Maximum likelihood estimation in nonlinear mixed effect models: adaptive Gaussian quadrature by sparse grid sampling

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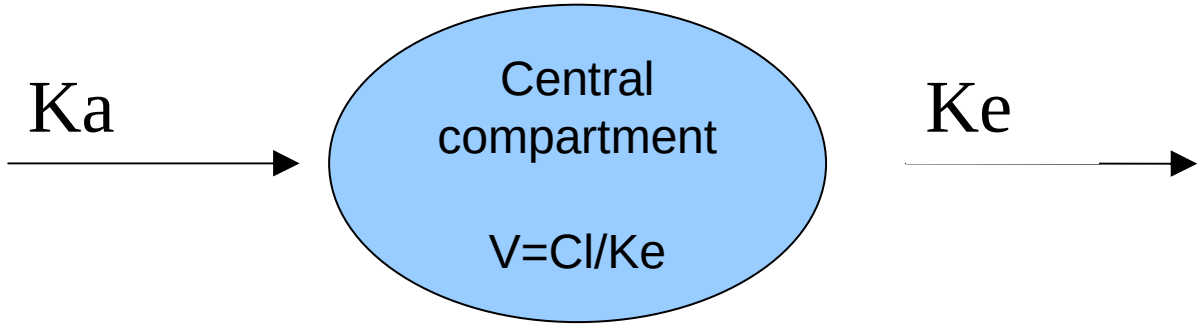
Estimation in nonlinear mixed effect models

- Pinheiro and Bates (1995):

  Comparison of estimation algorithms, NLME, Laplacian, AGQ and importance sampling

  Conclusion: AGQ precise, but less efficient

Compartment model for Theophyline data



$$c_t = \frac{DK_eK_a}{Cl(K_a - K_e)}(e^{-K_et} - e^{-K_at})$$

D: Dose
Ka: Absorption rate
Ke: Elimination rate
Cl: Clearance

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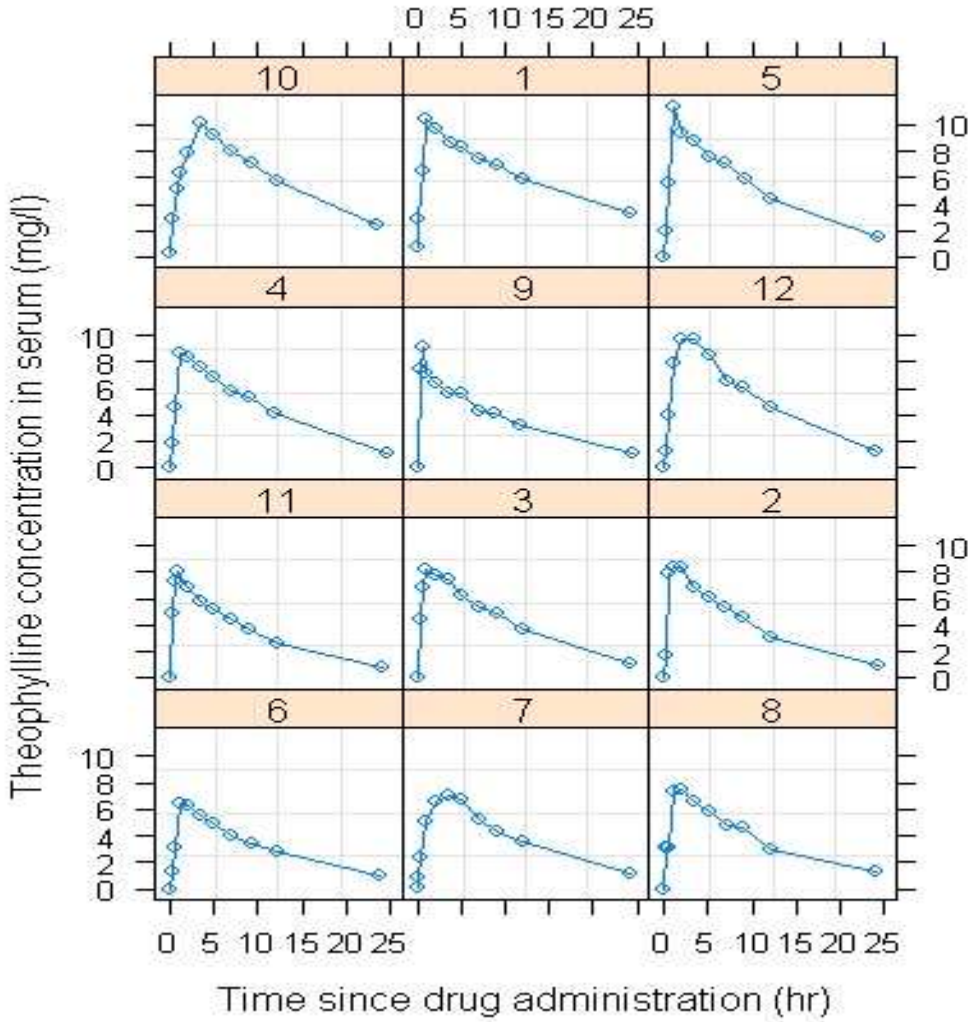
Theophyline serum concentrations
Boeckmann et al (1994)



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Maximum likelihood estimation

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Maximum likelihood estimation in non-linear mixed effects models

- Non-linear mixed effect model:

$$\underline{Y} = h(\underline{\beta}, \underline{b}) + \underline{\varepsilon}$$

where $\underline{Y}$ is the observation vector, h is the mean function, possible nonlinear in the fixed parameter vector, $\underline{\beta}$, and the random effect vector, $\underline{b}$.

