Predictive models using fusion methods to estimate pharmacodynamic properties of a recombinant botulinum toxin E in humans

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IPSEN AT A GLANCE

IPSEN
Innovation for patient care

Global specialty driven pharmaceutical company, created in 1929 in Dreux.

Total sales €1,275 m (+5.7% vs 2013).
At constant exchange rate

More than 4,500 employees worldwide.

R&D expenditure totaled close to €187m
(about 15% of sales)

3 MAJOR R&D CENTERS LOCATED AT THE HEART OF LEADING SCIENCE HUBS

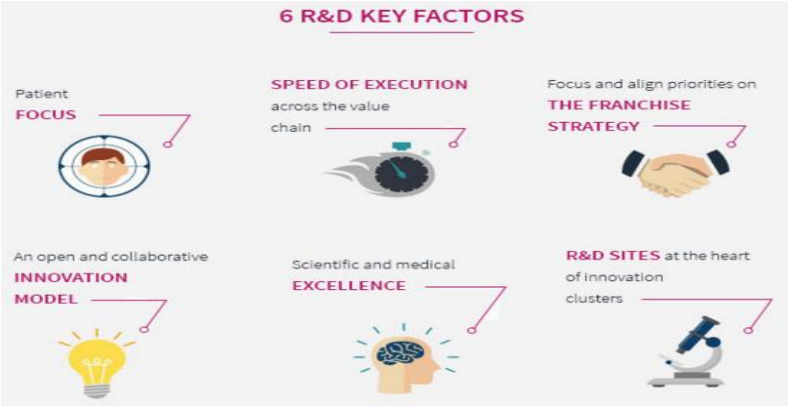
CAMBRIDGE
(Massachusetts - USA)

LES ULIS, PARIS-SACLAY
(France)

ABINGDON, OXFORD
(UK)

