UPPSALA UNIVERSITET

Population optimal experimental design for discrete type data

Joakim Nyberg, Mats O. Karlsson
and Andrew C. Hooker

Pharmacometrics research group
Department of Pharmaceutical Biosciences
Uppsala University

UPPSALA UNIVERSITET

Background

- Discrete type data are increasingly popular describing e.g. pharmacodynamic outcomes.

- Optimal design (OD) is a useful tool for optimizing studies.

=> Need for OD on models for discrete type data

UPPSALA UNIVERSITET

Some previous work in the area

- This concept is not new, e.g. Generalized Linear Models.*
- However, currently numerous issues arise with OD computation:
  - Exponential family (binomial, Poisson,…)
  - One must know link function, mean function for each model family

- In this work we attempt to provide a general method for categorical data models based on simulation of data.

* Longford, Breslow, Duffull, Ogungbenro etc.

Introduction Optimal design

UPPSALA UNIVERSITET

Cramér-Rao inequality*:

$$FIM\left(\vec{\Theta},\vec{x}\right)^{-1} \leq COV\left(\vec{\Theta},\vec{x}\right)$$

for an unbiased estimator

* holds regardless of whether the data is discrete or not

UPPSALA UNIVERSITET

Derivation of FIM for discrete type data

$$FIM\left(\vec{\Theta},\vec{x}\right)=E_x\left[FIM\left(\vec{\Theta},\vec{x}_{obs}\right)\right]$$

$$FIM\left(\vec{\Theta},\vec{x}_{obs}\right)=-\frac{\partial^2 \log L\left(\vec{\Theta},\vec{x}_{obs}\right)}{\partial\vec{\Theta}\partial\vec{\Theta}^T} \quad *$$

No analytic solution to likelihood for ME – models.

We need higher order approximation than FO=>
Pop likelihood calculate with Laplace or Monte Carlo

* FIM_{obs} is what you get from $COV MATRIX=R

UPPSALA UNIVERSITET

Design setup

- D-optimal design – maximizing the determinant of FIM

- Expectation over data evaluated by Monte Carlo Integration
    1. Generate a data set from some distribution
    2. Calculate FIM_{obs} given the data by calculating pop likelihood with:
        - Laplace Approximation
        - Monte Carlo Integration ("exact" if n->∞)

Dichotomous Model

1 random effect, 50 individuals with 30 doses/individual each split into 3 dose levels (one fixed to 0).