The random effects are assumed to follow a multivariate normal distribution, $\underline{b} \sim N(\underline{0}, \Omega)$, independent of the residual error, $\underline{\varepsilon}$, also assumed to follow a multivariate normal distribution, $\underline{\varepsilon} \sim N(\underline{0}, \Sigma)$

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Maximum likelihood estimation in non-linear mixed effects models

- Likelihood function:

$$L(\underline{Y},\underline{\beta},\Omega,\Sigma) = \int p(\underline{Y},\underline{\beta},\underline{b},\Omega,\Sigma)d\underline{b}$$

$$= \int p(\underline{Y},\underline{\beta},\Sigma \mid \underline{b})\, p(\underline{b},\Omega)d\underline{b}$$

where *p* is the density function for the relevant normal distributions

- MLE: parameter values of $\underline{\beta}$, Ω, Σ that maximize the likelihood function

The final integral cannot be solved explicitly, hence approximations is needed, e.g. first order approximation, Laplace or AGQ.

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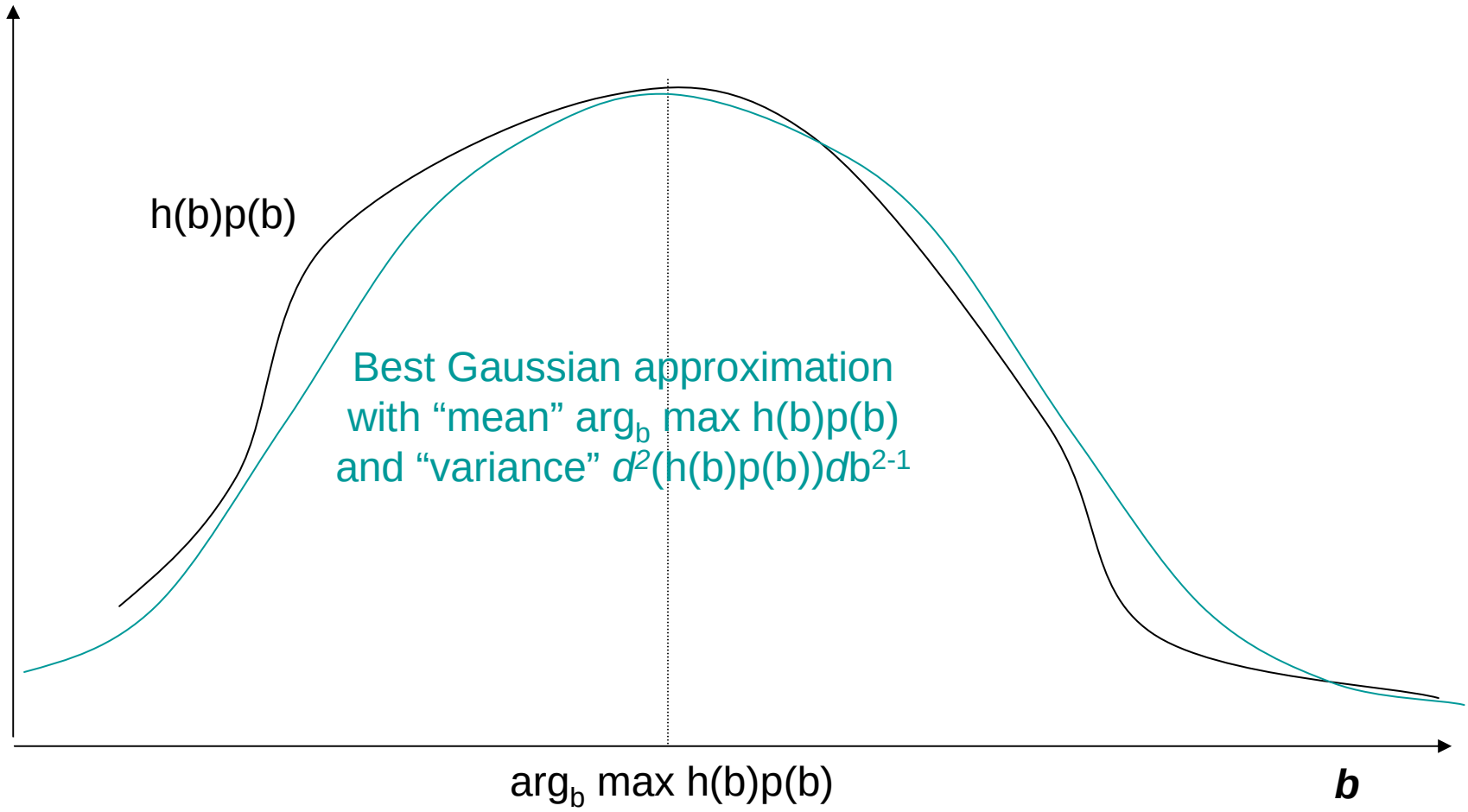
Laplace approximation to $\int h(b)\,p(b)db$



