Handling parameter constraints in complex/mechanistic population pharmacokinetic models

"An application of the multivariate logistic-normal distribution"

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Motivation

- Population PK model parameters often need to be constrained at the individual level due to the nature of the underlying process they represent.
  - e.g., model parameters are constrained to be positive through the assumption that they are log-normally distributed in the population

- Increased interest on the development of hierarchical-population PBPK models, as they offer significant advantages [1].

- Moving from empirical to complex mechanistic model structures constraining parameters can be challenging and particularly crucial, as they represent actual physiological processes.

Objective

Investigate approaches to incorporate stochastic variability in mechanistic PK model parameters which are subject to certain constraints.

[1]. Tsamandouras N et al, Br J Clin Pharmacol, 2013; doi: 10.1111/bcp.12234.

Constraints in population PBPK

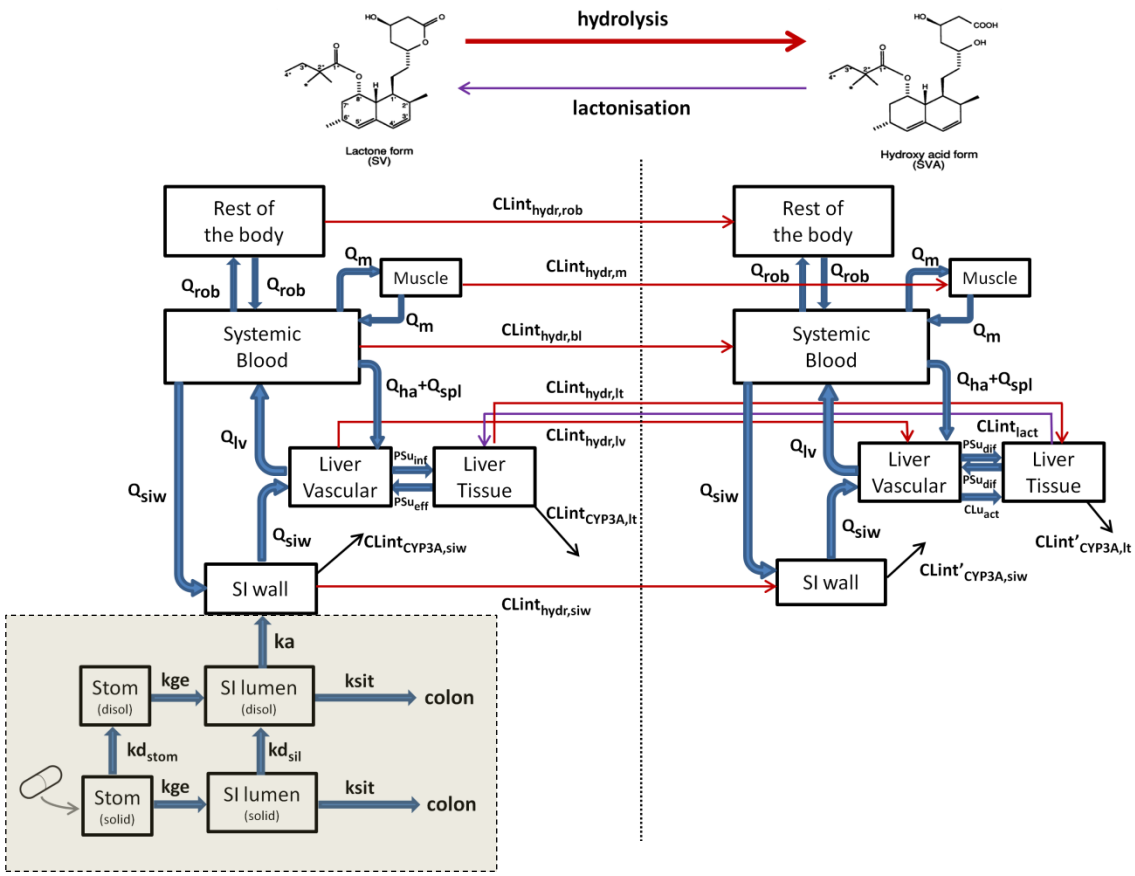
- Types of constraints that we are often faced with in population PBPK models:

Type 1: an independent model parameter that exhibits population variability and needs to be bound inside a specific physiological range

Type 2: multiple correlated model parameters that exhibit population variability and each of them is bound inside a physiological range

Type 3: multiple (potentially correlated) model parameters that exhibit population variability and their sum needs to add up to a specific physiological value in each individual (compositional parameters)

Type 1 constraint example



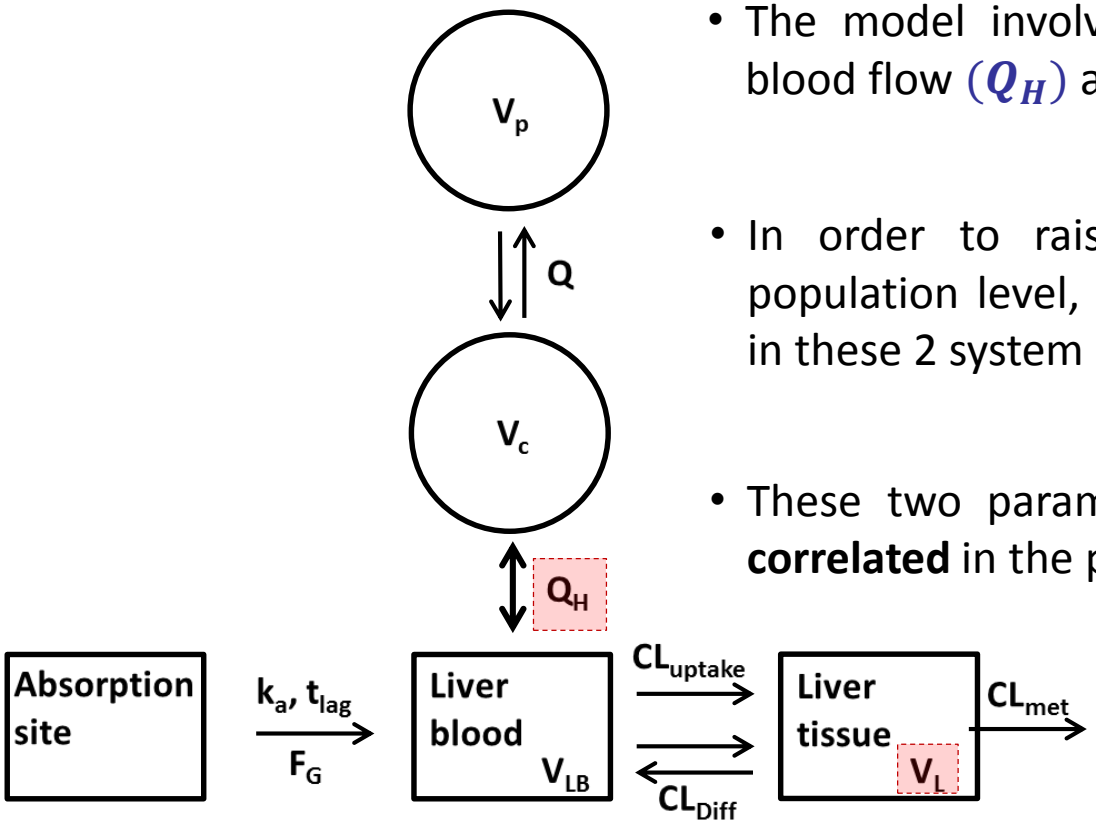
- A complex population PBPK model for simvastatin and its metabolite simvastatin acid [1]
- Absorption part of the model involves system parameters such as gastric and small intestinal residence time which we *a priori* know that are variable in the population
- Population variability in such system parameters should not be neglected in a hierarchical PBPK model.

- Incorporation of variability should be performed with caution as the **parameters should be constrained at the individual level to be within a specific physiological range.**

[1] Tsamandouras N et al, Submitted in Pharm Res

Type 2 constraint example

- A **semi-mechanistic repaglinide model** with focus on OATP1B1-mediated hepatic uptake [1]



- The model involves 2 system parameters, hepatic blood flow $(\boldsymbol{Q_H})$ and liver volume $(\boldsymbol{V_L})$
- In order to raise this structural model to the population level, variability should be also assigned in these 2 system parameters
- These two parameters are **known to be strongly correlated** in the population

- **The stochastic part should be able to describe this covariance structure but also ensure that each of them is constrained at the individual level within a physiological range**

[1] Gertz M et al, Pharm Res. 2014 Mar 13. [Epub ahead of print].

Solution to Type 1 & 2 constraints

Type 1 & 2 constrains can be satisfied by assuming that the parameter(s) of interest follow in the population **a generalisation of the logit-normal distribution.**

- The **logit-normal distribution** is routinely employed in PK/PD modelling to constrain parameters inside $(0, 1)$ (e.g., to model bioavailability, probability)

$$x \in (0,1) \sim logitN, \quad \text{if} \quad \underbrace{log\left(\frac{x}{1-x}\right)}_{\text{logit}} \sim N(\mu, \sigma^2) \qquad x = \underbrace{\frac{e^{logit}}{e^{logit}+1}}_{\text{logit}^{-1}}$$

- This distribution can be **generalised** to constrain parameters inside any (α, β)

$$x \in (a,\beta) \sim glogitN, \quad \text{if} \quad \underbrace{log\left(\frac{x-\alpha}{\beta-x}\right)}_{\text{glogit}} \sim N(\mu, \sigma^2) \qquad x = \alpha + \underbrace{\frac{(\beta-\alpha)\cdot e^{glogit}}{e^{glogit}+1}}_{\text{glogit}^{-1}}$$

Multivariate logit-normal generalisation

Generalisation of the multivariate logit-normal

⟹ Assume that $Y = [y_1, y_2, \dots, y_k]^T \sim N_k(M, \Sigma)$

⟹ A vector $X = [x_1, x_2, \dots, x_k]^T \sim glogitN_k$ can be generated by transformation of Y

$$x_i = a_i + \frac{(\beta_i - a_i) \cdot e^{y_i}}{1 + e^{y_i}}$$

, where the i_{th} element of X is constrained between

the i_{th} element of $A = [a_1, a_2, \dots, a_k]^T$ and the i_{th} element of $B = [\beta_1, \beta_2, \dots, \beta_k]^T$

Advantages of the logit-normal generalisation

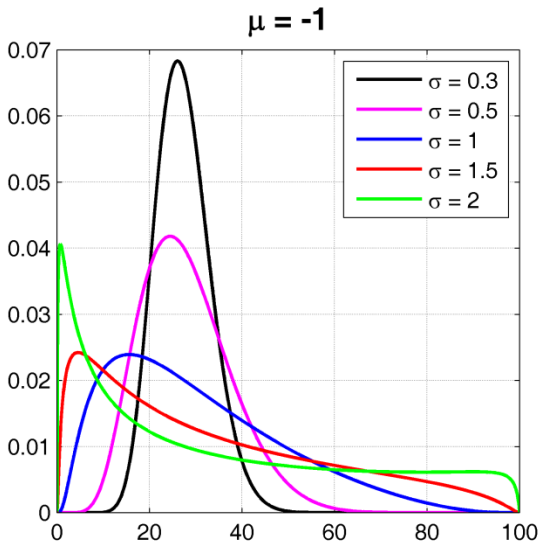
(+) Bounded support, non-physiological parameter values are avoided

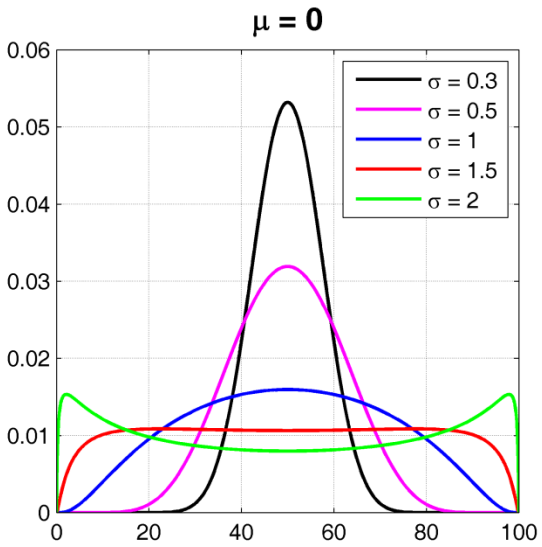
(+) Transformation of the normal, easily implemented in NMLEM software

