



PharmML – use of UncertML

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Communicating Uncertainty: UncertML 3.0

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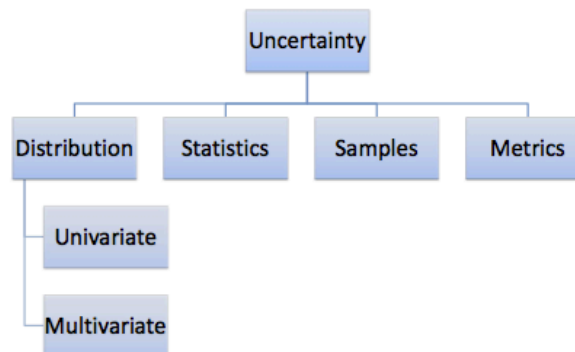
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The purpose of UncertML

UncertML was designed to allow the unambiguous communication of uncertain values between applications. Originally an XML schema developed for environmental applications, it is now a dictionary and a set of associated encodings in XML schema and JSON. Version 3.0 is currently in development and is designed to make UncertML easier to use in a wide variety of scientific XML encodings.

Design principles

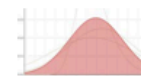
- Uncertainty is best represented by probabilistic approaches.
- The most complete description of uncertainty is the full distribution, from a predefined set of possible distributions.
- Sometimes only samples or summary statistics are available to describe uncertain quantities.
- It is useful to enable encoding of metrics which validate probabilistic beliefs using observations.
- We focus only on representing *uncertainty* – UncertML is domain-agnostic, and designed to be used within other schema which define units of measure, physical phenomena, etc.
- We avoid dependencies on other schema unless necessary for simplification.
- We allow for multiple encodings, and for independent use of the dictionary.



Existing uses of UncertML

- To represent observational uncertainties in Earth observation data.
- To encode uncertainties propagated through environmental processing chains.
- To represent uncertainties arising from the replacement of complex simulators with surrogate statistical models (emulators).

uncertweb
uncertainty-enabled model web



Use case

Oncology model, Ribba et al. 2012

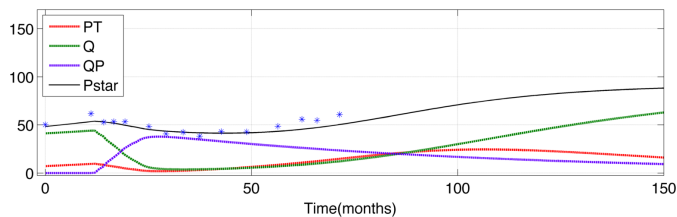
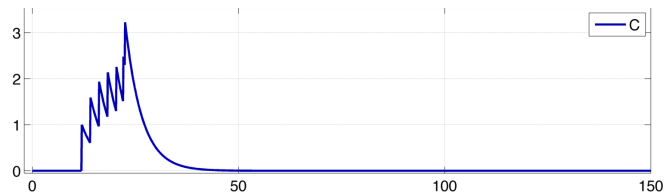
$$\frac{dC}{dt} = -KDE \times C$$

$$\frac{dP}{dt} = \lambda_p \times P \left(1 - \frac{P^*}{K}\right) + k_{QP} \times Q_P - k_{PQ} \times P - \gamma_P \times C \times KDE \times P$$

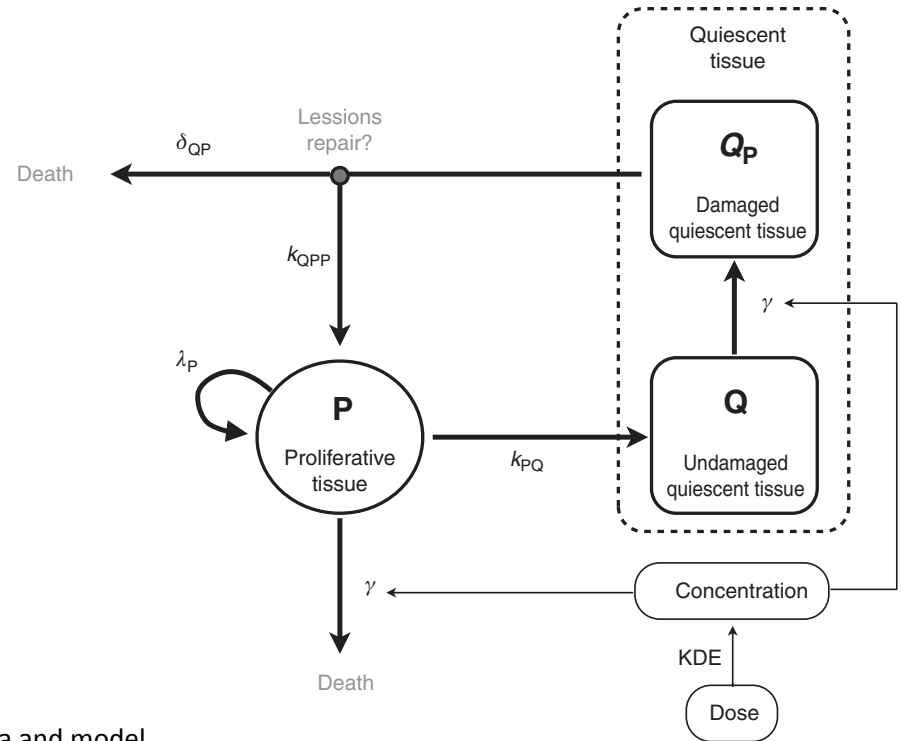
$$\frac{dQ}{dt} = k_{PQ}P - \gamma_Q \times C \times KDE \times Q$$