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Laplace approximation to $\int h(b)\,p(b)db$

- The integral is approximated by the exact integral of the approximation
- The approximation is exact when the random effects occur linearly in the mean function
- The approximation works well if h(b)p(b) is approximately quadratic in b

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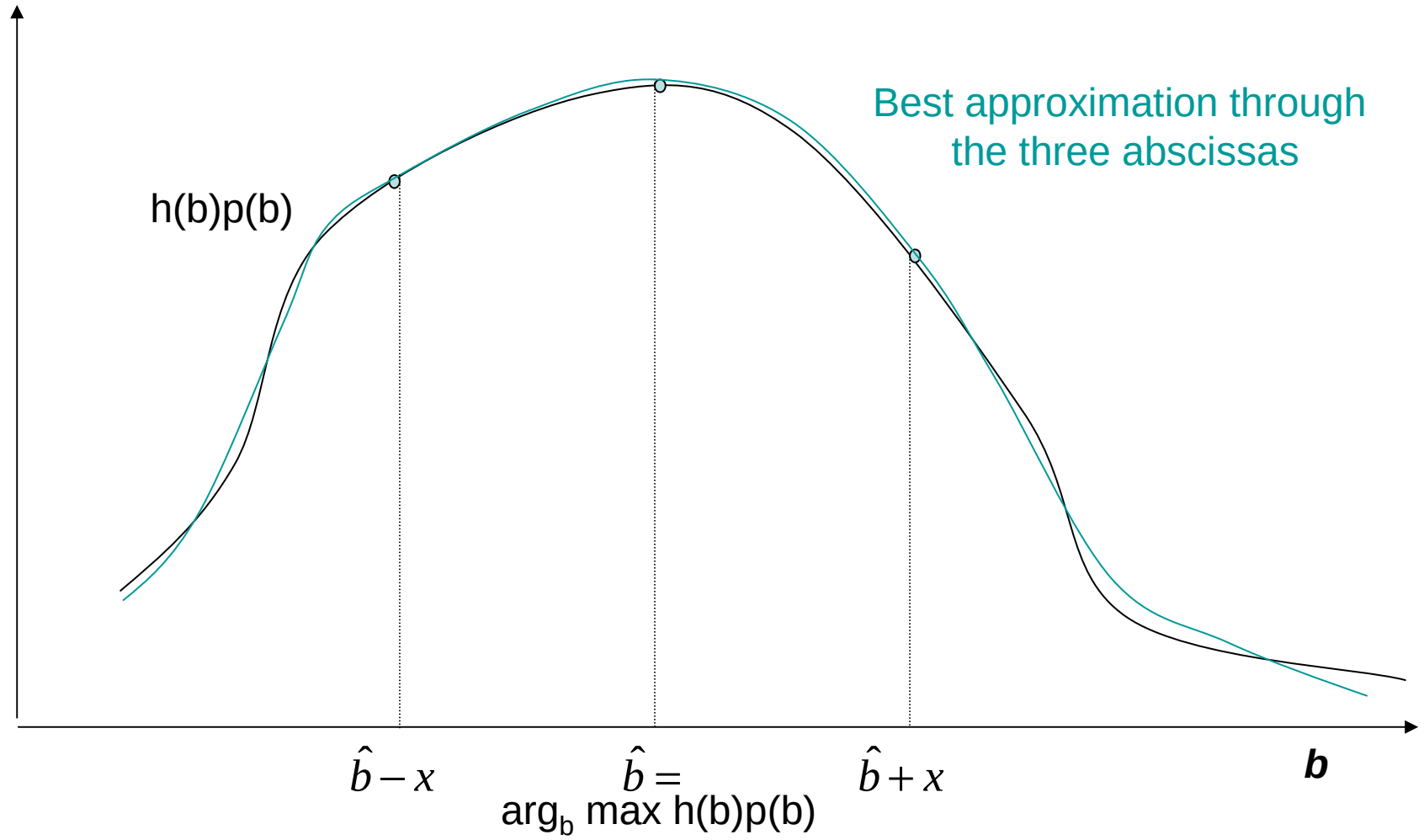
Adaptive Gaussian Quadrature of $\int h(b)\,p(b)db$