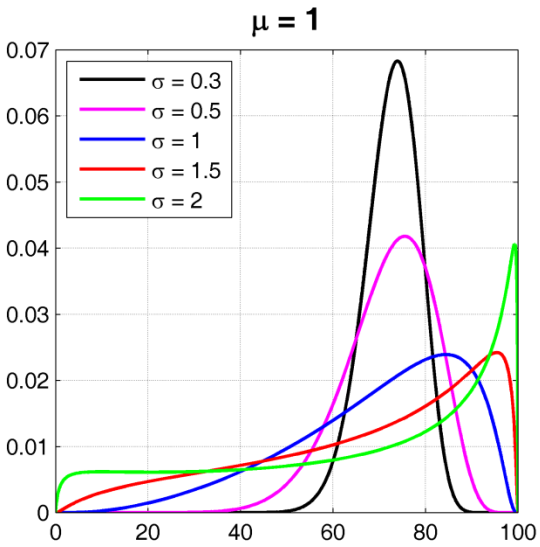
(+) Very flexible probability density function

Flexibility of the logit-normal generalisation

Univariate case:





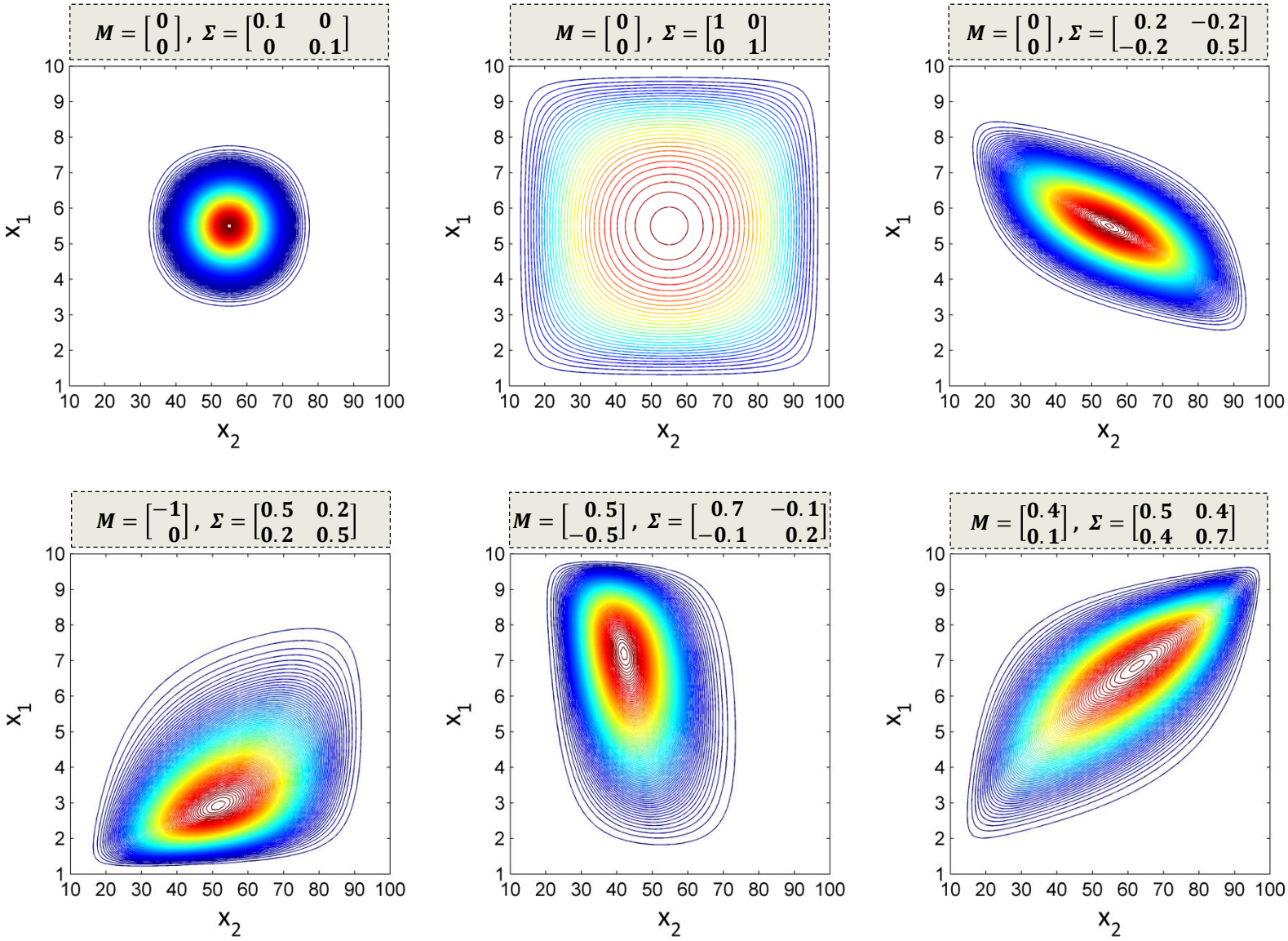


Flexible pdf that can describe both positively and negatively skewed distributions with variable degree of kurtosis or even bimodality [1].

[1]. Petersson K et al, Pharm Res. 2009;26(9):2174-2185.

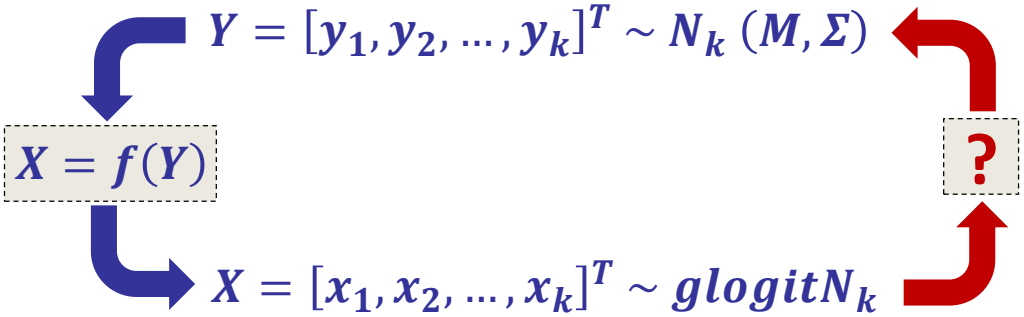
Flexibility of the logit-normal generalisation

Multivariate case:



Disadvantages of the logit-normal generalisation

(-) **Difficult to interpret** the population distribution of the physiologically meaningful variable directly from parameter estimates.



(-) **Difficult to set up prior information** when estimation is performed in a formal Bayesian or MAP method.

- As the prior information exists in the domain of X, how we can transmit this information in the Y variable domain?

(-) **The moments** of either the logit-normal or its generalisation **do not have an analytic solution**.

Providing priors in the transformation domain

- It can be easily derived that the $\boldsymbol{pdf}$ of $\boldsymbol{X \sim glogitN_k}$ is:

$$f(x_1, \dots, x_k) = \frac{1}{\sqrt{(2\pi)^k \cdot |\Sigma|}} \cdot e^{-\frac{1}{2}(Z-M)^T \cdot \Sigma^{-1} \cdot (Z-M)} \cdot \prod_{i=1}^{k} \left(\frac{(\beta_i - a_i)}{(x_i - a_i) \cdot (\beta_i - x_i)} \right) \quad , x_i \in (a_i, \beta_i)$$

, where $Z = [z_1, z_2, \dots, z_k]^T$ and $z_i = log\left(\frac{x_i - a_i}{\beta_i - x_i}\right)$

- The moments of the $\boldsymbol{glogitN_k}$ can be then computed by **numerical integration**

$$E(x_i) = \int_{a_k}^{\beta_k} \dots \int_{a_2}^{\beta_2} \int_{a_1}^{\beta_1} x_i \cdot f(x_1, \dots, x_k)\, dx_1 dx_2 \dots dx_k$$

$$Var(x_i) = \int_{a_k}^{\beta_k} \dots \int_{a_2}^{\beta_2} \int_{a_1}^{\beta_1} \left(x_i - E(x_i)\right)^2 \cdot f(x_1, \dots, x_k)\, dx_1 dx_2 \dots dx_k$$

$$Cov(x_i, x_j) = \int_{a_k}^{\beta_k} \dots \int_{a_2}^{\beta_2} \int_{a_1}^{\beta_1} \left(x_i - E(x_i)\right) \cdot \left(x_j - E(x_j)\right) \cdot f(x_1, \dots, x_k)\, dx_1 dx_2 \dots dx_k$$

Constraints in population PBPK

- Types of constraints that we are often faced with in population PBPK models:

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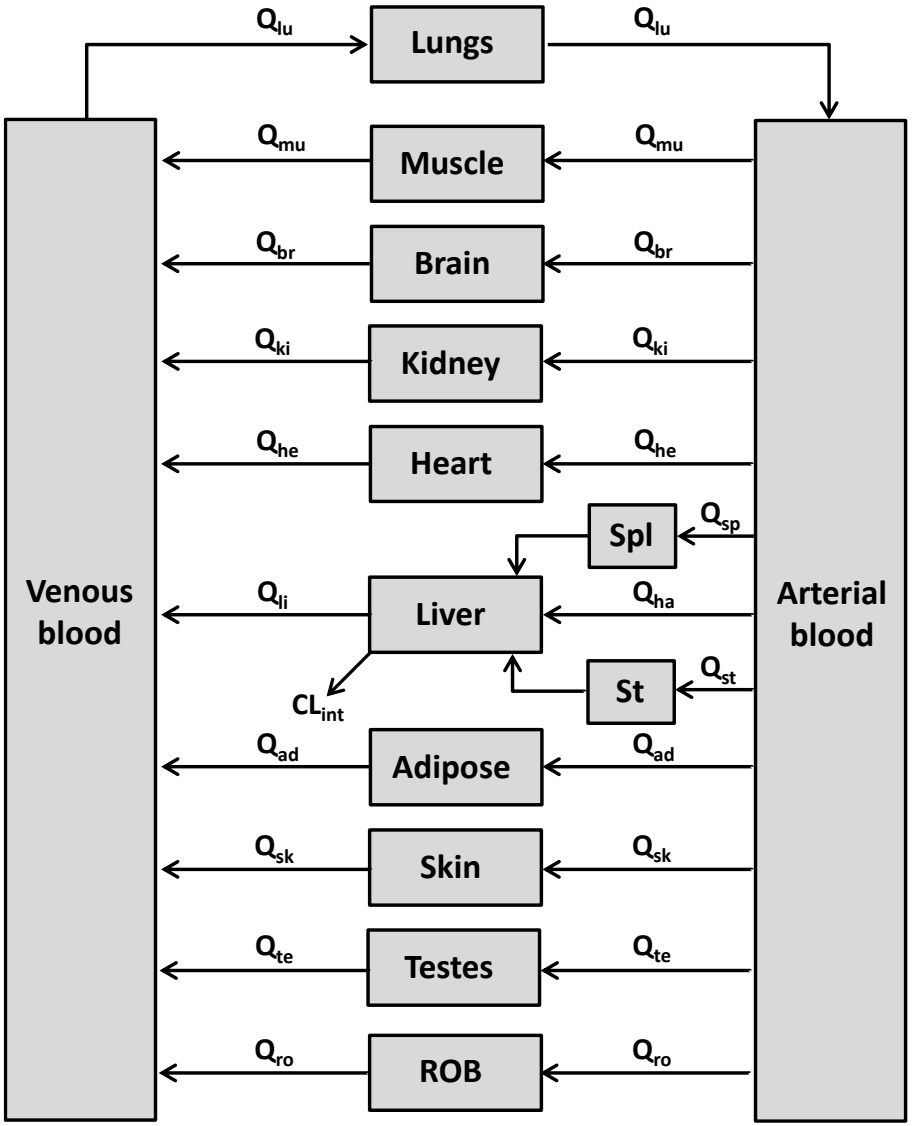
Type 3 constraint example

