Adaptive Bayesian Methods for Biomarker Trials: Application to Brain Imaging

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PSI Biomarker in Early Phase,

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Disclosure

- I work for a statistical CRO that develops and commercializes Decimaker, a software for Bayesian adaptive designs and decision analyses.

www.decimaker.com

Objective

- Develop a Bayesian Toolbox for Early Phase Biomarker Trials:
  - Show value of Bayesian methods
    - Case study using brain imaging
  - Leverage use of Bayesian methods
    - Sharing of programs and best practices

Outline

- Background: biomarkers in early phase
- Bayesian toolbox & use in a simple example
- Some more advanced problems
- Summary and Conclusions

Survey # 1

WHO KNOWS ABOUT BAYESIAN METHODS?

RE: ABOUT 20/30

WHO USES THEM FOR BIOMARKERS?

RE: 2/30

WHAT LANGUAGE?

RE: C (N=1) DURING PHD.

Biomarkers in Early Phase

- Proof of mechanism:
  - Drug-on-target assessment

    Receptor Occupancy PET
- Proof of principle:
  - Pharmacodynamic effect on disease phenotype

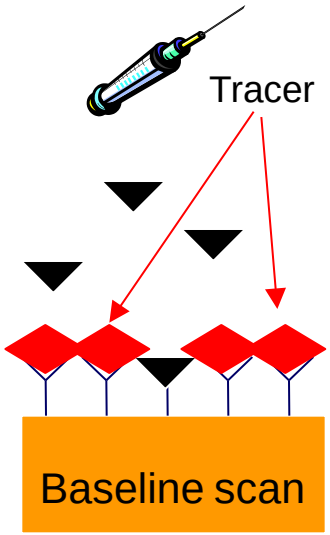
    β-CIT SPECT in Parkinson
- Proof of concept:
  - Clinical benefit to patient

    FDG-PET in Oncology

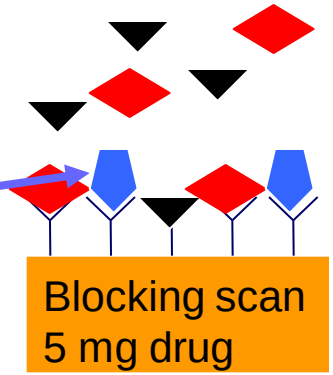
Opportunities and Challenges

- Streamline drug development:
  - Go/No go
  - Dose selection
- Some Challenges:
  - Complex technology, signal processing
  - Multiplicity of targets
  - Small sample size, expensive assay
  - Reliability of decisions
  - Trial failure: is it drug failure or biomarker failure?