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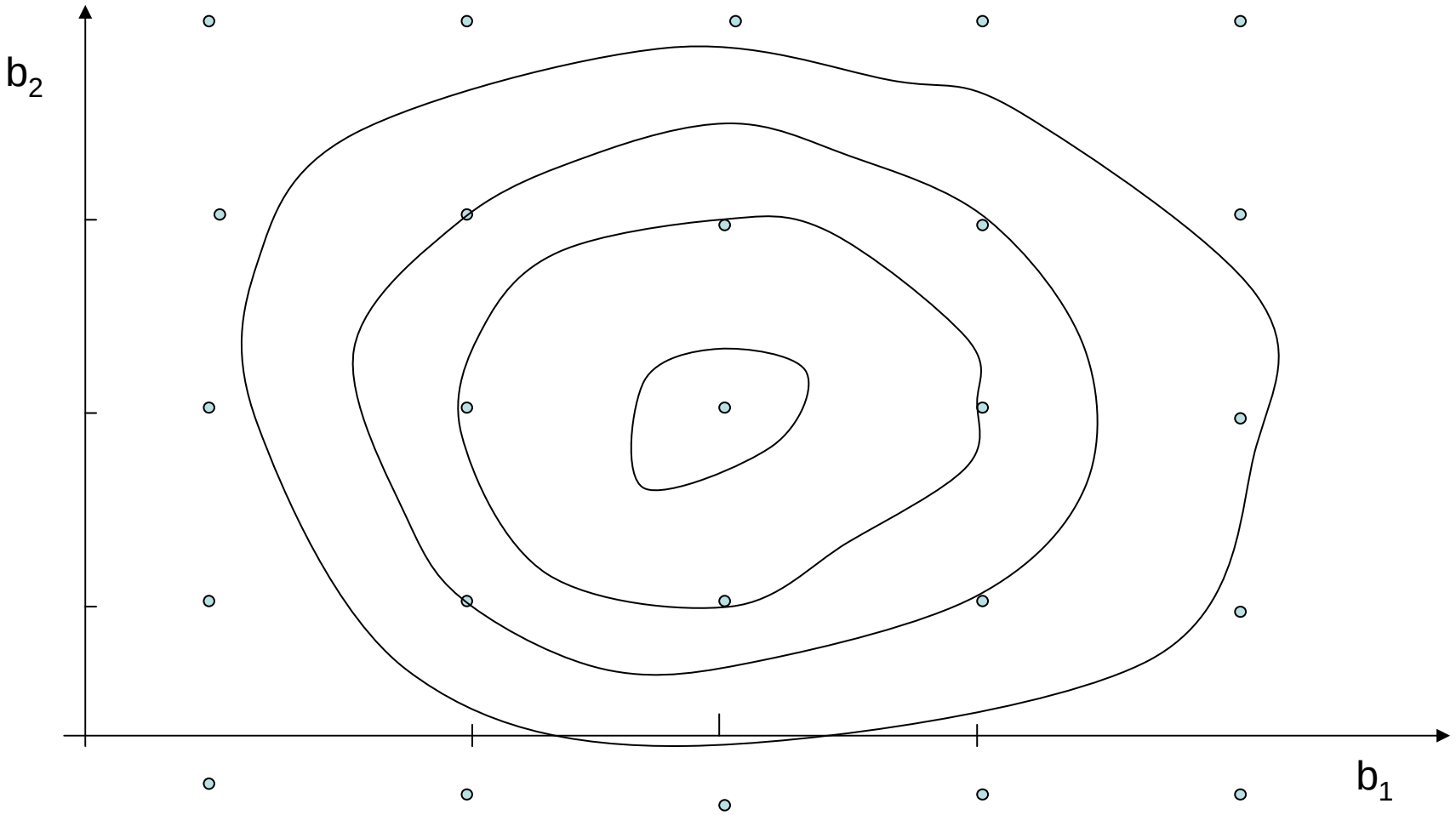
Adaptive Gaussian Quadrature of $\int h(b)\,p(b)db$

- The integral is approximated by a weighted sum:

$$\int h(b)\,p(b)db = \sum_{i=1}^{n} h(x_i)\,p(x_i)w_i$$

- Where the x_i, i=1, …, n are the abscissas and w_i the weight functions. Adaptive Gauss Hermite Quadrature have abscissas equal to roots of Hermite polynomials
- The approximation is exact when h(b)p(b) is a polynomial of degree 2n-1 (or less)

Adaptive Gaussian Quadrature, with 2-dim b and 5 abscissas, of $\int h(b)\,p(b)db$ (product rule)



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AGQ for multivariate random effect

- The number of function evaluations grow exponentially with dimension d of b:

	2	3	4	5	10
3	9	27	81	243	59049
7	49	343	2401	16807	$0.2*10^9$
13	169	2197	28561	371293	$138*10^9$

- AGQ becomes heavy computationally
- However, not all evaluation points are important for precision