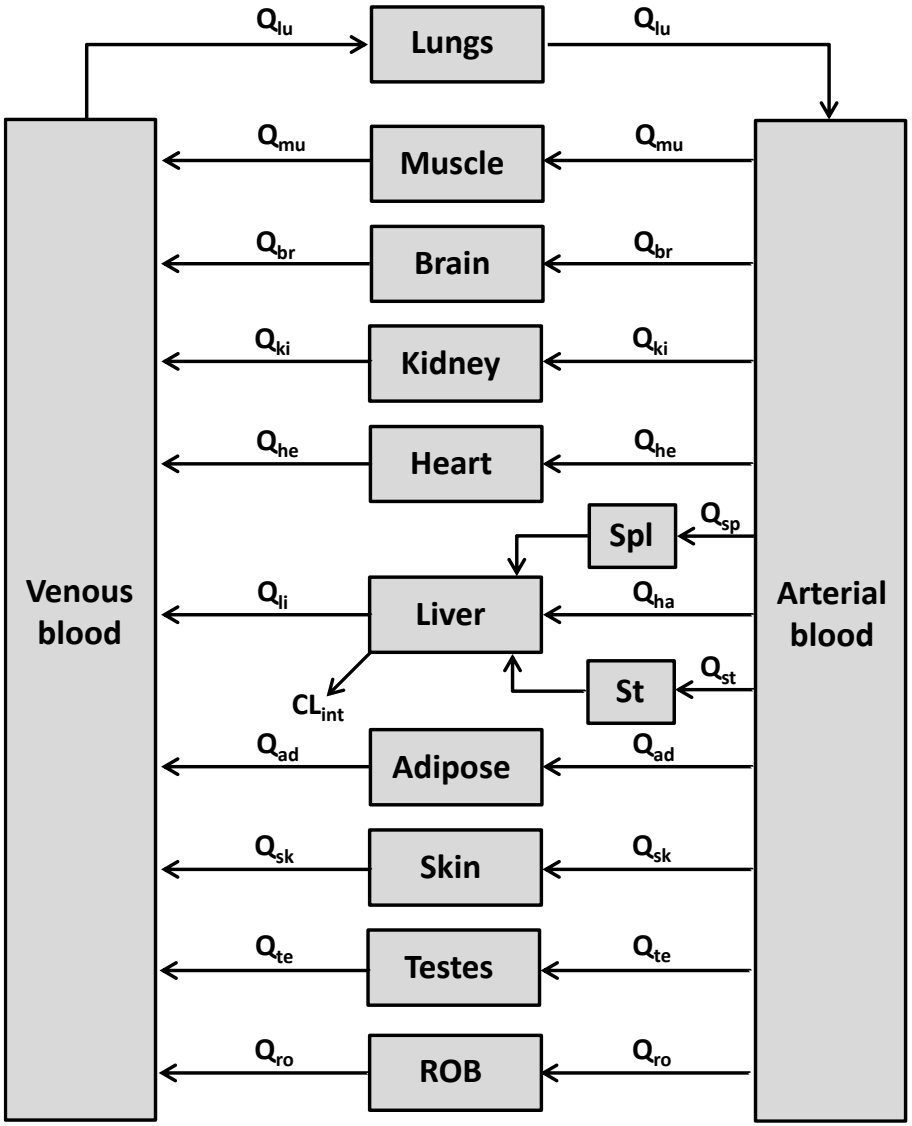


- A **whole-body PBPK** model
- Commonly employed at the **typical individual** level
- In an **hierarchical modelling** framework, population **variability in organ blood flows and volumes** should be considered

Major challenge:

- The **sum** of the organ blood flows in an individual should be equal to the cardiac output.
- The **sum** of the organ volumes in an individual should be equal to the total body volume.

Constraining compositional parameters



1st step: a useful parameterisation

$$Q_{j,i} = f_{Q_{j,i}} \cdot CO_i$$

$$0 < f_{Q_{j,i}} < 1 \ and \sum_{j=1}^{n_Q} f_{Q_{j,i}} = 1$$

$$V_{j,i} = f_{V_{j,i}} \cdot WTE_i$$

$$0 < f_{V_{j,i}} < 1 \ and \sum_{j=1}^{n_V} f_{V_{j,i}} = 1$$

Constraining compositional parameters

- In order to satisfy these constraints , it is usually proposed [1,2] that the fractional multipliers should be sampled from the **Dirichlet distribution**.

- A characteristic property of a k-dimensional **Dirichlet** is that **each of its k components is in the (0,1) interval and their sum is adding up to 1**.

- Although the Dirichlet has been used to satisfy the constraints in MC simulations, it **has not been applied in a NLME PBPK modelling framework**.

- Here we discuss the implementation of an approach using an alternative distribution, the **multivariate logistic-normal** which has similar properties to the Dirichlet, but **offers certain advantages for population PBPK modelling**.

[1] Farrar D et al, Toxicol Lett. 1989;49(2-3):371-385.

[2] Krewski D et al, J Biopharm Stat. 1995;5(3):245-271.

Multivariate logistic - N

Generate a logistic-N distribution

⟹ Assume that $U = [u_1, u_2, \dots, u_k]^T \sim N_k\,(M, \Sigma)$

⟹ Update U by adding an additional 0 element, so that $u_{k+1} = 0$

⟹ A vector $\Theta = [\theta_1, \theta_2, \dots, \theta_{k+1}]^T \sim logistic\text{ - }N$ can be generated by applying a logistic transformation on the updated vector U

$$\theta_i = \frac{e^{u_i}}{\sum_{i=1}^{k+1} e^{u_i}}$$

- The $(k+1)$-dimensional $logistic\text{ - }N$ is defined over the k-dimensional simplex and the drawn samples have components in **(0,1)** with **sum** adding up to **1**.

Aitchison J et al, Biometrika. 1980;67(2):261-272.

Multivariate logistic - N

3-dimensional logistic N example

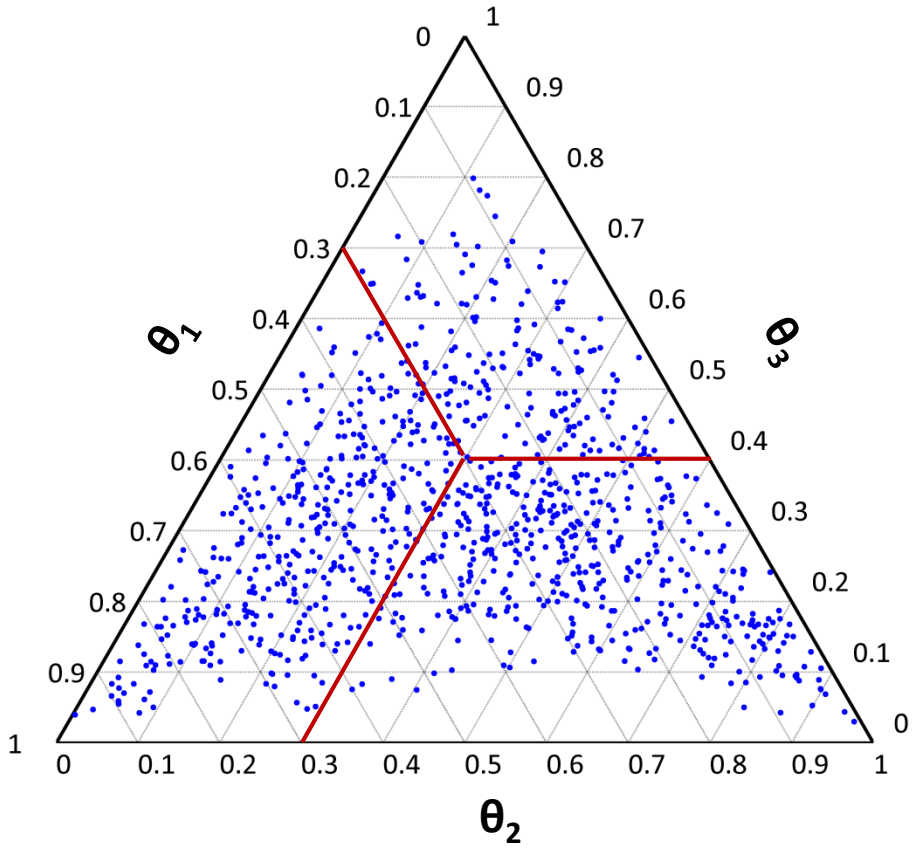
➡ Assume that $U = [u_1, u_2]^T \sim N_2(M, \Sigma)$ with $M = \begin{bmatrix} 0 \\ 0 \end{bmatrix}$ and $\Sigma = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$

➡ By updating U and applying transformation.

$$\theta_1 = \frac{e^{u_1}}{e^{u_1} + e^{u_2} + 1}$$

$$\theta_2 = \frac{e^{u_2}}{e^{u_1} + e^{u_2} + 1}$$

$$\theta_3 = \frac{1}{e^{u_1} + e^{u_2} + 1}$$



➡ $\theta = [\theta_1, \theta_2, \theta_3]^T \sim logistic\text{-}N$ is defined over the **2-simplex (triangle)**

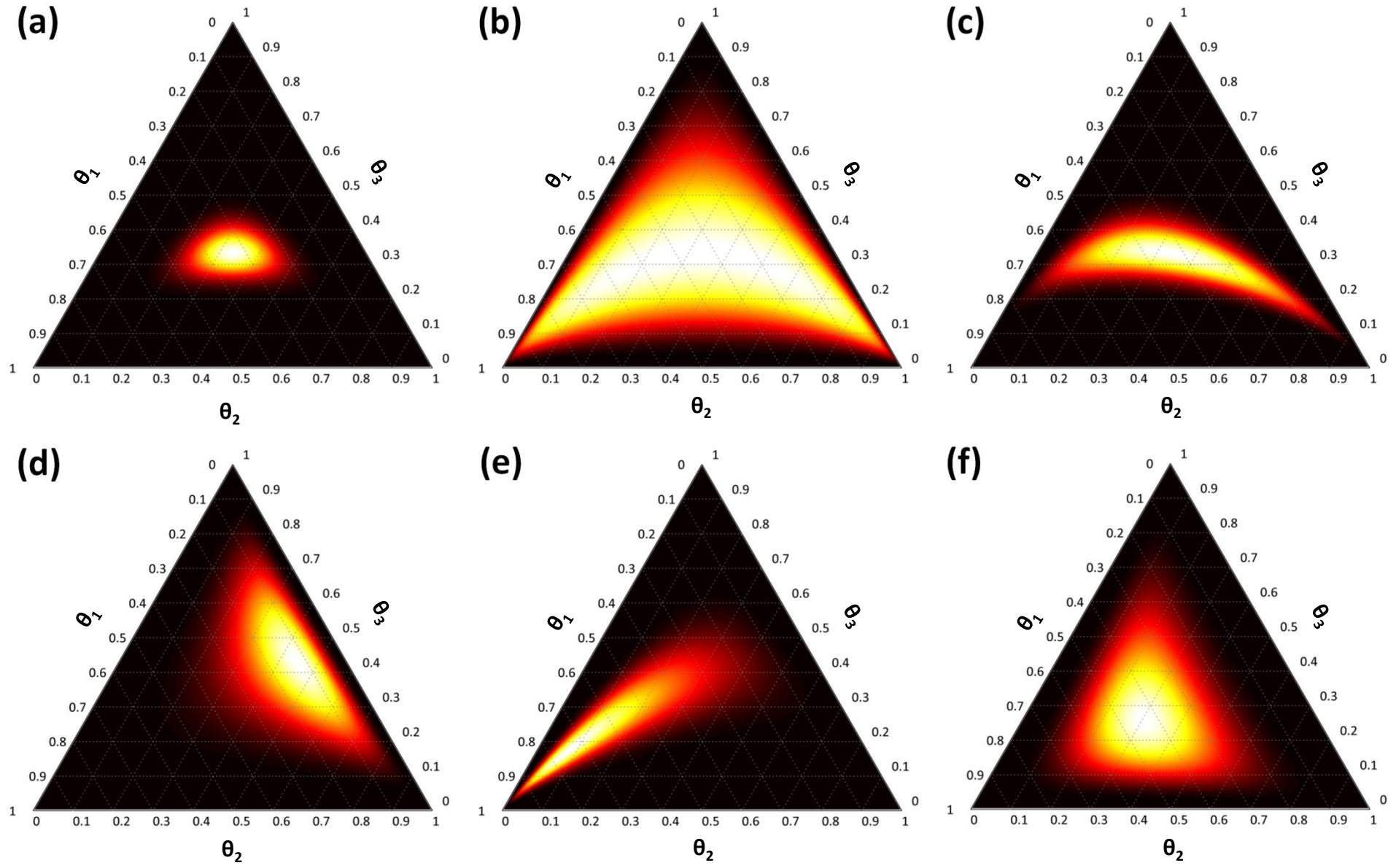
Advantages of the multivariate logistic - N

Flexibility and ability to adequately capture any inter-component correlations

- **Main drawback of the Dirichlet**: The components of a drawn sample have a **"near independence"** structure.