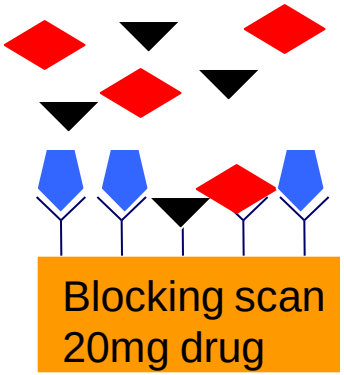
Example: Receptor Blockade PET



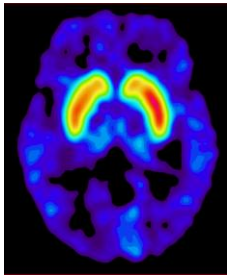

Drug

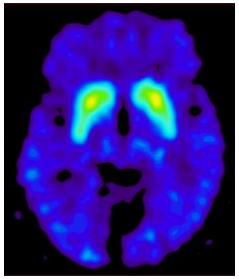


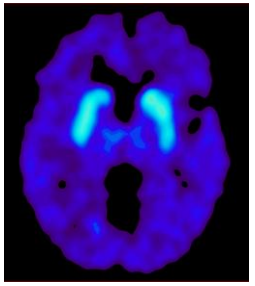
50%Occupancy



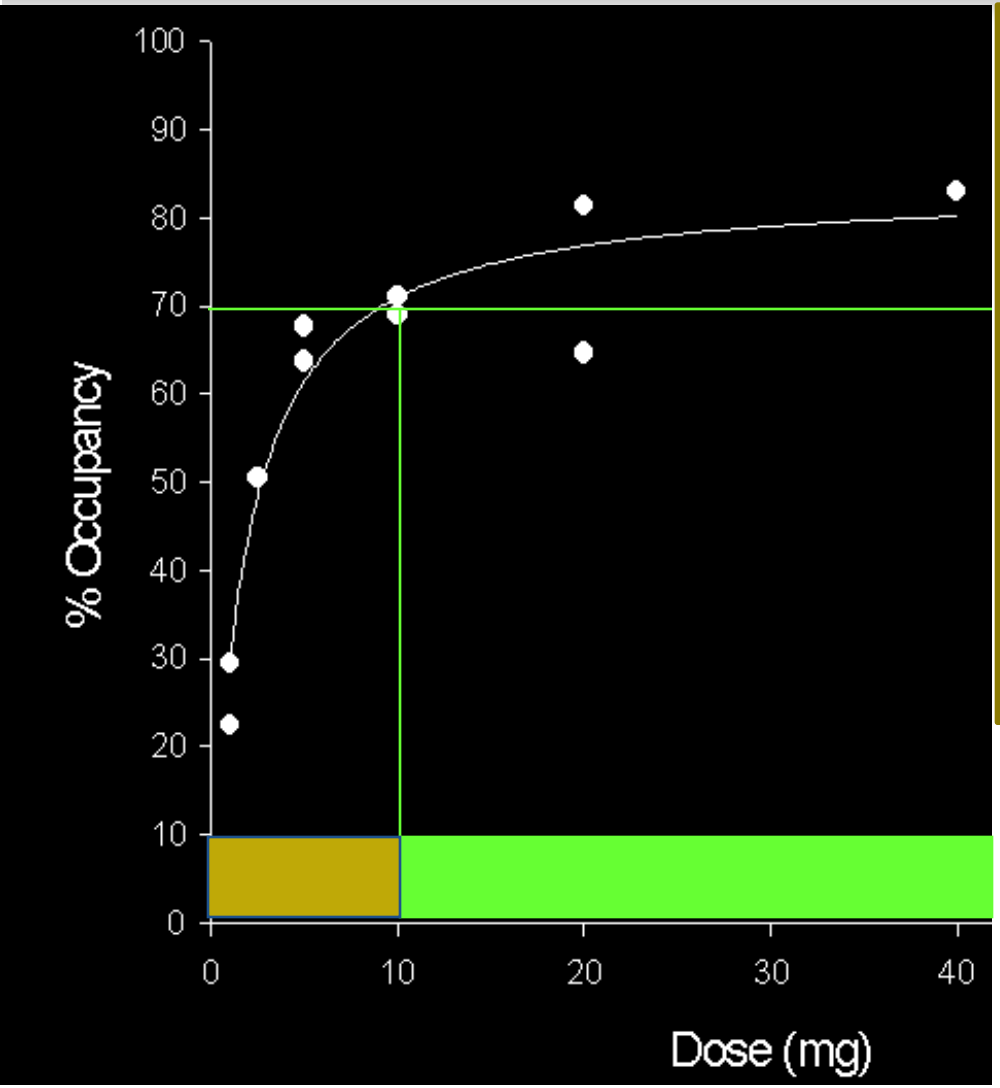
75%Occupancy







Dose-Occupancy Relationship



Strategy:
Fit dose-response model

Find dosage range producing meaningful response.

Examples:
- 11C-DASB PET for SSRI

J. Meyer et al., [11C]DASB uptake before and after fluoxetine, Toronto.

Statistical Techniques

Fixed-design, Frequentist

- Pre-specify design, doses, size.
- Fit model (e.g., Emax)
- Decide based on p-values, confidence intervals.

