Non-Clinical Statistics Conference | 2008

Design Space for analytical methods
A Bayesian perspective based on multivariate models and prediction

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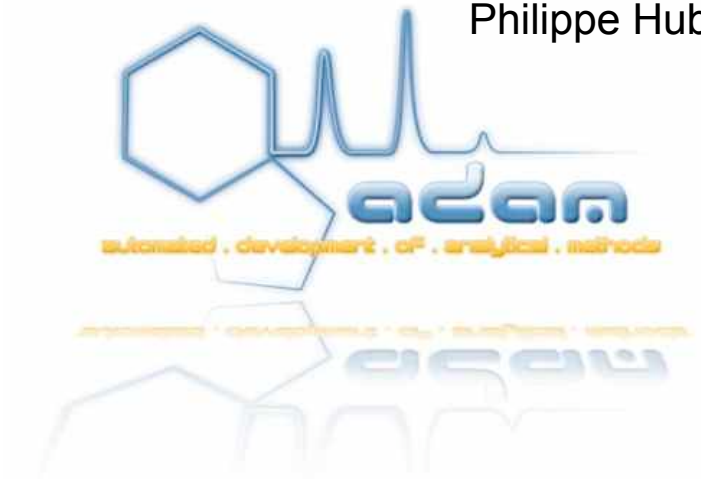


Wednesday, 24 September

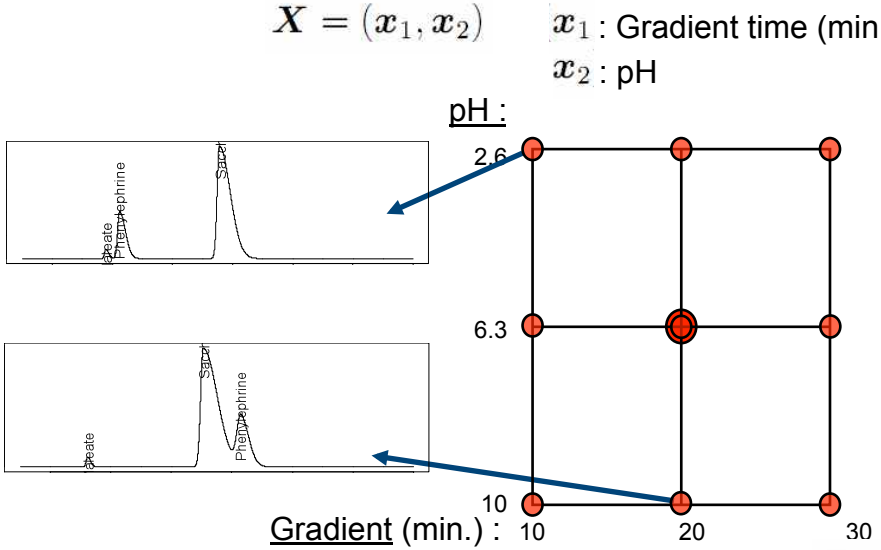
Overview

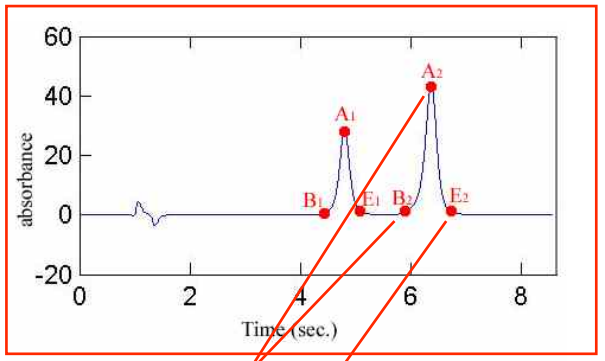
- The process
  - Liquid chromatography
  - Multivariate regression – correlated responses
- Definition
  - Design Space
  - Objective functions
- Bayesian model
  - Introduction
  - Priors
  - Introducing constraints in MCMC
  - Predictions
- Results
- Conclusions

Example of application

- A chromatographic method is to be optimized using DOE and response surface models
- *P*=3 peaks to be separated in the shortest time

$X = (x_1, x_2)$ x_1 : Gradient time (min.)
x_2 : pH





$$Y = ((B_1, A_1, E_1), (B_2, A_2, E_2), ..., (B_P, A_P, E_P))$$

$$\begin{cases} Y = XB + \epsilon \\ \text{with } \epsilon \sim N(0, \Sigma) \end{cases} \longleftarrow Y_{(N \times 3P)}$$

