Science For A Better Life

Bayesian Applications in Biomarker Detection

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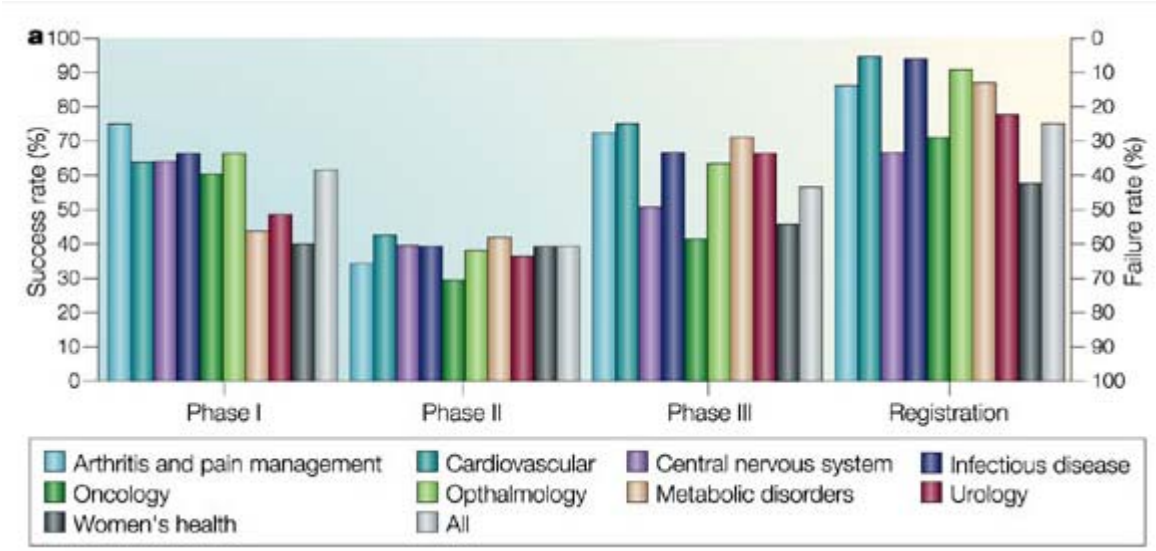
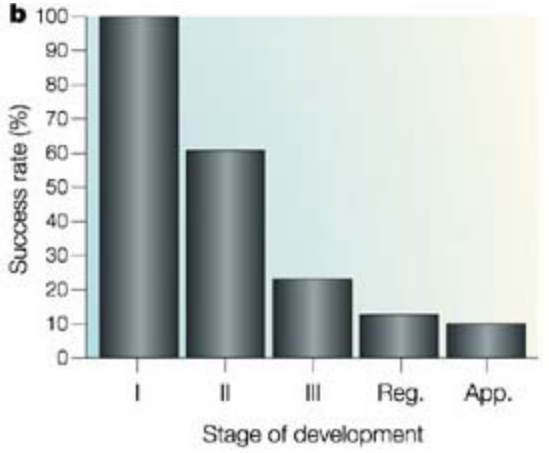
The views expressed in this presentation
are the personal views of the author,
and do not necessarily represent the view of his employer

Agenda

- Introduction
- Application to Enrichment Designs
- Bayesian Dose-Response
- Implementation
- Summary and Conclusion

Where Are We Now?





Kola, I, Landis, J. (2004). Can the pharmaceutical industry reduce attrition rates? Nature Reviews Drug Discovery, 3, 711-715

Old Stuff?

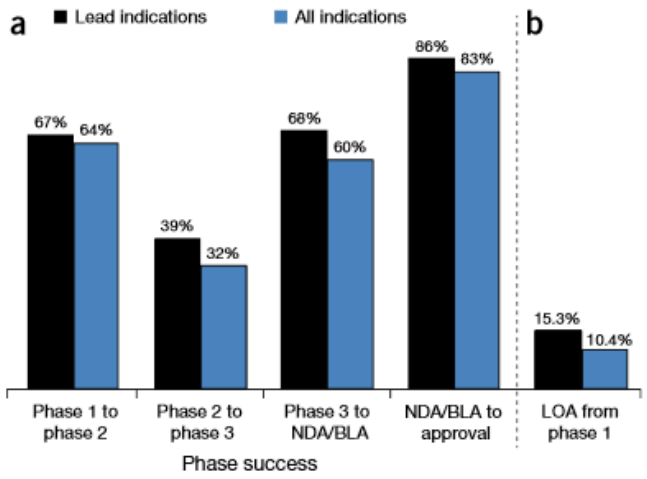


Figure 1 Phase success and LOA rates. (**a**) Phase success rates for lead and all indications. The rates represent the probability that a drug will successfully advance to the next phase. (**b**) LOA from phase 1 for lead and all indications. Rates denote the probability of FDA approval for drugs in phase 1 development.

"We found that approximately one in ten (10.4%, N = 5,820) of all indication development paths in phase 1 were approved by FDA"

Hay, M, Thomas, D, Craighead, J, Economides, C, Rosenthal, J (2014). Clinical development success rates for investigational drugs. Nature Biotechnology, 32, 40-51

Biomarkers to the Rescue…

Biomarkers: How good a cancer test are they?

