N-dimensional Likelihood Profiling (NLP)
An Efficient Alternative to Bootstrap

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Outline

- Motivation: Bootstrapping is hard!
- Solution: N-dimensional Likelihood Profiling
  - Faster solution than bootstrapping with easy convergence
- Examples of application
- Summary and conclusion

A day in the life of a quantitative clinical pharmacologist…

- A semi-mechanistic, highly nonlinear PK/PD model to assess drug effects.
- Need to discuss simulation with uncertainty with the study team... And we need it soon…
- …. But, bootstrapping takes forever
  - How can I simulate with uncertainty?

Photo: Bradley Gordon

How can I simulate with uncertainty?

Bootstrap	Covariance Matrix	LLP
Gold standard	Quick (if possible)	Reliable one parameter CI
Completes slowly Doesn't always complete May not have enough subjects	Sometimes not available Often not a good estimate of the CI Assumption heavy	Doesn't work with >1 parameter. Cannot simulate

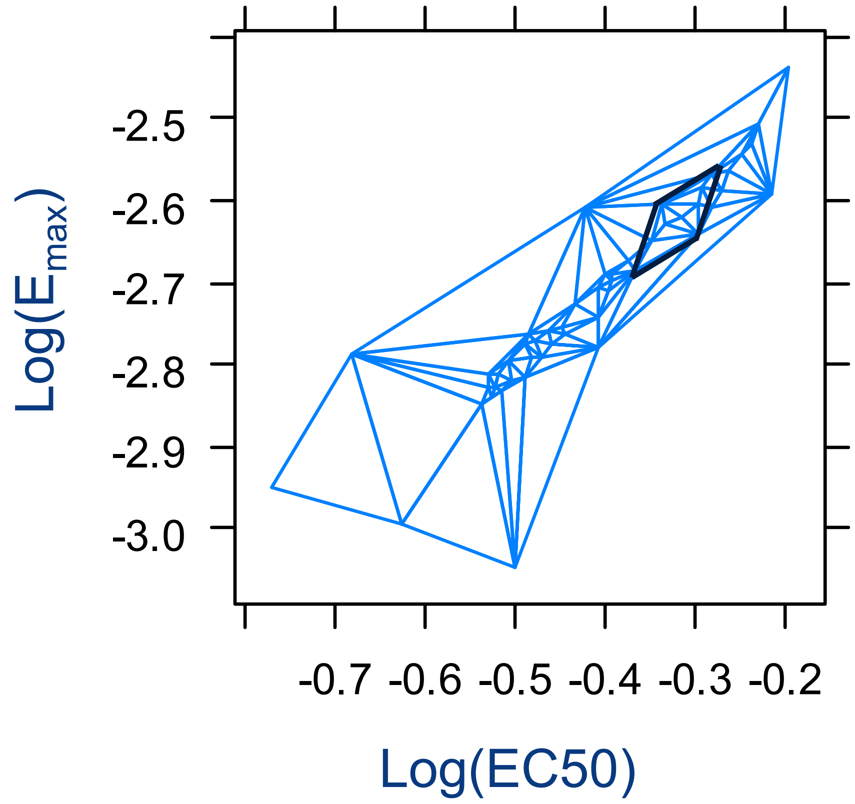
Photo: Jim Bowen

- The Idea:
  Extend LLP to higher dimensionality allowing to sample the empirical distribution for simulation.
  - Faster solution than bootstrapping with easy convergence.
- The Problem: Not so simple!
  - Requires integration of the likelihood surface in N dimensions.

Photo: Chris Lott

How does NLP work?

- From the initial estimates (θ_0)
- Relative likelihood values around θ_0 are searched maximizing information until convergence.