These 9 responses are correlated

Design Space: set of conditions (pH, Gradient,…) in the domain, such that separation and short run are guaranteed for the future

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ICH Q8 (may 2006) definition

Design Space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

→ The Design Space is the set of conditions giving solution within Acceptance Limits :

- "*…the established range of process parameters and formulation attributes that have been demonstrated to provide assurance of quality.*"
- "*Working within is not considered as a change in the analytical method.*"

n.b.: If the Design Space is large w.r.t. control parameters or conditions, the solution is considered as robust

Proposal : definition of Design Space

When the process is known

Design Space (DS) :

$$\{\boldsymbol{x}_k \in \chi \mid P(\boldsymbol{Y}(\boldsymbol{x}_k) \in \boldsymbol{\Lambda}) \geq \pi_{min}\}$$

χ omain of Factors

$\boldsymbol{x}_k$ et of Combinations of Factors

$\boldsymbol{Y}(\boldsymbol{x}_k)$ e Responses obtained for the $\boldsymbol{x}_k$ ndition (e.g. resolution)

$\boldsymbol{\Lambda}$ e set of Acceptance Limits (e.g. resolution>1.2)

π_{min} e Quality Level (e.g. *P*(resolution>1.2) > 0.8)

However :

- in development & validation, the process is unknown, its performances are estimated with uncertainty

- purpose : predict the space that will likely in the future provide most outputs within acceptance limits

Proposal : definition of design space

When the process is **un**known

Expected Design Space (DS) :

$$DS = \{\boldsymbol{x}_k \in \chi \mid E_{\hat{\boldsymbol{\theta}}}[P(\boldsymbol{Y}(\boldsymbol{x}_k) \in \boldsymbol{\Lambda}) \mid \hat{\boldsymbol{\theta}}] \geq \pi_{min}\}$$

Ex: $\hat{\boldsymbol{\theta}} = [\hat{\boldsymbol{\beta}}, \hat{\sigma}_{\epsilon}^2]$

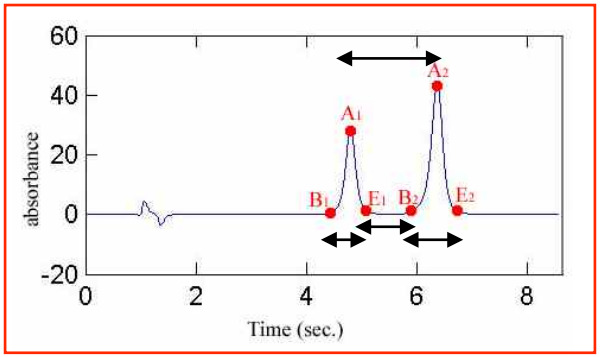
- The probability of achieving the acceptance limits is larger than π_{min}, the quality level
  - Given the estimates of process parameters $\hat{\theta}$
- The DS is located using predictions from models estimated during development & validation experiments

Chromatographic optimization

Specific problem:

Criteria / Objective functions

- Sum or product of the responses…
- Discontinuity
- Non linearity



Ex:

$$\left|\begin{array}{lll} O_1 = \text{Max. Time} & = \max\limits_{1\le j\le P}(A_j) & < \lambda_1 \\ O_2 = \text{Min. Separation} & = \min\limits_{1\le j\le P-1}(B_{(j+1)} - E_{(j)}) & < \lambda_2 \\ \ldots & \ldots & \ldots \\ O_Z = \text{Min. Resolution} & = \min\limits_{1\le j\le P-1}\left(\frac{2*(A_{(j+1)} - A_{(j)})}{(E_{(j+1)} - B_{(j+1)}) + (E_{(j)} - B_{(j)})}\right) & < \lambda_Z \end{array}\right|$$

$\boldsymbol{O}$ $\qquad$ $\boldsymbol{\Lambda}$

$$DS = \{\boldsymbol{x}_k \in \chi \mid E_{\hat{\boldsymbol{\theta}}}[P(\boldsymbol{O} \in \boldsymbol{\Lambda}) \mid \hat{\boldsymbol{\theta}}] \geq \pi_{min}\}$$

→ i.e. DS is the set of conditions, such that the probability that Objectives will be simultaneously (jointly) within the Acceptance Limits is higher than π_{min}

