2	denominator
Frechet1	α	shape	σ	scale
Frechet2	α	shape	σ	scale
			m	locationOfMinimum
Gamma1	k	shape	θ	scale
Gamma2	r	shape	μ	rate
GeneralizedGamma1	a	scale	d	shape1
			p	shape2

GeneralizedGamma2	a	location	b	scale
GeneralizedGamma3	c	shape1	k	shape2
	r	scale	μ	shape1
Gompertz1	η	shape	b	scale
Gumbel1	μ	location	β	scale
HalfNormal1	θ	inverseScale	—	—
HalfNormal2	μ	location	σ	scale
	—	—	—	—
HyperbolicSecant1	α	shape	β	scale
InverseGamma1	λ	shape	μ	mean
InverseGaussian1	μ	location	b	scale
Laplace1	μ	location	τ	tau
Laplace2	μ	location	s	scale
Logistic1	μ	location	τ	inverseScale
Logistic2	μ	location	σ	scale
LogNormal1	α	scale	β	shape
LogNormal2	λ	scale	κ	shape
LogNormal3	m	median	σ	stdevLog
LogNormal4	m	median	cv	coefVar
LogNormal5	μ	meanLog	σ	precision
LogNormal6	m	median	σ_g	geomStdev
LogNormal7	μ_N	mean	σ_N	stdev
LogUniform1	min	minimum	max	maximum
Lomax1	λ	scale	α	shape
Nakagami1	m	shape	Ω	spread
Normal1	μ	mean	σ	stdev
Normal2	μ	mean	v	var
Normal3	μ	mean	τ	precision
NormalInverseGamma1	μ	mean	λ	lambda
	α	alpha	β	beta
ParetoTypeII1	x_m	scale	α	shape
ParetoTypeIII1	μ	location	λ	scale
			α	tailIndex
Rayleigh1	σ	scale	—	—
Rice1	ν	noncentrality	σ	scale
ScaledInverseChiSquare1	ν	degreesOfFreedom	σ	scale
SkewNormal1	μ	location	σ	scale
			α	shape
StandardNormal1	$\mu=0$	mean	$\sigma=1$	stdev
StandardUniform1	$a=0$	minimum	$b=1$	maximum
StudentT1	ν	degreesOfFreedom	—	—
StudentT2	μ	mean	τ	scale
			ν	degreesOfFreedom
Trapezoidal1	a	lowerBound	b	levelStart
	c	levelEnd	d	upperBound
Triangular1	a	lowerLimit	b	upperLimit
			c	shape
TruncatedNormal1	μ	mean	σ	stdev
	a	lowerBound	b	upperBound
Uniform1	a	minimum	b	maximum
VonMises1	μ	location	κ	concentration
Weibull1	λ	scale	k	shape
Weibull2	λ	lambda	v	shape
WienerDiffusionModel1	α	boundSeparation	β	initialBias
	δ	driftRate	τ	nondecisionTime



Application of ProbOnto in PharmML

```

<!-- if (k > 0)
    log(P(Y=k)) = log(1-p0) - lambda + k*log(lambda) - factln(k)
  else
    log(P(Y=k)) = log(p0 + (1-p0)*exp(-lambda))
end -->

<PMF transform="log">
<math:LogicBinop op="eq">
  <ct:SymbRef symbIdRef="y"/>
  <ct:SymbRef symbIdRef="k"/>
</math:LogicBinop>
<ct:Assign>
  <math:Piecewise>
    <math:Piece>
      <!-- aux = log(1-p0) - lambda + k*log(lambda) - factln(k) -->
      <math:Binop op="minus">
        <math:Unop op="log">
          <math:Binop op="minus">
            <ct:Real></ct:Real>
            <ct:SymbRef blkIdRef="pm1" symbIdRef="p0"/>
          </math:Binop>
        </math:Unop>
      <math:Binop op="plus">
        <ct:SymbRef blkIdRef="pm1" symbIdRef="lambda"/>
        <math:Binop op="minus">
          <math:Binop op="times">
            <ct:SymbRef symbIdRef="k"/>
            <math:Unop op="log">
              <math:Binop op="minus">
                <ct:SymbRef blkIdRef="pm1" symbIdRef="lambda"/>
              </math:Binop>
            </math:Unop>
            <math:Unop op="factln">
              <ct:SymbRef symbIdRef="k"/>
            </math:Unop>
          </math:Binop>
        </math:Unop>
      <math:Binop op="times">
        <math:Binop op="gt">
          <ct:SymbRef symbIdRef="k"/>
          <ct:Real></ct:Real>
        </math:Binop>
      </math:Binop>
    </math:Piece>
    <math:Piece>
      <!-- aux = log(p0 + (1-p0)*exp(-lambda)) -->
      <math:Unop op="log">
        <math:Binop op="plus">
          <ct:SymbRef blkIdRef="pm1" symbIdRef="p0"/>
          <math:Binop op="times">
            <math:Binop op="minus">
              <ct:Real></ct:Real>
              <ct:SymbRef blkIdRef="pm1" symbIdRef="p0"/>
            </math:Binop>
            <math:Unop op="exp">
              <math:Unop op="minus">
                <ct:SymbRef blkIdRef="pm1" symbIdRef="lambda"/>
              </math:Unop>
            </math:Unop>
          </math:Binop>
        </math:Unop>
      </math:Binop>
    </math:Piece>
  </math:Piecewise>
</ct:Assign>
</PMF>