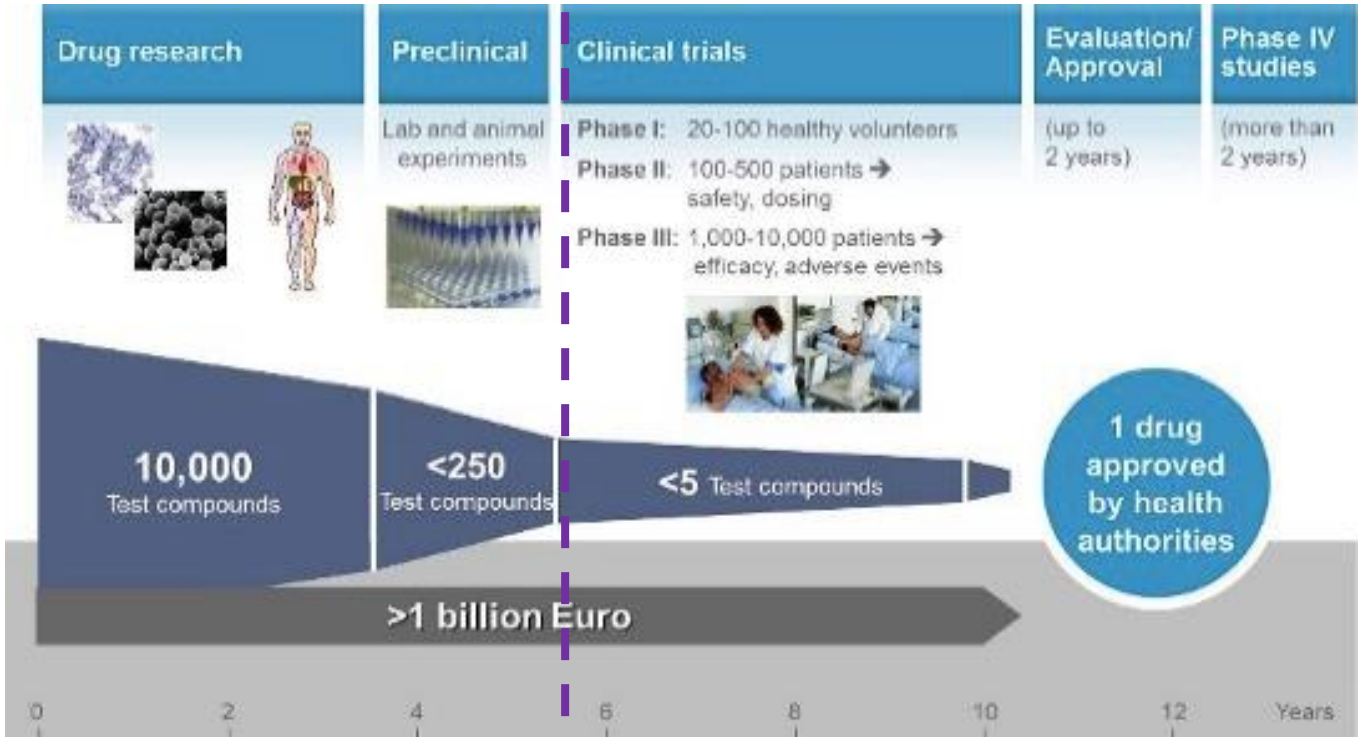
2014 sales by disease area

6 R&D KEY FACTORS



Drug Research and Development steps

CA LI LO CV PC PhI PhII PhIII LCM



Two main challenges in Devt :

- **Target the right population**
- **Select the right doses**

IPSEN question : is it possible to use available animal data and data of similar drugs in Humans to predict the behavior of a drug of interest ?

- One needs to identify dose of rBoNT-E for human that achieves 20% of maximum possible effect

- The given data is the following:
  - Rat, aboBoNT-A (Dysport)
  - Rat, rBoNT-E
  - Human, aboBoNT-A

- We are missing the data for human rBoNT-E and need to construct model by fusion of available data.

IPSEN's current way of solving the problem

- **Empirical methods**
  - **Using allometric factors :** translation from animal to human (minimal anticipated biological effect level (MABEL) approach, minimal pharmacological active dose (PAD), human equivalent dose (HED), no observed adverse effect level (NOAEL), maximum recommended starting dose (MRSD)
  - **Using safety factor :** non-clinical safety program on different species
  - **Cross-functional discussion** : select the most sensitive species with no observed adverse effects

- **In accordance to Food and Drug Administration guidance**
  - **No call into questions**

- **Strong interest and need in limiting the risks**

IPSEN investigations of methodologies and software tools
Innovation for Data Analysis and Modeling

- **Automatic construction of Data Predictive models :** multi inputs, multi outputs
- **Detect important parameters or combination of parameters in the models**
- **Help for Design of Experiments**
- **Take into account Multi Fidelity Data :** species, drugs, …
- **Calibration & Optimization of models :** drug design, …
- **Take into account Uncertainties in parameters**

