UPPSALA UNIVERSITET

Two applications (glucose-insulin and disease-progression) and the methods that we needed to use to compute these designs.

Andrew C. Hooker,

Joakim Nyberg, Stefanie Henning, Hanna Silber and Mats O. Karlsson

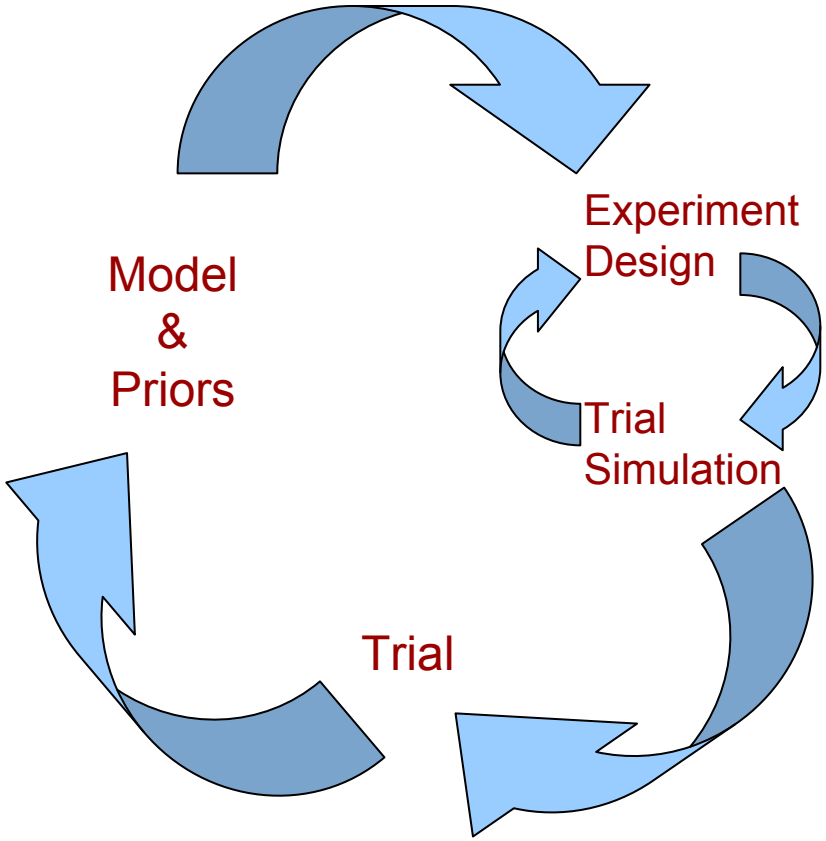
Division of Pharmacokinetics and Drug Therapy

Department of Pharmaceutical Biosciences

Uppsala University

UPPSALA UNIVERSITET

Model based drug development



UPPSALA UNIVERSITET

Limitations to making optimal design clinically relevant

1. Optimization only done on sample times in most cases
2. Must assume a model structure.
3. Point estimates of model parameters needed

UPPSALA UNIVERSITET

Making optimal design more clinically relevant

Sample time optimization

Theory does not stop us from optimization of 'other' design parameters

- Dose
- Covariates
- Number of samples/group
- Number of individuals/group
- Infusion start/stop/duration
- Start/stop times of studies
- Wash out period length
- Etc….

Foracchia, M., Hooker, A., Vicini, P. and Ruggeri, A., *POPED, a software for optimal experiment design in population kinetics.* Comput Methods Programs Biomed, 2004.

UPPSALA UNIVERSITET

Optimizing the IVGTT using optimal experimental design

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

Division of Pharmacokinetics and Drug Therapy
Department of Pharmaceutical Biosciences
Uppsala University

UPPSALA UNIVERSITET

Background / objective

Background

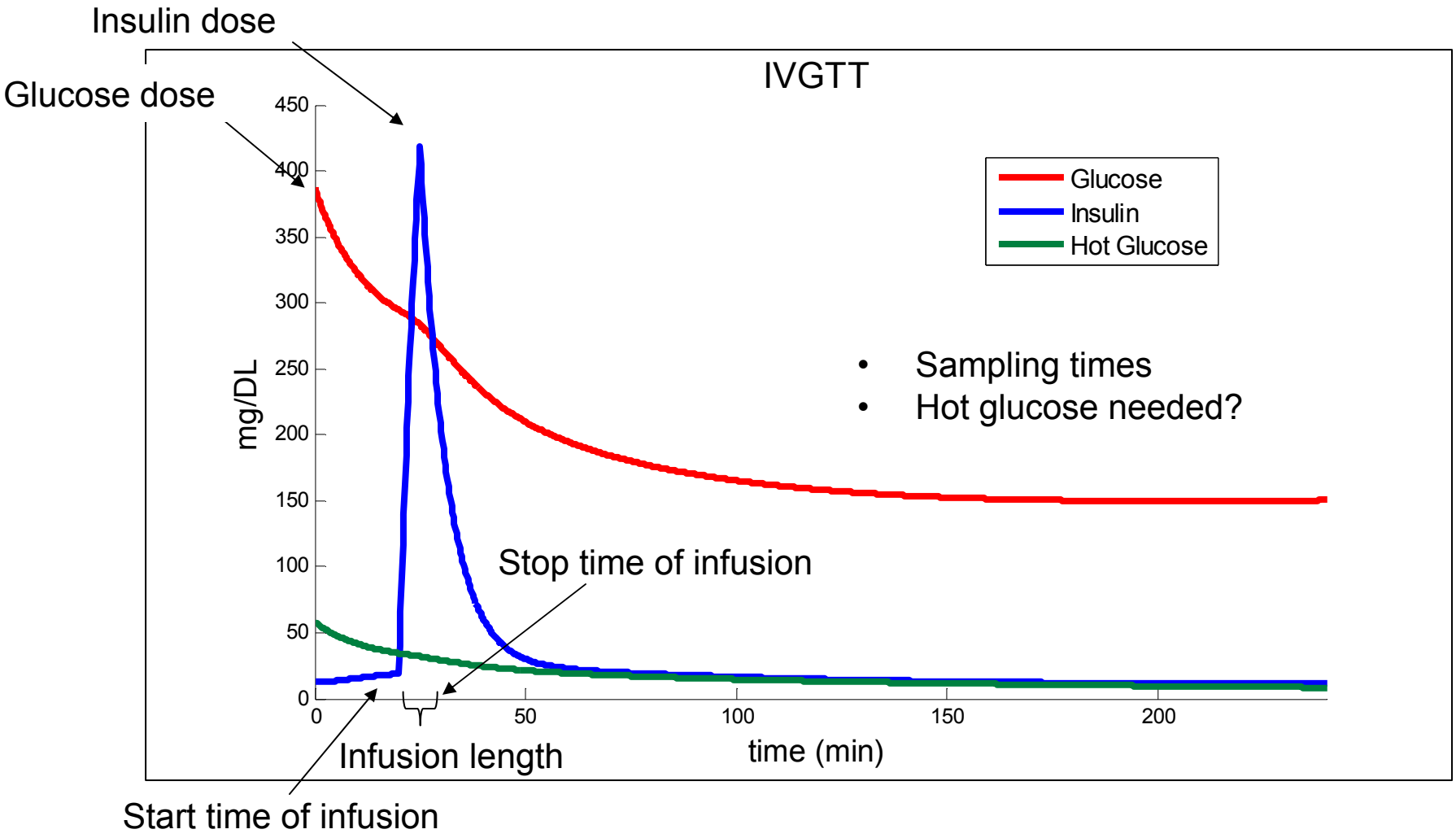
- Provocation experiments are performed in order to study the glucose insulin system
- The experiments are highly standardized and based on empiric design.
- Often rich in sampling