```

PMF implemented explicitly → error prone process and limited interoperability

Problem description:

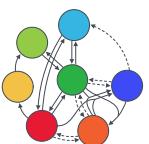
Count data models require the specification of the according PMF (probability mass function), here e.g. for the Zero-inflated Poisson

```

<PMF>
  <Distribution>
    <po:ProbOnto name="ZeroInflatedPoisson1">
      <po:Parameter name="rate">
        <ct:Assign>
          <ct:SymbRef blkIdRef="pm1" symbIdRef="lambda"/>
        </ct:Assign>
      </po:Parameter>
      <po:Parameter name="probabilityOfZero">
        <ct:Assign>
          <ct:SymbRef blkIdRef="pm1" symbIdRef="p0"/>
        </ct:Assign>
      </po:Parameter>
    </po:ProbOnto>
  </Distribution>
</PMF>

```

PMF implemented using ProbOnto → full interoperability by using the code names of the distribution and its parameters



Conclusions

PharmML and SO cover both *model definition* and *tool output* and have the potential to improve the way modelers work today by

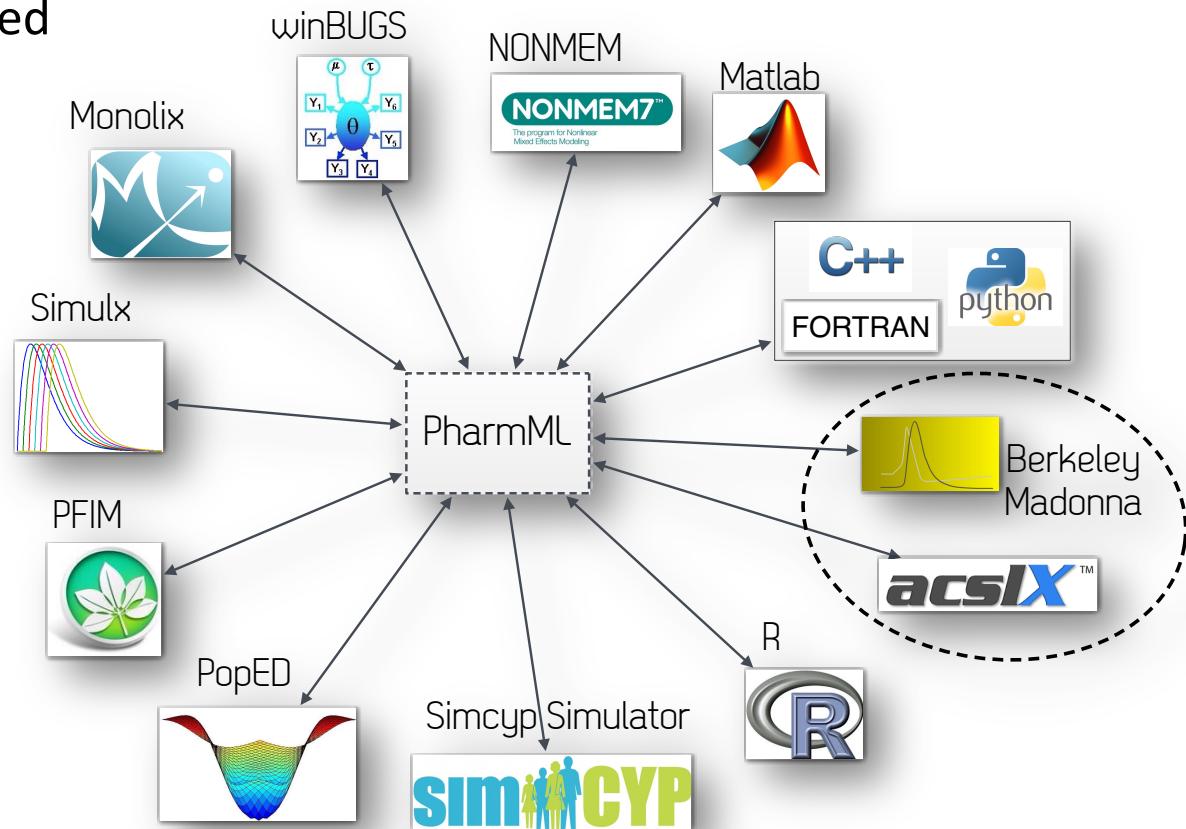
- Facilitating smooth and lossless transmission of models between tools.
- Enabling complex workflows based on standard model and output definition.
- Improving reproducibility of research.
- Easier reporting and bug tracking.
- Improving interaction with regulatory agencies.
- Facilitating the use of existing models, see e.g. BioModels database of computational models of biological processes (SBML).
- Stimulating development of new tools and methods.