➔ **IPSEN Innovation investigates DATADVANCE pSeven solution**

Using of pSeven to solve IPSEN problem

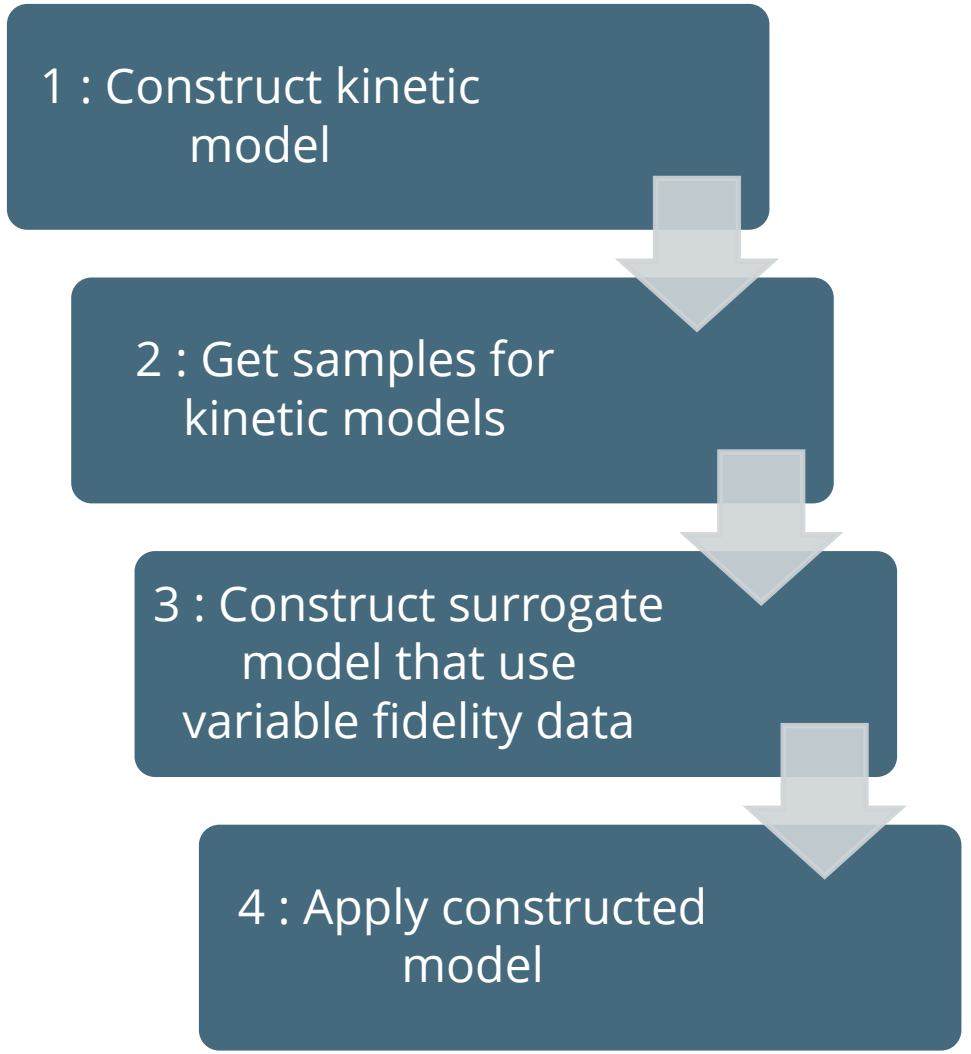
Simulation and Model construction Process

- **Construct kinetic models using available data for Rat aboBoNT-A, Rat rBoNT-E, Human aboBoNT-A**
  - Input for kinetic model is time and dose.
  - Output is obtained effect**, for all and for Human rBoNT-E**

- **Get dose–share of max effect at peak curve**
  - using obtained models
  - and generate samples on the base of these models.

- **Construct surrogate model for desired effect-dose curve using variable fidelity data. Two options are available:**
  - Generic Tool for Data Fusion : automatic, but only two fidelities available.
  - Generic Tool for Approximation : one has to specify weights for each sample (Human aboBoNT-A sample, Human rBoNT-E sample, …), number of fidelities is arbitrary.

- **Apply constructed model to get desired effect-dose curve.**



1 : Construct kinetic model

- For a given specie and a given drug, *y* is the drug rBoNT-E effect in Human , function of dose *d* and time *t*

$$y(d,t) = \frac{k_a d}{v(k_a - k_e)}[\exp(-k_e t) - \exp(-k_a t)].$$

Here d is a dose, t is a measurement time. Model has three parameters k_a, c_l, v:

- k_a is the fractional absorption rate;
- c_l is the clearance rate;
- v is volume of distribution;
- parameter $k_e = \frac{c_l}{v}$.