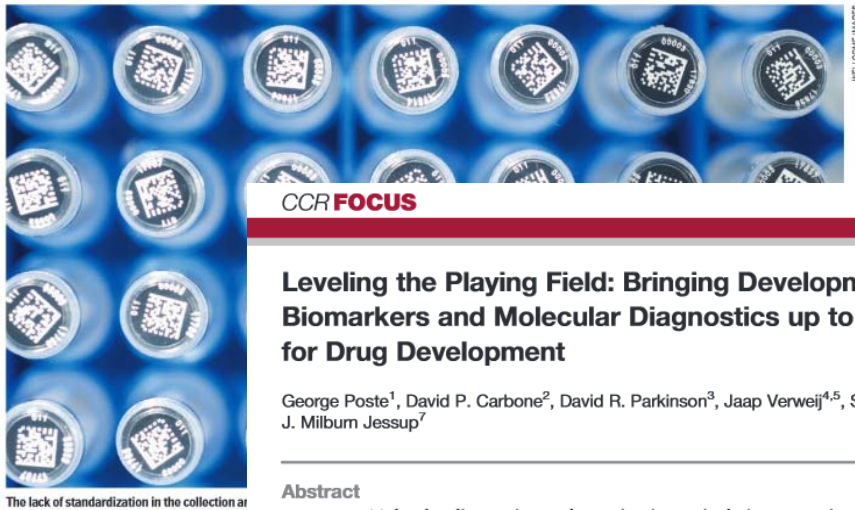
COMMENT

Cancer biomarkers have changed the way we detect and treat the disease. I they all they're cracked up to be?

Herceptin targets breast cancer via the biomarker HER-2, which was discovered in the 80s. Photograp Life Pictures/Getty Images Time Life Pictures/Getty

Barely a week goes by without headlines blaring some new way of understa detecting or treating cancer. It could be a newly identified gene or a protein

TheGuardian, August 2010



WELLCOME IMAGES

The lack of standardization in the collection ar

Bring

The dismal patchwork should be replaced by

If researchers could establish correlatio between diseases and changes in bioma kers, the ability of physicians to diagnc disease and tailor treatments to individua would be radically improved[1]. Howev research into biomarkers — disease-ass ciated molecular changes in body tissu and fluids — hasn't yet delivered on

Poste G 2011 Bring

CCR FOCUS

Leveling the Playing Field: Bringing Development of Biomarkers and Molecular Diagnostics up to the Standards for Drug Development

George Poste[1], David P. Carbone[2], David R. Parkinson[3], Jaap Verweij[4,5], Stephen M. Hewitt[6], and J. Milburn Jessup[7]

Abstract

Molecular diagnostics are becoming increasingly important in clinical research to stratify or identify molecularly profiled patient cohorts for targeted therapies, to modify the dose of a therapeutic, and to assess early response to therapy or monitor patients. Molecular diagnostics can also be used to identify the pharmacogenetic risk of adverse drug reactions. The articles in this *CCR Focus* section on molecular diagnosis describe the development and use of markers to guide medical decisions regarding cancer patients. They define sources of preanalytic variability that need to be minimized, as well as the regulatory and financial challenges involved in developing diagnostics and integrating them into clinical practice. They also outline a National Cancer Institute program to assist diagnostic development. Molecular diagnostic clinical tests require rigor in their development and clinical validation, with sensitivity, specificity, and validity comparable to those required for the development of therapeutics. These diagnostics must be offered at a realistic cost that reflects both their clinical value and the costs associated with their development. When genome-sequencing technologies move into the clinic, they must be integrated with and traceable to current technology because they may identify more efficient and accurate approaches to drug development. In addition, regulators may define progressive drug approval for companion diagnostics that requires further evidence regarding efficacy and safety before full approval can be achieved. One way to accomplish this is to emphasize phase IV postmarketing, hypothesis-driven clinical trials with biological characterization that would permit an accurate definition of the association of low-prevalence gene alterations with toxicity or response in large cohorts. *Clin Cancer Res; 18(6); 1515–23. ©2012 AACR.*

From Qualitative to Quantitative

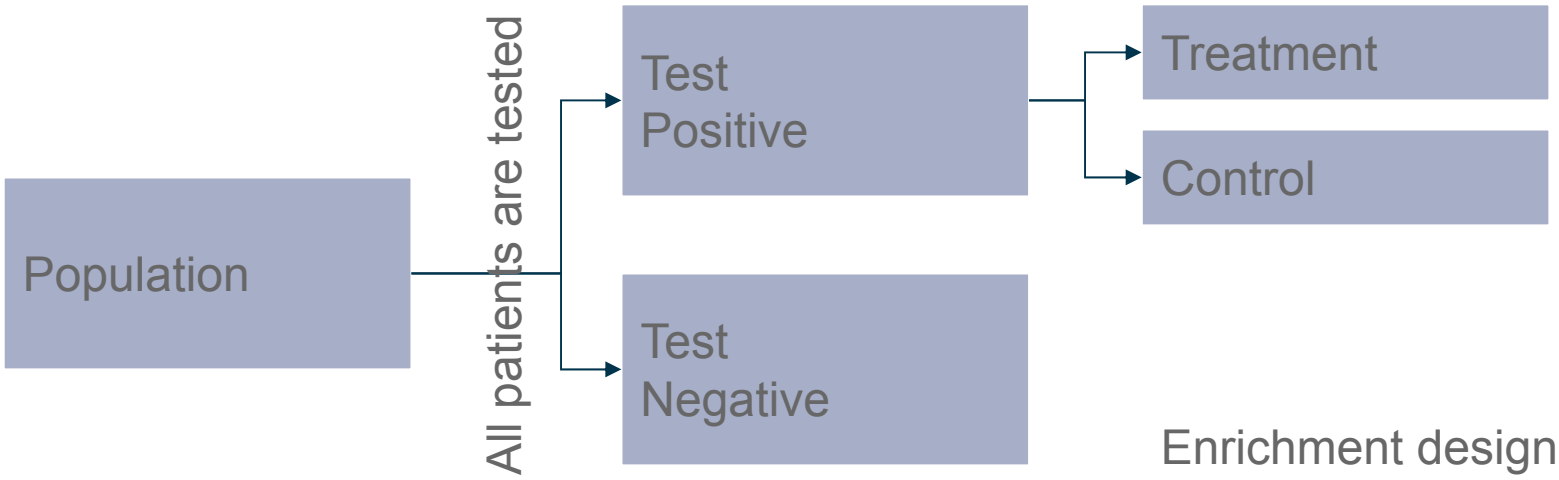
We have to move from qualitative to quantitative decision making in biomarker identification and development