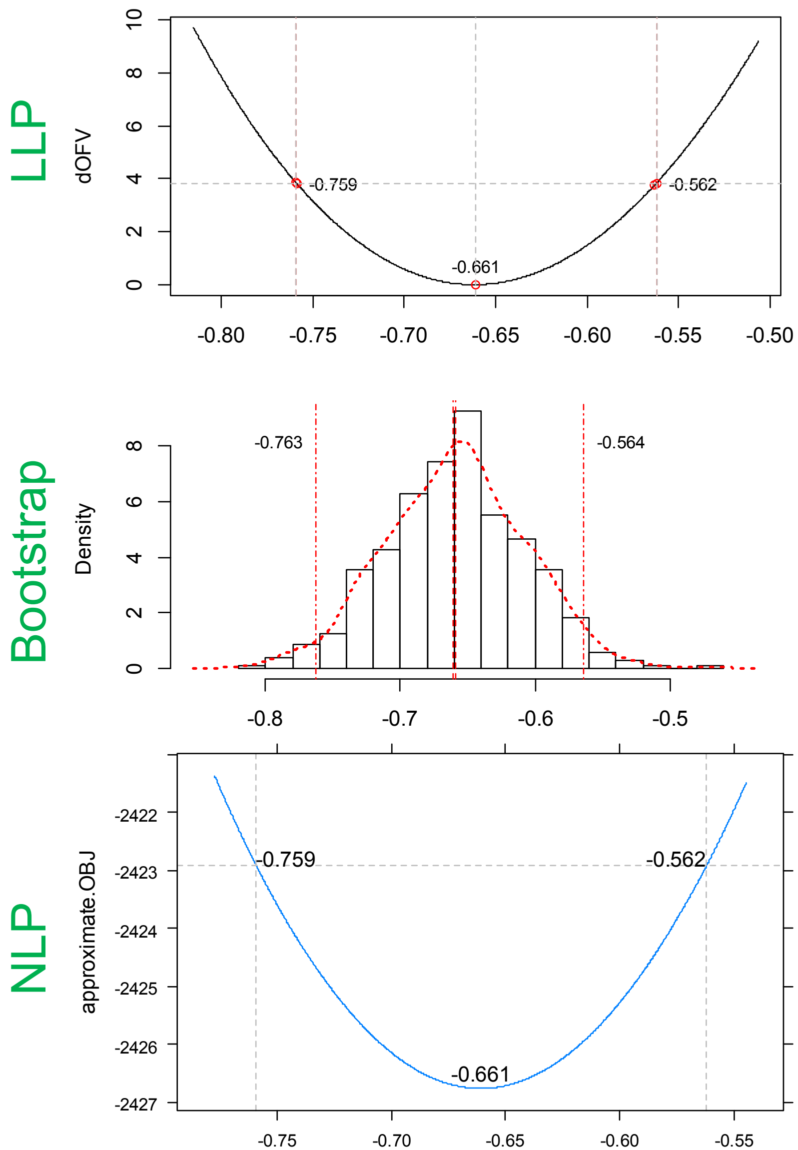


NLP in one dimension

- Compare LLP, Bootstrap, and NLP with one parameter of a two compartment PK model.

- All provide equal results.

- Model evaluations :
  - LLP - 5
  - Bootstrap - 1000
  - NLP - 8



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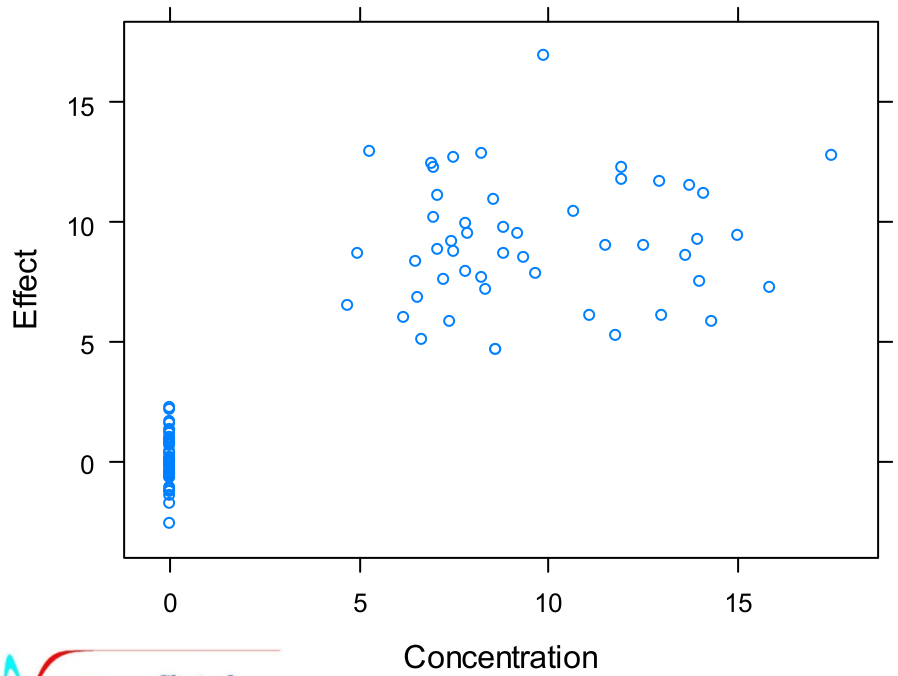
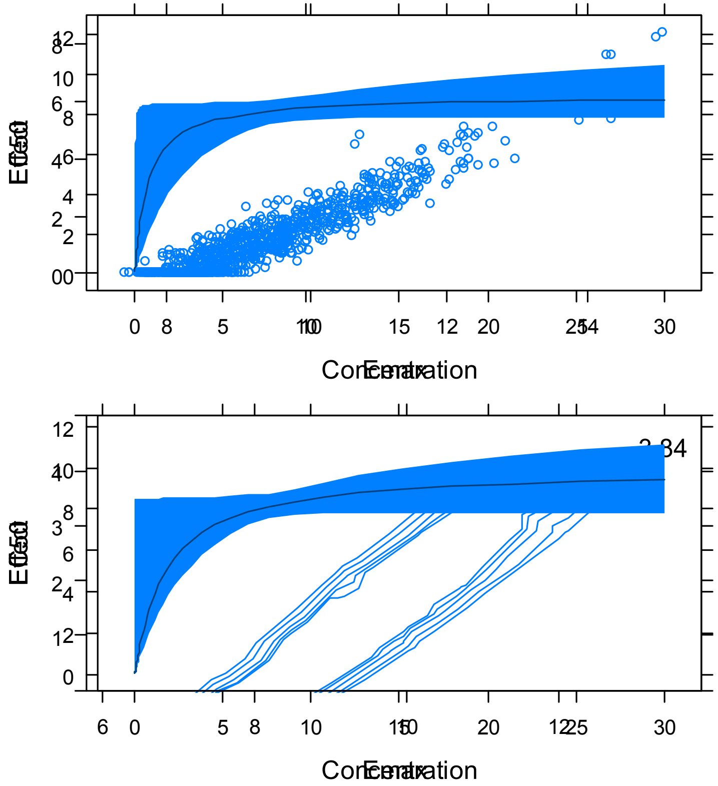
- In a “no regrets dose” study…
- What can we infer about Emax/EC50?