$$\theta_1 = -0.5 \quad \omega_1^2 = 0.1$$

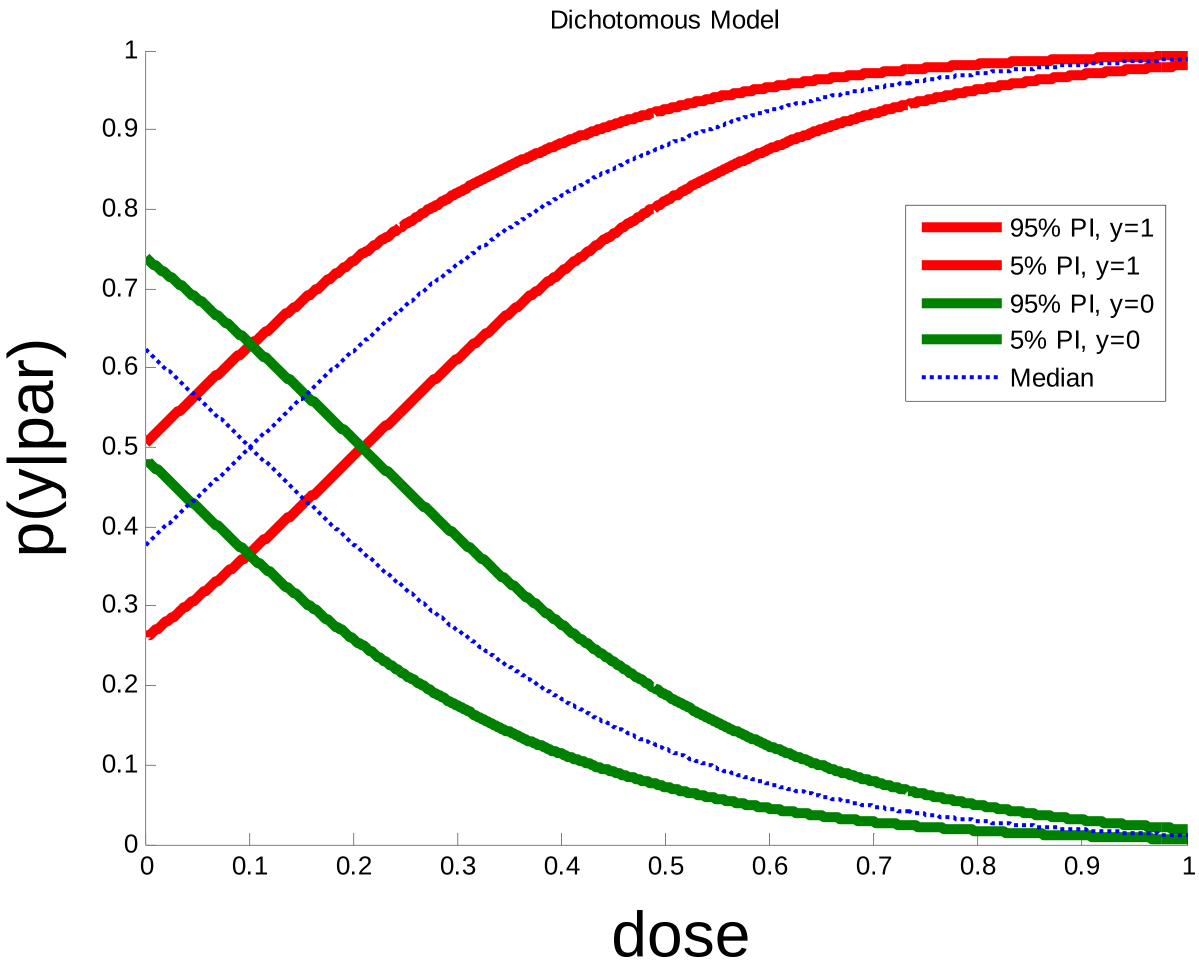
$$\theta_2 = 5 \quad D = [0,1]$$

$$p = \frac{e^{\theta_1 + \eta_1 + \theta_2 \cdot D}}{1 + e^{\theta_1 + \eta_1 + \theta_2 \cdot D}}$$

$$like = \begin{cases} p & \text{if } DV = 1 \\ 1 - p & \text{if } DV = 0 \end{cases}$$

UPPSALA UNIVERSITET

Dichotomous Model – PI



UPPSALA
UNIVERSITET

Dichotomous Model - Results

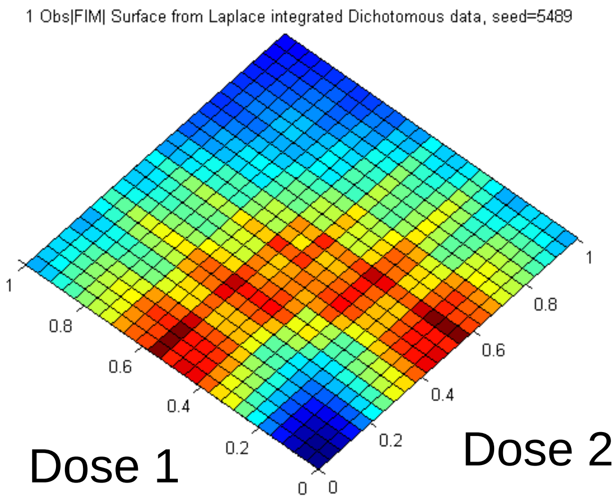
	NONMEM Laplace	PopED Laplace	PopED MC
-2LL observed	1631.912	1631.912	1631.877
Avg RSE(FIM_{obs})	26.8%	26.8%	26.0%
Avg RSE(E[FIM_{obs}])	27.9%*	26.8%	26.8%

* 1000 sim/est empirical SE calculated from estimates
Observed: For each individual: 10 obs at placebo, 0.25 & 0.45 units.