- Find answers to questions, instead of finding questions to answers
  - Clear hypotheses
  - Account for false-positive findings
  - Appropriate validation / cross-validation
- Estimations instead of p-values
- More interdisciplinary work!
- Consider use of Bayesian Techniques in biomarker identification process
  - Two examples today:
    - Enrichment designs
    - Biomarker dose / time - response relations

Enrichment Designs - Background

Targeted clinical trials:

- Evaluation of efficacy and safety for patient with certain (biomarker) characteristics – “biomarker positive patients”
- Evaluation of best treatment regimen depending on prognostics of clinical outcome
- Investigation of association of treatment effect with test results



Enrichment design

Challenges

High degree of certainty that relevant drug response only occurs in “marker positive” patients

- Exclusion of test negative patients prevents description of test characteristics (sensitivity, specificity)
- Effects on drug development:
  - Lower number of patients necessary,
  - but potentially longer recruitment times,
  - and potentially higher costs (screening)

Further, more generic, challenges:

- Estimation of recruitment rates
- Estimation of prevalence

Example

Assume that we need 50 marker (test) positive patients, and the recruitment rate is 10 patients per month. Depending on the prevalence, how many patients are we expected to screen, and what is the accrual time?

Prevalence	n_{tested}	Accrual time
1	50	5
0.8	63	6.25
0.5	100	10
0.3	167	16.7

```
DATA example1;
     n_plus = 50;
     lambda = 10;
     DO theta = 1, 0.8, 0.5, 0.3;
        n_screen = n_plus / theta;
        time = n_plus / (theta*lambda);
        OUTPUT;
     END;
RUN;
```

Notation

Let

- $\mathbf{N_t^+}$ denote the recruitment process for the marker (test) positive patients, respectively
- $\mathbf{n^+}$ be the required number of marker (test) positive patients
- $\boldsymbol{\lambda} > 0$ be the recruitment rate in the unselected population
- $0 < \boldsymbol{\theta} \leq 1$ be the prevalence of the marker (test) positive population
- $\mathbf{T^+(n)}$ denote the accrual time for n patients in the marker positive recruitment process, respectively

Process with Fixed Parameters

Let **λ** and **θ** be **fixed and known**

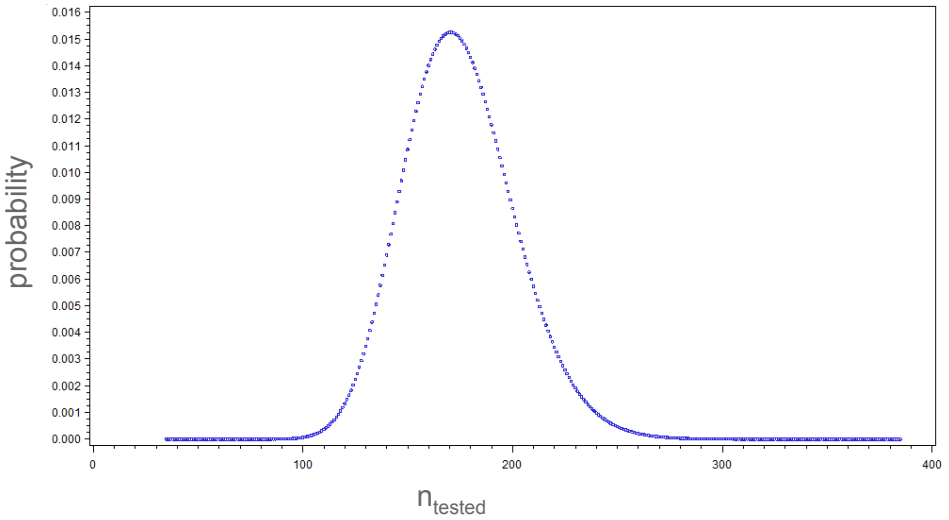
Then

- N_t^+ is a Poisson process with parameter θλ
- Therefore, the jump-times (waiting times) of the process are i.i.d. exponentially distributed with rate θλ
- Thus, $T^+(n^+) \sim \Gamma(n^+, \theta\lambda)$
  - (sum of n^+ independent exponentially distributed variables, each with rate parameter θλ)
  - $E(T^+(n^+)) = n^+/ \theta\lambda$, $Var(T^+(n^+)) = n^+/ (\theta\lambda)2$
  - = Erlangen distribution, as n^+ is an integer.

Costs

Let n_{tested} be the number needed to be screened in order to obtain n^+ patients, given prevalence θ

- Expected n^+/ θ
- $n_{tested} \sim NegBin(n^+, \theta)$
- Example:
  - $n^+ = 35$, $\theta = 0.2$;
    expected $n_{tested} = 35/0.2 = 175$




```
DATA tt;
  theta = 0.2; n_plus = 35;
  DO x = 0 TO 350;
      probnb=PDF("NEGB", x, theta, n_plus);
      n_tested = x + n_plus;
      OUTPUT;
  END;
RUN;

symbol1 v=circle height=0.3;
PROC GPLOT;
     PLOT probnb * n_tested;
RUN;QUIT;
```

Prediction

- Use Gamma(n^+, $\theta\lambda$) distribution to obtain prediction intervals for $T^+(n^+)$
- Use NegBin(n^+, θ) to obtain information on number of patients that are screened, and derive associated costs from this
- In SAS® use the GAMINV, and/or QUANTILE function.
  - Caveat: parameterization of the Gamma distribution for GAMMA and GAMINV function (no scale parameters!)
  - Note Gamma distribution in SAS based on waiting times (thus, uses scale parameters, not rate parameters!)