Bayesian Adaptive

- Choice of relevant priors
- Pre-specify analysis plan and max. size.
- Enroll iteratively groups of patients
- Fit model (e.g., Emax)
- Decide based on posterior distribution :
  - Stop/Go
  - Adaptive dose selection
- Predict future events

Bayesian Methods

- Posterior update

$$p(\theta \mid y) \propto p(\theta)\, p(y \mid \theta)$$

- Intuitive idea : cumulative learning of historical and trial information
- Immediate applications to drug development:
  - Summary of relevant information
  - Probability of success
  - Utility-based decisions
  - Prediction of future results

SIMPLE BAYESIAN TOOLBOX FOR RO-PET

Simple Illustration

- Dose-Response Emax Model for One Brain Region:

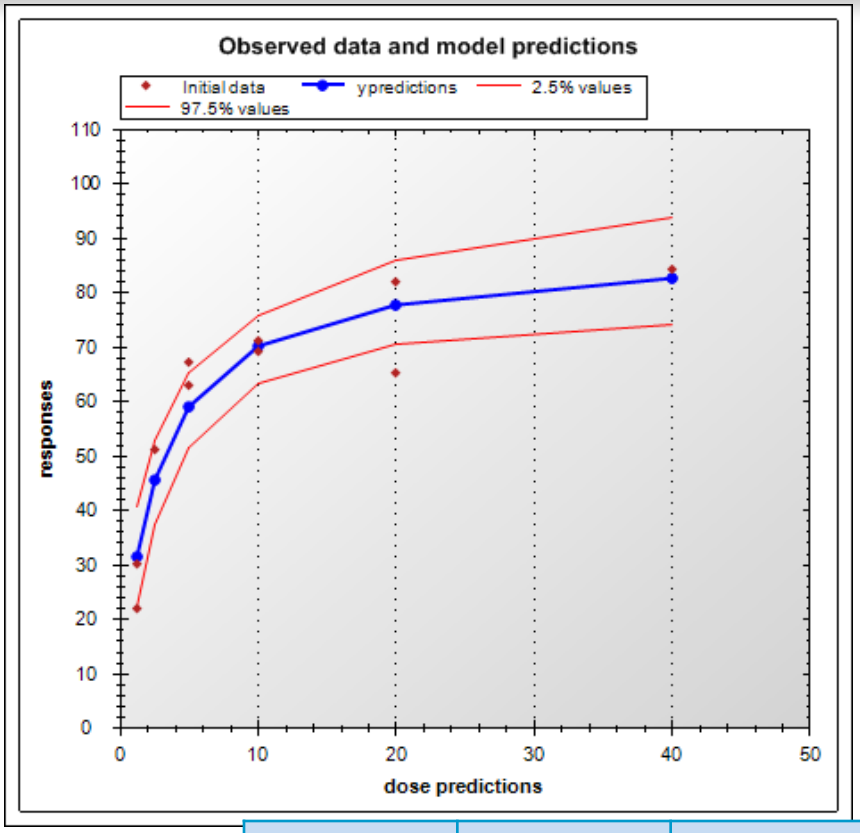
$$\mu = E0 + \frac{E\max dose}{ED_{50} + dose}$$

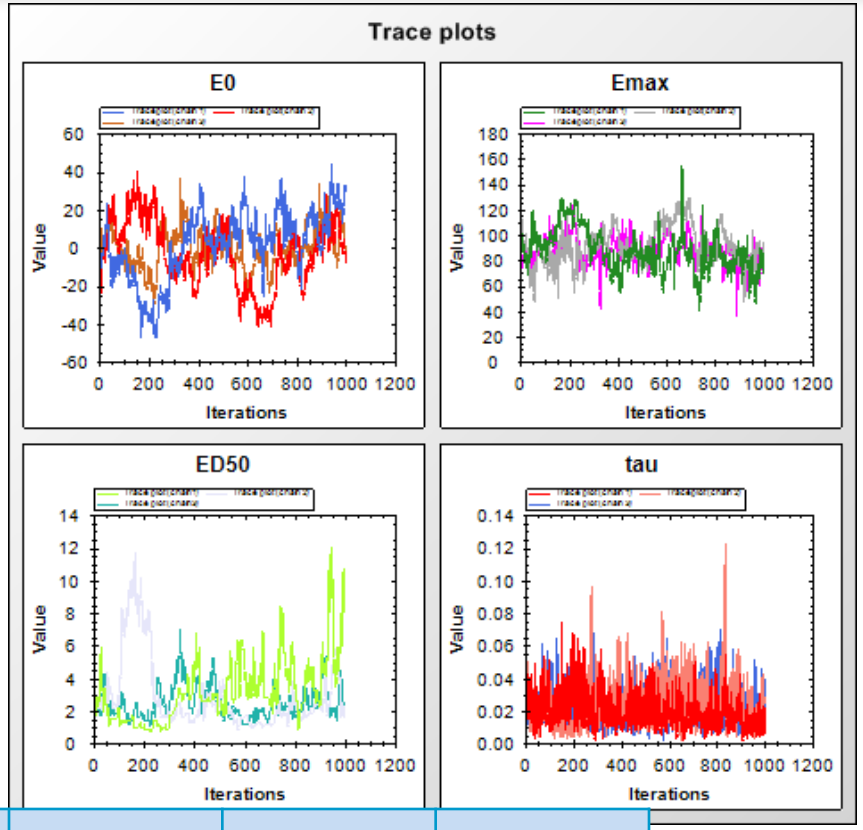
- Priors:
  - Flat on Emax and ED50.
  - Informative on E0: normal; mean=0, std=20.