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Smolyak's rule

- Old news: Smolyak (1963)
- We follow the tensor product construction by Gerstner and Griebel (2003)
- Example:

  Smolyak's level 2 rule for d-dimensions:

$$\int h(b)e^{-\frac{1}{2}b^2}\,db \approx \sum_{i=1}^{d}\left\{h(-\sqrt{3}e_i)+h(\sqrt{3}e_i)\right\}+(1-\frac{d}{3})h(0)$$

- Weights equals 1/6 for the 2d axial points and 1-1/3 for center
- Exact for polynomials of degree 3 or less

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Function evaluation with multivariate parameter

- Number of function evaluations reduced significantly:

	2	3	4	5	10
3	9 5	27 7	81 9	243 11	59049 21
7	49 7	343 31	2401 49	16807 71	$0.2*10^9$ 241
13	169 45	2197 105	28561 201	371293 341	$138*10^9$ 1981

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Examples

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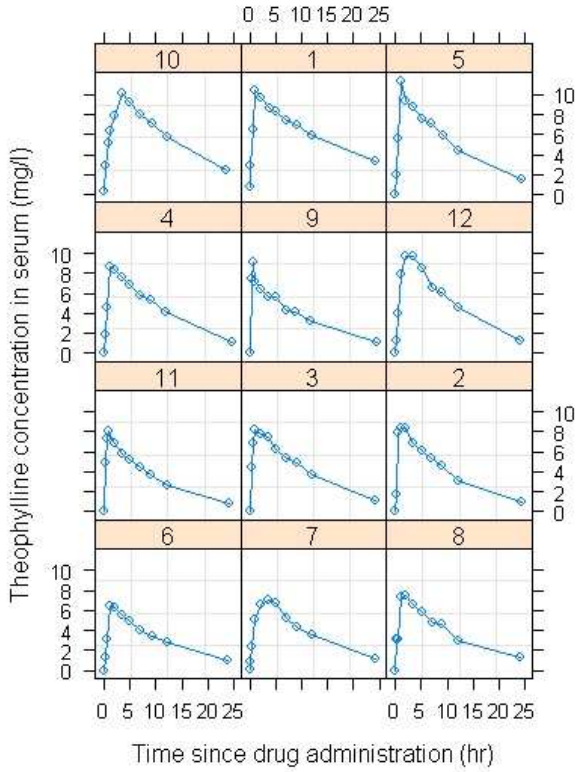
Theophyline serum concentrations

- Model:

$$c_t = \frac{DK_eK_a}{Cl(K_a - K_e)}(e^{-K_et} - e^{-K_at})$$

- Absorption rate, elimination rate and clearance are random
- Smolyak algorithm converged with non-singular covariance matrix of parameter estimates
- Smaller (slightly) residual variance compared to Laplace



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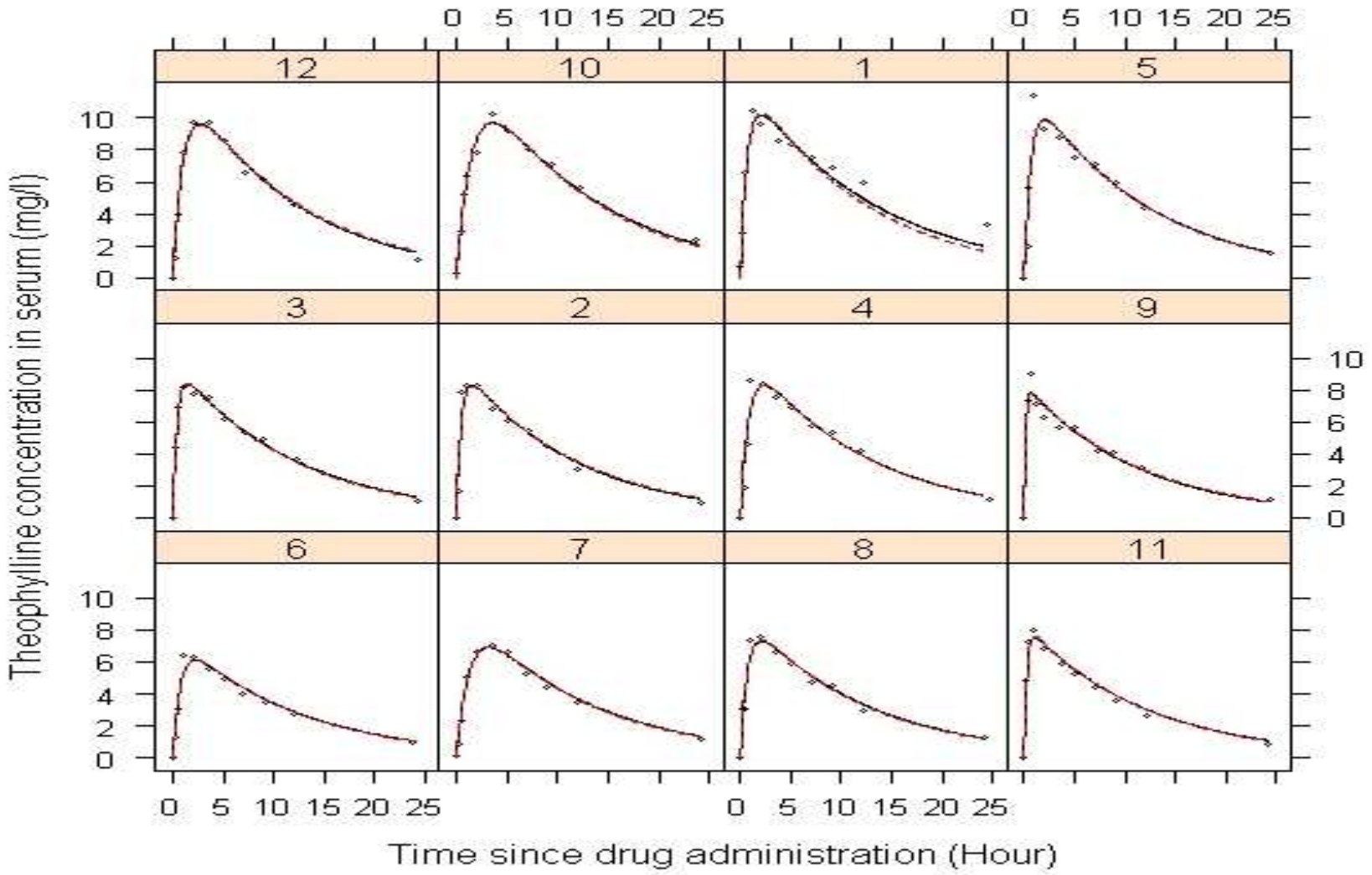
Theophyline data
- observed and predicted profiles