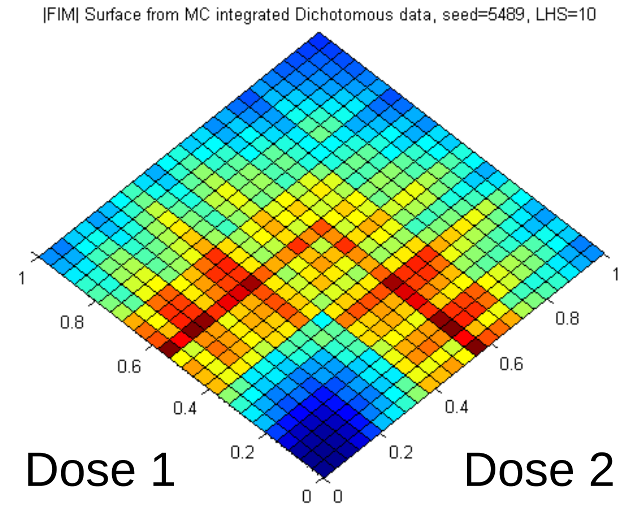
UPPSALA
UNIVERSITET

1 Observed |FIM| versus Dose

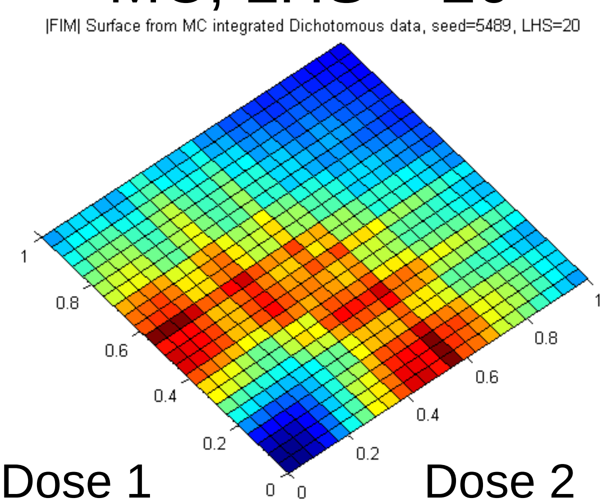
Laplace



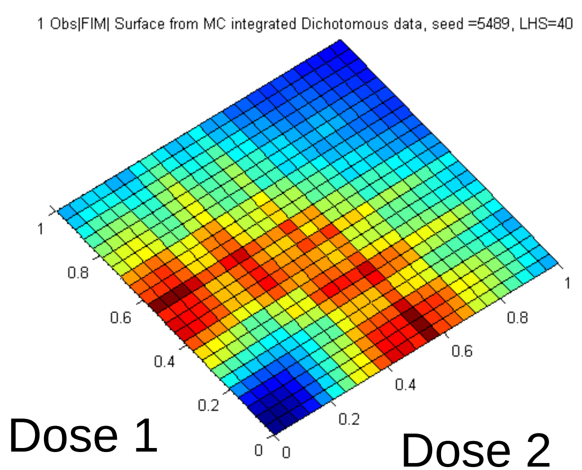
MC, LHS = 10



MC, LHS = 20



MC, LHS = 40



UPPSALA UNIVERSITET

Results - Optimal Designs – 100 obs FIM