Example with Process Variability

Again, we need 50 marker (test) positive patients, and the recruitment rate is 10 patients per month.

Prevalence	n_{tested}		Accrual time $T(n^+)$	
1	50	--	5	(3.90, 6,22)
0.8	63	[56, 69]	6.25	(4.87, 7.77)
0.5	100	[84, 117]	10	(7.79, 12.43)
0.3	167	[136, 201]	16.7	(12.99, 20.72)

Numbers are estimates and 90% prediction intervals

```
DATA example2;
     n_plus = 50;
     lambda = 10;
     DO theta = 1, 0.8, 0.5, 0.3;
        n_screen = n_plus / theta;
        ll_screen = n_plus + QUANTILE("NEGBIN", 0.05, theta, n_plus);
        ul_screen = n_plus + QUANTILE("NEGBIN", 0.95, theta, n_plus);

        time = n_plus / (theta*lambda);
        ll_time = QUANTILE("GAMMA", 0.05, n_plus, 1/(theta*lambda));
        ul_time = QUANTILE("GAMMA", 0.95, n_plus, 1/(theta*lambda));
        spread_time = ul_time - ll_time;

        OUTPUT;
     END;
RUN;
```

Using Random Recruitment Rate

Now, assume that **$\lambda \sim \Gamma(\alpha, \beta)$**, and **$\theta$ fixed and known**

- Easy interpretation: $E(\lambda) = \alpha / \beta$; $Var(\lambda) = \alpha / \beta^2$
- E.g. assume expected recruitment rate *e*, and variance *v*:
  $\beta = e/v$, $\alpha = e^2/v = 1 / cv^2$ of recruitment rates

- Now, $T^+(n^+) \sim \Gamma(n^+, \theta\Gamma(\alpha,\beta))$
- This is equivalent to:
  - $T^+(n^+) \sim (\beta/\theta)\, \Gamma(n^+, 1) / \Gamma(\alpha,1)$
    since $\Gamma(\alpha,\beta) = \Gamma(\alpha,1) / \beta$
    aka Type IV Pearson distribution
  - Extension of Negative Binomial Distribution on real numbers
  - Expected value: $n^+ \beta / \theta\, (\alpha - 1)$ for $\alpha > 1$
  - Variance: $\beta^2 n^+(n^+ + \alpha - 1) / \theta^2(\alpha-1)^2(\alpha-2)$, for $\alpha > 2$

Prediction Intervals

For the prediction interval of the recruitment time, we use a large sample approximation:

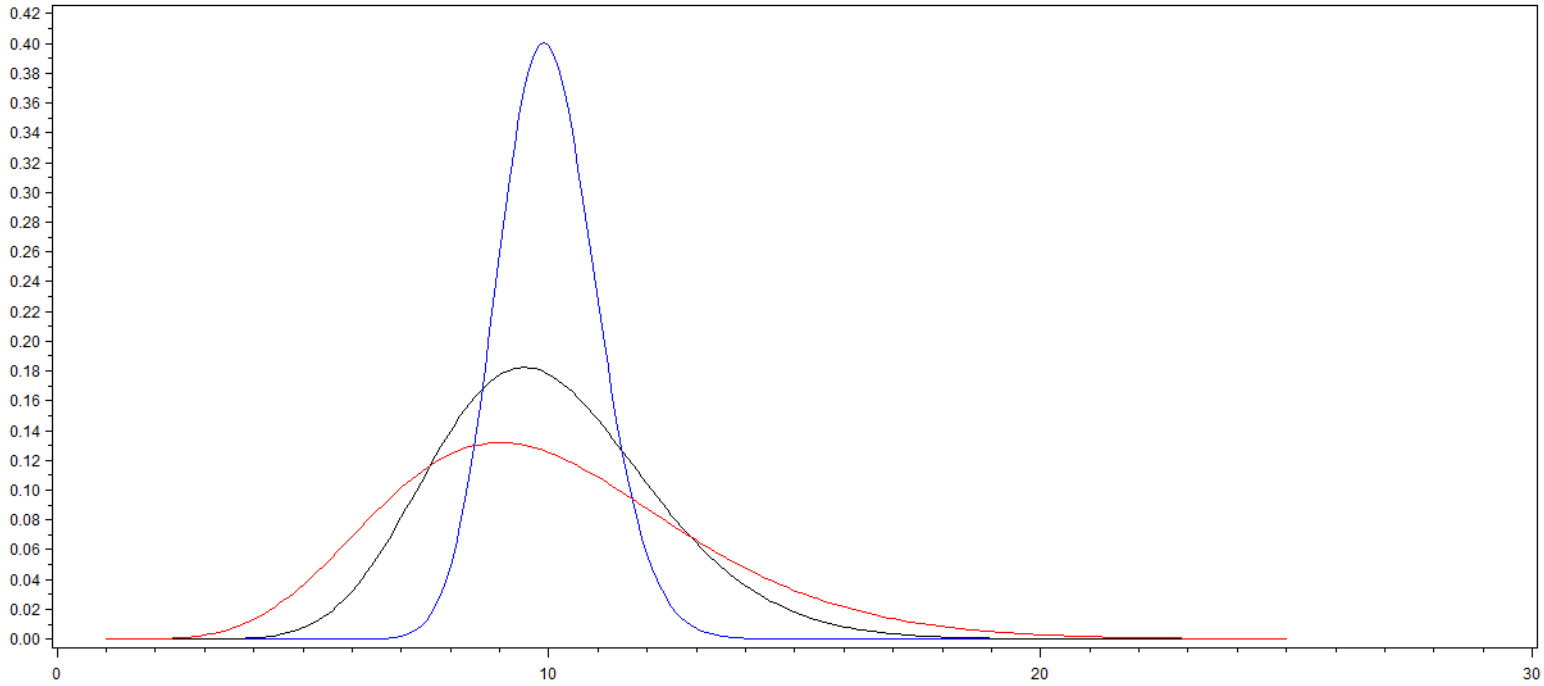
- $$PI(T^+(n)) = \left[\frac{n\beta}{\theta(\alpha-1)} \pm Z\sqrt{\frac{\beta^2 n(n+\alpha-1)}{\theta^2(\alpha-1)^2(\alpha-2)}} \right]$$