$$\frac{dQ_P}{dt} = \gamma_Q \times C \times KDE \times Q - k_{QP}Q_P - \delta_{QP} \times Q_P$$

$$P^* = P + Q + Q_P$$



* Experimental data for subject #2



Real data and model simulation for one subject

Model in PharmML

Model Definition extended

```
1 <?xml version="1.0" encoding="UTF-8"?>
2 <PharmML xmlns="http://www.pharmml.org/2013/03/PharmML"
3   xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
4   xsi:schemaLocation="http://www.pharmml.org/2013/03/PharmML http://www.pharmml.org/2013/03/PharmML"
5   xmlns:ct="http://www.pharmml.org/2013/03/CommonTypes"
6   writtenVersion="0.1">
7   <ct:Name>Ribba et al. 2012 - growth tumor model</ct:Name>
8   <ct:Description>based on A Tumor Growth Inhibition Model for Low-Grade Glioma Treated with Chemotherapy or Radiotherapy
9     Benjamin Ribba, Gentian Kaloshi, Mathieu Peyre, et al. Clin Cancer Res Published OnlineFirst July 3, 2012.</ct:Description>
10
11   <IndependentVariable symbId="time"/>
12
13   <ct:FunctionDefinition symbId="constantErrorModel" symbolType="real"> [5 lines]
14
15   <ModelDefinition xmlns="http://www.pharmml.org/2013/03/ModelDefinition">
16
17     <VariabilityModel blkId="model" type="model"> [2 lines]
18
19     <VariabilityModel blkId="obsErr" type="error"> [2 lines]
20
21     <ParameterModel blkId="pm1"> [243 lines]
22
23     <StructuralModel blkId="sm1"> [158 lines]
24
25     <ObservationModel blkId="om1"> [38 lines]
26
27   </ModelDefinition>
28
29   <TrialDesign xmlns="http://www.pharmml.org/2013/03/TrialDesign"> [92 lines]
30
31   <ModellingSteps xmlns="http://www.pharmml.org/2013/03/ModellingSteps">
32
33     <EstimationStep oid="estTask1"> [204 lines]
34
35     <StepDependencies> [4 lines]
36   </ModellingSteps>
37 </PharmML>
```

Model Definition

Parameter Model

All parameters are log-normally distributed, e.g.