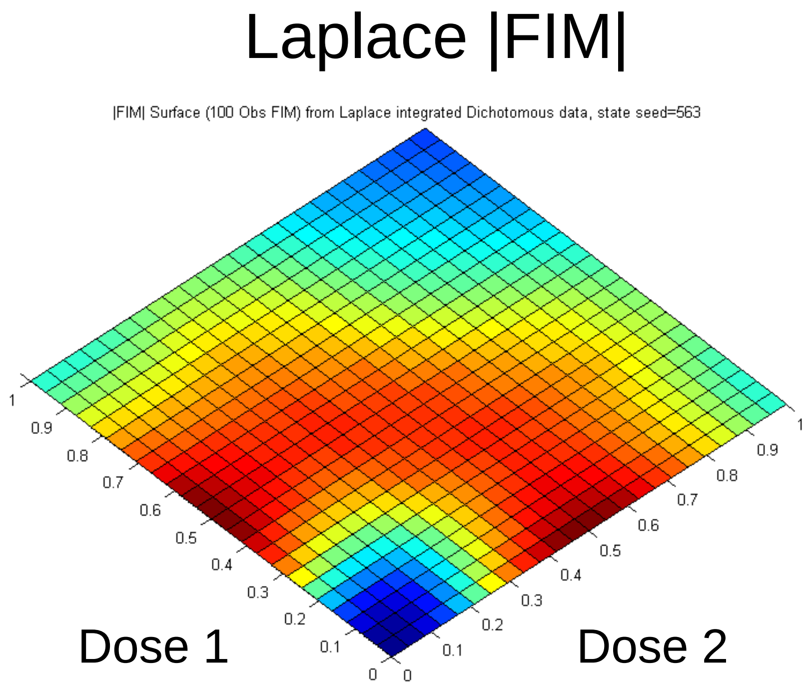
Dose1 = 0, Dose2 dependent on the method

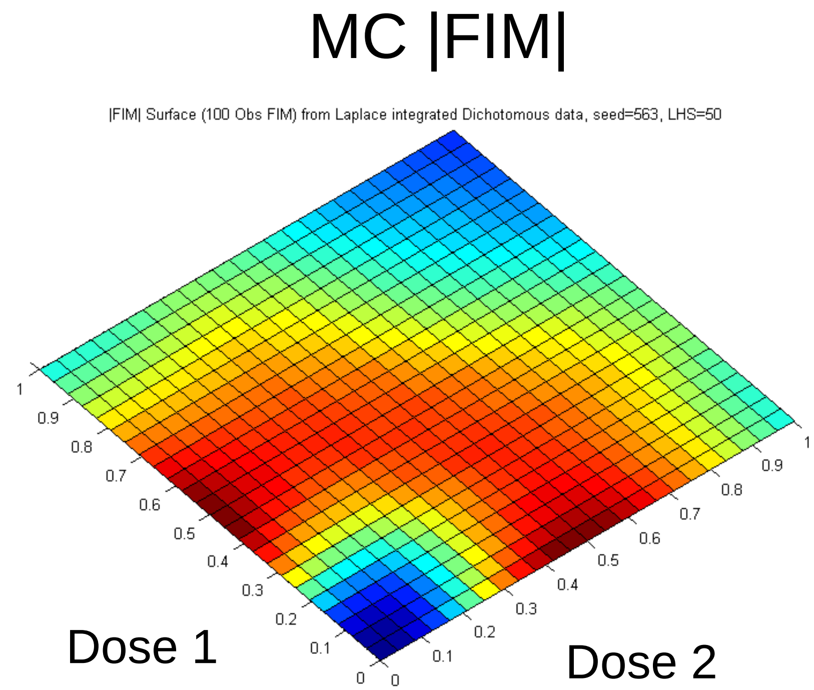
Dose2 (units)	Laplace, det(FIM)	MC, det(FIM)
0.44	5.89e+5	**6.00e+5**
0.50	**5.91e+5**	5.98e+5

Red = optimal

Different results with different calculation methods!