For the number of patients needed to screen, same as before

- because $n_{tested} \sim NB(n^+, \theta)$, and thus independent from λ

Random Recruitment Rates

Rate λ = 10, different variances v: Gamma distributions



v=1; Γ(100,10)
v=5; Γ(20, 2)
v=10; Γ(10, 1)

Example Random Recruitment Rates

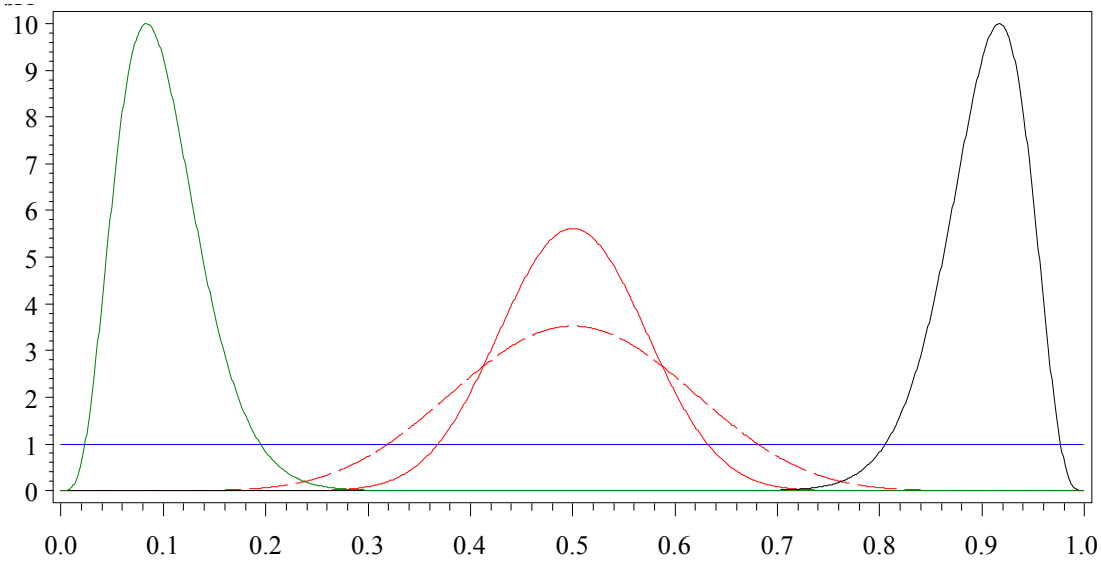
Assume n+ = 50, rate λ around 10, different variances v, different prevalences θ

v	θ	α	β	Expected $T^+(n^+)$	90% Prediction Interval
1	1.0	100	10	5.1	(3.6, 6.5)
1	0.8	100	10	6.3	(4.5, 8.1)
1	0.5	100	10	10.1	(7.2, 13.0)
1	0.3	100	10	16.8	(12.0, 21.7)
5	1.0	20	2	5.3	(2.9, 7.7)
5	0.8	20	2	6.6	(3.6, 9.6)
5	0.5	20	2	10.5	(5.7, 15.3)
5	0.3	20	2	17.5	(9.6, 25.5)
10	1.0	10	1	5.6	(2.0, 9.1)
10	0.8	10	1	6.9	(2.6, 11.3)
10	0.5	10	1	11.1	(4.1, 18.1)
10	0.3	10	1	18.5	(6.8, 30.2)

Thoughts about the Prevalence

In the previous models, it was assumed that the prevalence θ is known and fixed.

- Often estimated from small studies
- Use Bayesian methods to derive (posterior) “belief in the estimated prevalence θ
- Prior may be non-informative or informative. Quantify the prior belief by Beta-Distribution.
- Beta(α, β),
  where
  α = n * prior and
  β = n * (1-prior);



Recruitment using Random Prevalence

.Now, use Bayesian framework to quantify uncertainty about the prevalence

- Using non-informative prior, and p(θ) = a/b, then θ|data ~ Beta(a+1, b+1)

We incorporate that into our previous recruitment model, and now use simulation to determine the expected recruitment time, and expected number of patients to be screened

- Results based on 10,000 simulations

```
DATA tt;
    e=10; nobs=50;
    DO v= 1, 5, 10;
       DO theta = 1, 0.8, 0.5, 0.3;
          DO priorsize = 10, 50;
             DO tryout = 1 TO 10000;
                alpha = e*e/v;
                beta = e/v;
                lambda = RAND("GAMMA", alpha)/beta;
                theta2 = RAND("BETA", priorsize*theta + 1, priorsize*(1-theta) + 1);
                obs = 0; time=0; nscreen = 0;
                DO UNTIL (obs=nobs);
                   IF theta2 < 1 THEN x = RANBIN(-1, 1, theta2);
                   ELSE x=1;
                   nscreen = nscreen + 1;
                   time = time + RAND("exponential")/lambda;
                   IF x=1 THEN obs = obs + 1;
                END;
                OUTPUT;
             END;
          END;
       END;
    END;
RUN;
```

Example Recruitment Time

Assume $n^+ = 50$, accrual rate around 10, different prevalences θ, different sizes of prior trial to estimate θ

v	α	β	θ	Prior Size	Median Time	5%, 95% pctl
5	20	2	0.8	10	6.8	(4.2, 11.9)
5	20	2	0.8	50	6.5	(4.1, 10.3)
5	20	2	0.5	10	10.3	(5.7, 21.3)
5	20	2	0.5	50	10.2	(6.3, 17.1)
5	20	2	0.3	10	15.9	(7.8, 41.7)
5	20	2	0.3	50	16.7	(9.7, 29.7)