LLP

Bootstrap

NLP



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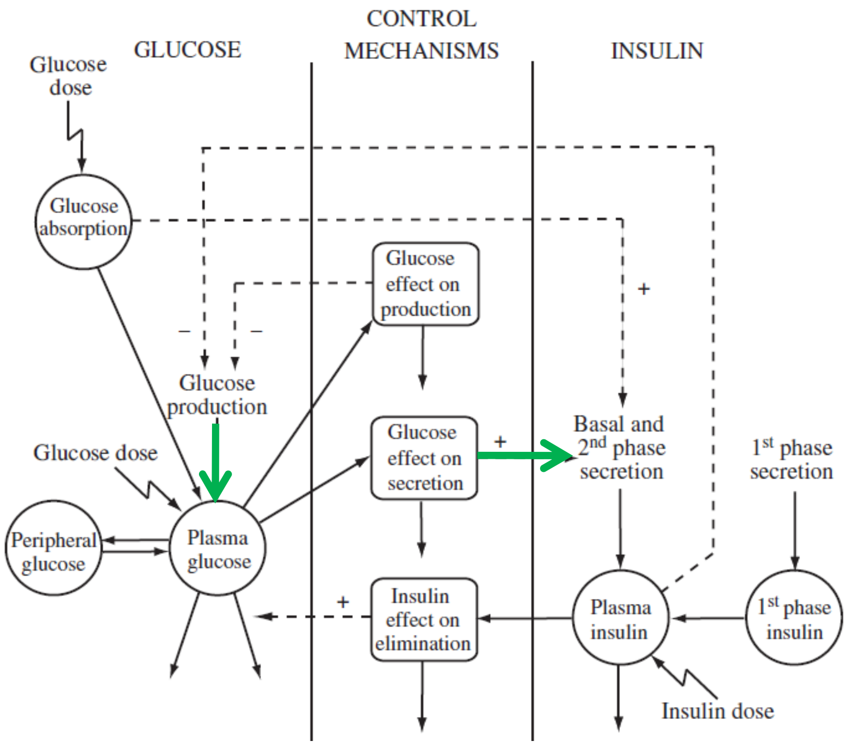
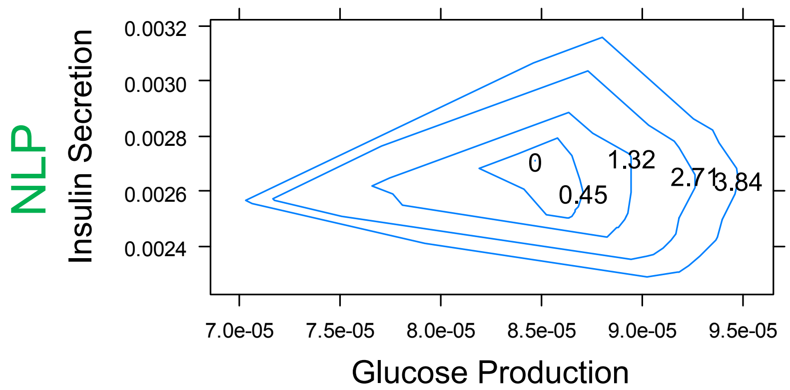
A day in the life of a quantitative clinical pharmacologist… made simpler.