1: Construct kinetic model

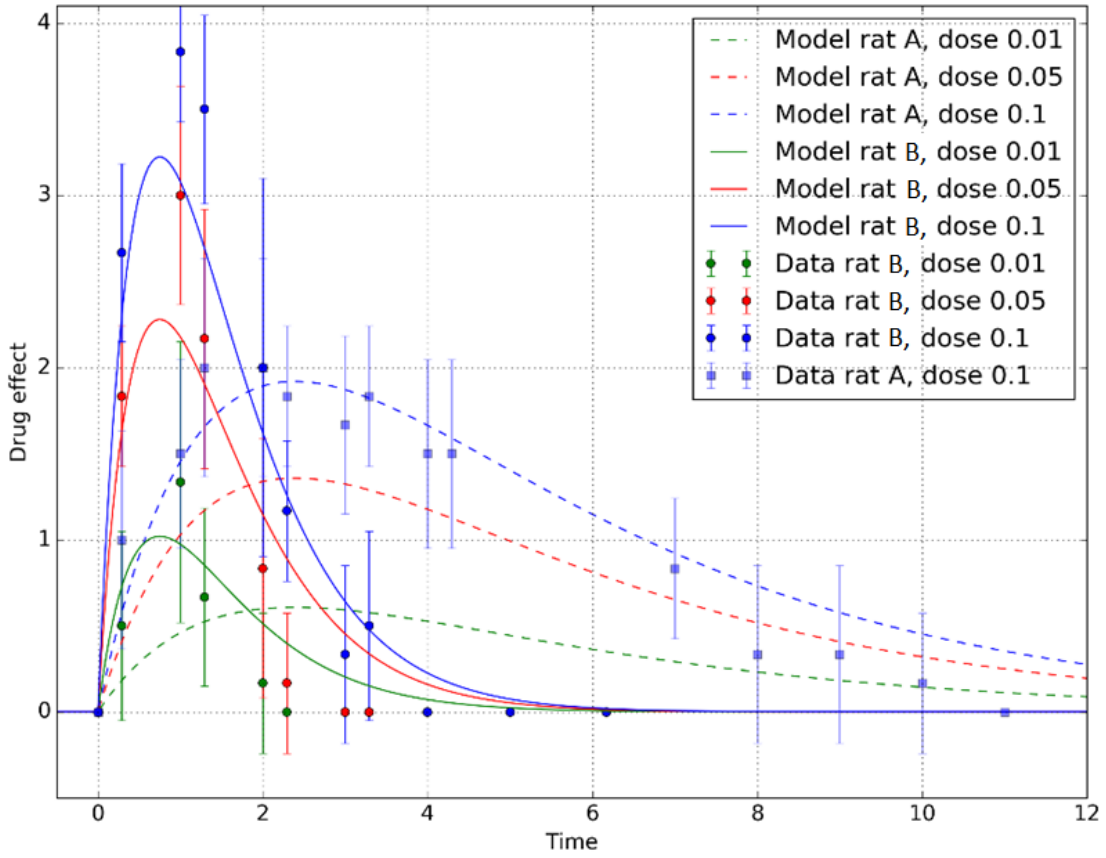
- To fit the model we minimize squared differences between true and model values using **Generic Tool for Optimization** from pSeven Core.

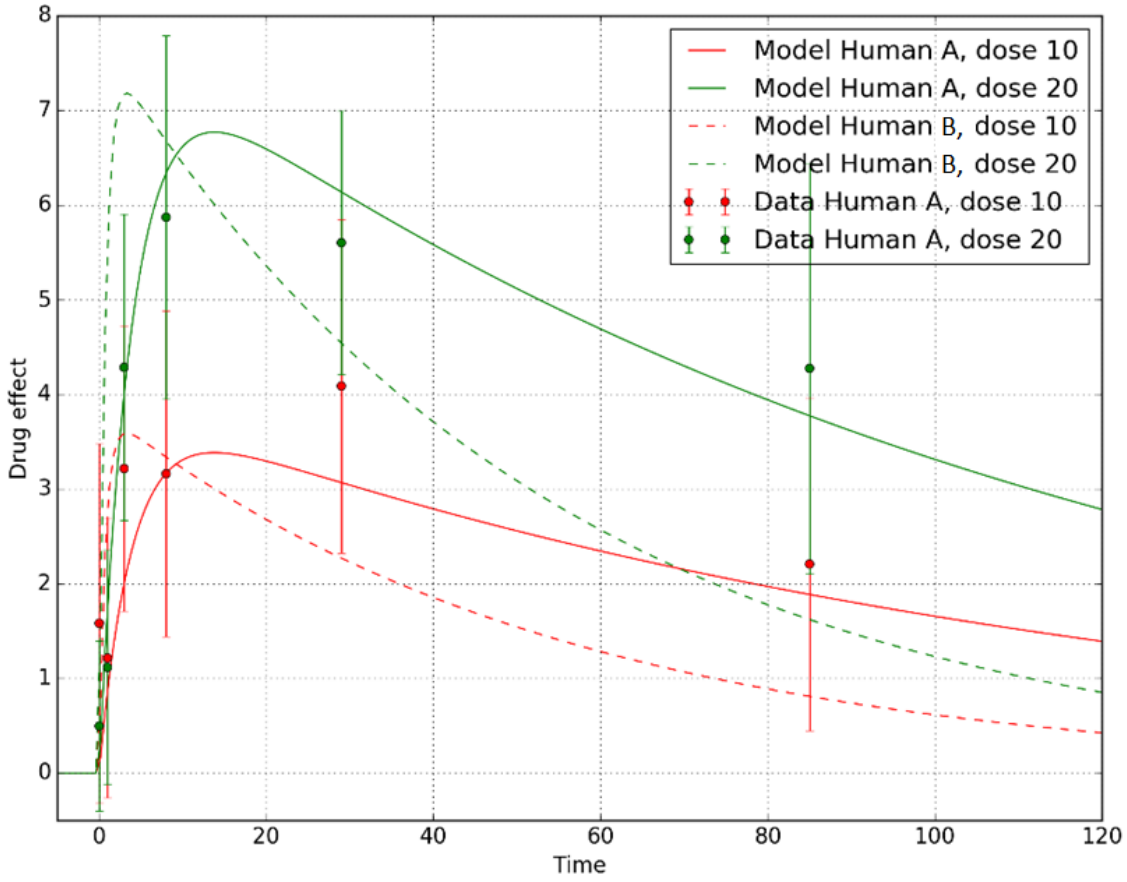
- We take into account that models are different for different drugs and species