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Bayesian model

- Multivariate multiple linear regression model

$$(\boldsymbol{Y}|X_1 = x_{01}, ..., X_F = x_{0F}, I) \sim N(\boldsymbol{B}'\boldsymbol{x}_0, \boldsymbol{\Sigma})$$

$$\boldsymbol{\theta} = [\boldsymbol{B}, \boldsymbol{\Sigma}]$$

- The joint posterior distribution for $\boldsymbol{\theta}$ is obtained as follow :

$$p(\boldsymbol{B}, \boldsymbol{\Sigma}|data, I) \propto p(data|\boldsymbol{B}, \boldsymbol{\Sigma}, I).p(\boldsymbol{B}, \boldsymbol{\Sigma}|I)$$

- $\boldsymbol{B}$ and $\boldsymbol{\Sigma}$ are assumed independent, therefore

$$p(\boldsymbol{B}, \boldsymbol{\Sigma}|data, I) \propto p(data|\boldsymbol{B}, \boldsymbol{\Sigma}, I).p(\boldsymbol{B}|I).p(\boldsymbol{\Sigma}|I)$$

Priors and hyperpriors

- Non informative priors for $\boldsymbol{B}$

$$\beta_{jf} \sim N(b_{jf}, \tau_{jf}) \qquad 1 \leq j \leq 3P, \quad 1 \leq k \leq F$$

(# responses; # factors)

with

$$b_{jf} \sim N(0, 1e-6)$$
$$\tau_{jf} \sim \Gamma(0.1, 0.1)$$

- Non informative Priors for $\boldsymbol{\Sigma}$ [Dokoumetzidis & Aarons, J. Pharm. and Pharm., 32, 2005]

$$\boldsymbol{\Sigma}^{-1} \sim W_{3P}(\nu.\boldsymbol{\Omega}, \nu)$$

with

$$\boldsymbol{\Omega} = 0.1 * \boldsymbol{I}_{3P}$$
$$\nu = 3P$$

$\boldsymbol{\Omega}$: covariance matrix

Informative priors

- Setting informative priors
  - Responses are known to be correlated
    - The begin, the end, the apex of one peak move together
  - Retention times can be accurately modelled as a function of factors using classical response surface model [Schoenmakers, 1986] [Dewé *et al*., 2004]

$$\longrightarrow \boldsymbol{\Sigma}^{-1} \sim W_{3P}(\nu.\boldsymbol{\Omega}, \nu)$$

$$\boldsymbol{\Omega} = \boldsymbol{I}_P \otimes \boldsymbol{V}$$

$$cov(\boldsymbol{Y}_j, \boldsymbol{Y}_j) = \text{diag}(\boldsymbol{V}) = 0.01 * \boldsymbol{I}_3$$

$$cov(\boldsymbol{Y}_i, \boldsymbol{Y}_j) = \text{non-diag}(\boldsymbol{V}) = 0.008, \quad i \neq j$$

$$\nu = 3P + cst$$

- The higher the correlation
- The higher ν

} The more informative the prior

Ex :

Peak 1 Peak 2

$$\boldsymbol{\Omega} = \begin{bmatrix} 0.01 & 0.008 & 0.008 & 0 & 0 & 0 & \cdots \\ 0.008 & 0.01 & 0.008 & 0 & 0 & 0 & \cdots \\ 0.008 & 0.008 & 0.01 & 0 & 0 & 0 & \cdots \\ 0 & 0 & 0 & 0.01 & 0.008 & 0.008 & \cdots \\ 0 & 0 & 0 & 0.008 & 0.01 & 0.008 & \cdots \\ 0 & 0 & 0 & 0.008 & 0.008 & 0.01 & \cdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots \end{bmatrix}$$

Introduction of constraints in MCMC

- As stated, the prior on Σ takes into account the correlation between the *begin*, the *apex* and the *end* of one peak

- But, no constraint is put on some obvious relations between *begin*, *apex* and *end*
  - During MCMC simulations, one can observe for instance ***A***<***B*** or ***E***<***A***