Bootstrap did not complete after 10 days on a computational cluster.

NLP converged in 1 day on my laptop.



Silber, H. E., Jauslin, P. M., Frey, N. and Karlsson, M. O. Basic & Clinical Pharmacology & Toxicology, 106: 189–194.

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Conclusions

- NLP allows estimation and sampling of the likelihood surface in multiple dimensions (≤5).
- Faster solution than bootstrap with easy convergence for
  - Long parameter estimation times,
  - Small populations,
  - Fixed parameters,
  - High bootstrap non-convergence rates.

Acknowledgements

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- Ted Rieger
- Avi Ghosh

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THANK YOU!

Photo: Rose Robinson

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BACKUPS

Theory

- Covariance matrix
  - Assumes that local curvature at the minimum defines full distribution.
- LLP
  - Find the point where OBJ increases by X (3.84 = 95% CI) through iteration.
- NLP
  - Find the (piecewise, continuous) equation that defines the OBJ surface as a function of model parameters.
  - Can be used like LLP for one dimension, but allows sampling.
  - Provides multivariate empirical distribution.
- Bootstrap
  - Find parameter estimates through population resampling.

Summary

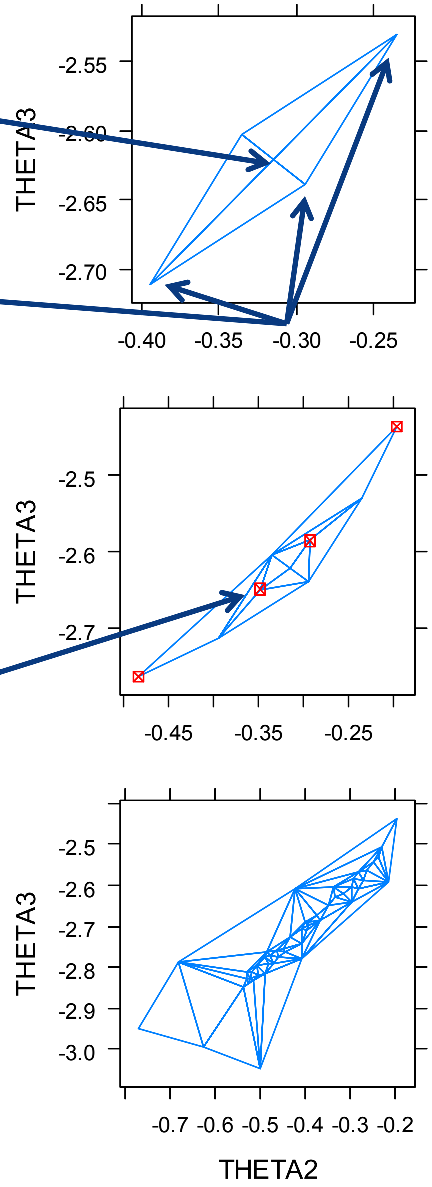
	LLP	Bootstrap	NLP
Can Sample for Simulation	No	Yes	Yes
CPU Time	~1x N	~1000-2000x N	~5-100x N
Dimensions	1	Full	Intermediate
Uncertainty in FIXED Parameters	Yes	No	Yes

Green indicates two best for row.

How does NLP work?

- Start with the initial parameter estimates (θ_0).
- Fix the parameters of interest at values away from θ_0 forming an initial set of simplexes.
- For each simplex (i):
  While ($\int new_i\, d\theta$ - $\int old_i\, d\theta$) > tol
  - Store $\int old_i\, d\theta = \int new_i\, d\theta$
  - Refine points and run model at new points.
    - Adding where error was previously observed; allows parallelization.
  - Compute $\int new_i\, d\theta$

- User-defined parameters are for point selection and Δ integration tolerance.



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Future extensions

- Analytical integration of n-dimensional likelihood surface will very significantly decrease estimation time in higher dimensions.
  - Improved interpolation methods will similarly reduce integration time and number of iterations required.
- If estimating full dimensionality of the problem (all non-fixed θs, ηs, and σs), faster methods (using maxeval=0) can be used to simply sample the likelihood surface at that point.
  - Typically will require above improvements in integration and/or interpolation.