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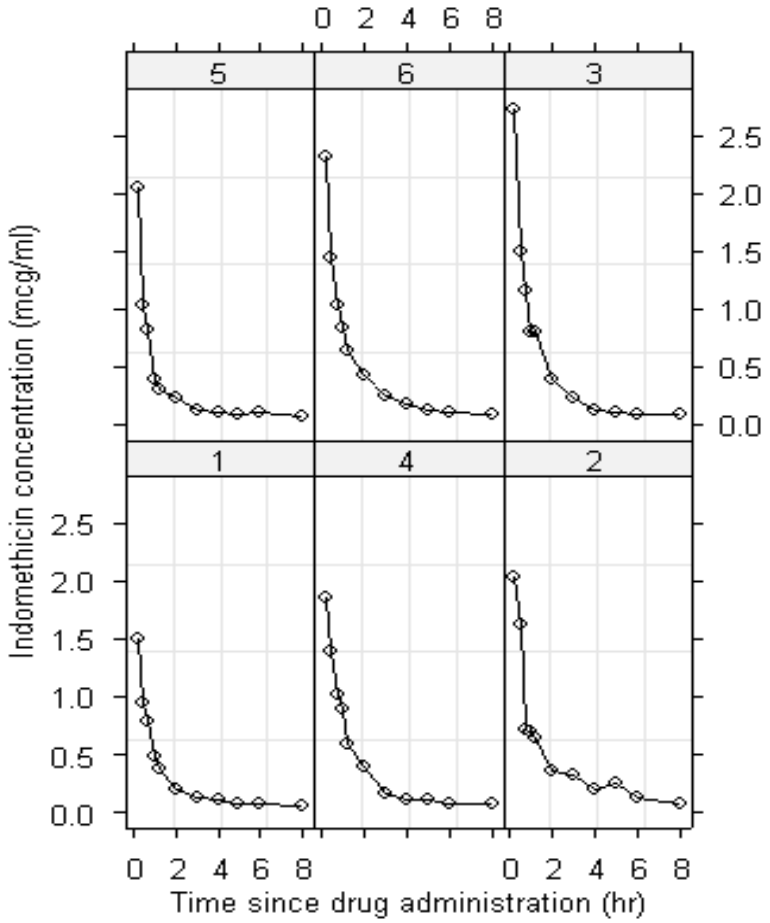
Indomethecin data
- observed and predicted profiles

- Model:

$$c_t = A_1 \exp(-rc_1 \cdot time) + B_1 \exp(-rc_2 \cdot time)$$

- A1, log(rc1) and B1 are random
- Smolyak algorithm converged with nonsingular covariance matrix