Winbugs code for Emax model

```
model{
for (i in 1:n.obs) {
   y[i]~dnorm(mean[i],tau)
   mean[i]<-E0 + Emax * x[i]/(ED50+ x[i])}
E0~dnorm(0,.0025)
Emax~dflat()
ED50~dflat()
tau~dgamma(0.0001,0.0001)
}
```

Model fit to PET data





Param	mean	sd	2.5%	median	97.5%
E0	-0.823	15.99	-36	0.359	28.58
Emax	88.74	14.63	60.43	87.58	120.8
ED50	2.84	1.836	0.95	2.34	8.618
tau	0.021	0.012	0.005	0.019	0.05

Bayesian Decisions

Principle: Based on posterior distribution of functions of parameters.

Examples:

- Probability of success
  - Pr[μ(dose)>70%|data]
- Estimation of a target dose
  - Predicted dose where μ=70%

Pr(40mg)=99%

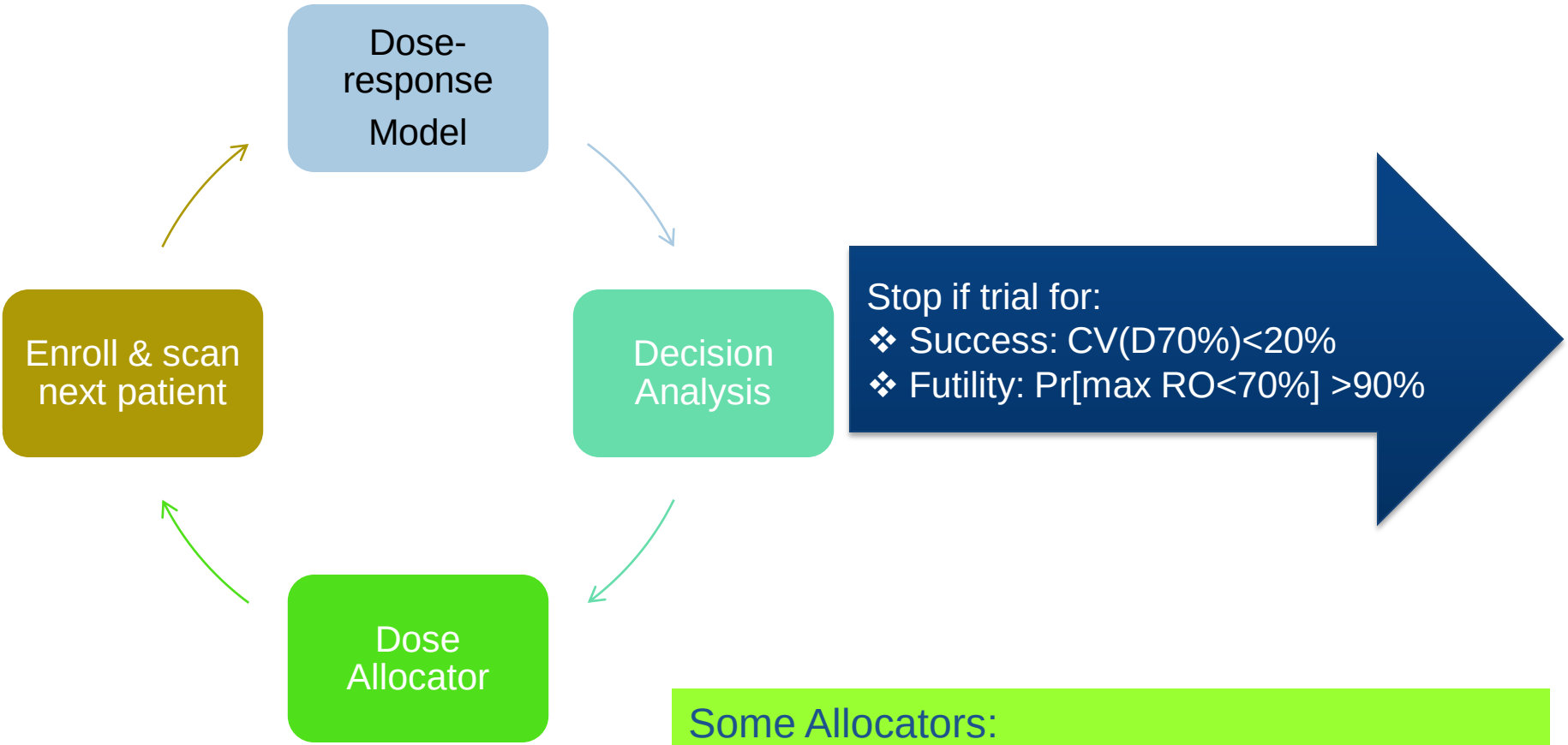
$$D_{70\%} = \mathrm{ED50}\,\frac{70\% - \mathrm{E0}}{\mathrm{Emax} - 70\% + \mathrm{E0}}$$