- One can introduce the constraint on the relations between *begin*, *apex* and *end* by rejecting the generated B^s and Σ^s from the MCMC sample that do not fulfil the following conditions, for each $\boldsymbol{x}_0$:

$$\begin{aligned} \boldsymbol{A}(\boldsymbol{x}_0) - \boldsymbol{B}(\boldsymbol{x}_0) < 0 \\ \boldsymbol{E}(\boldsymbol{x}_0) - \boldsymbol{A}(\boldsymbol{x}_0) < 0 \\ (\boldsymbol{E}(\boldsymbol{x}_0) - \boldsymbol{B}(\boldsymbol{x}_0) < 0) \end{aligned} \quad \forall \boldsymbol{x}_0 \in \chi$$

Prediction

- Plausible values of one prediction $\tilde{Y}$, conditional to the available information : predictive posterior distribution

$$p(\tilde{\boldsymbol{Y}}|data, I) = \int\int p(\tilde{\boldsymbol{Y}}|\boldsymbol{B}, \boldsymbol{\Sigma}, data, I).p(\boldsymbol{B}, \boldsymbol{\Sigma}|data, I)dBd\Sigma$$

→ A draw from the joint posterior of parameters

→ A draw from the Normal (model) conditionally to the posterior of parameters

(1) For s=1 to nsim
(2) Sample $\boldsymbol{\theta}^s = [\boldsymbol{B}^s, \boldsymbol{\Sigma}^s]$ from $p(\boldsymbol{B}, \boldsymbol{\Sigma}|data, I)$
(3) Sample $\tilde{\boldsymbol{Y}}$ from $p(\tilde{\boldsymbol{Y}}|\boldsymbol{B}^s, \boldsymbol{\Sigma}^s, I) = N(\boldsymbol{B}^{s\prime}\tilde{\boldsymbol{X}}, \boldsymbol{\Sigma}^s)$
(4) End

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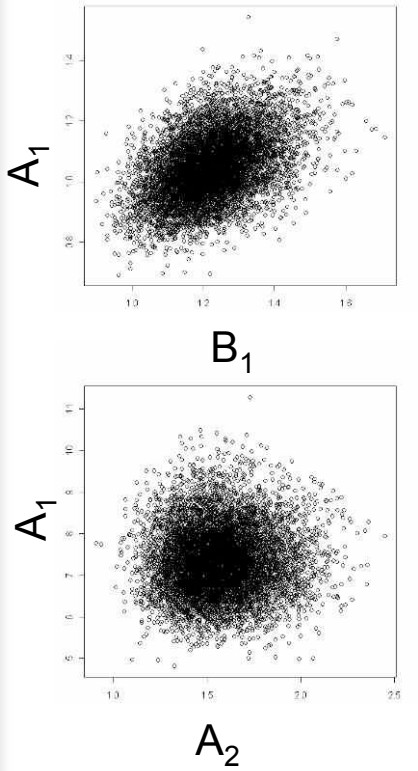
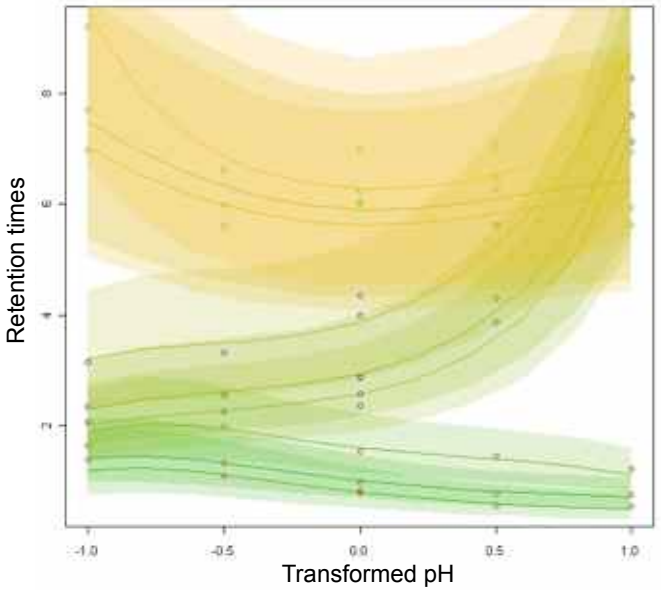
Results (non informative prior and no constraint)