- This independence assumption is **very strong for physiological systems** where **parameters** may exhibit complicated **covariance structures**

- **Logistic-N** takes a **draw of the MVN** and **maps it via transformation to the simplex**. Therefore, takes advantage of the **covariance structure of the MVN** to create **random variables** in the simplex with **various patterns** of **variability** and **correlation**.



(a): $M = \begin{bmatrix} 0 \\ 0 \end{bmatrix}$, $\Sigma = \begin{bmatrix} 0.1 & 0 \\ 0 & 0.1 \end{bmatrix}$

(b): $M = \begin{bmatrix} 0 \\ 0 \end{bmatrix}$, $\Sigma = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$

(c): $M = \begin{bmatrix} 0 \\ 0 \end{bmatrix}$, $\Sigma = \begin{bmatrix} 0.2 & -0.2 \\ -0.2 & 0.5 \end{bmatrix}$

(d): $M = \begin{bmatrix} -1 \\ 0 \end{bmatrix}$, $\Sigma = \begin{bmatrix} 0.5 & 0.2 \\ 0.2 & 0.5 \end{bmatrix}$

(e): $M = \begin{bmatrix} 0.5 \\ -0.5 \end{bmatrix}$, $\Sigma = \begin{bmatrix} 0.7 & -0.1 \\ -0.1 & 0.2 \end{bmatrix}$

(f): $M = \begin{bmatrix} 0.4 \\ 0.1 \end{bmatrix}$, $\Sigma = \begin{bmatrix} 0.5 & 0.4 \\ 0.4 & 0.7 \end{bmatrix}$

Advantages of the multivariate logistic - N

Flexibility and ability to adequately capture any inter-component correlations

- **Main drawback of the Dirichlet**: The components of a drawn sample have a **"near independence"** structure.

- This independence assumption is **very strong for physiological systems** where **parameters** exhibit complicated **covariance structures**

- **Logistic N** takes a **draw of the MVN** and **maps it via transformation to the simplex**. Therefore, takes advantage of the **COV structure of the MVN** to create **random variables** in the simplex with **various patterns** of **variability** and **correlation**.

Practical advantage in terms of implementation

- **Transformation of the normal** and can be **easily coded** and **implemented** in any NLMEM software.

Disadvantages of the multivariate logistic - N

- Parameter estimation is performed in the $N_k(M, \Sigma)$ parameter domain and not on the domain of the parameter of interest ($logistic\text{ - }N$)

  (-) Difficult to interpret results with regard to the physiological parameter of interest

  (-) Difficult to accurately specify priors

- It can be derived that the pdf of $\Theta = [\theta_1, \theta_2, \dots, \theta_{k+1}]^T \sim logistic\text{ - }N$ is:

$$f(\theta_1, \dots, \theta_k) = \frac{1}{\sqrt{|2\pi \cdot \Sigma|}} \cdot \left(\prod_{i=1}^{k+1} \theta_i \right)^{-1} \cdot e^{-\frac{1}{2}(Z-M)^T \cdot \Sigma^{-1} \cdot (Z-M)} \quad , \theta_i \in Simplex^{\,k}$$

, where $Z = [z_1, z_2, \dots, z_k]^T$, $z_i = log\left(\frac{\theta_i}{\theta_{k+1}}\right)$ and $\theta_{k+1} = 1 - \sum_{i=1}^{k} \theta_i$

Providing priors in the transformation domain

- The moments of the $\boldsymbol{logistic\text{-}N}$ for the first k-components are not reducible to a simple form but can be computed by **numerical integration**:

$$E(\theta_i) = \int_0^1 \int_0^{1-\theta_1} \dots \int_0^{1-\sum_{n=1}^{k-1}\theta_n} \theta_i \cdot f(\theta_1, \dots, \theta_k)\, d\theta_k \dots d\theta_2 d\theta_1$$

$$Var(\theta_i) = \int_0^1 \int_0^{1-\theta_1} \dots \int_0^{1-\sum_{n=1}^{k-1}\theta_n} \left(\theta_i - E(\theta_i)\right)^2 \cdot f(\theta_1, \dots, \theta_k)\, d\theta_k \dots d\theta_2 d\theta_1$$

$$Cov(\theta_i, \theta_j) = \int_0^1 \int_0^{1-\theta_1} \dots \int_0^{1-\sum_{n=1}^{k-1}\theta_n} \left(\theta_i - E(\theta_i)\right) \cdot \left(\theta_j - E(\theta_j)\right) \cdot f(\theta_1, \dots, \theta_k)\, d\theta_k \dots d\theta_2 d\theta_1$$

- Depending on the prior information in hand we can either **fit M and Σ to match the prior moments** or **directly fit M and Σ to any raw prior data**.

Application in an empirical absorption model

- The example derived during the population PK modelling of plasma data after a mavoglurant oral formulation dose [1]. Several individuals exhibited irregular concentration profiles with multiple peaks.

- The complex absorption process was described with a flexible empirical input function [2], the **weighted sum of n inverse Gaussian density functions, $IG_j(t)$**.

$$I(t) = FD \sum_{j=1}^{n} f_j IG_j(t)$$

Note that $\sum_{j=1}^{n} f_j = 1$ should hold in each individual !!!

- Csajka *et al* [2] used a specific parameterisation that assure $\sum_{j=1}^{n} f_j = 1$ in each individual, however f_j is allowed to take negative values to meet the constraint.

- Here, we propose that f_j can be efficiently modelled on the simplex with the $logistic\text{-}N$

[1] Wendling T et al, Pharm Res, Submitted.

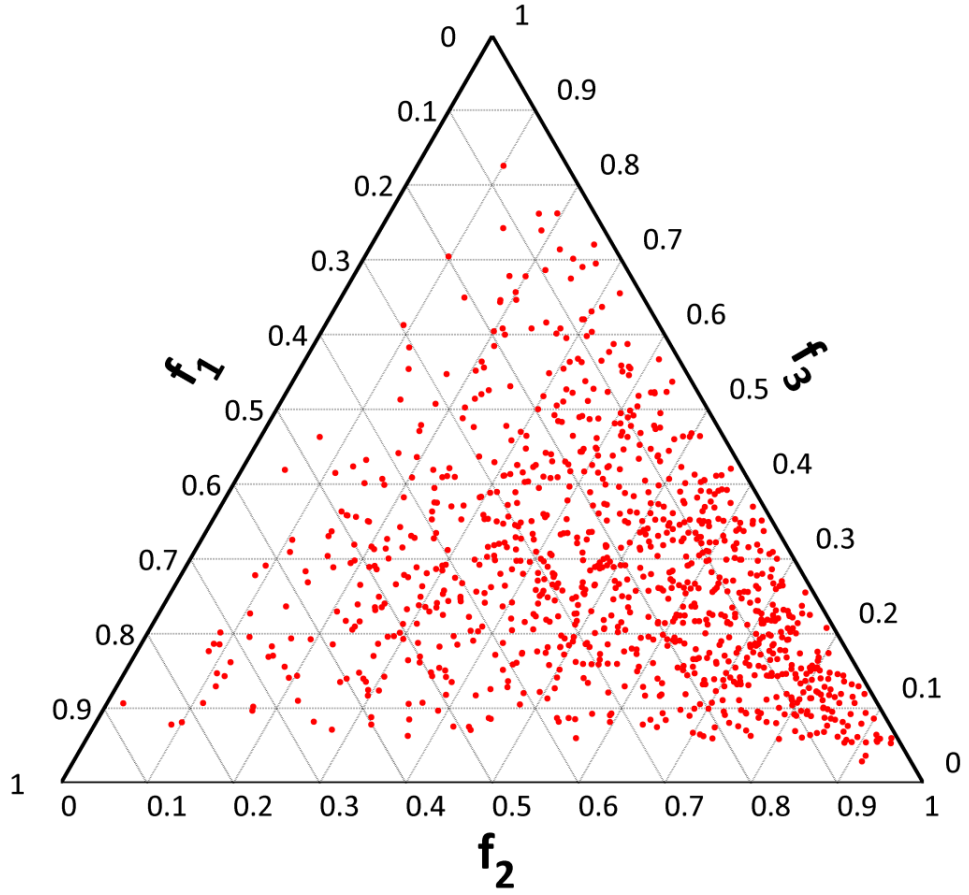
[2] Csajka C et al, Pharm Res. 2005;22(8):1227-1235.

Application in an empirical absorption model

- 1000 individuals were simulated with the final PK model and their f_j parameters were plotted on the simplex

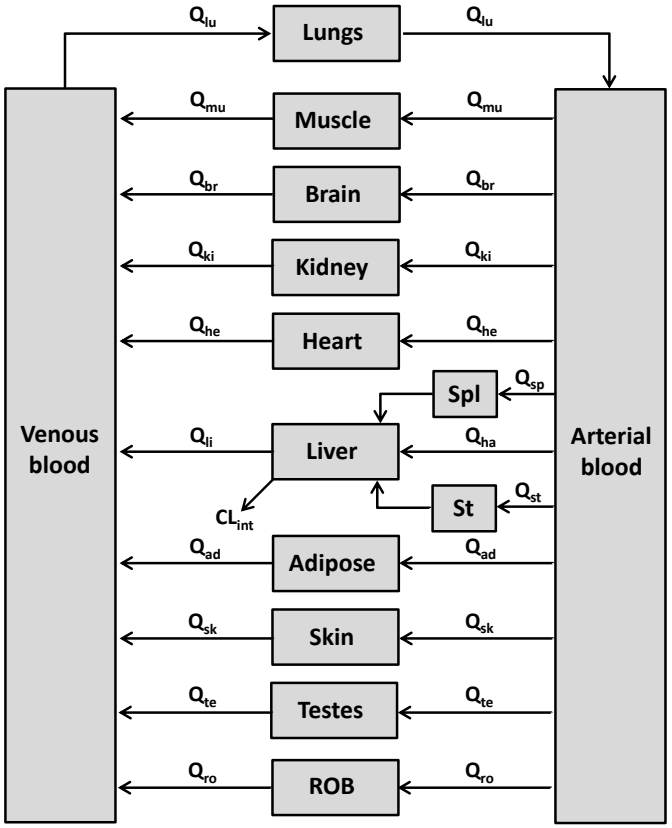
	f_1	f_2	f_3
mean	0.23	0.50	0.27
SD	0.17	0.20	0.14

Corr	f_1	f_2	f_3
f_1	1	-0.73	-0.17
f_2	-0.73	1	-0.55
f_3	-0.17	-0.55	1



Application in a whole-body PBPK model

- We applied ***logistic-N*** in order to incorporate population variability in organ blood flows and volumes of a **previously published diazepam PBPK model** [1,2].