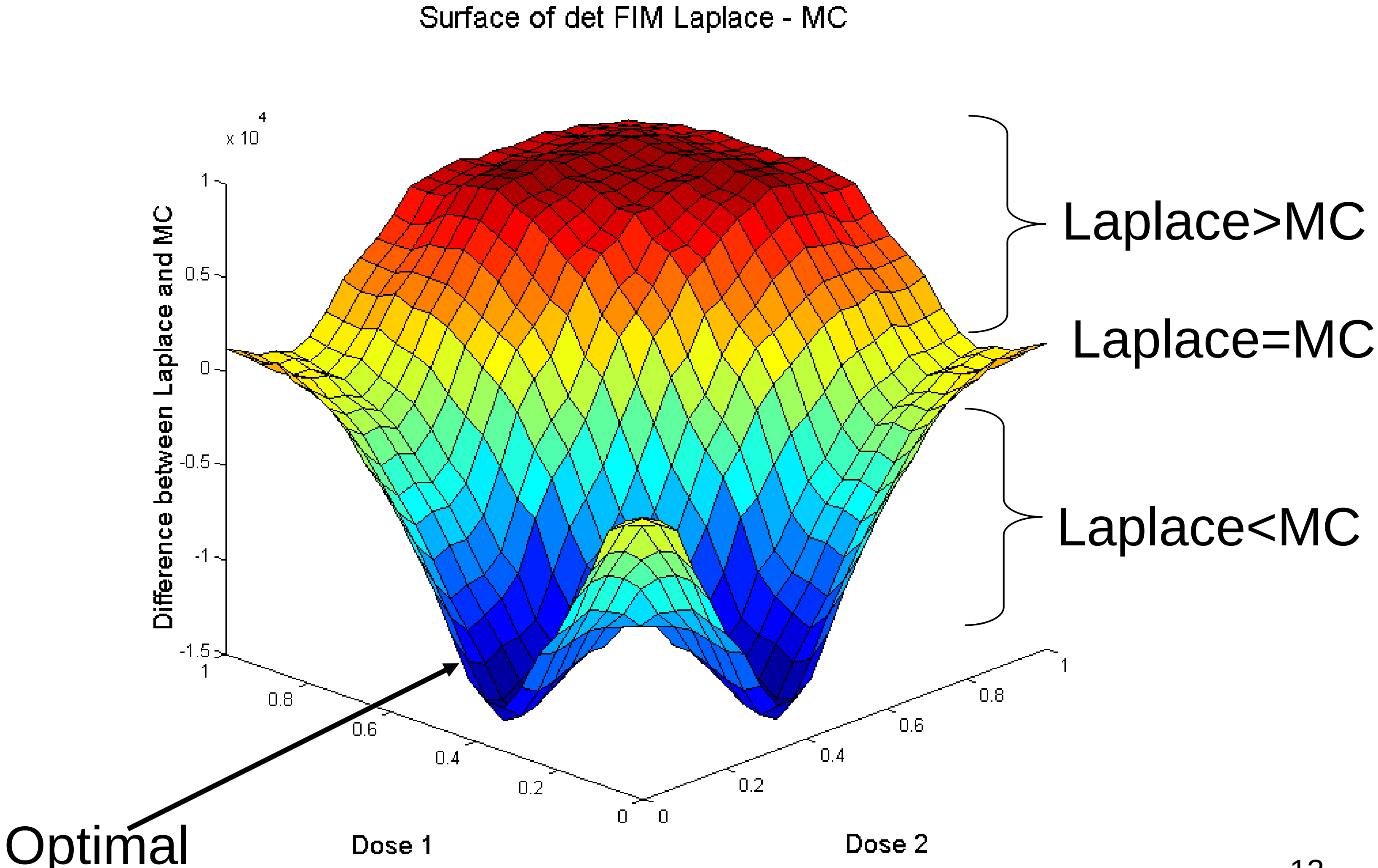
Expected |FIM| – Laplace vs. MC





Expected FIM, calculated as 100 Obs FIM

Expected |FIM| – Differences (Lap, MC)