Aim

- To evaluate different design aspects of the insulin modified IVGTT for the patient population using the optimal design software PopED

UPPSALA UNIVERSITET

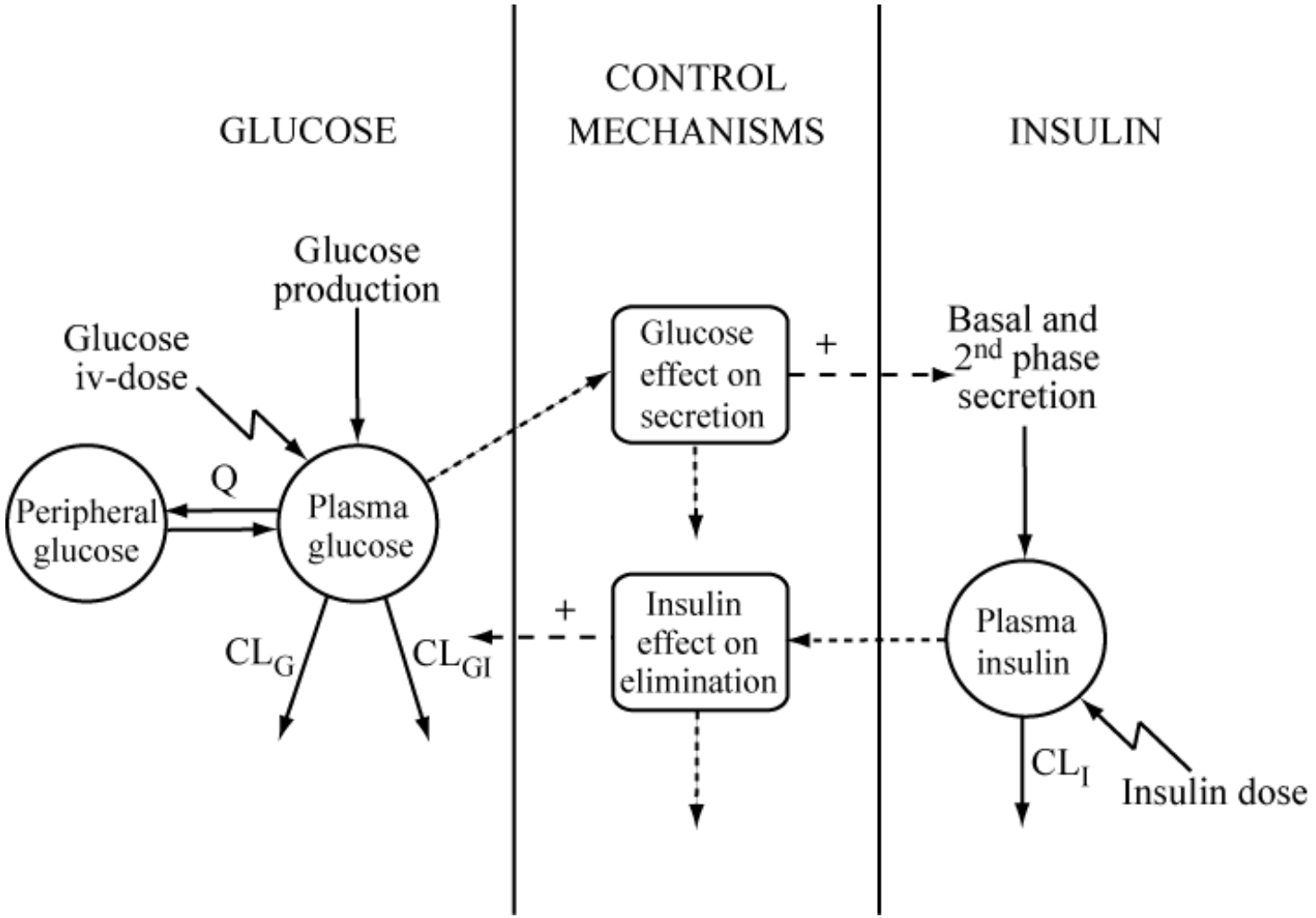
What can we optimize on?