$$\lambda_{P_i} = \lambda_{P_{pop}} e^{\eta_{\lambda_P}};$$

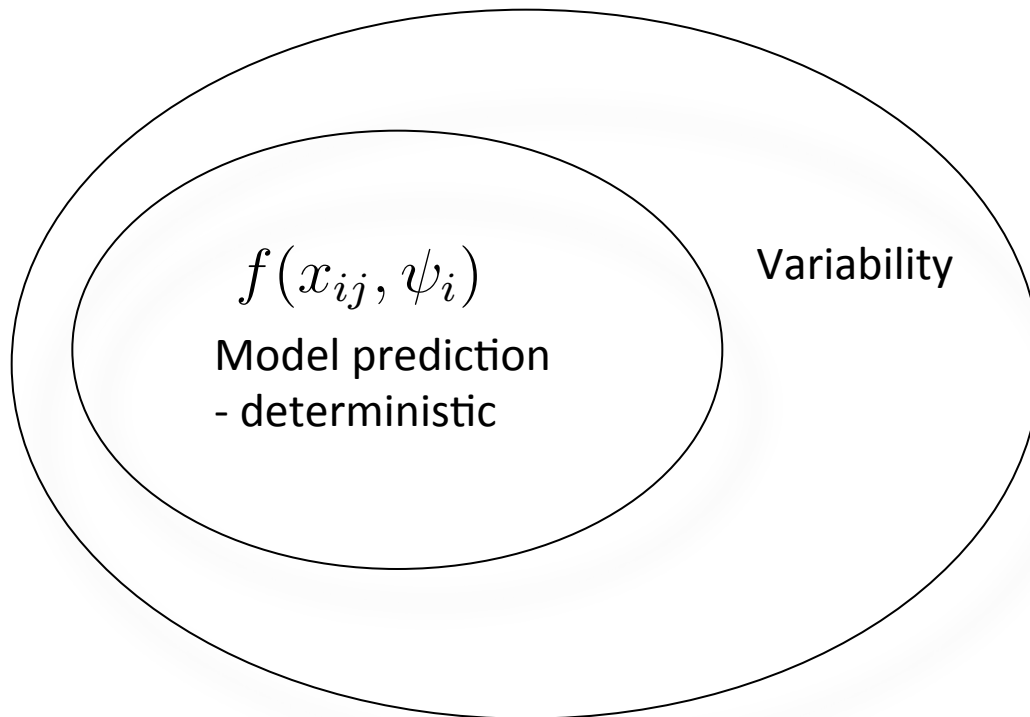
$$\log(\lambda_{P_i}) = \log(\lambda_{P_{pop}}) + \eta_{\lambda_P}; \quad \eta_{\lambda_P} \sim N(0, \omega_{\lambda_P})$$

```
<!-- LAMBDAP log-normal distributed -->
<RandomVariable symbId="eta_LAMBDAP">
  <ct:VariabilityReference>
    <ct:SymbRef blkIdRef="model" symbIdRef="indiv"/>
  </ct:VariabilityReference>
  <NormalDistribution xmlns="http://www.uncertml.org/3.0" definition="http://www.uncertml.org/distributions/normal">
    <mean>
      <rVal>0</rVal>
    </mean>
    <stddev>
      <var varId="omega_LAMBDAP"/>
    </stddev>
  </NormalDistribution>
</RandomVariable>
<IndividualParameter symbId="LAMBDAP">
  <GaussianModel>
    <Transformation>log</Transformation>
    <LinearCovariate>
      <PopulationParameter>
        <ct:Assign>
          <ct:SymbRef symbIdRef="pop_LAMBDAP"/>
        </ct:Assign>
      </PopulationParameter>
    </LinearCovariate>
    <RandomEffects>
      <ct:SymbRef symbIdRef="eta_LAMBDAP"/>
    </RandomEffects>
  </GaussianModel>
</IndividualParameter>
```

Basic comparison to SB

- The details are in the parameter model
 - Population/typical value of a parameter
 - Covariates
 - Continuous – Age, Height, Body weight,...
 - Discrete – Gender, Ethnicity, Pharmacogenomics, ...
 - Correlations
 - Variability, e.g. inter-individual variability
 - Explained – e.g. by covariates
 - Random