	Mean	Sd	Median
D70%	10.51	5.30	9.78

Winbugs code for Decisions

```
model{
for (i in 1:n.obs) {
Likelihood…
Pr.70[i]<-step(mean[i]-70)}
Priors…
Dtarget<-ED50*(70-E0)/(Emax-70+E0)
}
```

Adaptive Dose Selection



Some Allocators:

1. To minimize the variance (D-, C-optimality)
2. To find a target dose (D70%)

Utility-based dose allocators

- Let $\{d_1, \ldots, d_N\}$ be the set of possible doses:
  - E.g., 1.25, 2.5, 5, 10, 20, 40mg
- We choose as next dose the candidate that maximizes the expected utility function:

$$E(d) = \int U(d, \theta)\, p(\theta \mid y) d\theta$$

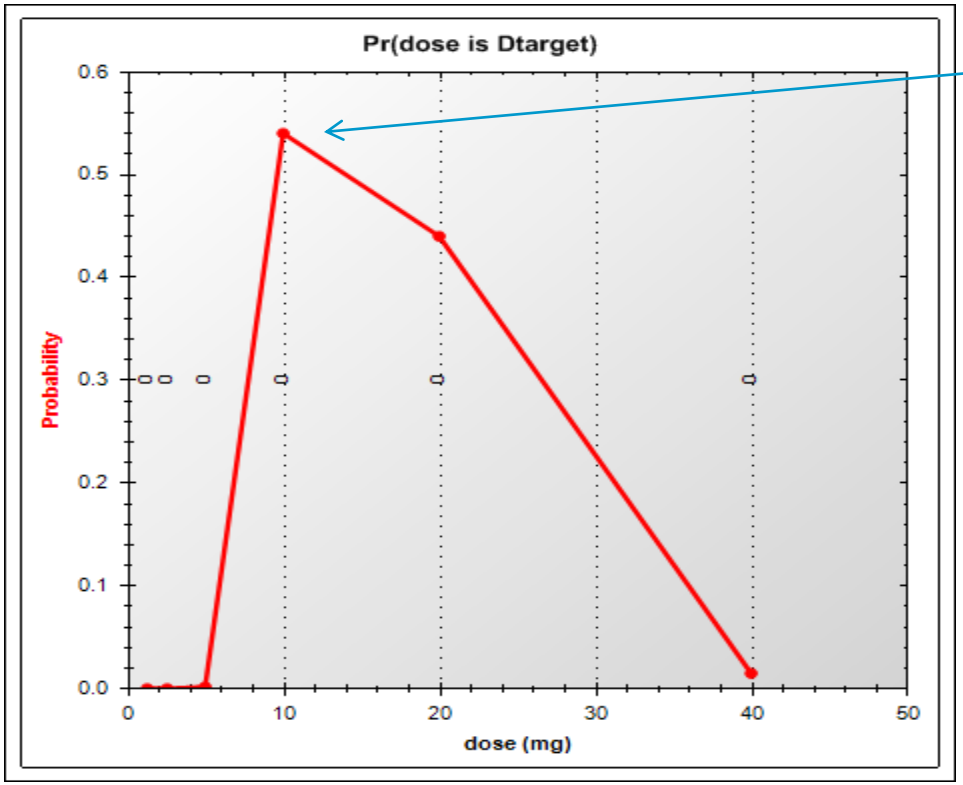
Some utility examples:

- Variance:
  - D-optimality: $U(d,\theta) = \det[M(d,\theta)]$
  - C-optimality: $U(d,ED50) = \mathrm{var}[ED50(d)]$

- Minimum dose producing desired effect:
  - $dTarget(\theta) = \min_d \mu(d, \theta) \geq 70\%$
  - $U(d,\theta) = \{d == dTarget(\theta)\}$

Results: DTarget Allocator

Probability that dose is the minimum dose where RO>70% versus dose.



Largest probability at 10 mg (54%).

Winbugs/R code for DTarget

Remember: Pr.70 : matrix (#col=#doses) equal to TRUE if mean[i]>=70%, FALSE otherwise.

Then, in R:

```
dose<-c(1.25,2.5,5,10,20,40)
```

We calculate for each row(j) of Pr.70:

```
min.dose[j]<-min(dose[pr.70[j,]])
```

The Dtarget distribution is computed from frequencies in:

```
table(min.dose)
```

Survey #2:

We have discussed :

- the choice of relevant priors to gain efficiency & decrease size
- Bayesian Go/Stop and adaptive allocation decisions based on posterior distribution functions.

WHAT ELSE CAN BE ACCOMPLISHED USING BAYESIAN METHODS?

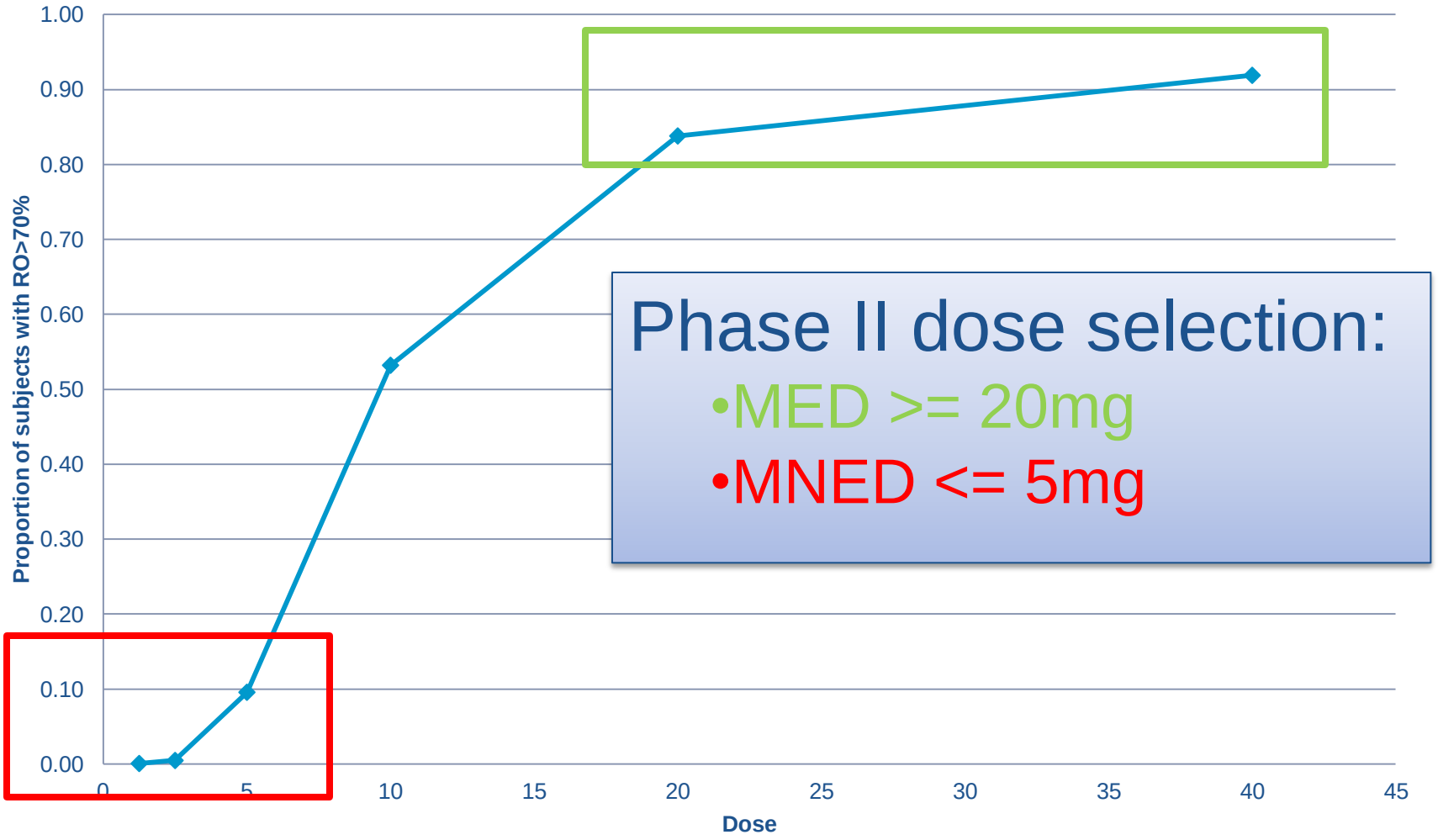
Predictions

- Posterior predictive distribution
  - Look at what is most likely next:
    - Given current data, and