UPPSALA UNIVERSITET

The glucose-insulin model

for the T2DM patient population



Silber et. al. *JCP*, 2007

UPPSALA UNIVERSITET

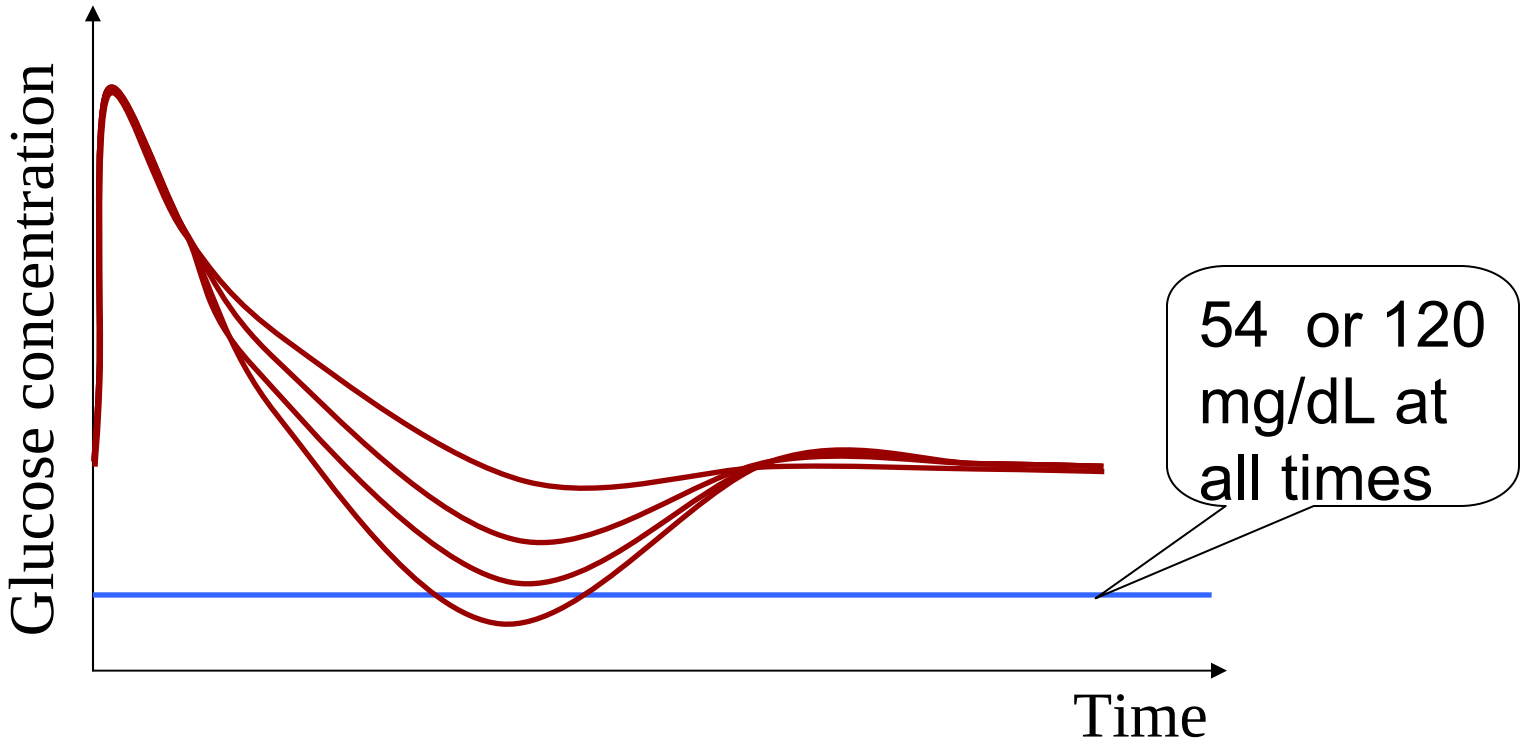
Practical considerations

- ✓ Complex model
  - ✓ 3 submodels (glucose, insulin, hot glucose)
  - ✓ 25 parameters
  - ✓ 30 observations
- ➢ Long run times – design reduction necessary
  - ✓ Reduce sampling scheme (10 observations)
  - ✓ FO method (for now)
  - ✓ Optimize one design aspect at the time