Basic comparison to SB



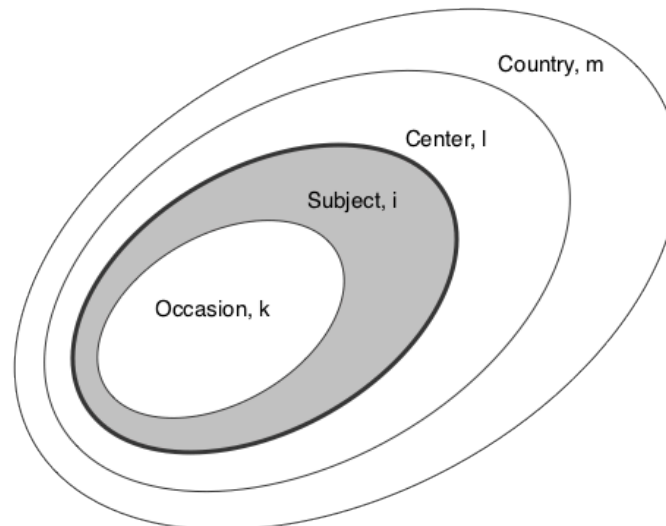
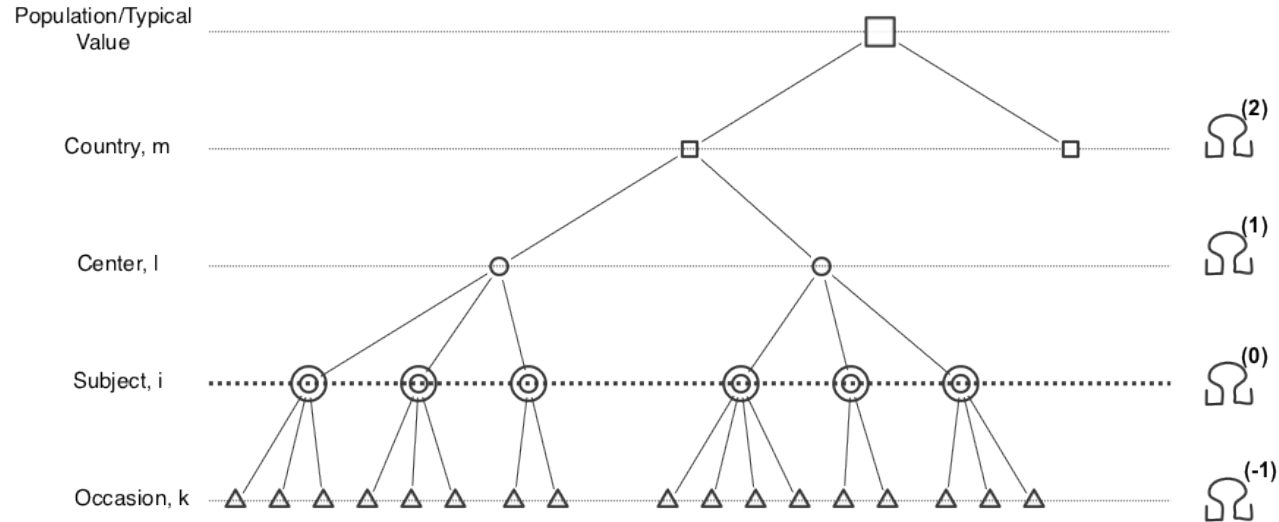
Variability

- Explained – e.g. by covariates
- Random

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

- N subjects
- n_i measurements per subject i

Variability – nested hierarchy

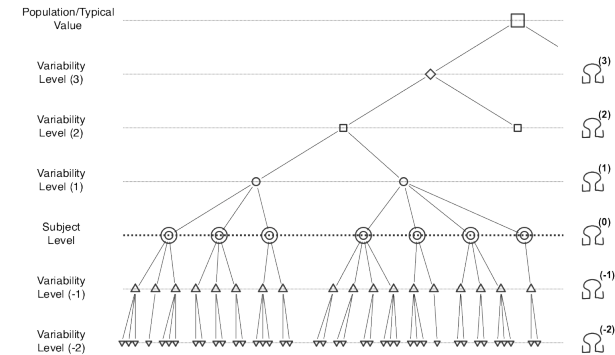


Model Definition

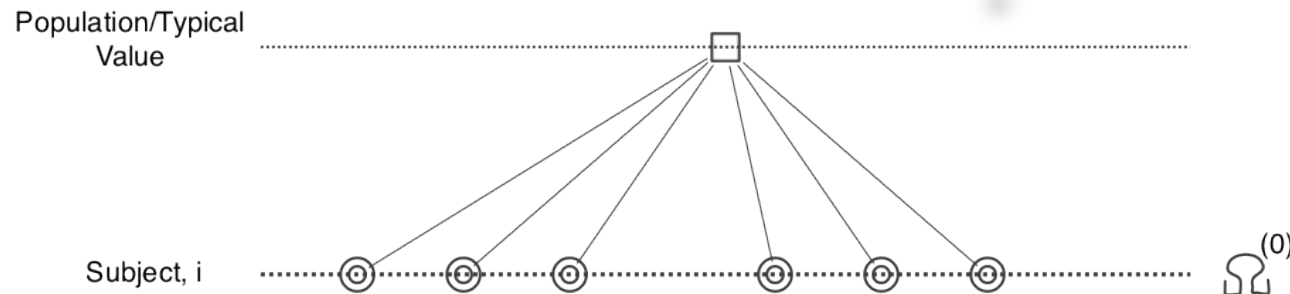
Simple Variability Model

There is only one level of variability
- inter-individual variability (IIV)