- Of the very few examples in the pharmaceutical arena where PBPK was used in a NLME data analysis framework
- Diazepam plasma concentrations available for 12 individuals sampled up to 72h after a 7mg IV infusion.
- Prior information from pre-clinical species was utilised to facilitate KP estimation.
- However, the **stochastic part of the model was minimal** including IIV only in CL_{int} and a residual error component.

[1] Gueorguieva I et al, J Pharmacokinet Pharmacodyn. 2006;33(5):571-594. [2] Langdon G et al, Eur J Clin Pharmacol. 2007;63(5):485-498.

Variability in organ blood flows and volumes

- Population **variability in organ blood flows** was incorporated as:

$$Q_{j,i} = f_{Q_{j,i}} \cdot CO_i \qquad f_Q \sim logistic\text{-}N\,(M_Q, \Sigma_Q)$$

- Population **variability in organ volumes** was incorporated as:

$$V_{j,i} = f_{V_{j,i}} \cdot WTE_i \qquad f_V \sim logistic\text{-}N\,(M_V, \Sigma_V)$$

- Note that $f_{Q_{j,i}}$ and $f_{V_{j,i}}$ are sampled from separate distributions, so correlation between them cannot be captured with a covariance structure.

- When data are available it is advisable to at least relate CO_i with WTE_i through a fixed covariate relationship (e.g., allometry).

Variability in organ blood flows and volumes

- As only plasma concentrations are observed we do not expect to be able to estimate the values of system parameters and the related random effect terms.

- Prior physiology knowledge should be utilised in order to either fix the system parameters and their variability terms or provide strong informative priors in a Bayesian or MAP method.

- A crucial step was the derivation of $\boldsymbol{M, \Sigma}$ of the respective multivariate normal, which will provide a $\boldsymbol{logistic\text{-}N}$ distribution with the desirable characteristics that match our prior knowledge for the system parameters.

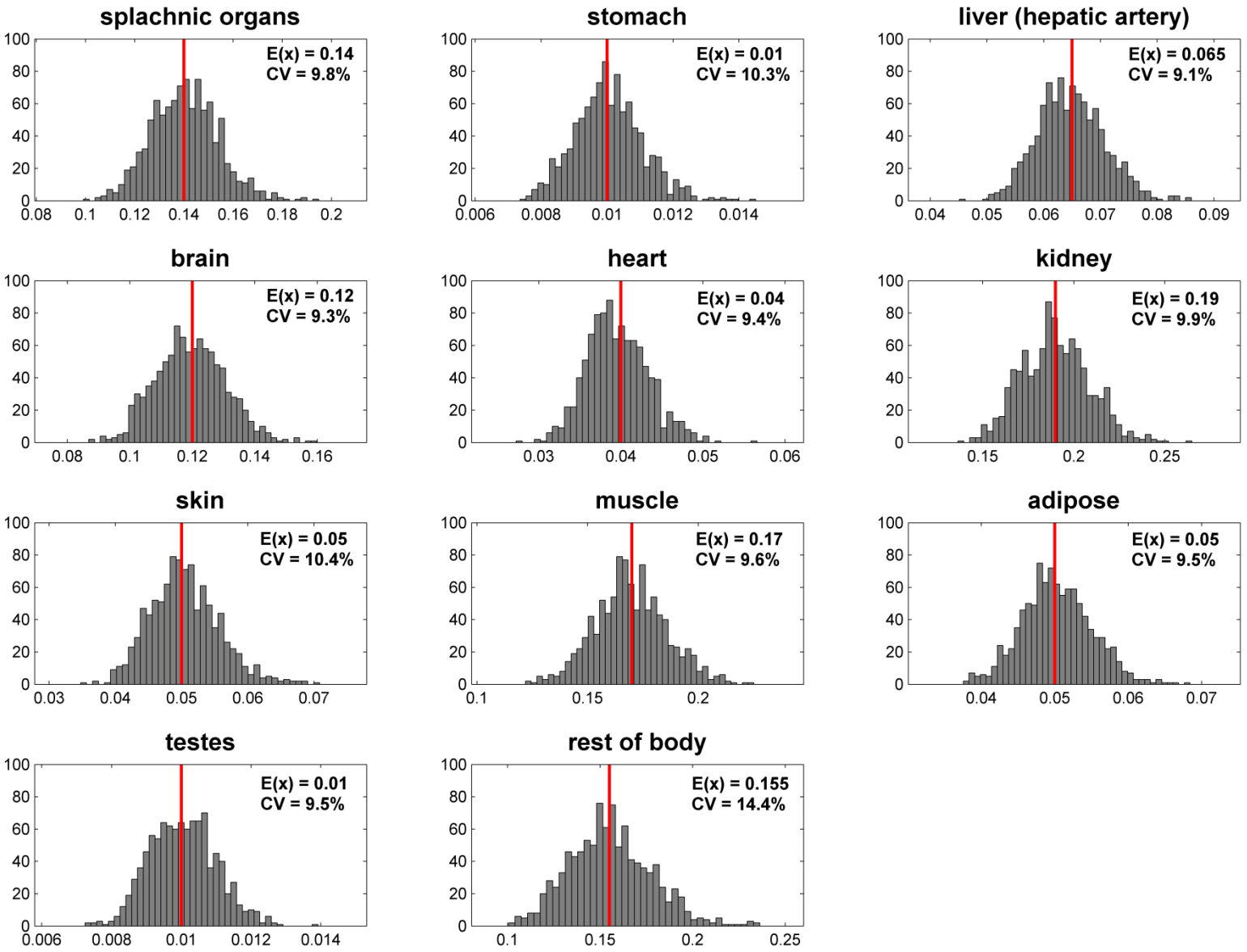
- In the current work we controlled (fixed) $\boldsymbol{M, \Sigma}$ to generate population distributions of organ blood flows and volumes that have

  (-) means matching the known from physiology average individual values [1]

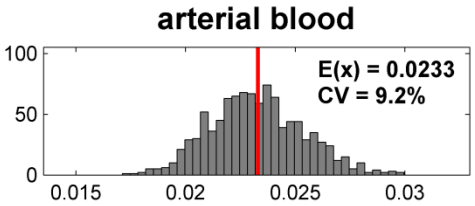
  (-) CV in the range of 10%-30% as assessed in different scenarios

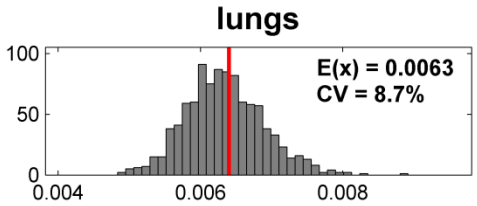
[1] Brown RP et al, Toxicol Ind Health. 1997;13(4):407-484.

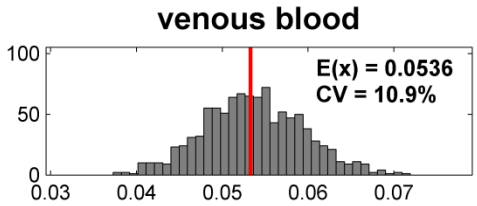
Variability in fractional organ blood flows

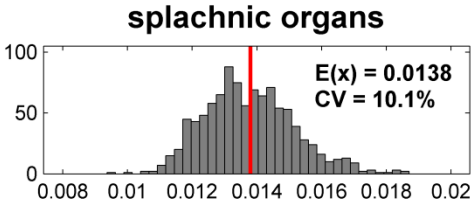


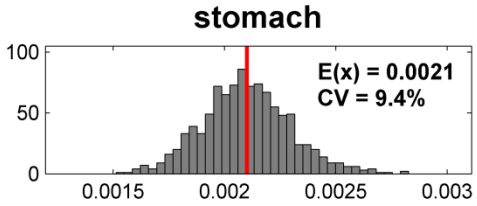
Variability in fractional organ volumes

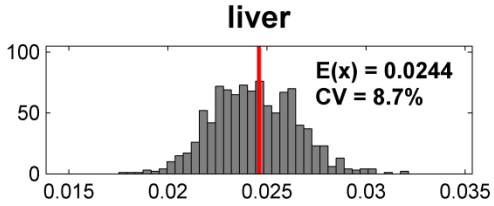


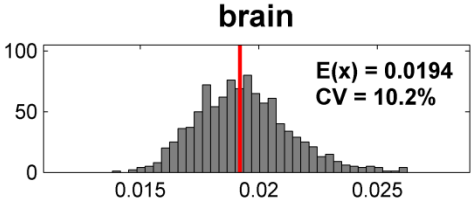


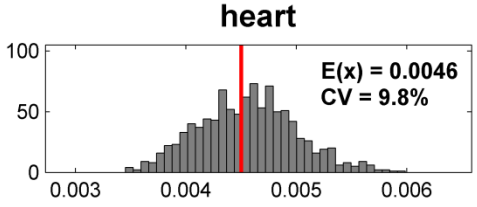


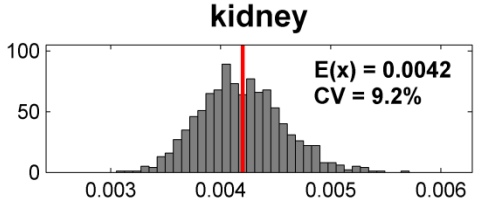


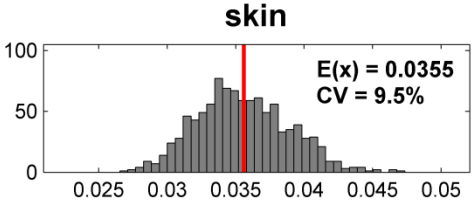


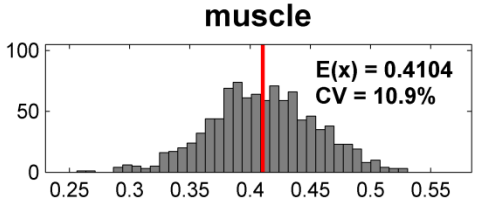


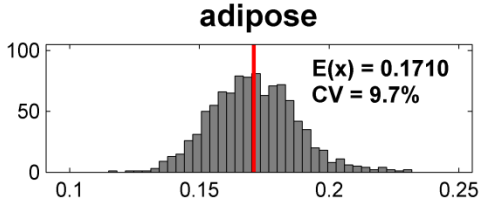


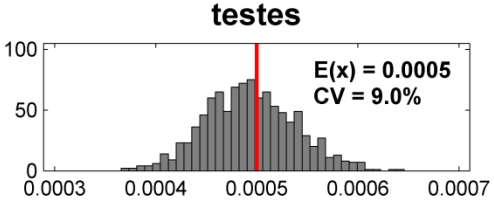


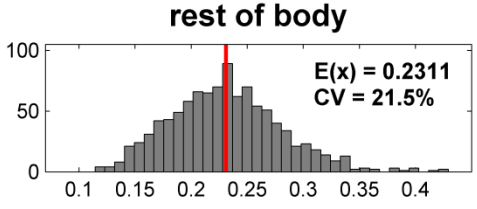












System parameters variability in pop-PBPK

- Investigate the importance of taking into account system parameter variability when performing population data analysis with a PBPK model structure.

- To formally assess the degree of bias that can arise if we omit population variability in PBPK system parameters, we performed a simulation study.