    - Unconditionally to any fixed parameter value.
  - Predicting Receptor Occupancy in future patient:

$$p(y_{new} \mid y) = \int p(y_{new} \mid \theta, y)\, p(\theta \mid y)\, d\theta$$

Virtual patient model

Proportion of Future Patients with Receptor Saturation



Phase II dose selection:

- MED >= 20mg
- MNED <= 5mg

Winbugs code for prediction

```
model{
for (i in 1:n.obs) {
Likelihood…
next.RO[i]~dnorm(mean[i],tau)
pr.next.70[i]<-step(next.RO[i]-70)
}…}
```

Predictive Power

- We would like to use the current knowledge summarized in the posterior distribution to calculate sample size for a next study:
  - Goal is to show that μ>70%

- We compute the predictive power:

$$PP(\mu > 70\%) = \int CP(\mu > 70\% \mid \theta, y)\, p(\theta \mid y)\, d\theta$$

WinBugs/R Code for Conditional Power

- Step 1 - WinBUGS: We predict the mean RO for the target sample size N as:

```
N<-4;  sd<- sqrt(1/tau);
se<-sd/sqrt(N);inv.se2<-1(se*se);
mean.N~dnorm(mean,inv.se2)
```

- Step 2 – R: We calculate the power for the t-test statistic using:

```
cp<-power.t.test(n=N,delta=mean.N-70 ,sd=sd,
alternative="one.sided",type="one.sample“)
```