UPPSALA UNIVERSITET

Constraints on glucose concentrations

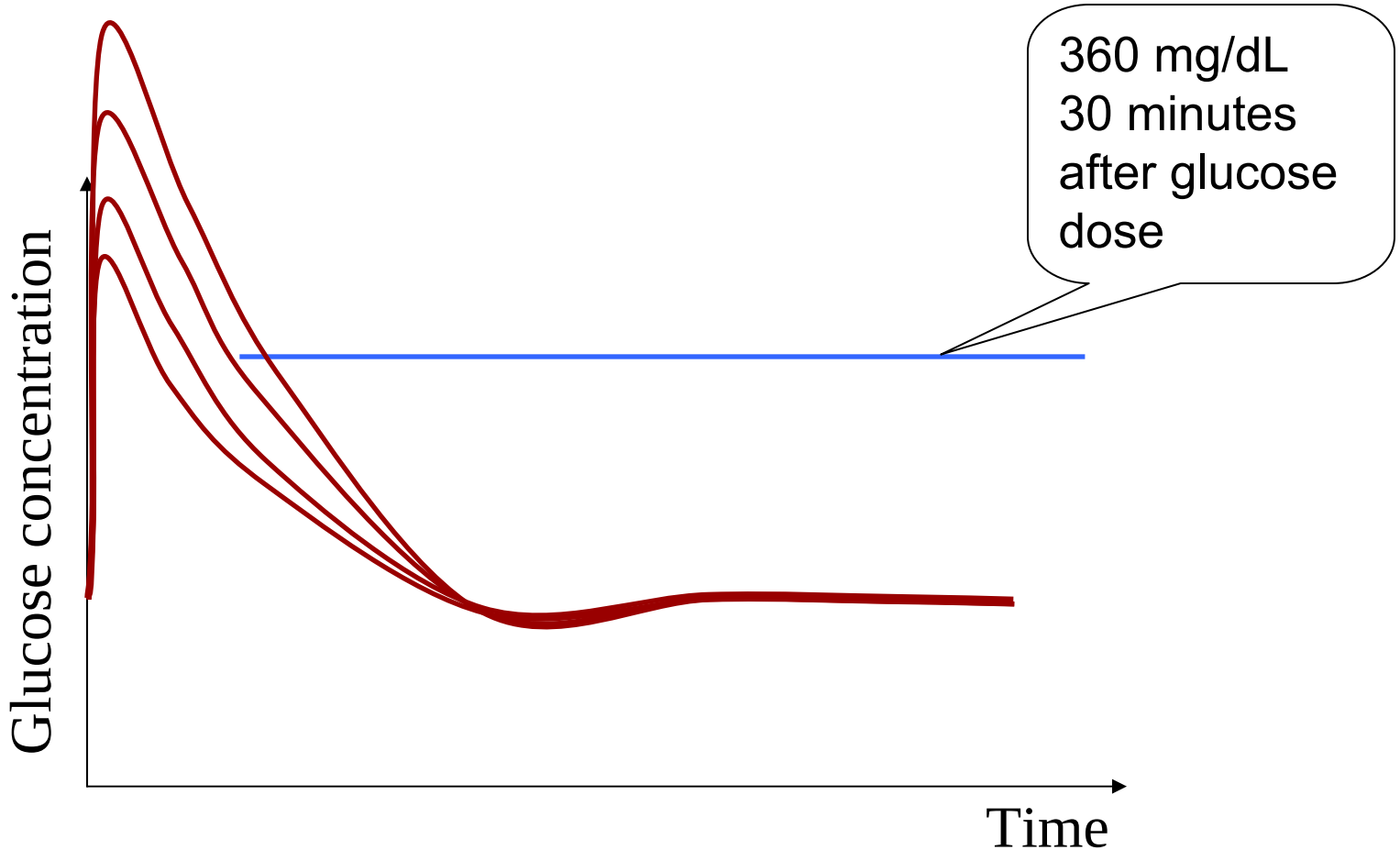
Effect of changing the insulin dose



UPPSALA UNIVERSITET

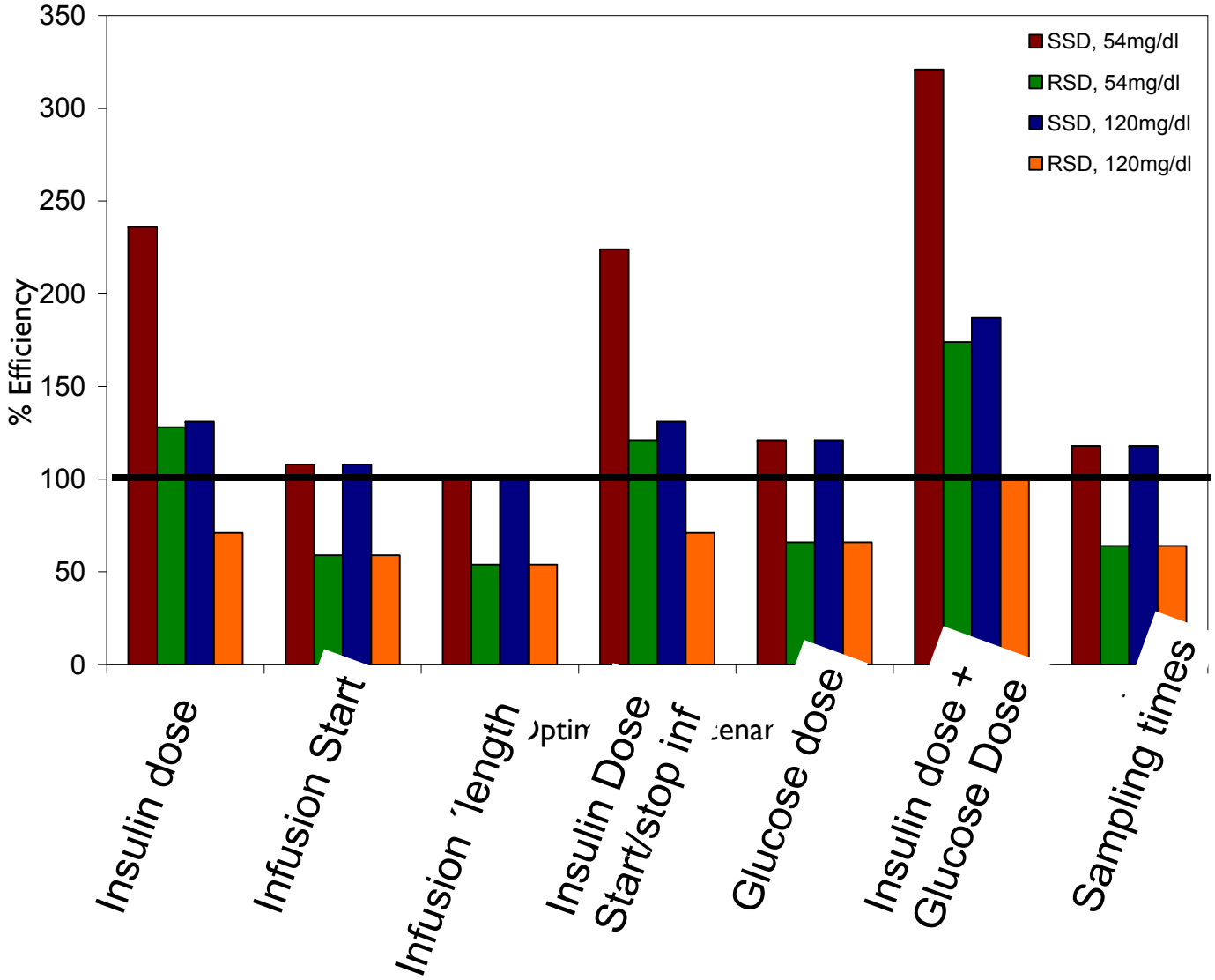
Constraints on glucose concentrations

Effect of changing the glucose dose



UPPSALA UNIVERSITET

Results



UPPSALA UNIVERSITET

Summary and conclusion

- ✓ It is possible to improve on the design of the insulin modified IVGTT
- ✓ Changing the insulin dose has the greatest impact on the efficiency of the design

- ✓ These type of provocation experiments can be improved by the use of population modeling and optimal experimental design

UPPSALA UNIVERSITET

Limitations to making optimal design clinically relevant

1. Optimization only done on sample times in most cases
2. Must assume a model structure.
3. Point estimates of model parameters needed

UPPSALA
UNIVERSITET

Application of Optimal Design for Disease Progression Studies

Stefanie Hennig, Sebastian Ueckert, Joakim Nyberg, Andrew Hooker, Mats O. Karlsson

Division of Pharmacokinetics and Drug Therapy
Department of Pharmaceutical Biosciences
Uppsala University

UPPSALA UNIVERSITET

Disease Progression

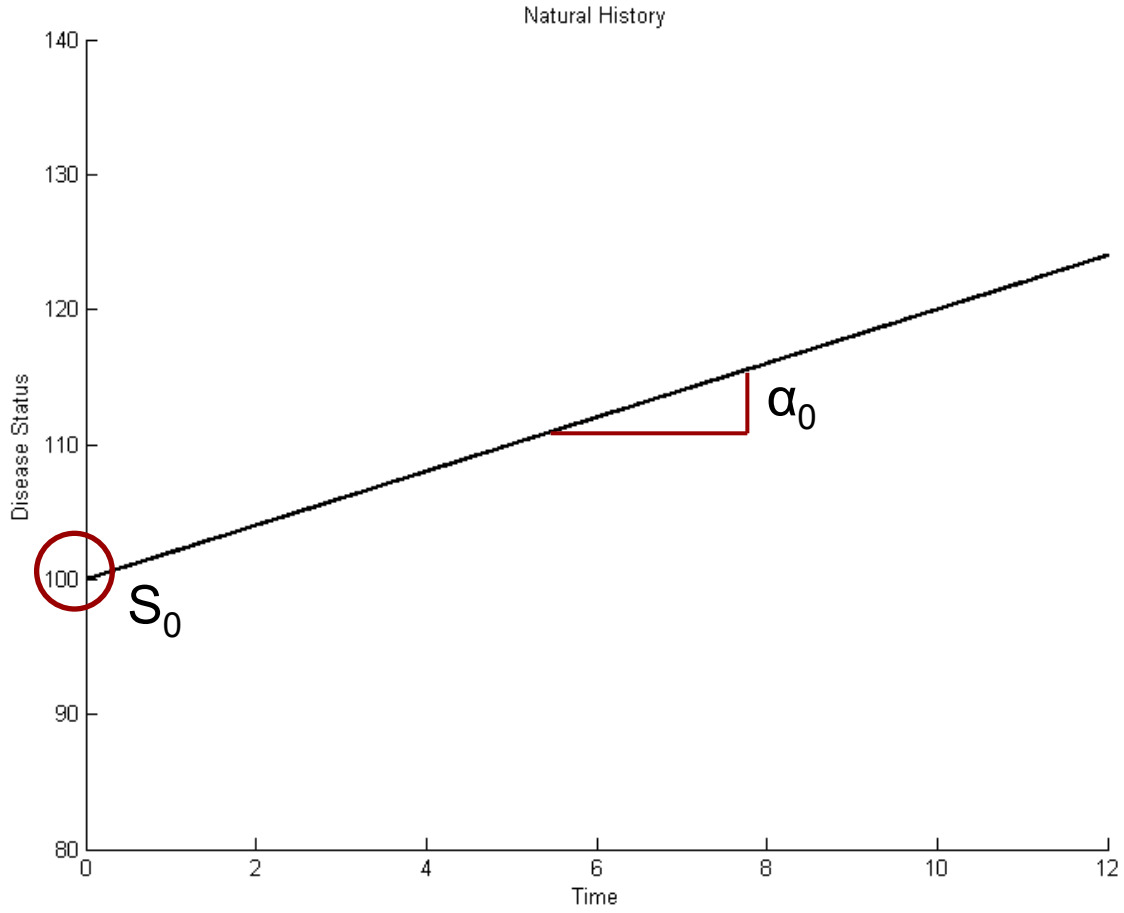
- Disease status (S) of degenerative diseases (Alzheimer's, Parkinson, osteoporosis) worsens over time
- Rate of deterioration determined by natural rate of disease progression and the effect of drug treatment
- Drug treatment in these diseases should slow down disease progression not just relieve clinical symptoms
- Disease progression studies are performed to obtain information on the effect of drugs for the long term prognosis on a disease