Simulation study procedure (A)

1st step: Use a diazepam PBPK that **incorporates IIV not only on CL_{int} but also on system parameters** to simulate 1000 datasets with the design of the original study and the following scenarios:

- **Scenario A1:** CV of **10%** on organ blood flows and volumes
- **Scenario A2:** CV of **20%** on organ blood flows and volumes
- **Scenario A3:** CV of **30%** on organ blood flows and volumes

2nd step: Fit the simulated datasets with the same model but omitting variability on organ blood flows and volumes

3rd step: For each scenario, among N successfully minimised runs calculate the relative bias in random effect terms estimates

$$REE_n = \frac{\hat{\chi}_n - \chi^*}{\chi^*} \cdot 100$$

$$R_{bias} = \frac{1}{N} \cdot \sum_{n=1}^{N} REE_n$$

Simulation study procedure (B)

1st step: Use a diazepam PBPK that **incorporates IIV not only on CL_{int} and system parameters but also on adipose KP** to simulate 1000 datasets with the design of the original study and the following scenarios:

- **Scenario B1:** CV of **10%** on organ blood flows and volumes
- **Scenario B2:** CV of **20%** on organ blood flows and volumes
- **Scenario B3:** CV of **30%** on organ blood flows and volumes

2nd step: Fit the simulated datasets with the same model but omitting variability on organ blood flows and volumes

3rd step: For each scenario, among N successfully minimised runs calculate the relative bias in random effect terms estimates

$$REE_n = \frac{\hat{\chi}_n - \chi^*}{\chi^*} \cdot 100$$

$$R_{bias} = \frac{1}{N} \cdot \sum_{n=1}^{N} REE_n$$

Simulation study results

Case A

R_{bias} (%) in random effect estimates

CV	N	$IIV\ CL_{int}$	$Res\ V$
10%	981	-2.5% (-8.3 , 3.7)	**+2.2%** (1.1 , 3.3)
20%	982	+3.8% (-2.0 , 10.1)	**+9.0%** (7.6 , 10.3)
30%	992	**+47.3%** (35.8 , 62.2)	**+34.9%** (31.4 , 39.5)

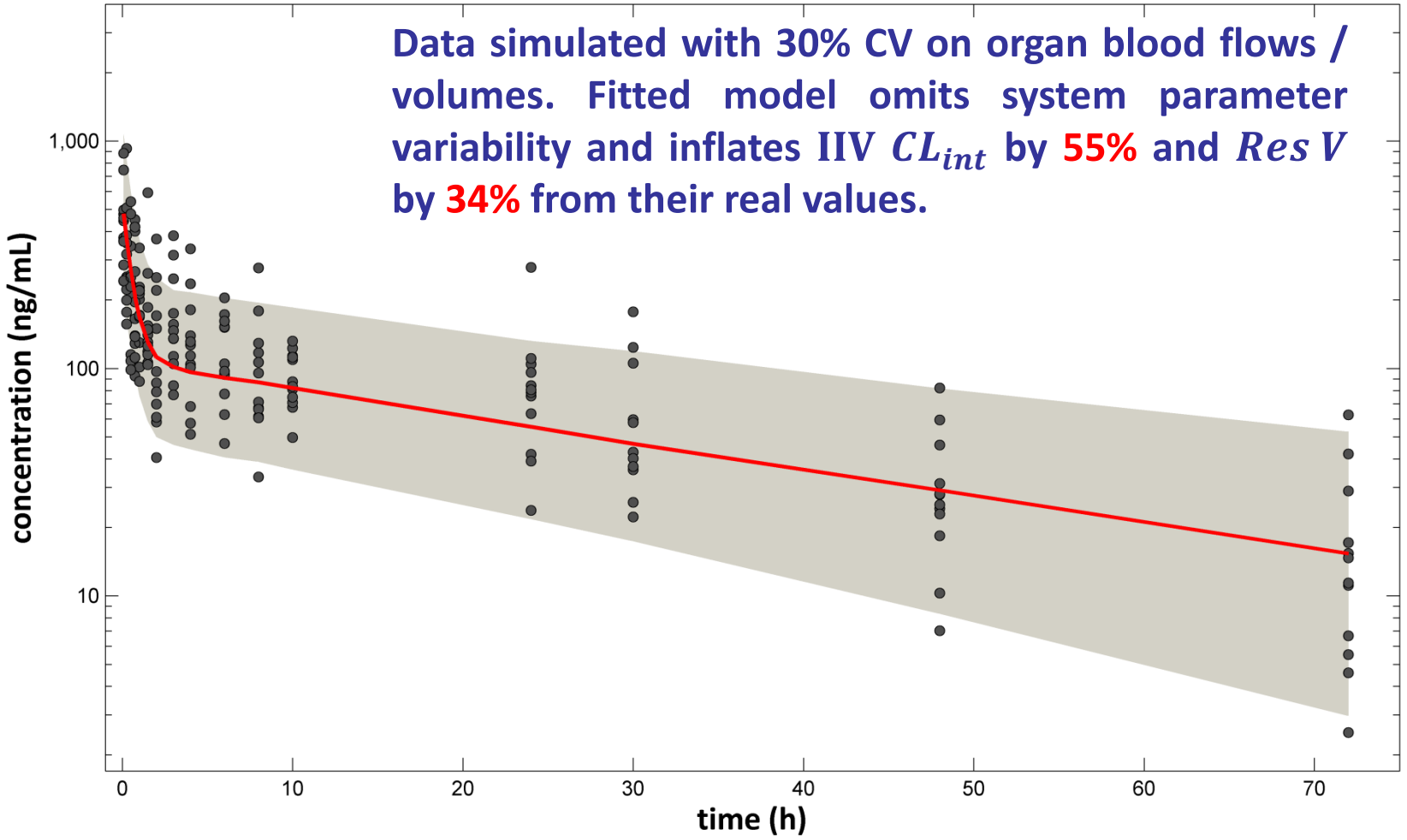
Case B

R_{bias} (%) in random effect estimates

CV	N	$IIV\ CL_{int}$	$IIV\ KP_{adi}$	$Res\ V$
10%	920	-3.6% (-8.7 , 2.0)	**+8.4%** (2.3 , 15.2)	+0.6% (-0.6 , 1.8)
20%	905	-3.2% (-8.7 , 2.6)	**+45.7%** (37.2 , 54.9)	**+2.9%** (1.7 , 4.2)
30%	904	-5.4% (-10.5 , 0.2)	**+202%** (173 , 241)	**+7.8%** (6.5 , 9.1)

VPC of a simulated dataset fit

- Even in cases where the stochastic model is substantially biased we can't always be able to spot this problem by looking at the model fit.



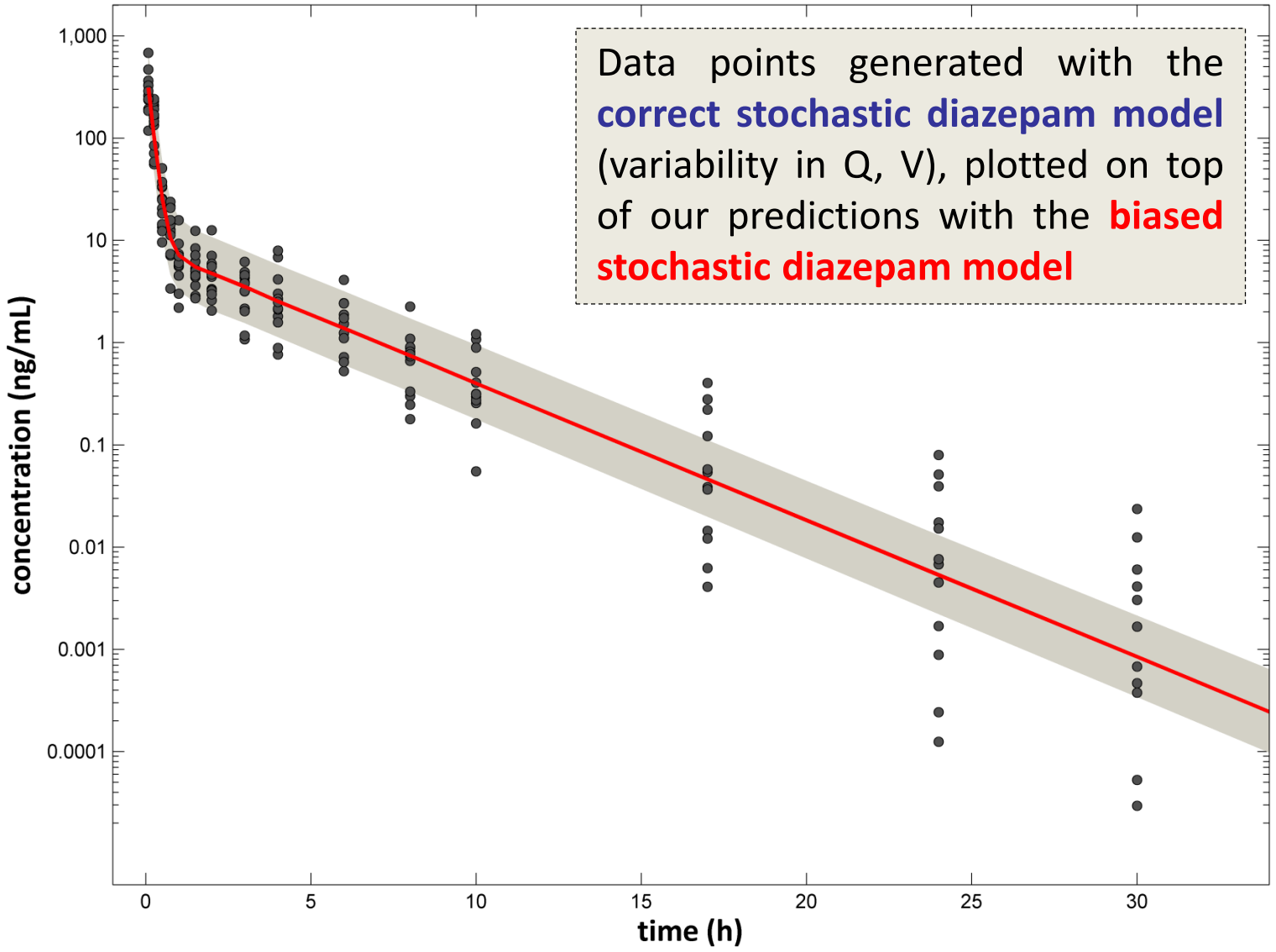
A biased stochastic model affects extrapolation

- Population PBPK models are rarely developed solely to describe the data, but mainly for their ability to extrapolate and perform predictions.
- If the stochastic part of the population PBPK model is biased its predictive performance may decline.

Extrapolation example:

- Diazepam is compound with low E_h and high plasma binding.
- Assume now a hypothetical scenario where due to a specific situation (e.g. enzyme induction, polymorphism, change in binding), E_h increases to 0.8.
- In such a situation, the PBPK model with the biased variability structure will fail to extrapolate and correctly predict variability in plasma concentrations.

A biased stochastic model affects extrapolation



Conclusions

- The use of **hierarchical - population PBPK models to analyse clinical data** is an approach with a **progressively increasing impact**.

- This **approach may be even more popular in the future** with the advance of experimental methods to determine tissue concentrations noninvasively.

- In this work **we examined the most common types of constraints** in such models that arise due to the fact that **parameters represent actual physiological processes**.

- **Transformations of the normal** not only can **satisfy these constraints** but also **offer high flexibility** during characterisation of the parameters distribution.

- Development of the stochastic part of a population PBPK model is **methodologically challenging but crucial for the ability to perform extrapolation** outside the studied dataset and conditions.