Specie	Drug	Parameters
Rat	aboBoNT-A	*kaA, ClA,vR*
Rat	rBoNT-E	*kaE, ClE, vR*
Human	aboBoNT-A	*kaA, ClA, vH*
Human	rBoNT-E	*kaE, ClE, vH*

1 : Construct kinetic model

- Results of fit correspond to the data well.

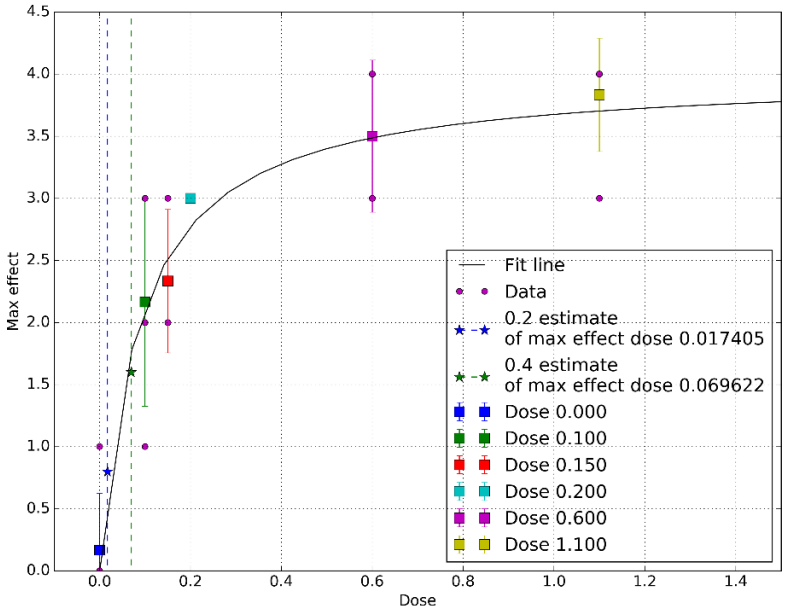




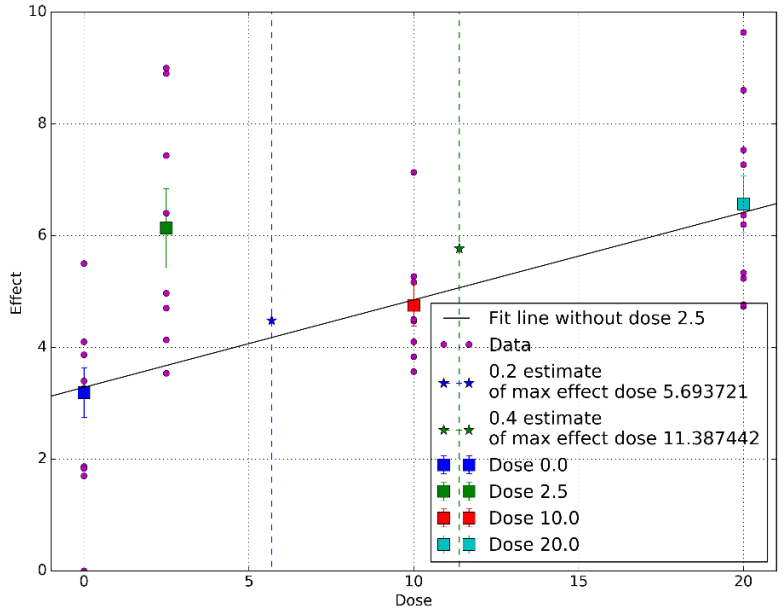
2 : Get samples for kinetic models

- Identification of desired dose (in units)

Rat aboBoNT-A model



Human aboBoNT-A model



Human rBoNT-E model

Etc …..