ProbOnto

- Facilitates encoding, and annotation of statistical models

Future directions

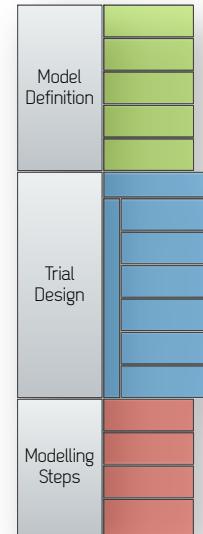
- DDMoRe foundation – post August 2016
 - keeping products updated
 - developing further the software infrastructure
- Get in touch with DDMoRe foundation
- Write your own translator for **Berkeley Madonna** or **acslX** or hire an expert



Contributions

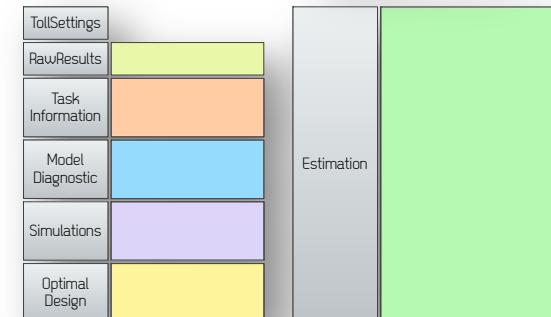
PharmML

- Swat MJ, S Moodie, SM Wimalaratne, NR Kristensen, M Lavielle, A Mari, P Magni, MK Smith, R Bizzotto, L Pasotti, E Mezzalana, E Comets, C Sarr, N Terranova, E Blaudez, P Chan, J Chard, K Chatel, M Chenel, D Edwards, C Franklin, T Giorgino, M Glont, P Girard, P Grenon, K Harling, AC Hooker, R Kaye, R Keizer, C Kloft, JN Kok, N Kokash, C Laibe, C Laveille, G Lestini, F Mentre, A Munafo, R Nordgren, HB Nyberg, ZP Parra-Guillen, E Plan, B Ribba, G Smith, IF Troconiz, F Yvon, PA Milligan, L Harnisch, M Karlsson, H Hermjakob and N Le Novère



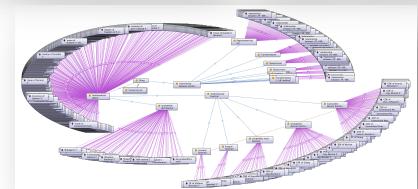
SO

- Nadia Terranova, Marc Lavielle, Mike K Smith, Emmanuelle Comets, Kajsa Harling, Rikard Nordgren, Duncan Edwards, Andrew Hooker, Celine Sarr, France Mentre, Florent Yvon, Maciej J Swat



ProbOnto

- Maciej J Swat, Pierre Grenon, Sarala M Wimalaratne



References & Resources

DDMoRe

- DDMoRe project website, URL: www.ddmore.eu
- <http://www.ddmore.eu/product/interoperability-framework>

PharmML

- Swat et al. (2015). Pharmacometrics Markup Language (PharmML): Opening New Perspectives for Model Exchange in Drug Development. CPT PSP, 4(6):316-9.
- URL: pharmml.org

SO

- URL: ddmore.eu/projects/so-standard-output

ProbOnto

- Swat MJ, Grenon P, Wimalaratne S. ProbOnto - ontology and knowledge base of probability distributions, Bioinformatics 2016; doi: 10.1093/bioinformatics/btw170.
- URL: www.probonto.org