UPPSALA UNIVERSITET

Poisson Model – 1 Random effect

1 random effect, 20 individuals with 90 obs./ind. split into 3 dose levels.

$$\theta_1 = 1 \qquad \omega_1^2 = 0.1$$

$$\theta_2 = 0.5 \qquad D = [0,1]$$

$$B = \theta_1 \cdot e^{\eta_1}$$

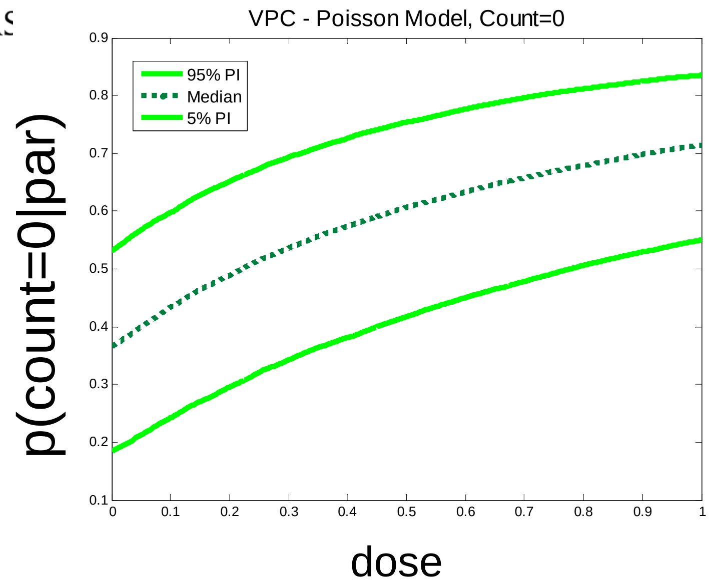
$$D_{50} = \theta_2$$

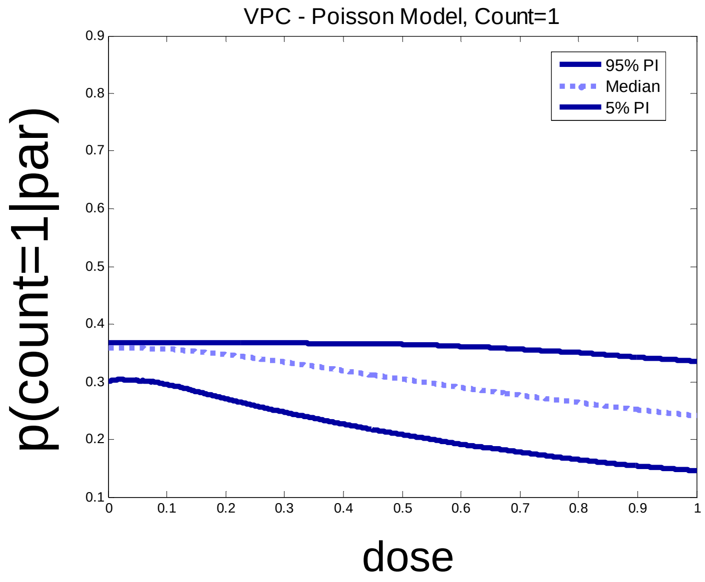
$$\lambda = B \cdot \left(1 - \frac{D}{D + D_{50}}\right)$$