3 : Construct surrogate model that use variable fidelity data

Model generation

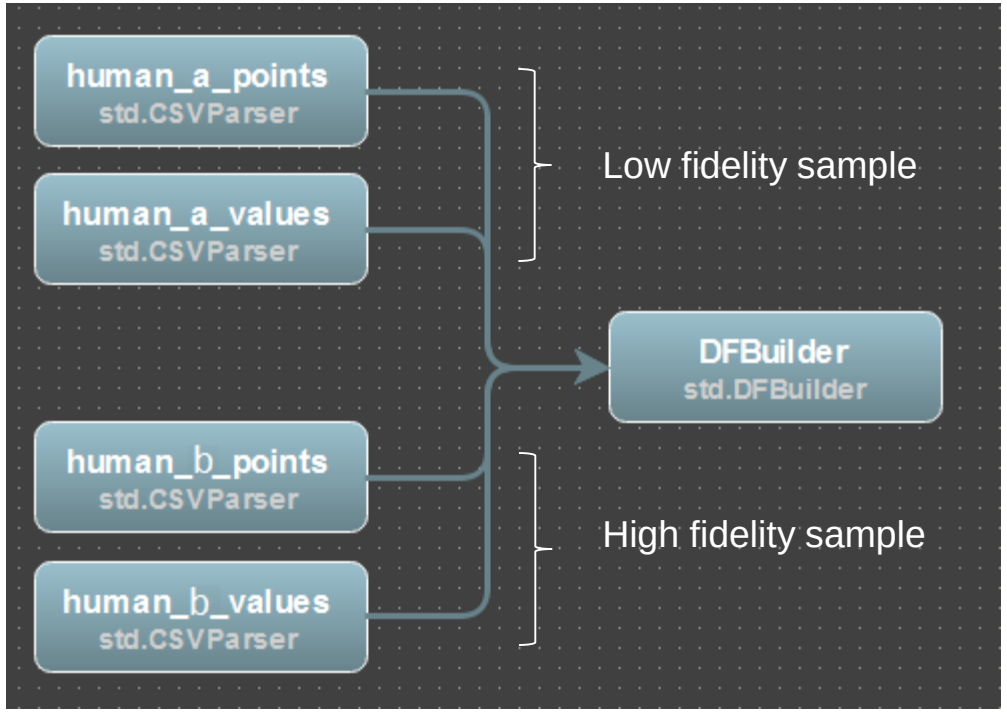
- **Generic Tool for Data Fusion** : automatic, only two fidelities available (Human aboBoNT-A, Human rBoNT-E)

- **Generic Tool for Approximation** – one has to specify weights for each sample (Rat aboBoNT-A, Rat rBoNT-E, Human aboBoNT-A sample, Human rBoNT-E sample, …), number of different fidelity samples is arbitrary.