$$\lambda_{P_i} = \lambda_{P_{pop}} e^{\eta_{\lambda_P}};$$



Complex hierarchy
reduces to



Model Definition

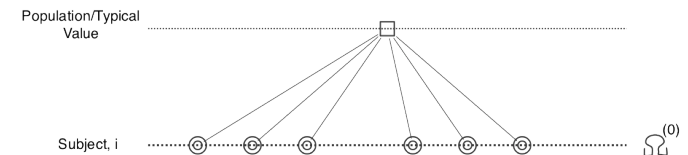
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    </mean>
    <stddev>
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        </ct:Assign>
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    </RandomEffects>
  </GaussianModel>
</IndividualParameter>
  
```

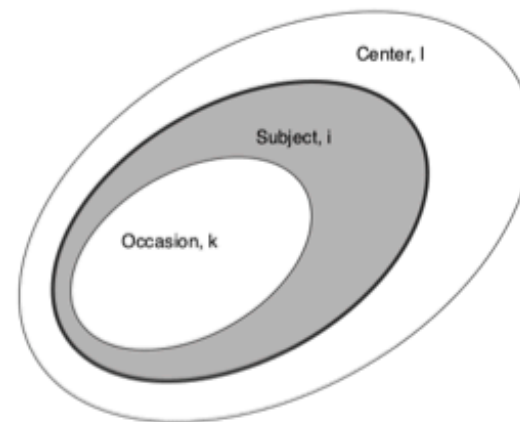
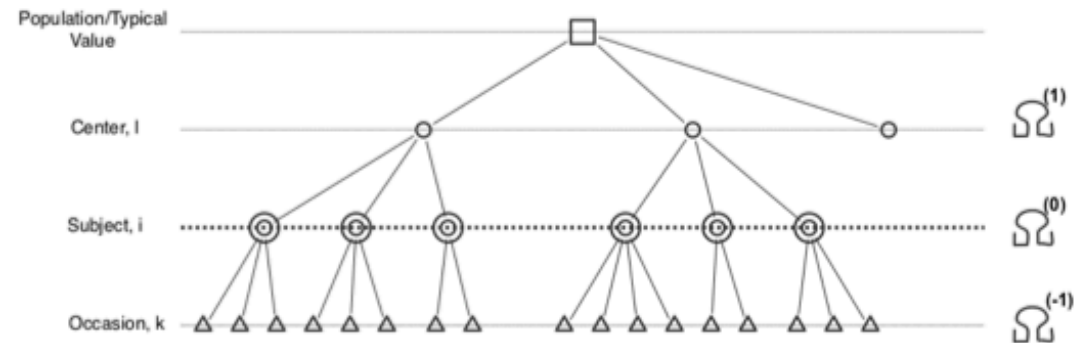
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$$\log(\lambda_{P_i}) = \log(\lambda_{P_{pop}}) + \eta_{\lambda_P}; \quad \eta_{\lambda_P} \sim N(0, \omega_{\lambda_P})$$



Model Definition

Complex Variability Model

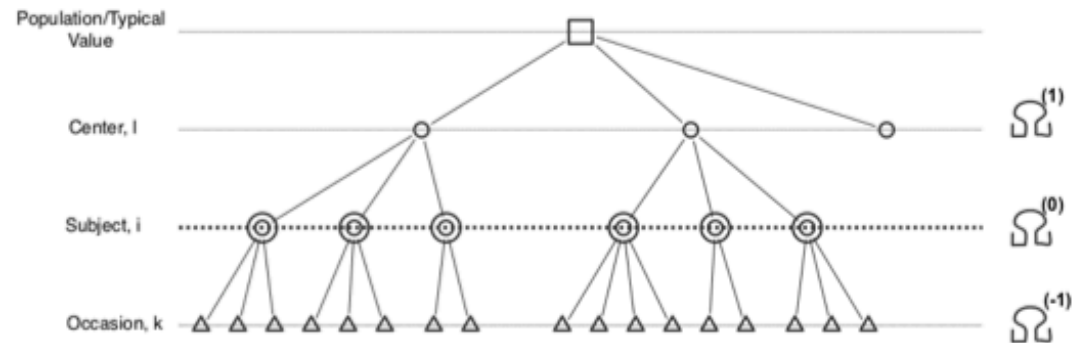


Three levels of variability

- inter-center variability
- inter-individual within center variability
- inter-occasion within individual within center variability

Model Definition

Complex Variability Model



$$\underbrace{\log(V_{lik})}_{\text{transformed individual value}} = \underbrace{\log(V_{pop})}_{\text{transformed typical value}} + \underbrace{\beta_{V,1} 1_{Sex_i=F}}_{\text{categorical covariate model}} + \underbrace{\beta_{V,2} \log\left(\frac{W_i}{70}\right)}_{\text{continuous covariate model}} + \underbrace{\eta_{l,V}^{(1)}}_{\text{inter-centre variability}} + \underbrace{\eta_{li,V}^{(0)}}_{\text{inter-individual within centre variability}} + \underbrace{\eta_{lik,V}^{(-1)}}_{\text{inter-occasion within individual within centre variability}}$$

Three levels of variability

- inter-center variability
- inter-individual within center variability
- inter-occasion within individual within center variability