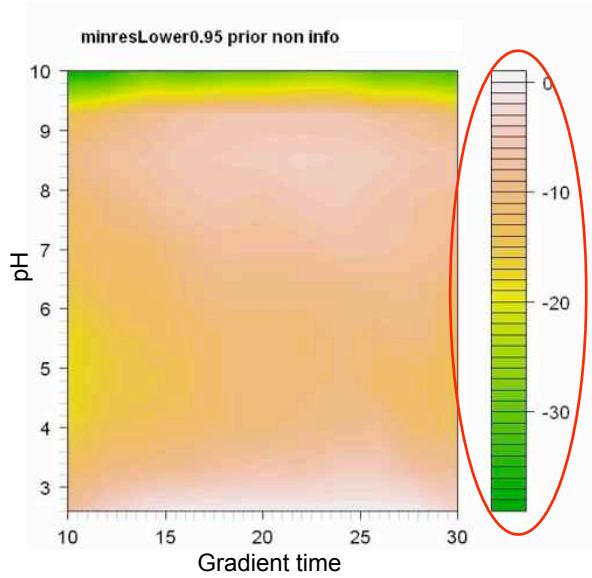
1) From the joint predictive posterior of the responses…

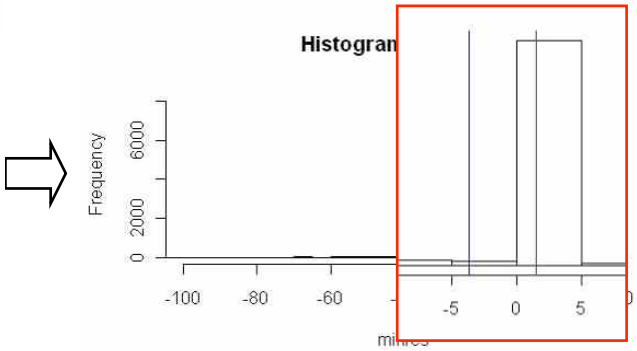


2) Regression lines + Predictive Intervals

Gradient time fixed at 20 min.







>summary(minres)

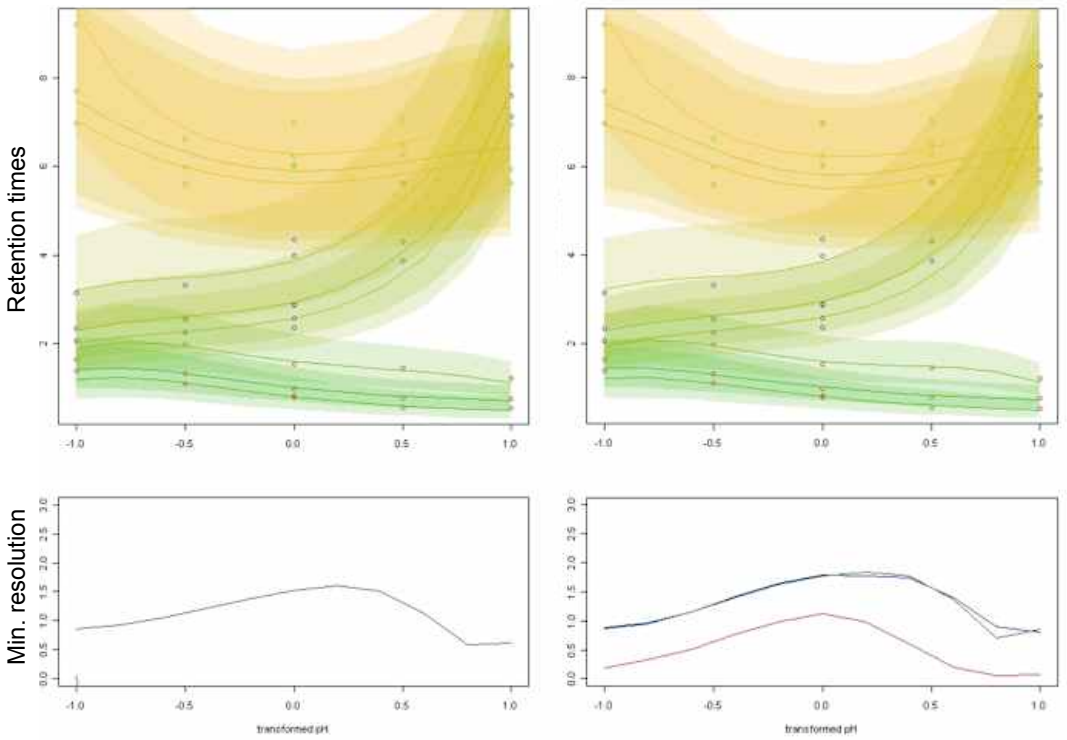
Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
-3356.0000	0.4441	0.8260	-4.1640	1.3040	16.9500

Results (comparison of priors)

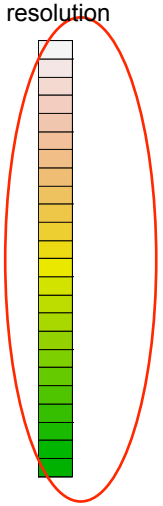
Non informative prior

Informative prior

Gradient time fixed at 20 min.