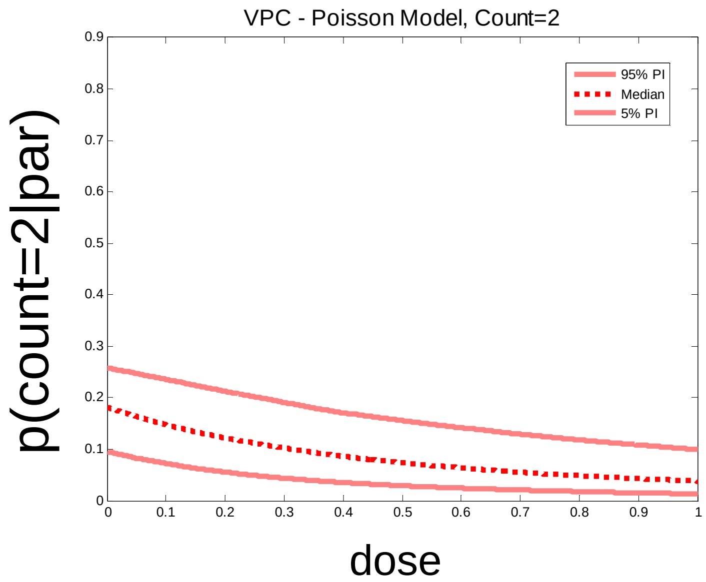
$$-2ll = -2 \cdot \left(-\lambda + n \cdot \ln(\lambda) - \ln(n!)\right)$$

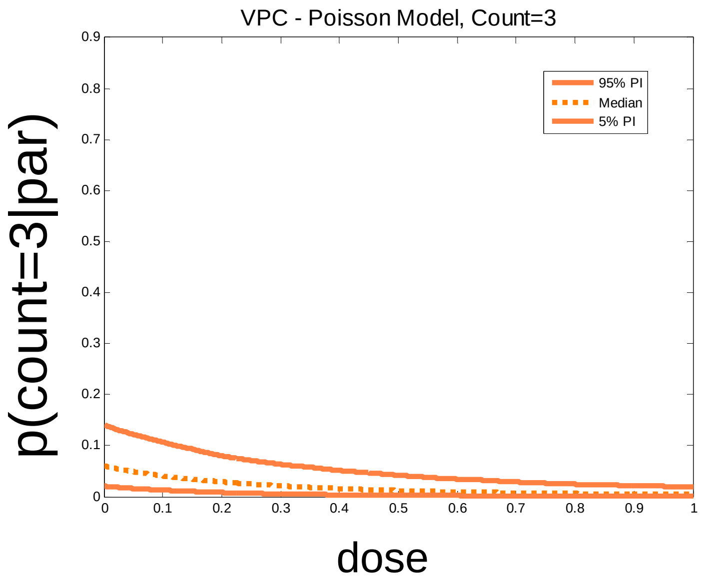
$$\ln(n!) = \begin{cases} n \cdot \ln(n) - n + \frac{\ln\left(n \cdot \left(1 + 4n \cdot (1 + 2n)\right)\right)}{6} + \frac{\ln(\pi)}{2} & if \;\; n > 0 \\ 0 & if \;\; n = 0 \end{cases}$$

PI - Poisson Model









UPPSALA UNIVERSITET

Poisson Model - Results

	NONMEM Laplace	PopED Laplace	PopED MC (1 000 000 samples)
-2LL observed	3809.66	3809.66	3809.63
Avg RSE(FIM_{obs})	22.0%	21.9%	22.2%
Avg RSE(E[FIM_{obs}])	19.1%*	18.6%	18.4%