Chan, Holford. Annu Rev Pharmacol Toxicol 2001;41:625-59
Holford. PAGE 2007

UPPSALA UNIVERSITET

Natural History

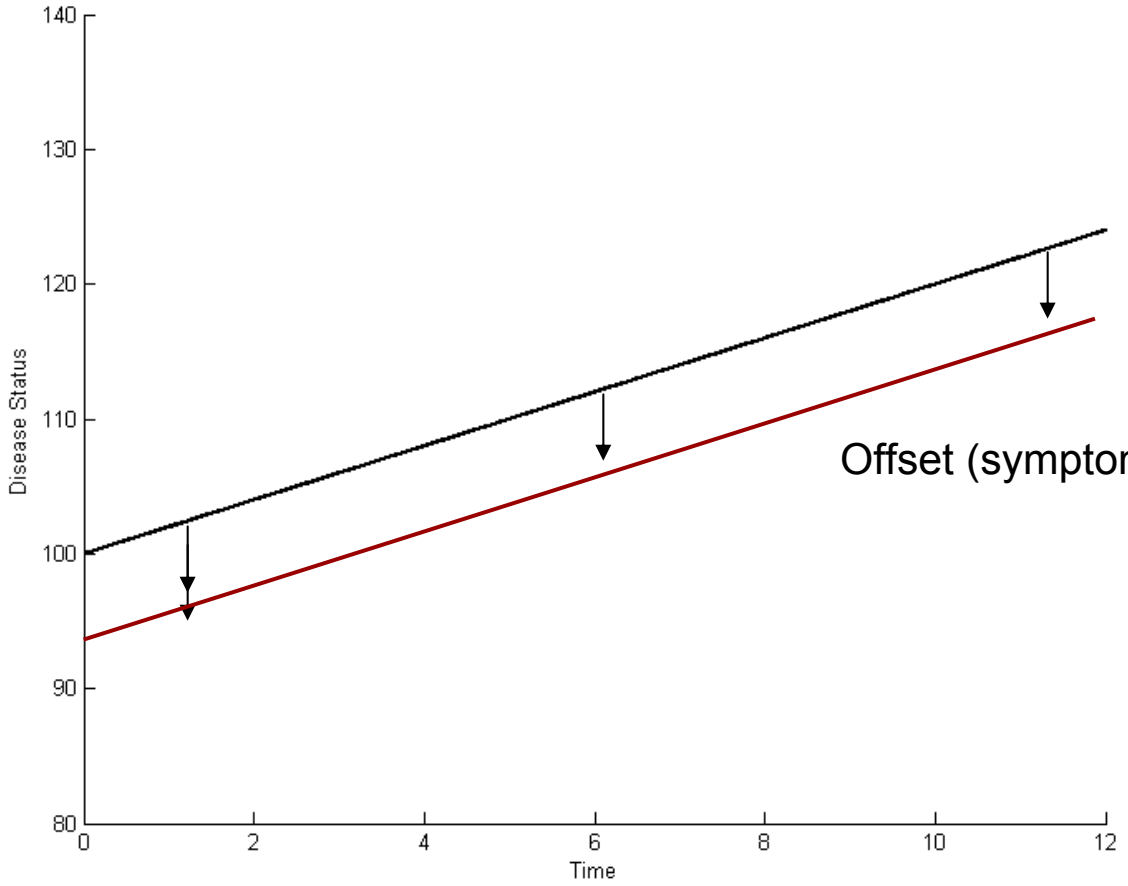
$$DS_{NH} = S_0 + \alpha_0 \times t$$



UPPSALA UNIVERSITET

Symptomatic treatment Effects

$$DS_{dt} = S_s + \alpha_0 \times t$$

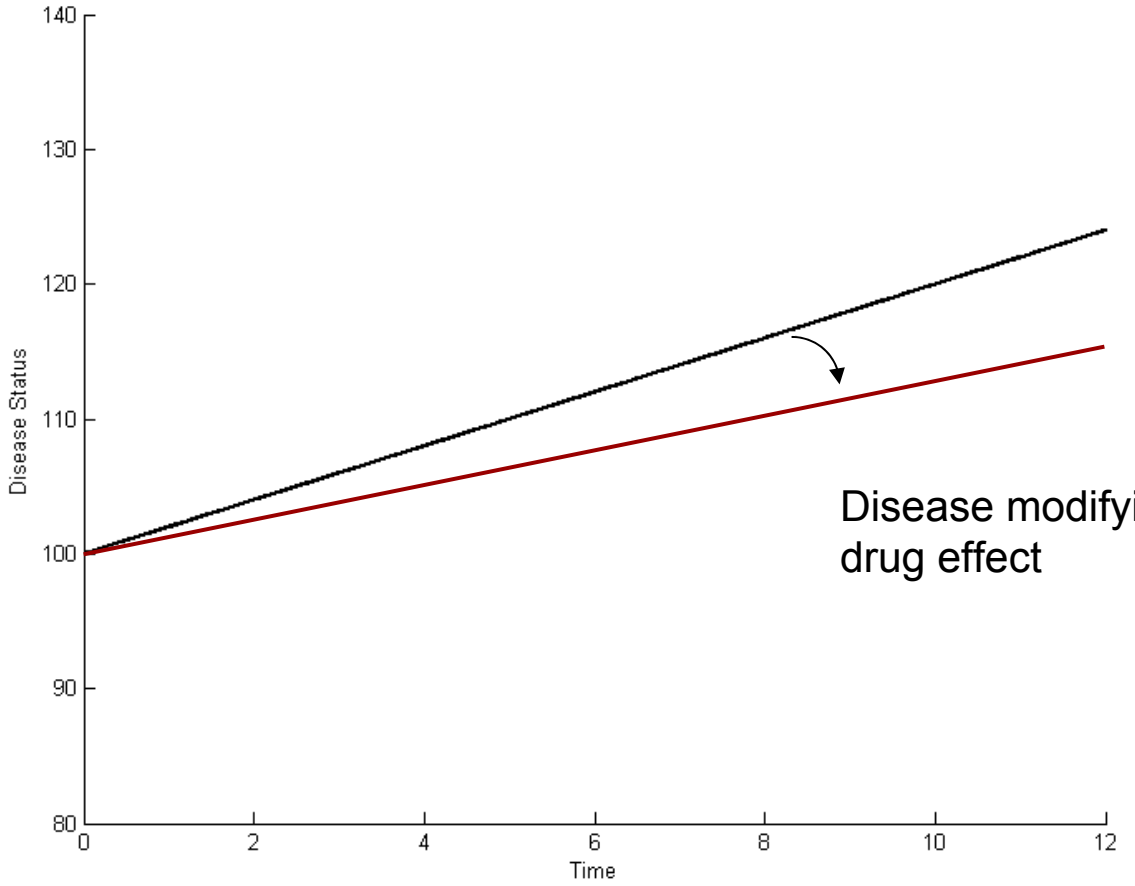


Offset (symptomatic, S) drug effect

UPPSALA UNIVERSITET

Protective treatment Effects

$$DS_{dt} = S_0 + \alpha_p \times t$$

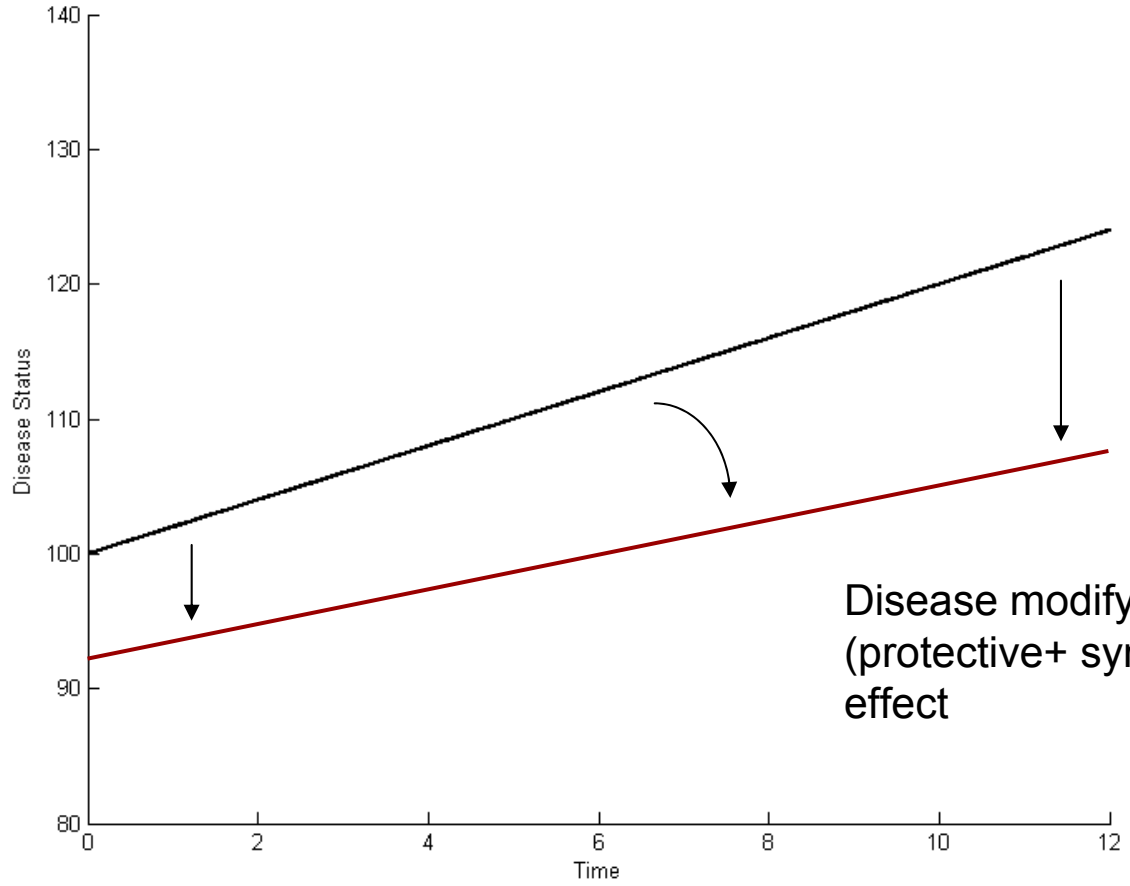


Disease modifying (protective, P) drug effect

UPPSALA UNIVERSITET

Disease modifying + symptomatic effects

$$DS_{DT} = S_S + \alpha_P \times t$$



Disease modifying + offset (protective+ symptomatic, PS) drug effect

UPPSALA UNIVERSITET

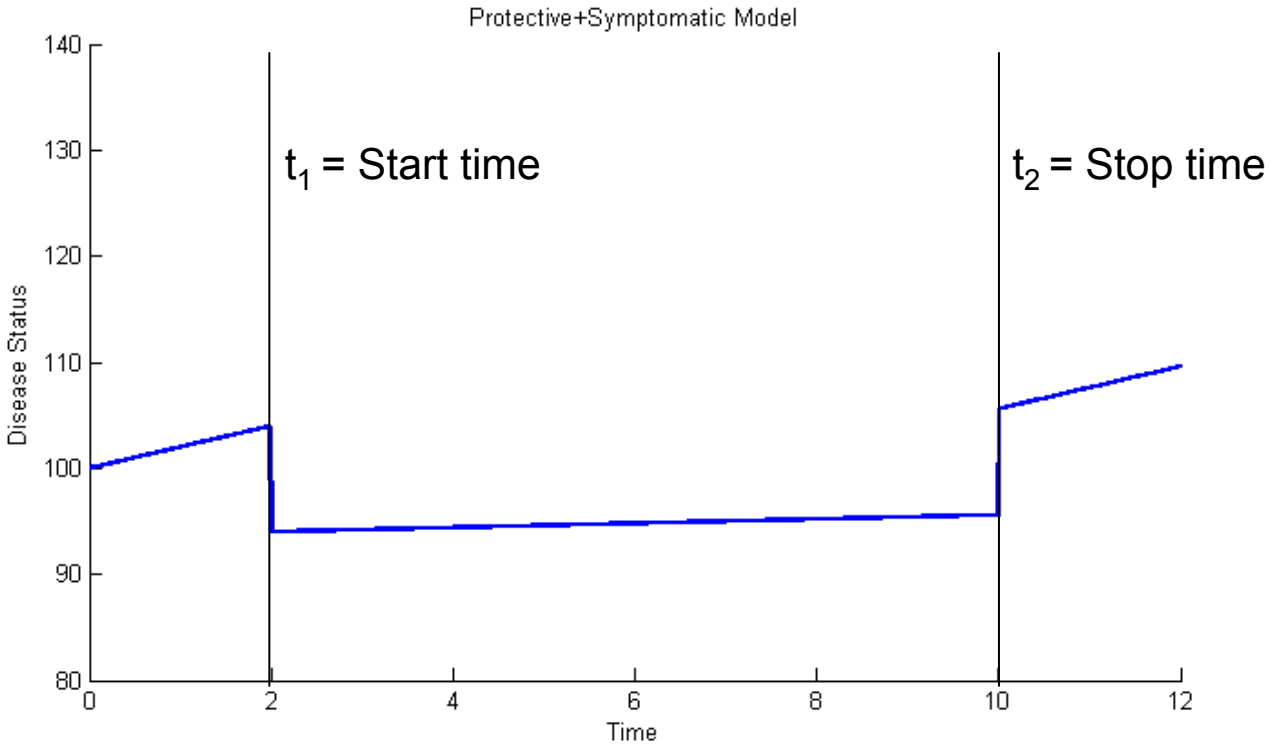
Treatment periods

$$DS = \begin{cases} S_0 + \alpha_0 t & t < t_1 \\ S_S + \alpha_P (t - t_1) & t_1 < t < t_2 \\ S_0 + \alpha_0 (t - t_2) & t > t_2 \end{cases}$$

Delayed start period

Treatment period

Wash-out period



UPPSALA UNIVERSITET

Aim

- Demonstrate an application of optimal design optimizing period lengths (delayed start, treatment, wash-out) for DP studies
  - Determine optimal start time and stop time of treatment for separate models
  - Determine efficiency loss if no observations taken after stopping the treatment (during washout)

- Characterize drug effects across different mechanisms and magnitudes for model discrimination
  - using uncertainty on parameter values (ED-optimality)

Design Parameters – flexible start/stop time of treatment

Parameters:

- Baseline S_0 = 100
- Slope α_0 = 2
- Baseline $_{\text{symptomatic effect}}$ S_s = 90
- Slope $_{\text{protective effect}}$ α_p = 0.2
- BSV on all parameters = 30%
- Residual error
  - additive = 10
  - proportional = 22%

Parameter Uncertainty (ED-design)

- Slope of disease progression, α_0 =15%

Design:

- Total Study Period (t): 12
- Observations (n):
  - 13 evenly spread
  - [0-12] h
  - fixed
- Number of patients: 200 (1 Group same design)
- Treatment Period: flexible
- Optimizations performed using PopED v.2