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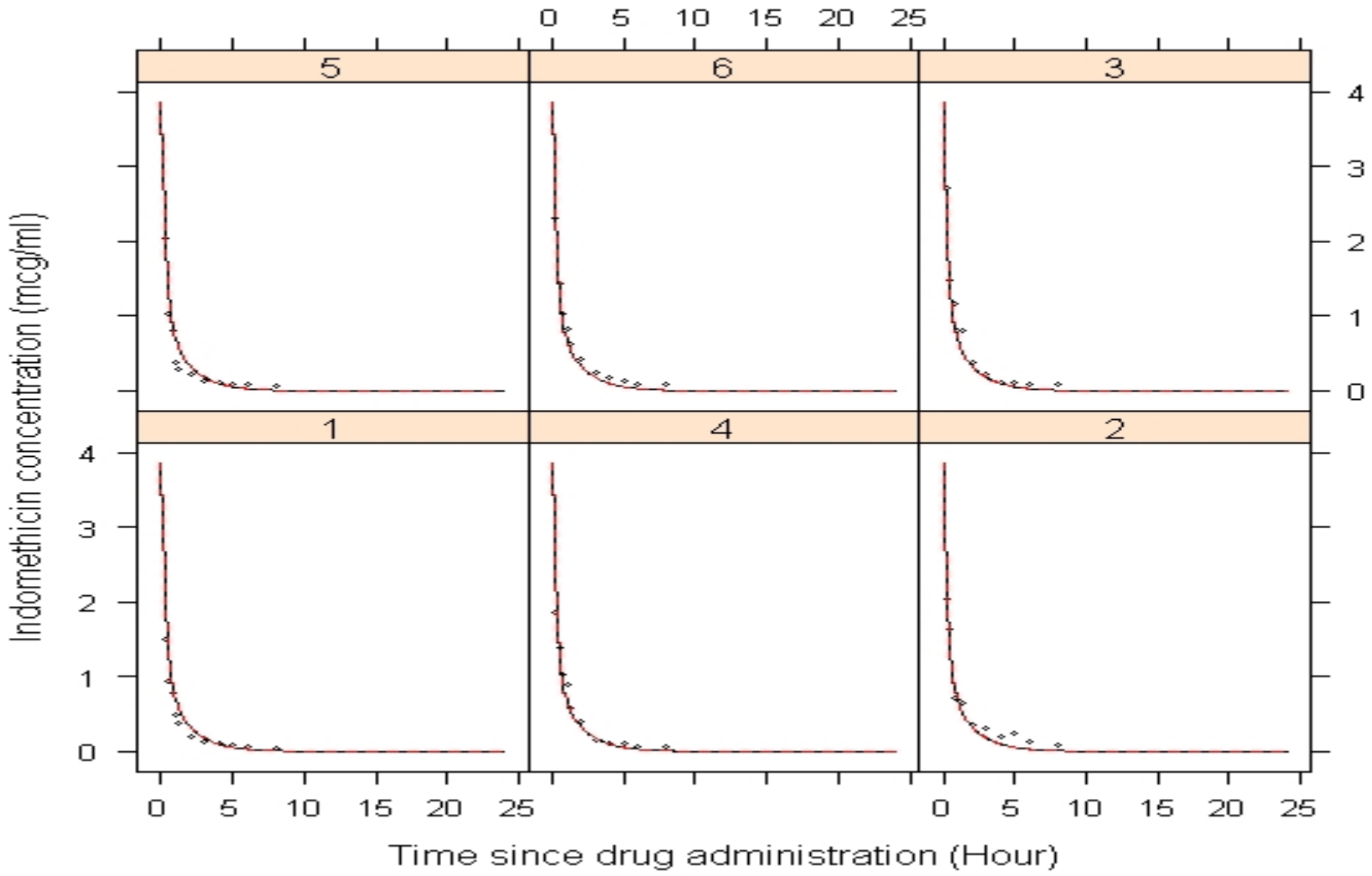
Indomethecin data



Simulations

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Simulation: First-order open compartment model (Theophyline data)

- 500 simulations
- 12 subjects
- 10 concentrations at

  t=0, 0.25, 0.5, 1, 2, 3.5, 7, 9, 12, 24h
- Dose=4.5mg
- lKa = 0.5, lCl=-3, lKe = -2.5
- lKa and lCl are allowed to vary randomly, $b_i \sim N(0, \psi)$, where ψ is diagonal, 0.36 and 0.04 respectively

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Simulation results (Theophyline data)

500 simulations based on Theophylline data

	lKe	lKa	lCl	psi.lKa	psi.lCl	sigma
True Value	**-2.5**	**0.5**	**-3**	**0.6**	**0.2**	**0.7**
NLME (starting values)	-2.4940	0.4792	-3.0040	0.5799	0.1928	0.6993
sd	0.0403	0.1174	0.0405	0.0853	0.0300	0.0296
Smolyak	-2.5010	0.5057	-3.0010	0.5716	0.1935	0.6929
sd	0.0407	0.1210	0.0410	0.1087	0.0313	0.0361
AGQ	-2.5010	0.5004	-3.0010	0.5893	0.1952	0.6984
sd	0.0404	0.1196	0.0406	0.0889	0.0304	0.0296