95% Lower predictive interval of minimal resolution



Green : median
Blue : mean
Red : 95% Lower predictive interval

- Slightly smaller intervals
- Consistent

Multicriteria Decision Method

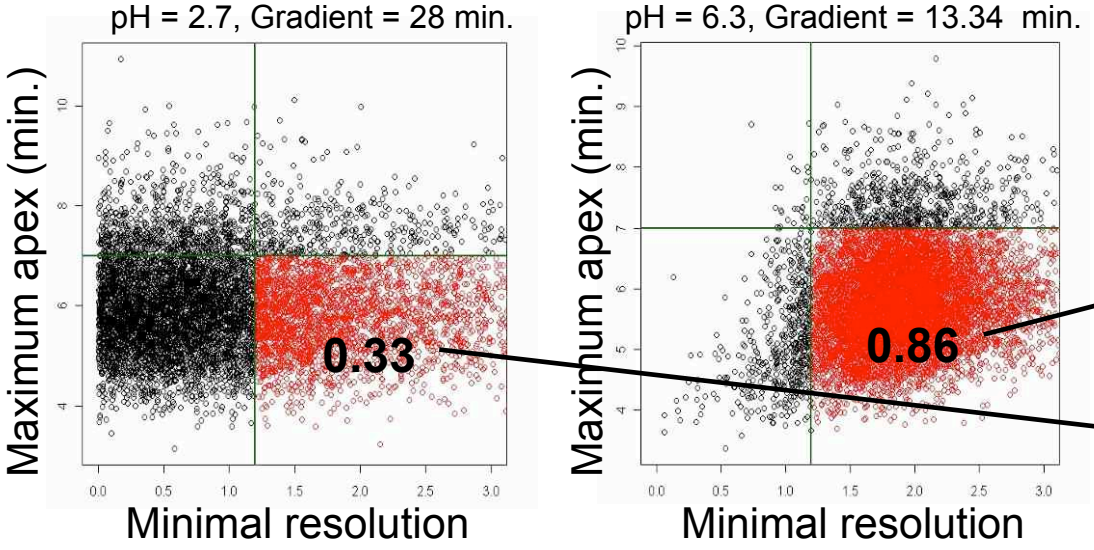
- From the joint distribution of criteria, design space definition suggests a multicriteria approach

$$DS = \{\boldsymbol{x}_k \in \chi \mid E_{\hat{\boldsymbol{\theta}}}[P(\boldsymbol{O} \in \boldsymbol{\Lambda}) \mid \hat{\boldsymbol{\theta}}] \geq \pi_{min}\}$$

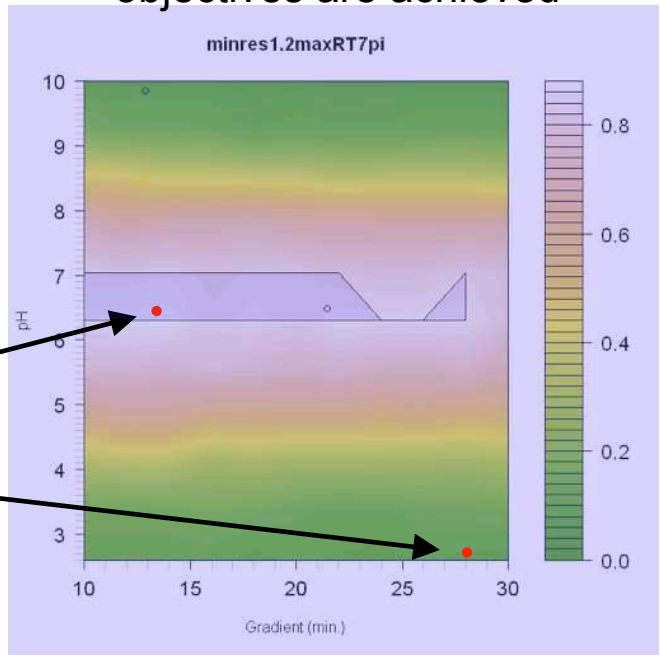
  - Using the joint distribution, correlation between objective functions is taken into account