UPPSALA UNIVERSITET

Results – Flexible start and stop time

- Number of observations during different study periods

	Number of observations (%)		
Model	**Before Treatment**	**During Treatment**	**After Treatment**
Protective	0%	50%	50%
Symptomatic	20%	50%	30%
Protective+Symptomatic	10%	40%	50%

UPPSALA UNIVERSITET

Results – No Washout Period

Efficiency of designs decreased between 10-40% per parameter

	Number of observations (%)		
Model	**Before Treatment**	**During Treatment**	**After Treatment**
Protective	46%	54%	0%
Symptomatic	8%	92%	0%
Protective+Symptomatic	54%	46%	0%

UPPSALA UNIVERSITET

Results – Model Discrimination

- Results of comparison from 100 simulation from true model and estimations using the true model and 2 alternative models
- Design: Combined models design
- Based on significant reduction in OFV

True	Test	% True model accepted
Symptomatic Model	Protective	100
	P+S	91
Protective Model	Symptomatic	100
	P+S	100
Protective+Symptomatic Model	Symptomatic	100
	Protective	100

UPPSALA UNIVERSITET

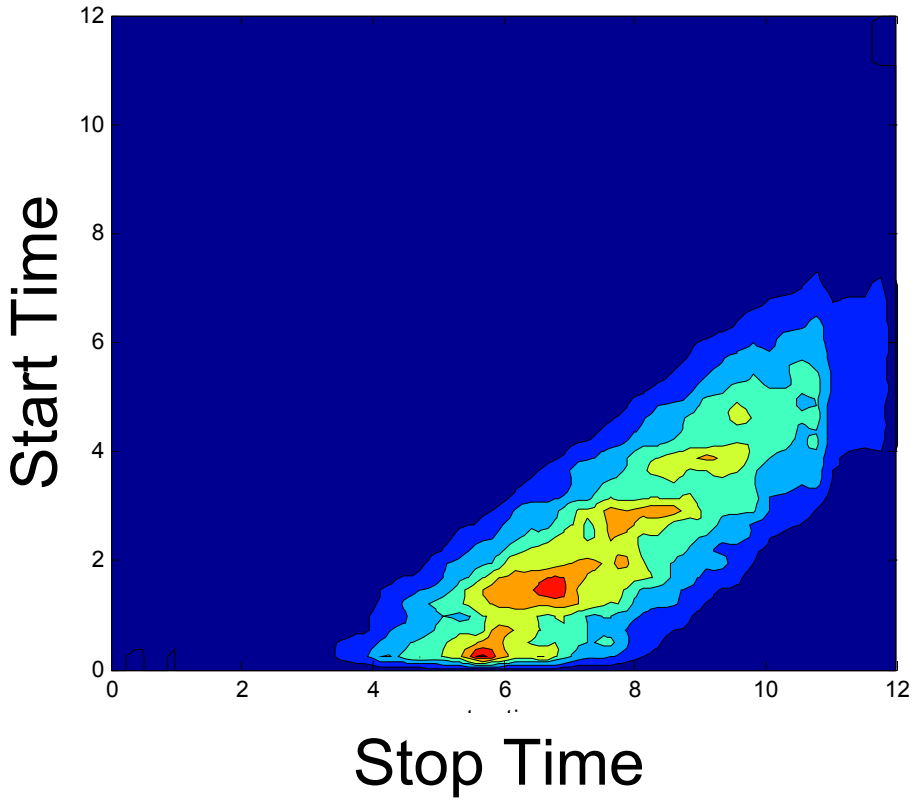
Effect Discrimination

- Assumed a uniform distribution of P and S effect between 0% and 100% of the total effect
- Find an ED optimal design
- Simulate and estimate 9 different scenarios from the indefinite number of combinations using NONMEM VI
- Look at the 95% confidence region around the estimates