Acknowledgements

Supervisors:

Leon Aarons

Aleksandra Galetin

Amin Rostami-Hodjegan

Colleagues in UoM:

Kayode Ogungbenro

Alison Margolskee

Adam Darwich

Andres Olivares-Morales

Thierry Wendling

Supplementary Slides

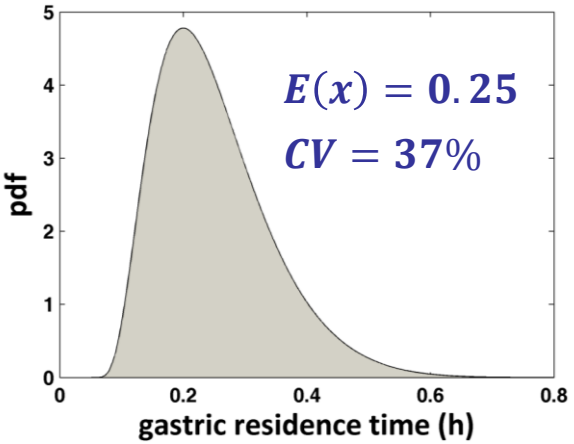
Application in Type 1 example

- **Depending on the prior information** in hand we can either:
  - **Fit M and Σ to the moments of the prior distribution (Gastric residence time)**

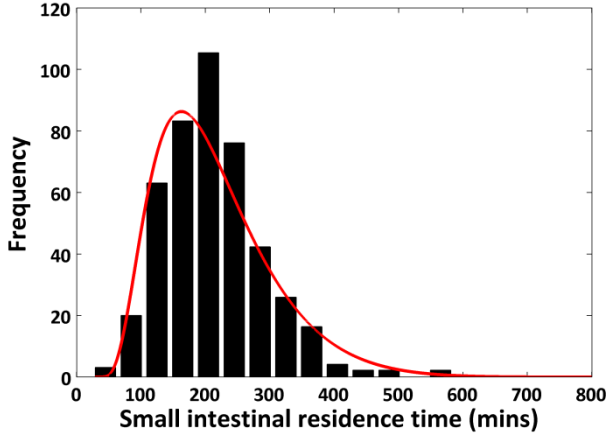
    Prior knowledge suggests that GRT has a population mean of 0.25 h with a 37% CV. Fit $\boldsymbol{M}$ and $\boldsymbol{\Sigma}$ to the suggested moments using numerical integration and an optimisation algorithm.

    $\boldsymbol{M = -1.4225}$ $\quad$ $\boldsymbol{\Sigma = 0.6065}$

    $\alpha = 0.05\ h$ $\quad$ $\beta = 1\ h$



  - **Directly fit M and Σ to the actual prior distribution (Small intestinal residence time)**



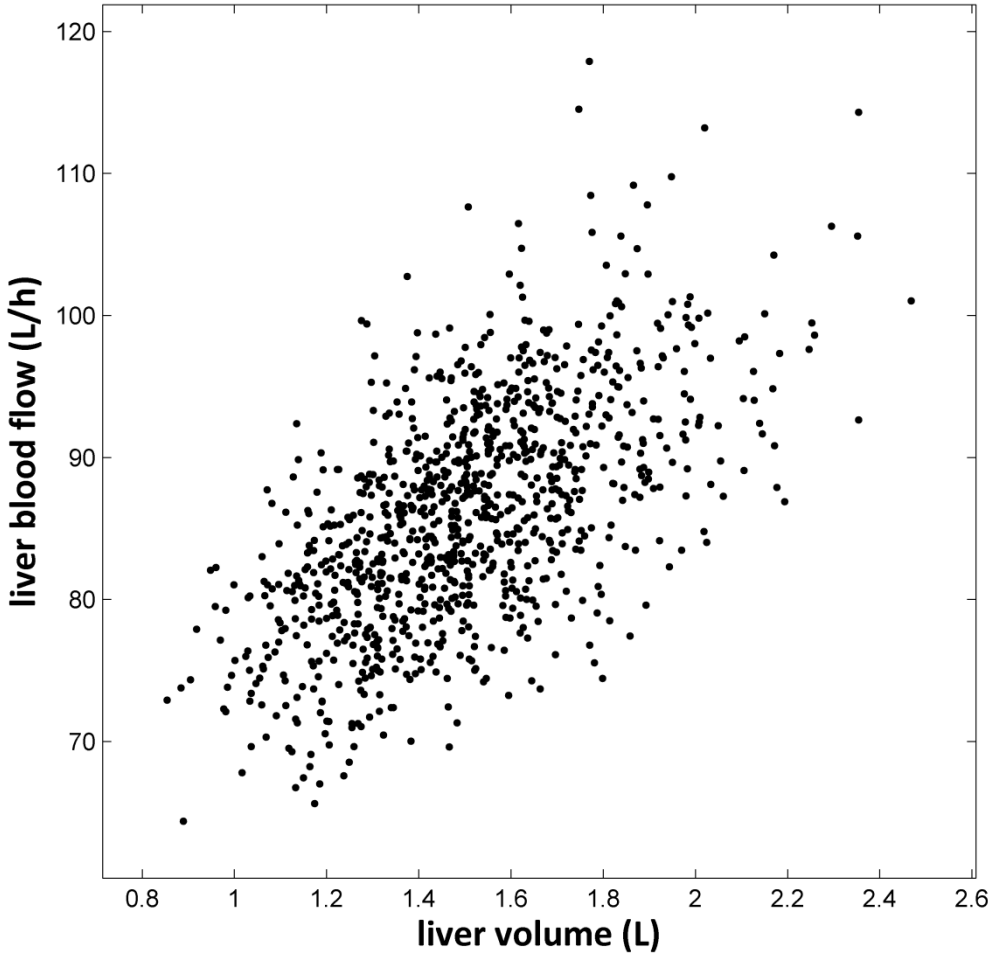
Extract observed data (Yu, 1996) with regard to SIRT and then directly use these data to obtain maximum likelihood estimates of the $\boldsymbol{M}$ and $\boldsymbol{\Sigma}$ parameters of the pdf.

$\boldsymbol{M = -1.56}$ $\quad$ $\boldsymbol{\Sigma = 0.62}$

$\alpha = 29\ mins$ $\quad$ $\beta = 999\ mins$

Application in Type 2 example

- Plotted below are liver volumes and blood flows from 1000 individuals randomly sampled from Simcyp's default virtual population.



$0.85 < liver\ volume\ (L) < 2.47$

$mean(liver\ volume) = 1.50\ L$

$SD(liver\ volume) = 0.26\ L$

$64.38 < liver\ bl.flow\ (L/h) < 117.89$

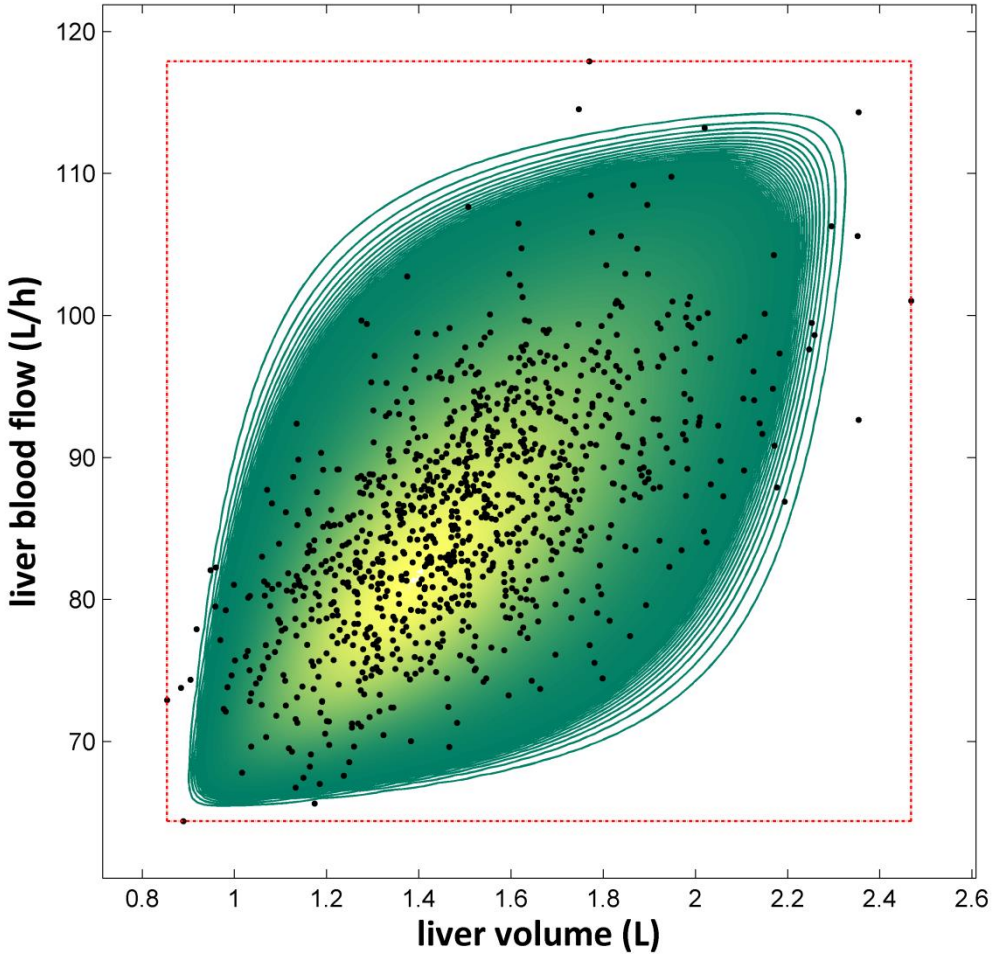
$mean(liver\ bl.flow) = 86.02\ L/h$

$SD(liver\ bl.flow) = 7.97\ L/h$

$Corr(volume, bl.flow) = 0.61$

Application in Type 2 example

- Fit M and Σ to the moments of the prior distribution



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$SD(liver\ bl.flow) = 7.97\ L/h$

$Corr(volume, bl.flow) = 0.61$

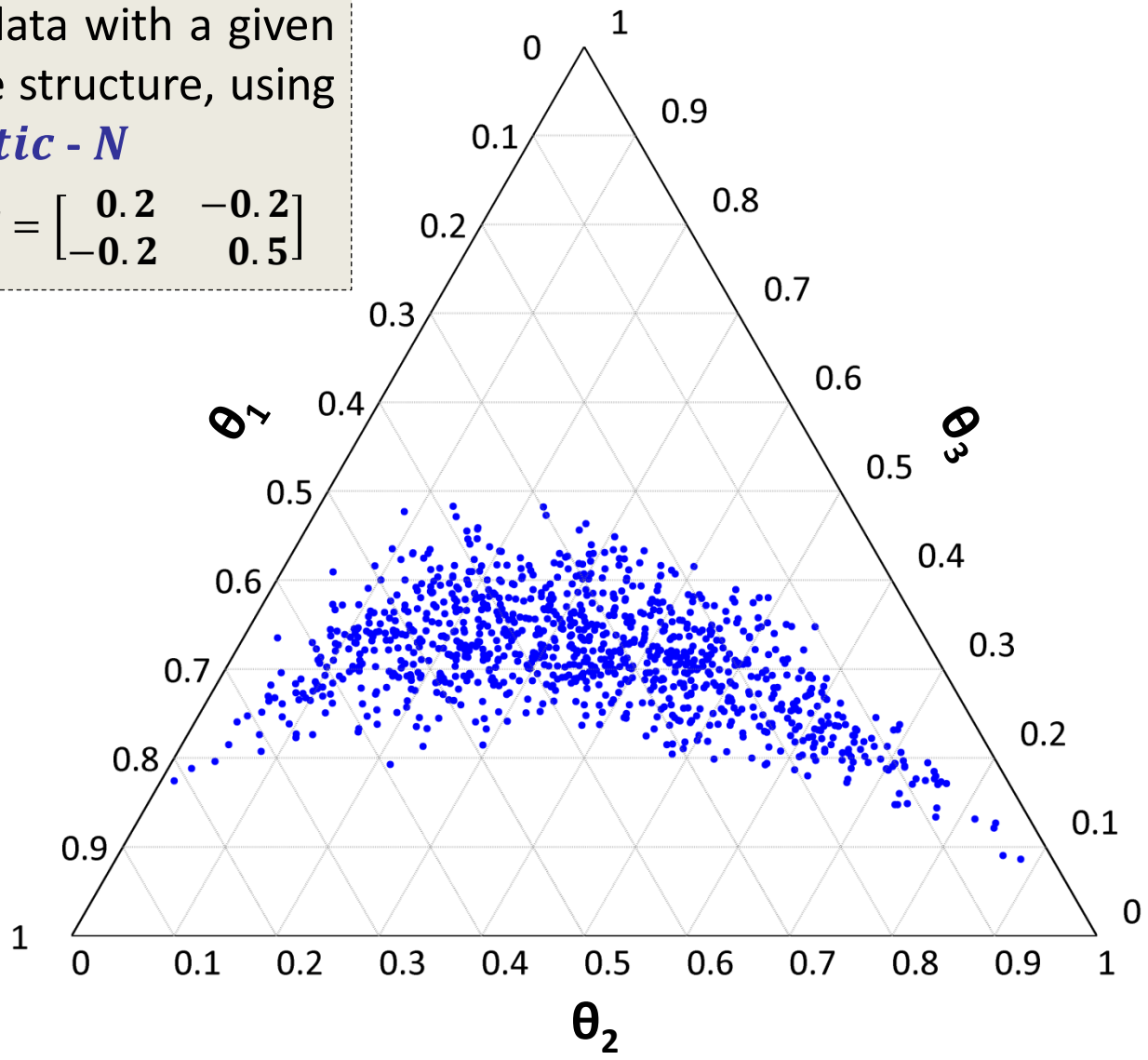
$$A = \begin{bmatrix} 0.85 \\ 64.38 \end{bmatrix} \qquad B = \begin{bmatrix} 2.47 \\ 117.89 \end{bmatrix}$$