- Ex: $E_{\hat{\boldsymbol{\theta}}}[P(Obj_1 > \lambda_1, Obj_2 > \lambda_2) \mid \hat{\boldsymbol{\theta}}] \geq \pi_{min}$

$E_{\hat{\boldsymbol{\theta}}}[P(resolution_{min} > 1.2, apex_{max} < 7) \mid \hat{\boldsymbol{\theta}}] \geq 0.8$

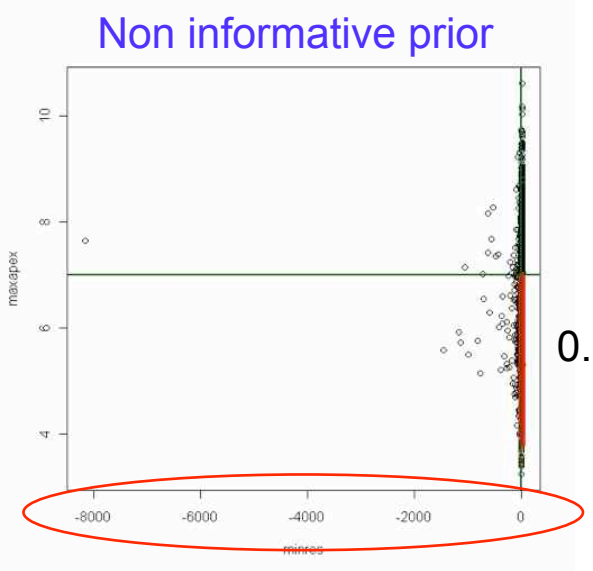
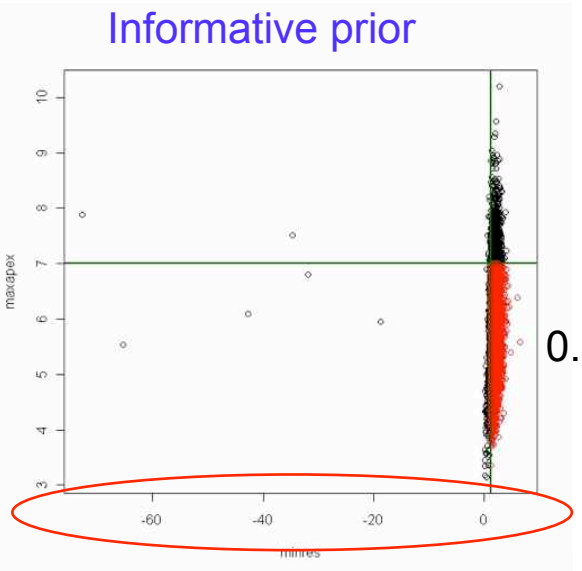
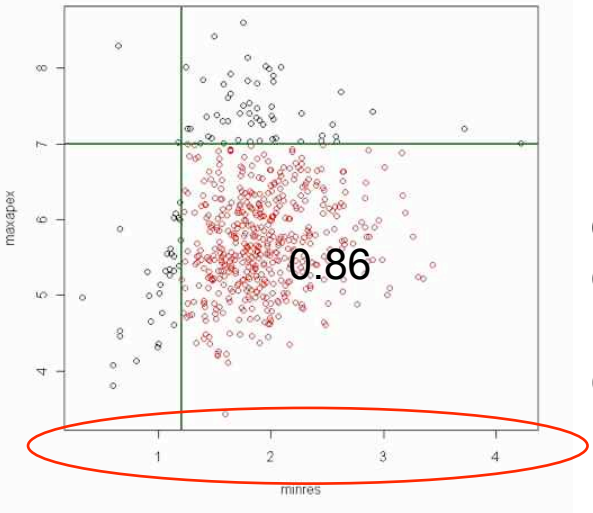