3 : Construct surrogate models that use variable fidelity data

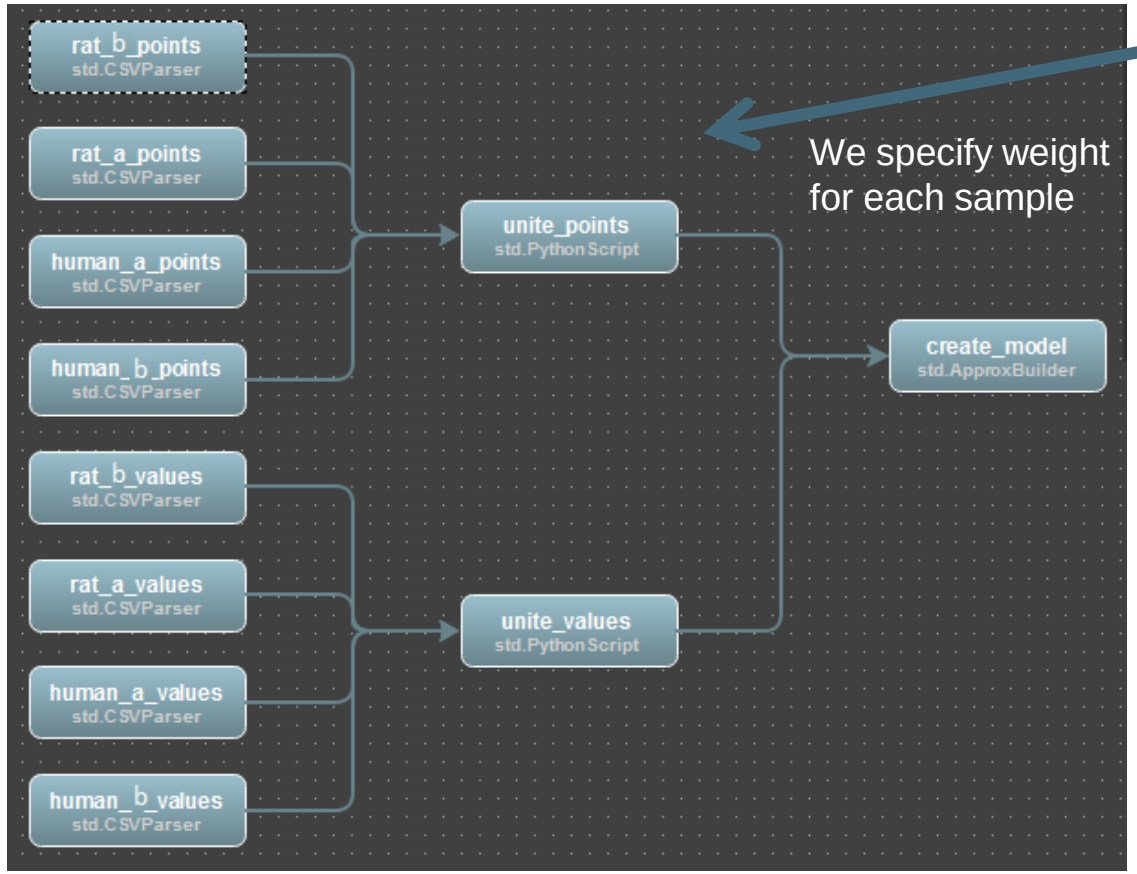
Construction of GT DF surrogate model

- Load low fidelity inputs and outputs
- Load high fidelity inputs and outputs
- Construct surrogate model for a high fidelity function



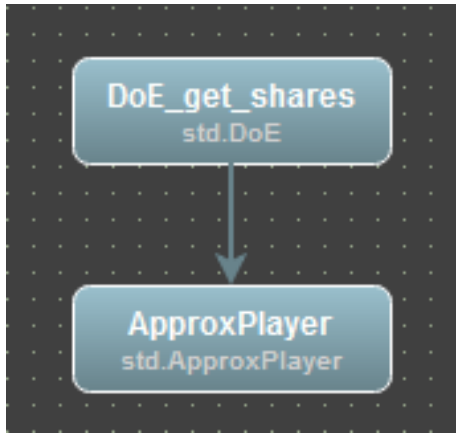
3 : Construct surrogate models that use variable fidelity data

Construction of GT Approx surrogate model



We specify weight for each sample

Parameter	Value
human_a_weight Sets script variable value.	10
human_b_weight Sets script variable value.	100
rat_a_weight Sets script variable value.	1
rat_b_weight Sets script variable value.	10