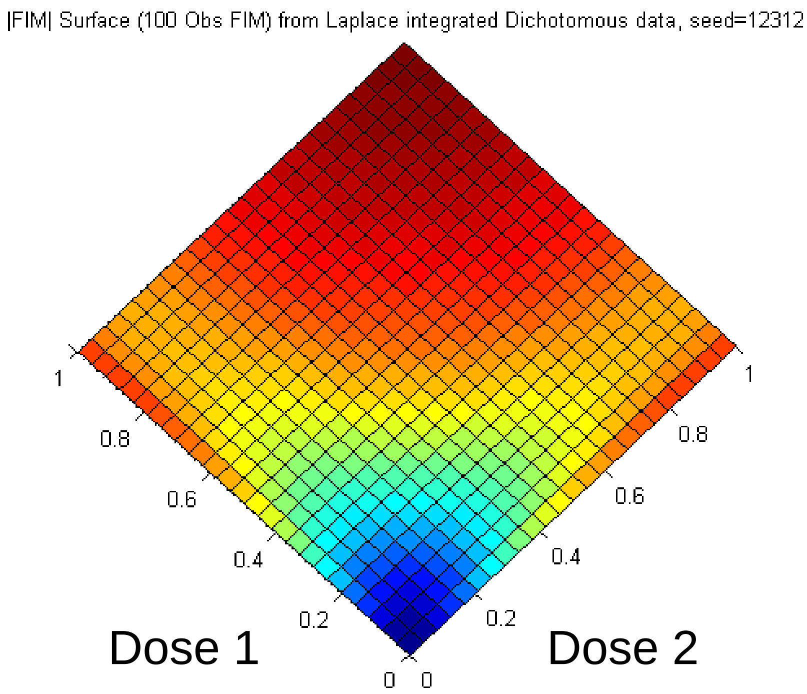
* 1000 sim/est empirical SE calculated from estimates

30 obs/ind at dose 0, 0.4 0.7

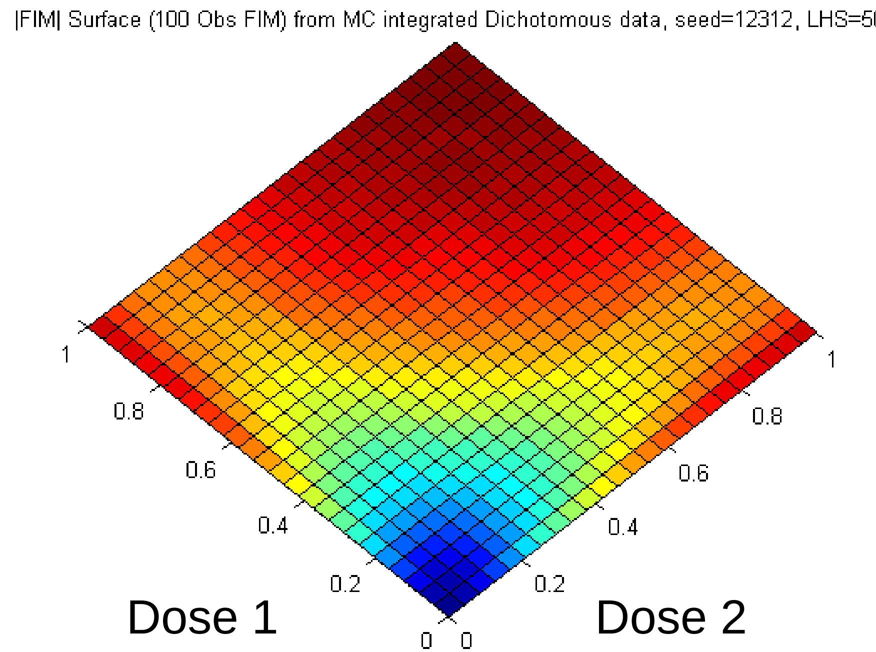
UPPSALA UNIVERSITET

Expected |FIM| Laplace versus MC

Laplace |FIM|



MC |FIM|



UPPSALA UNIVERSITET

Conclusions

- Optimal design on Mixed Effects models for discrete type data was successfully implemented in PopED 2.09 with:
  - Laplace approximation
  - Monte Carlo Integration
- Optimal design differs between calculation methods
- Time consuming => faster/more efficient algorithms are needed, e.g. parallelization, SAEM.
- This technique is general (if likelihood can be calculated method should work). Applicable for OD on models for other types of data/models, e.g. BQL-data, TTE/RTTE, Order/Non-order categorical, Markov model, discrete distributions etc.

UPPSALA UNIVERSITET

Thank you

Thank you for your attention!