Example Screening

Assume $n^+ = 50$, accrual rate around 10, different prevalences θ, different sizes of prior trial to estimate θ

v	α	β	θ	Prior Size	Median n_{tested}	5%, 95% pctl
5	20	2	0.8	10	65.0	(53.0, 97.0)
5	20	2	0.8	50	63.0	(55.0, 76.0)
5	20	2	0.5	10	100.0	(67.0, 187.0)
5	20	2	0.5	50	100.0	(77.0, 136.0)
5	20	2	0.3	10	154.0	(86.0, 377.0)
5	20	2	0.3	50	163.0	(113.0, 251.0)

Summary Accrual Time

N+=50, accrual rate λ ≈10

v	α	β	θ	Prior Size	Median Time	"Likely Range"
--	--	--	0.5	--	10.0	(7.8, 12.4)
1	100	10	0.5	--	10.1	(7.2, 13.0)
1	100	10	0.5	50	10.0	(7.0, 14.4)
1	100	10	0.5	10	10.2	(6.2, 19.7)
5	20	2	0.5	--	10.5	(5.7, 15.3)
5	20	2	0.5	50	10.2	(6.3, 17.1)
5	20	2	0.5	10	10.3	(5.7, 21.3)
10	10	1	0.5	--	11.1	(4.1, 18.1)
10	10	1	0.5	50	10.5	(5.7, 20.5)
10	10	1	0.5	10	10.6	(5.3, 24.5)

Summary Screening / Costs

$N^+ = 50$

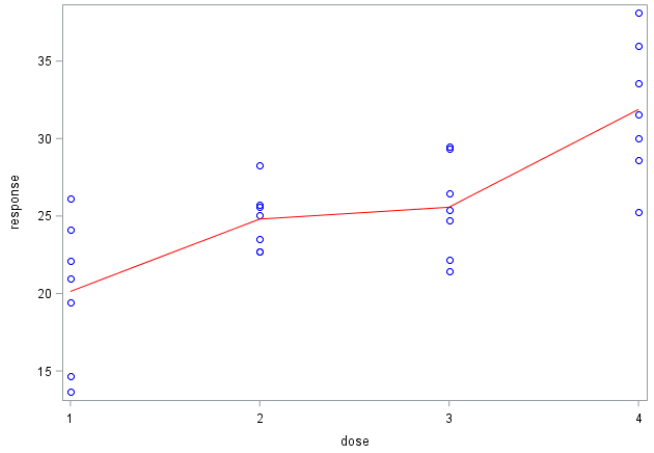
θ	Prior Size	"expected n_{tested}"	"likely range"
0.5	--	100	(84, 117)
0.5	10	100	(67, 187)
0.5	50	100	(77, 136)

Further Challenges

- Inclusion of Bayesian models for accrual
  - ~IG(nP, TP), where T is expected time to accrue n patients, P is confidence level for accrual
  - Eg. Gajewski BJ, Simon SD, Carlson S (2008), "Predicting accrual in clinical trials with Bayesian posterior predictive distributions“, Statistics in Medicine 27(13); 2328-2340.
- Inhomogeneous Poisson models
  - Multiple centers, time-dependent λ_t
- Other recruitment models
  - Using feedback mechanisms: INGARCH(1,1) process, as studied by Ferland, Latour, and Oraichi (2006), extended by Fried and Foskianos (2010)
  - $N_t \sim Pois(\theta \lambda_t)$
    $\lambda_t = \beta_0 + \beta_1 \lambda_{t-1} + \alpha_1 N_{t-1}$

Dose – Response / Expression

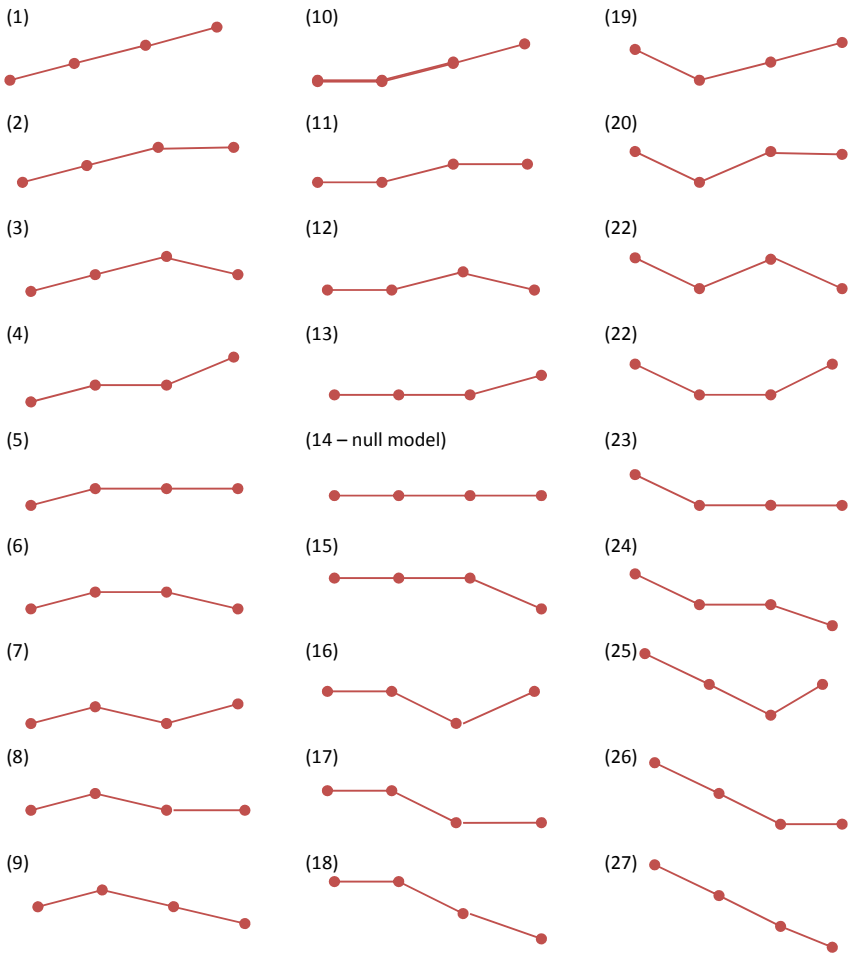
- Interest to classify potential biomarkers according to dose-expression profiles
  - Any relationship
  - Shape of profile
- Order constraints: higher (lower) expression as dose increases
  - Monotone increases / decreases
  - No parametric assumptions about dose – expression profiles