Probability map that both objectives are achieved



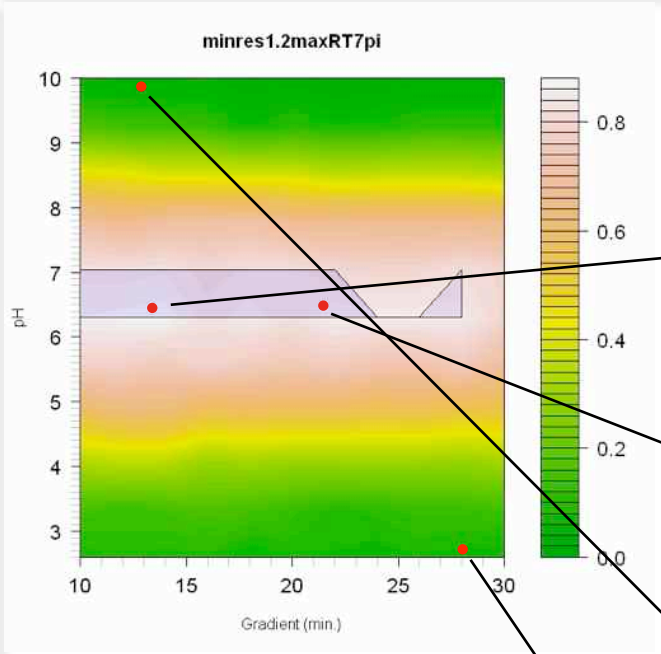
Comparison of priors and constraints

Joint predictive posterior distribution of $resolution_{min}$ and $apex_{max}$ at pH = 6.3, Gradient = 13.34

	Non informative prior	Informative prior
No constraint	 0.6	 0.86
Constraints	No elements left in the chains of parameters	 0.86

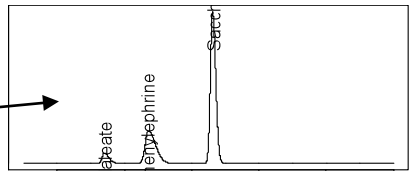
But,
only 10% of elements are kept in the chains

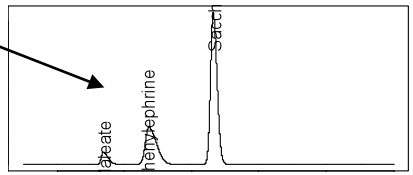
Validation

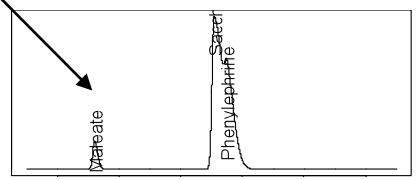


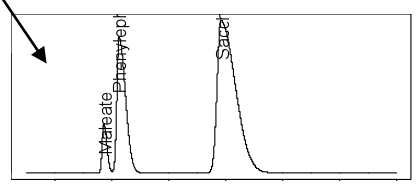
2 points belonging to DS
2 points out of DS

Mean predicted

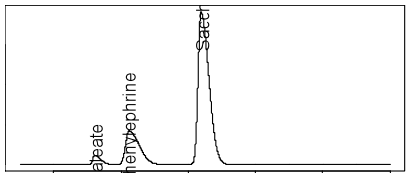


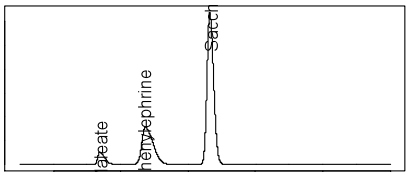


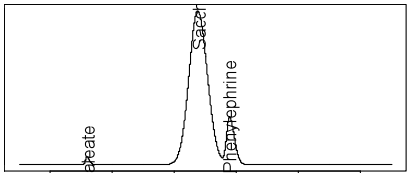


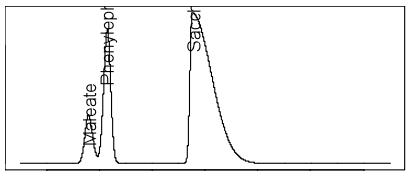


Real









Conclusions

- Design Space must be defined on prediction of future results given past experiments
- Uncertainty of models should be taken into account in predictions
- Bayesian multivariate multiple regression is powerful and flexible to model correlated responses and to manage uncertainty
  - The Design Space is straightforward to obtain with Bayesian models
- The joint predictive posterior distribution of objective functions allows the development of Multicriteria Decision Methods (MCDM)
  - About expected future performance
  - under uncertainty
  - taking into account dependencies between criteria
- Bayesian models in chromatography can take advantage from the long history of the domain, e.g. to set up informative priors
- Further works
  - MCMC sampling method should be adapted for constraints

Thank you !

Convergence