R Code for Predictive Power

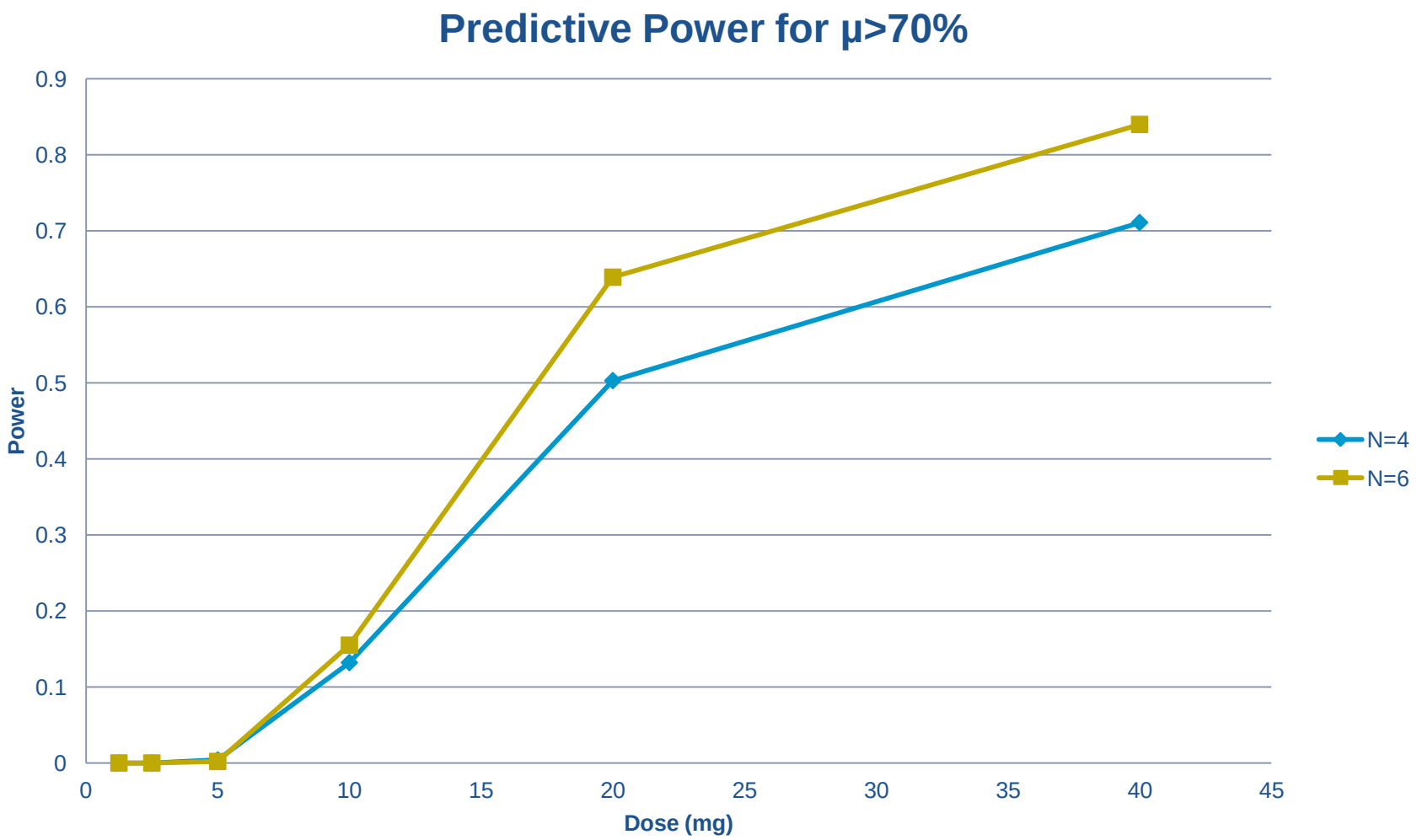
- We start out of cp$power: the MCMC chain of conditional powers:

Mean.N	Sd	cp$power
84.5	10.1	0.7686
72.4	9.7	0.5673
78.7	12.3	0.6575
…	…	…
81.7	9.2	0.7889

- The predictive power is then calculated as:

mean(cp$power)

Result for PET trial



Use of Discrete Priors

- Discrete probability distribution for selected parameters
  - E.g.: Instead of Emax~flat(), we define:

Emax	Prior Prob.	Posterior Prob.
0	33.3%	0.03%
50	33.3%	7.27%
70	33.3%	92.70%

- Utility:
  - Dichotomous decisions
  - Dose selection (eg, ED50)
  - Use of posterior MCMC samples as a new prior

Winbugs code for discrete priors

Inits…

Emax<-Emax.v[Emax.k]

Emax.k~dcat(Emax.p[])

}

Data:

Emax.v=c(0, 50, 70)

Emax.p=c(0.33, 0.33,0. 33)

Summary and Conclusions

- We illustrated the Bayesian logic applied to early phase biomarker trials.
- We discussed:
  - Choice of priors
  - Bayesian posterior analysis for decision, adaptive designs, predictions and power.
- Extensions to more complex models is « easy ».
- Main obstacles to Bayesian methods:
  - Know-how: need sharing of best practices
  - Programming:
    - Winbugs is a standard but not really user-friendly
    - Proc MCMC in SAS 9.2 (new & not tested yet).

Thank you!

Any Question?