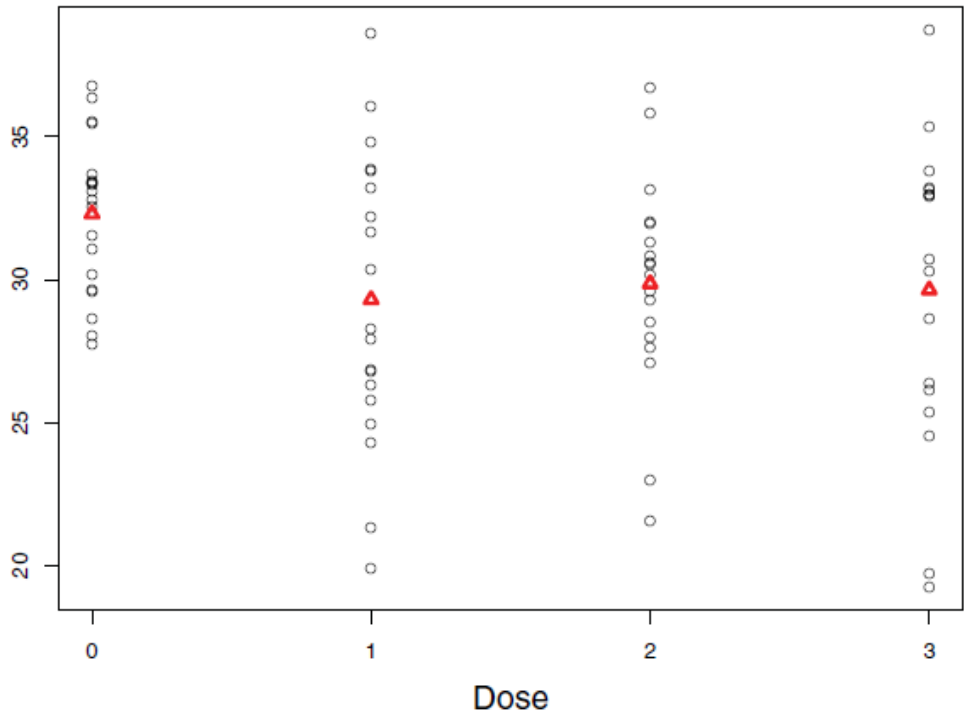
Dose – Response

Dose – Biomarker Expression Relation(s)

- Maximum Test
- Bayesian approach



Dose Response Example



Otava M., Shkedy Z., Lin D., Göhlmann H.W.H., Bijnens L., Talloen W., Kasim A. (2014). Dose–Response Modeling Under Simple Order Restrictions Using Bayesian Variable Selection Methods. *Statistics in Biopharmaceutical Research*, 6:3, 252-262.
Otava M. (2014). Bayesian variable selection in dose-response relationship concept. International Biometric Conference, Florence.
Otava M. (2013). Bayesian Variable Selection Method for Modeling Dose-Response Microarray Data Under Simple Order Restrictions. Bayes2013, Rotterdam.

Monotone Dose-Response

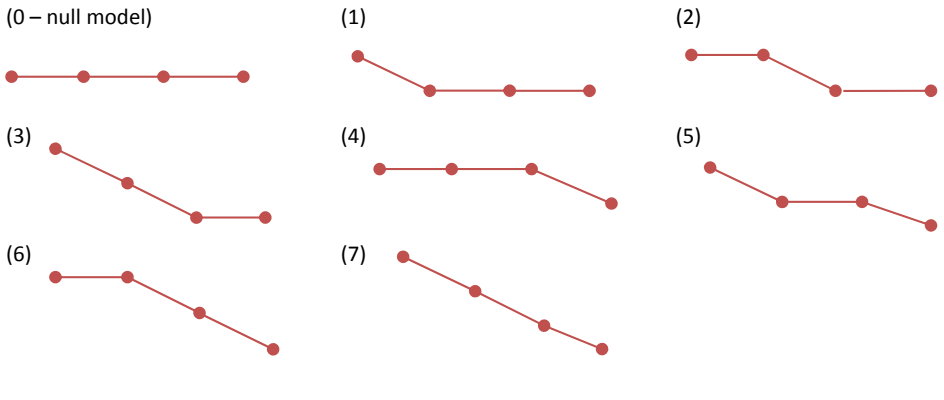
Order-restricted alternative as an example:

- ANOVA model: $Y_{ij}=\mu_i + \varepsilon_{ij}$, $\varepsilon_{ij}\sim N(0,\sigma^2)$, i=0,…3, j=1,…, n_i
- H_0: $\mu_0 = \mu_1 = \mu_2 = \mu_3$ versus
  H_{down}: $\mu_0 \geq \mu_1 \geq \mu_2 \geq \mu_3$ with at least one strict inequality

- Decompose into $2^K - 1$ sub-alternatives
- K=3: 7 sub-alternatives (downward trend!)

$$H_1^3 = \bigcup_{k=1}^{7} H_{1,k}^3 \quad \text{where}$$

$$H_{1,1}^3 : \mu_0 > \mu_1 = \mu_2 = \mu_3$$
$$H_{1,2}^3 : \mu_0 = \mu_1 > \mu_2 = \mu_3$$
$$H_{1,3}^3 : \mu_0 > \mu_1 > \mu_2 = \mu_3$$
$$H_{1,4}^3 : \mu_0 = \mu_1 = \mu_2 > \mu_3$$
$$H_{1,5}^3 : \mu_0 > \mu_1 = \mu_2 > \mu_3$$
$$H_{1,6}^3 : \mu_0 = \mu_1 > \mu_2 > \mu_3$$
$$H_{1,7}^3 : \mu_0 > \mu_1 > \mu_2 > \mu_3$$



Example: Biomarker

Assume possible downward trend.