$$\boldsymbol{M} = \begin{bmatrix} \boldsymbol{-0.45} \\ \boldsymbol{-0.43} \end{bmatrix} \qquad \boldsymbol{\Sigma} = \begin{bmatrix} \boldsymbol{0.55} & \boldsymbol{0.31} \\ \boldsymbol{0.31} & \boldsymbol{0.46} \end{bmatrix}$$

Advantages of the multivariate logistic - N

Simulate data with a given covariance structure, using the ***logistic - N***

$$\boldsymbol{M} = \begin{bmatrix} \mathbf{0} \\ \mathbf{0} \end{bmatrix}, \boldsymbol{\Sigma} = \begin{bmatrix} \mathbf{0.2} & \mathbf{-0.2} \\ \mathbf{-0.2} & \mathbf{0.5} \end{bmatrix}$$



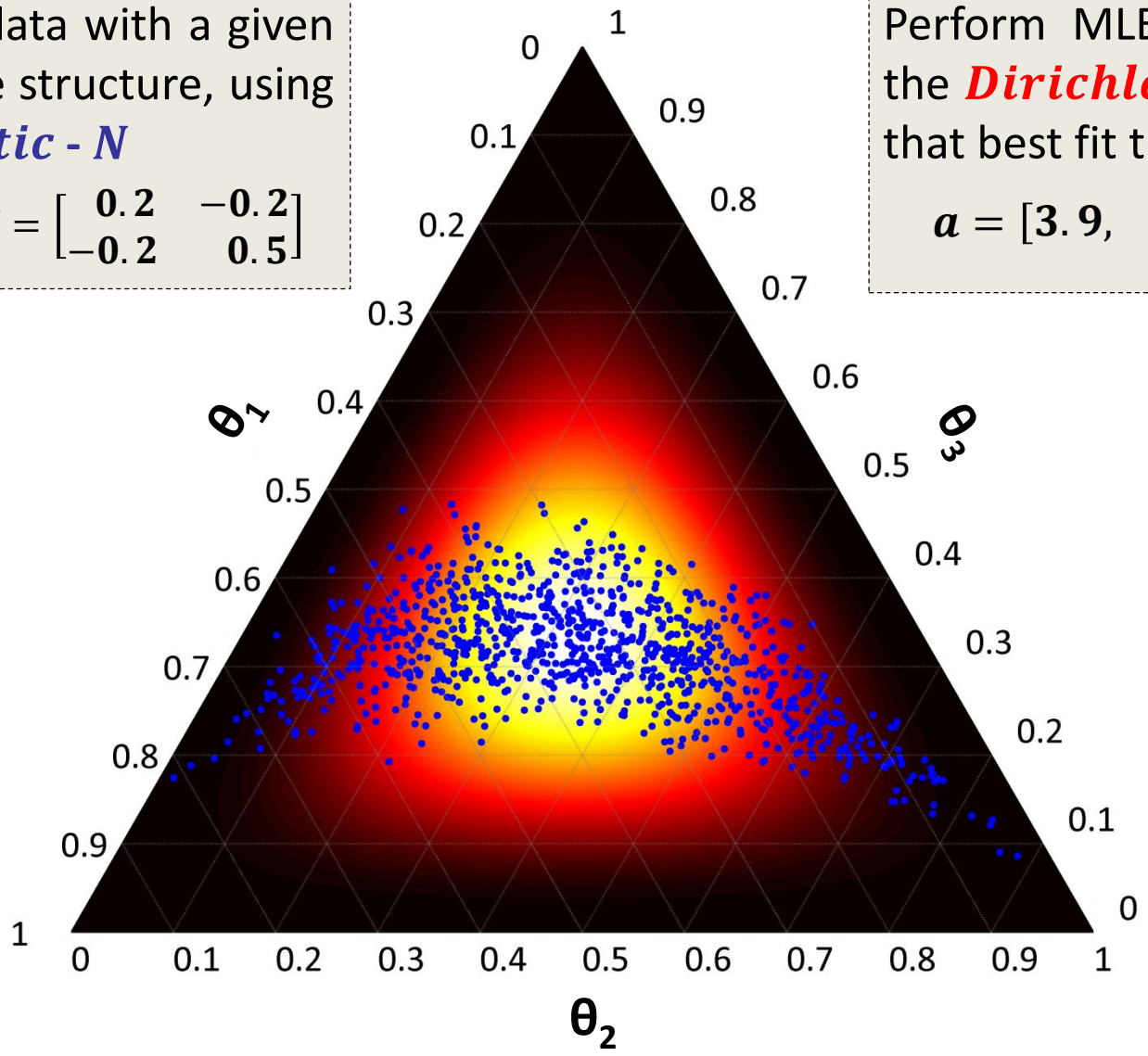
Advantages of the multivariate logistic - N

Simulate data with a given covariance structure, using the ***logistic - N***

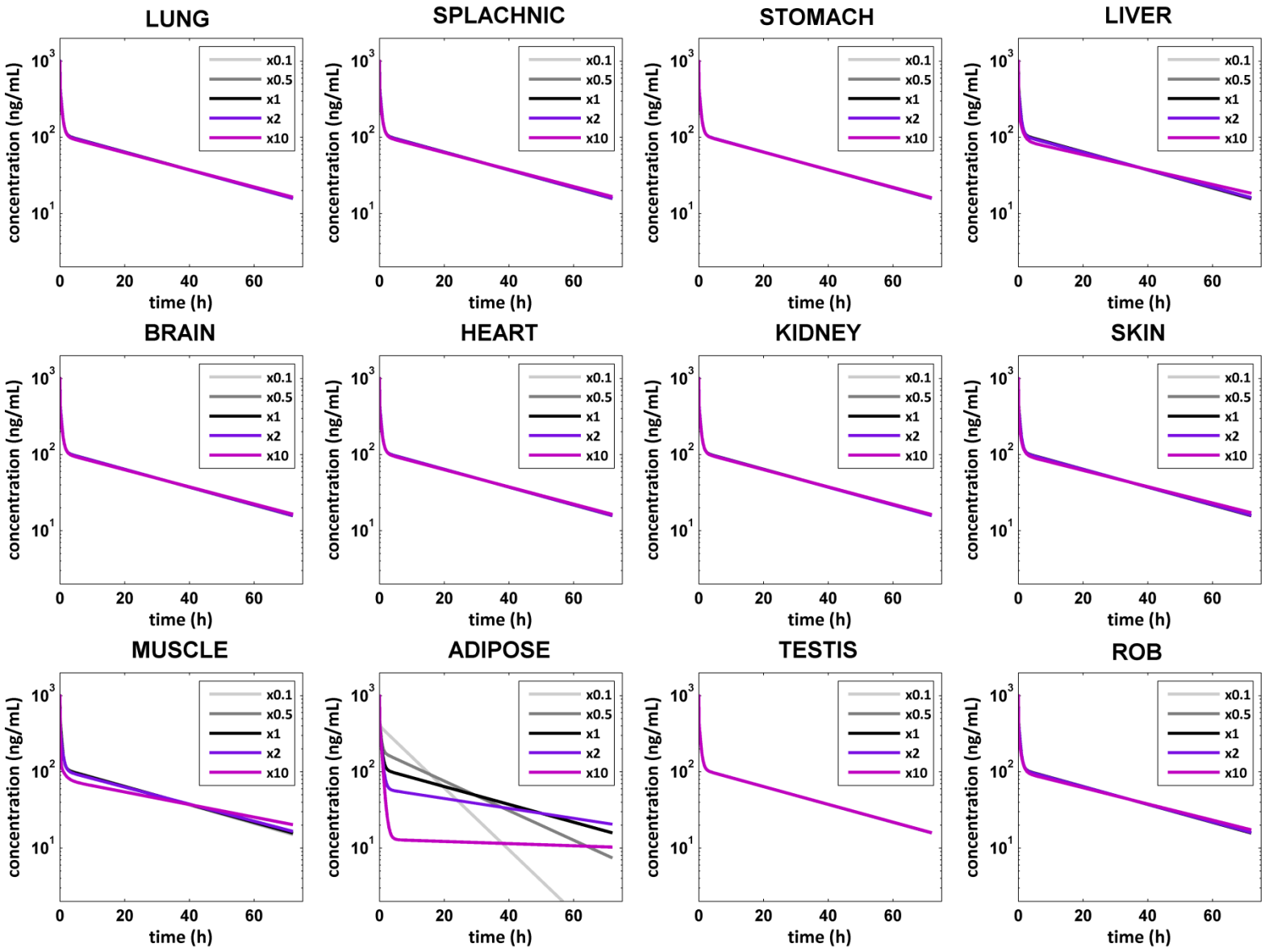
$$\boldsymbol{M} = \begin{bmatrix} \mathbf{0} \\ \mathbf{0} \end{bmatrix}, \boldsymbol{\Sigma} = \begin{bmatrix} \mathbf{0.2} & \mathbf{-0.2} \\ \mathbf{-0.2} & \mathbf{0.5} \end{bmatrix}$$

Perform MLE to estimate the ***Dirichlet*** parameters that best fit the data

$$\boldsymbol{a} = [\mathbf{3.9}, \quad \mathbf{3.8}, \quad \mathbf{3.9}]$$



Sensitivity of plasma output on tissue KP values



Application in an empirical absorption model

```
; Assume the 2-d untransformed variable U ~ N (M, Σ)
  U1 = THETA (1) + ETA (1)
  U2 = THETA (2) + ETA (2)

; Create the 3-d variable FR ~ logistic-N referring to the f_j parameters
  FR1 = EXP (U1) / (EXP (U1) + EXP (U2) + 1)
  FR2 = EXP (U2) / (EXP (U1) + EXP (U2) + 1)
  FR3 = 1 / (EXP (U1) + EXP (U2) + 1)

; Initial estimates for the M and Σ parameters of the 2-d normal
  $ THETA
    M1          ; first element of the 2-d mean vector M
    M2          ; second element of the 2-d mean vector M

  $ OMEGA BLOCK (2)
    Σ11         ; 2 x 2 covariance matrix Σ
    Σ21  Σ22
```