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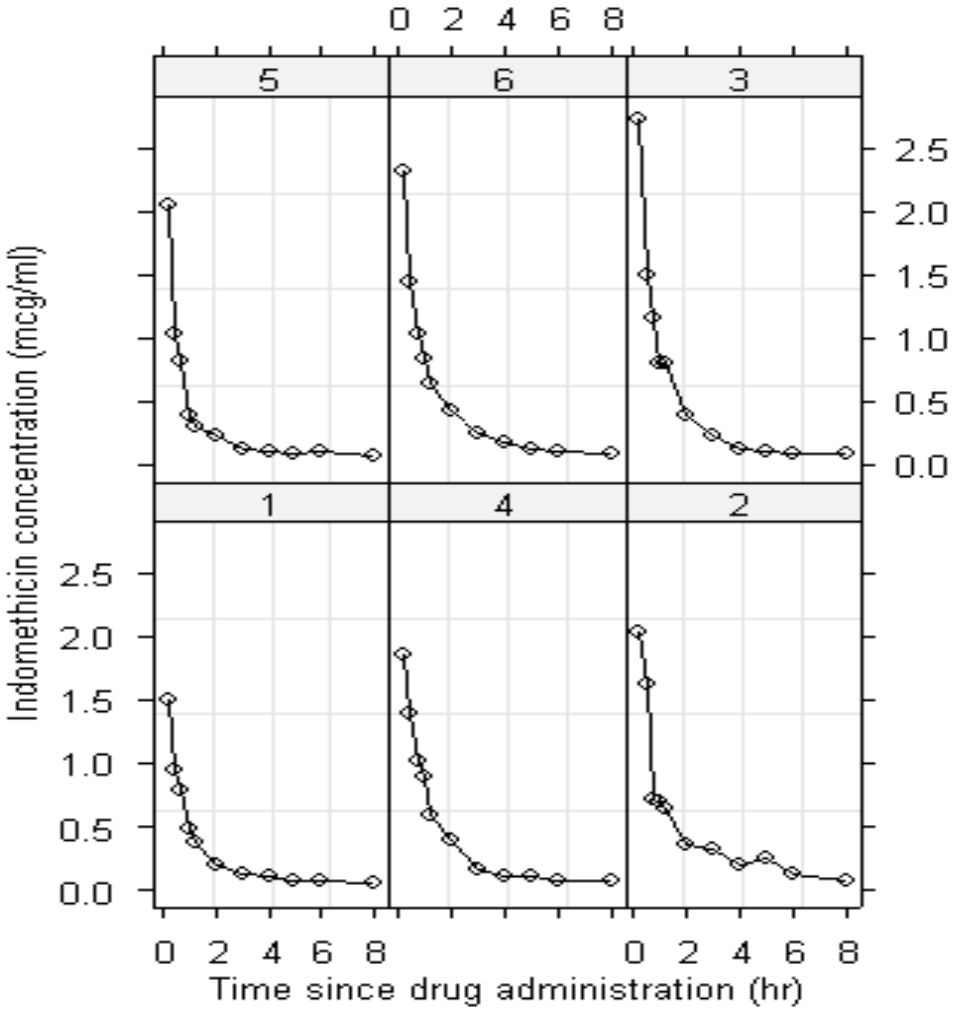
Serum Concentration of Indomethecin



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Simulation: Biexponential model (Indomethacin data)

- 1000 simulations
- 6 subjects
- 11 concentrations at

  t=0.25, 0.5, 0.75, 1, 1.25, 2, 3, 4, 5, 6, 8h
- α =2.8, lKe1=0.7, β =0.4, lKe2=-1.5
- α and lKe1 are allowed to vary randomly, $b_i \sim N(0, \psi)$, where ψ is diagonal, 0.36 and 0.04 respectively

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Simulation results (Indomethecin data)

1000 simulation based on Indomethecin data

	A1	lrc1	A2	lrc2	psiA1	psilrc1	sigma
True value	**2.8**	**0.7**	**0.4**	**-1.5**	**0.6**	**0.2**	**0.09**
Starting values (NLME)	2.806	0.6644	0.3637	-1.6967	0.4975	0.1636	0.08772
sd	0.2701	0.1242	0.0953	0.3856	0.1859	0.0700	0.0089
Smolyak	2.814	0.7122	0.4169	-1.5432	0.5151	0.1920	0.08661
sd	0.2690	0.1335	0.11547	0.35370	0.1712	0.06829	0.008654
AGQ	2.798	0.7039	0.4111	-1.5572	0.4738	0.1817	0.08758
sd	0.2701	0.1311	0.11434	0.35904	0.1828	0.06894	0.008803

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Conclusion

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Conclusion

- AGQ precise method for MLE in nonlinear mixed effects models
- For multivariate parameters AGQ becomes difficult
- Smolyaks rule reduces the number of function evaluations significant
- The method works well on the examples aswell as in the simulation study

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Thank you!

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  - Gerstner, T. and Griebel, M.: Dimension-Adaptive Tensor-Product Quadrature, Computing 71, 65-87 (2003)

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