Model construction

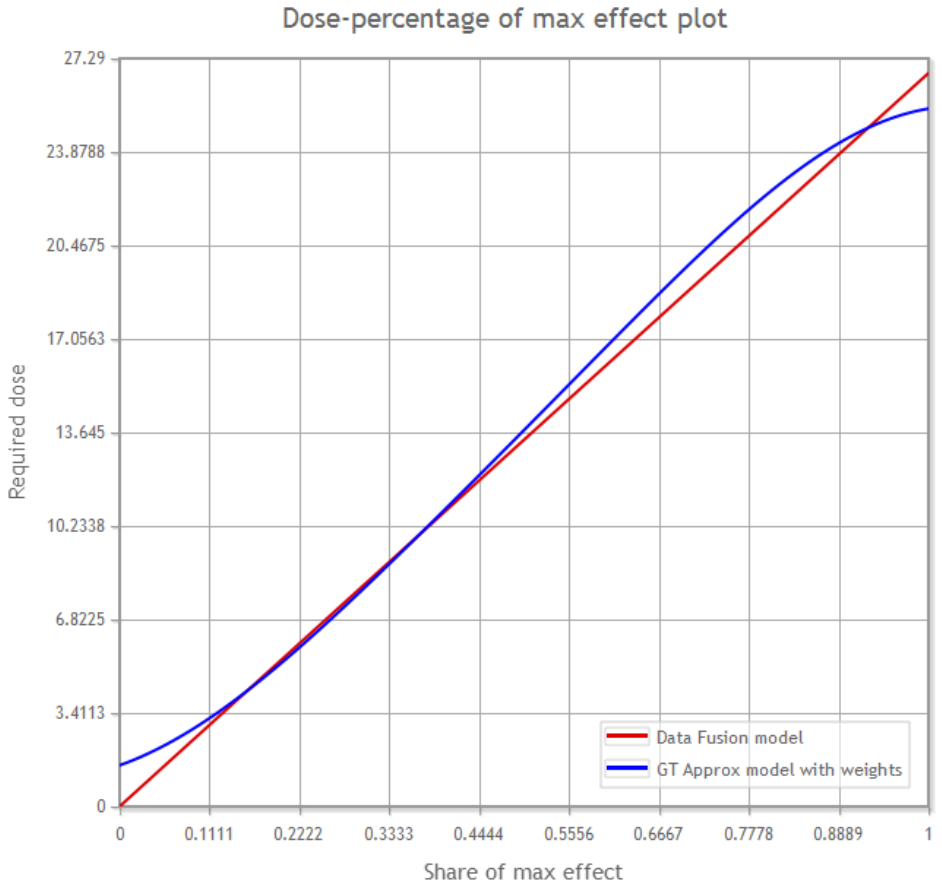
Model usage

4 : Apply constructed model

Obtained models and Results

- **Generic Tool for Data Fusion** : automatic, but only two fidelities available.
  - **Linear model.**

- **Generic Tool for Approximation** – one has to specify weights for each sample (Human A sample, Human E sample, …), number of different fidelity samples is arbitrary.
  - **Nonlinear model.**



Results

Outputs

Estimated dose (ng) of rBoNT-E to achieve percent of Emax					
Emax achieved (%)	Model 1	Model 2	Model 3	Model 4	Model based on rBoNT-E data only
10		0.001	0.012	0.003	0.0035
20	5	0.002	0.028	0.008	0.0107
30		0.004	0.049	0.016	0.0233
40		0.009	0.077	0.029	0.0445
50		0.019	0.117	0.051	0.0812
60		0.041	0.177	0.087	0.149
70		0.099	0.279	0.157	0.291
80		0.288	0.487	0.323	0.6673
90		1.451	1.125	0.946	2.4453

Table: Fusion models predicting the dose of rBoNT-E required to achieve a given percentage of maximum effect (Emax) in humans

Results analysis

- Models 3 and 4 accurately predicted the true effect.
- Adding new data to Model 3 slightly improved results
- Introducing Human rBoNT-E data to Model 4 improved results further.

Conclusions / Perspectives

IPSEN

- **Some simulations projects** at IPSEN will require re-using the same workflow, with different species / drugs / phase
  - Data has to be well-collected, prepared, understood
  - Intermediate results have to be investigated before concluding on a method

- **Selecting the right doses in clinical trials** is crucial in Development, but it is hard to bring new innovative methods due to regulatory constraints
  - The strategy is to use it to support and reassure for decision, even though it is not specified in current guidelines
  - Until it is recommendd in guidelines

DATADVANCE

- **Interesting generic methodologies developed by Datadvance** to automatically build Predictive models and Data Fusion Models (data with different species, drugs, ..) and **adding our own models and use estimation parameters feature is enabled.**

- **And possible extension of other methods available in pSeven : we would like to add and automatise the multi-endpoints**
  - Compromise that we would like to automatise/optimize

Thank you all for your attention

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