UPPSALA UNIVERSITET

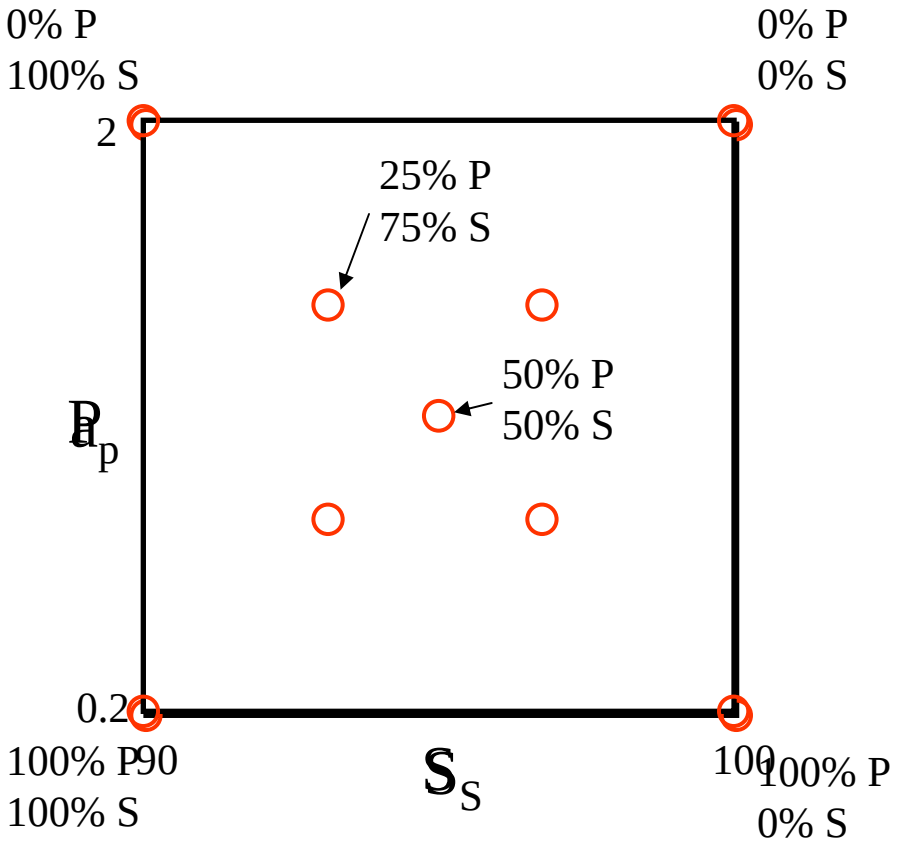
Results - Effect Discrimination

Start Time	1.07
Stop Time	6.11
OFV	3.49e11



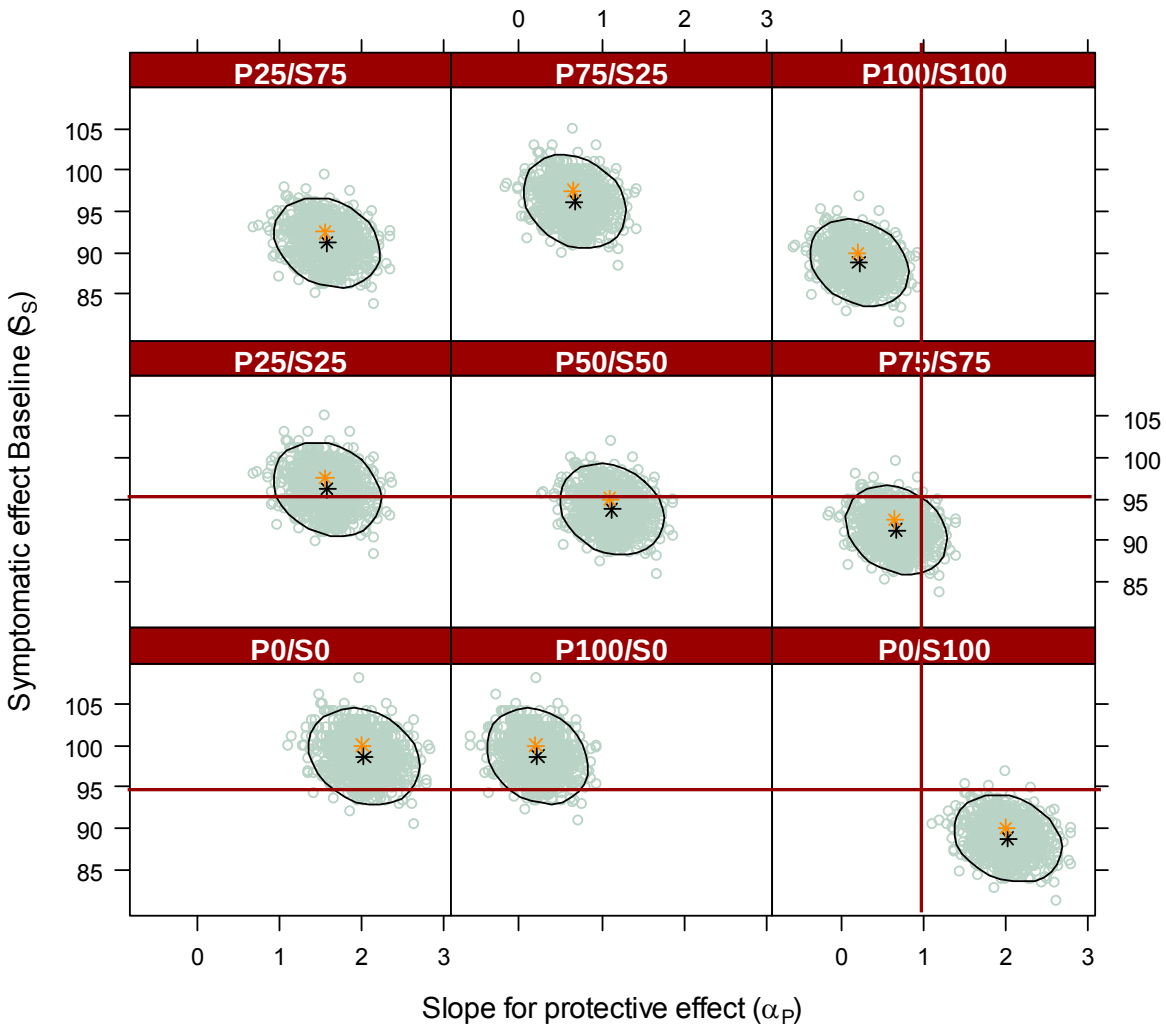
Results - Effect Discrimination Simulation and Estimation

- 1000 Simulation of 9 different effect scenarios



UPPSALA UNIVERSITET

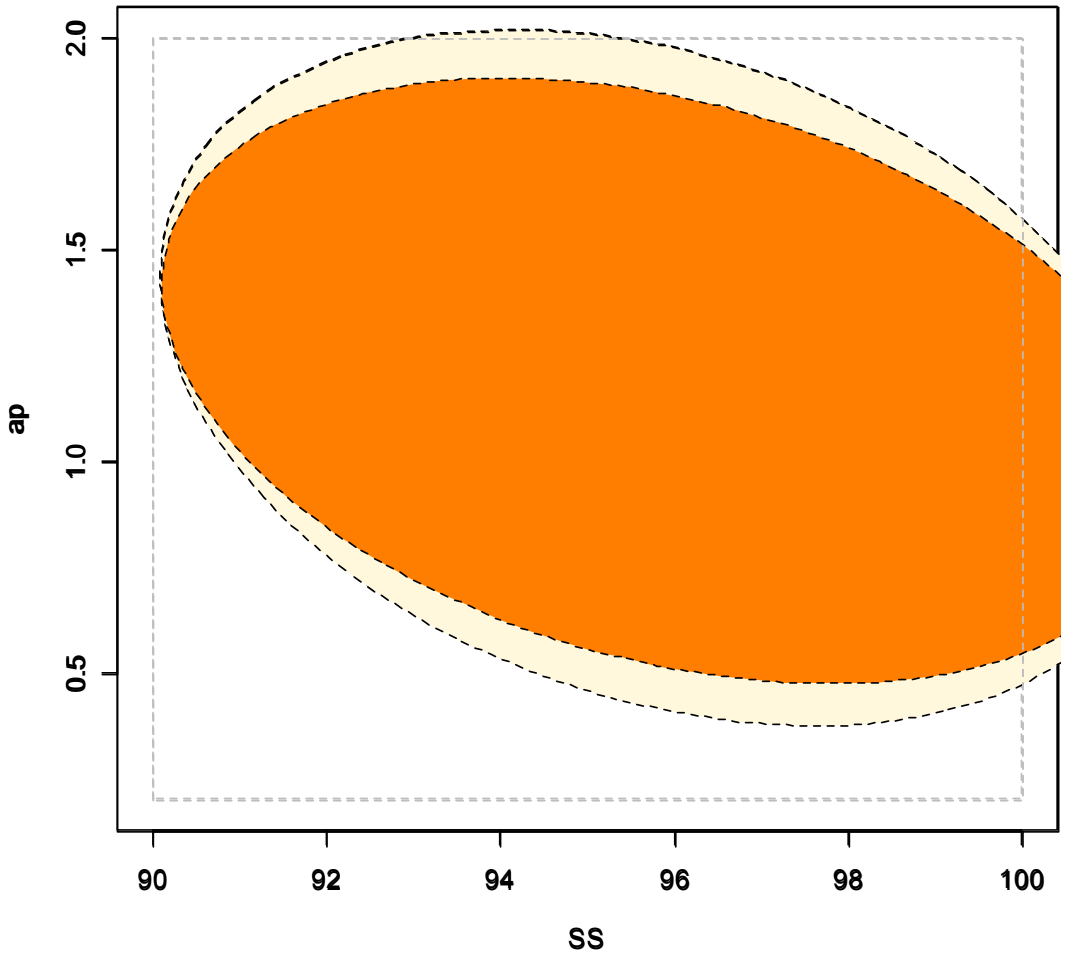
Results - Effect Discrimination Confidence Regions



UPPSALA UNIVERSITET

Results - Effect Discrimination CR

OD for full effect range versus OD on a specific effect (P50%S50%)



UPPSALA UNIVERSITET

Conclusion for disease progression example

- Efficiency of the design increases if we have washout observations
- Optimization for a uniform distribution of effects showed good performance
- CR spanning large parts of the parameter range made differentiating between some close effects impossible

UPPSALA UNIVERSITET

Conclusions

1. Optimization on “other” design variables needed and can be more informative than sample times

2. If model structure not known this uncertainty should be taken into account
   a. Multiple model structures
   b. Distributions around assumed parameter values

3. Design constraints on the dependent variable useful