- Re-parametrisation:

$$\mu_i = \begin{cases} \mu_0, & i = 0 \\ \mu_0 - \sum_j^i I_j \beta_j, & i = 1,...,K \text{ with indicator variable } I_j \text{ and } \beta_j \geq 0 \end{cases}$$

- Use priors and hyperpriors as discussed by Otava

Hypothesis/Sub - alternative	(I_1, I_2, I_3)	$g = \sum_{j=1}^{3} I_1 2^{j-1}$
$H_0^3 : \mu_0 = \mu_1 = \mu_2 = \mu_3$	$(0,0,0)$	0
$H_{1,1}^3 : \mu_0 < \mu_1 = \mu_2 = \mu_3$	$(1,0,0)$	1
$H_{1,2}^3 : \mu_0 = \mu_1 < \mu_2 = \mu_3$	$(0,1,0)$	2
$H_{1,3}^3 : \mu_0 < \mu_1 < \mu_2 = \mu_3$	$(1,1,0)$	3
$H_{1,4}^3 : \mu_0 = \mu_1 = \mu_2 < \mu_3$	$(0,0,1)$	4
$H_{1,5}^3 : \mu_0 < \mu_1 = \mu_2 < \mu_3$	$(1,0,1)$	5
$H_{1,6}^3 : \mu_0 = \mu_1 < \mu_2 < \mu_3$	$(0,1,1)$	6
$H_{1,7}^3 : \mu_0 < \mu_1 < \mu_2 < \mu_3$	$(1,1,1)$	7

Otava M., Shkedy Z., Lin D., Göhlmann H.W.H., Bijnens L., Talloen W., Kasim A. (2014). Dose–Response Modeling Under Simple Order Restrictions Using Bayesian Variable Selection Methods. *Statistics in Biopharmaceutical Research*, 6:3, 252-262.
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Priors and Hyperpriors

As priors, we have

- $\mu_0 \sim N(\eta_0, \sigma_0^2)$
- $\beta_i \sim N\left(\eta_{\beta_i}, \sigma_{\beta_i}^2\right) I(0, A)$; *A* denotes the expected difference in the response
- $I_i \sim Bernoulli(\pi_i)$

And hyperpriors

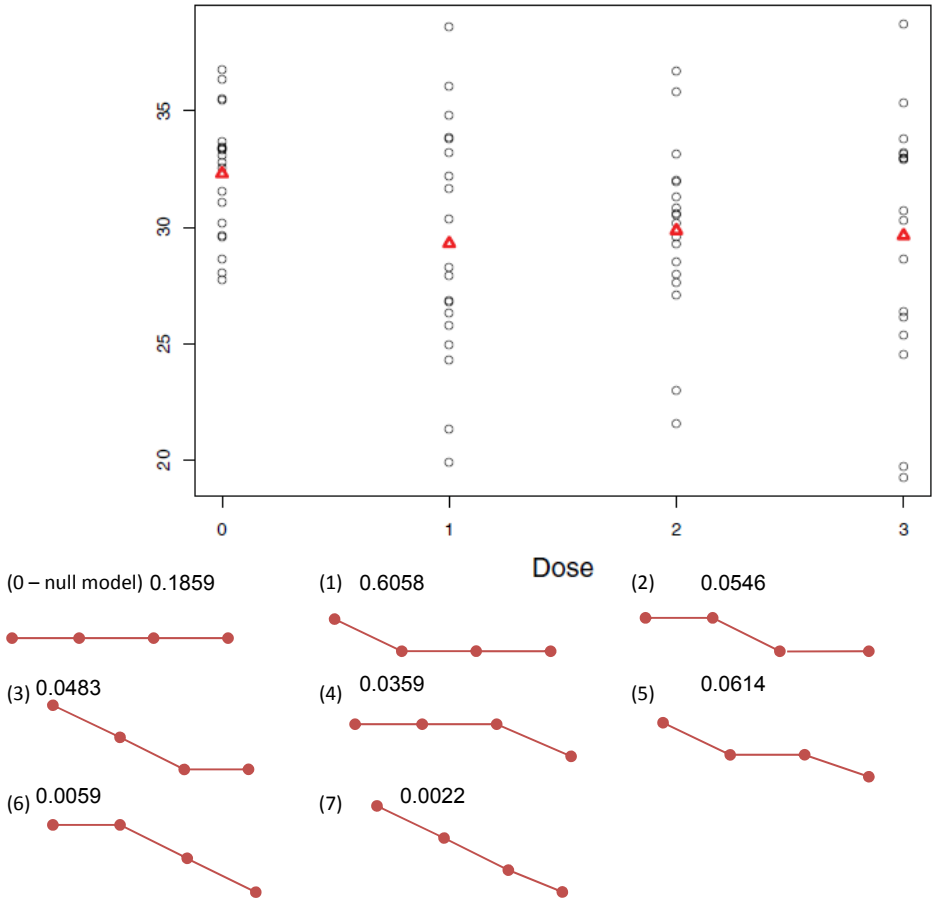
- $\pi_i \sim Uniform(0,1)$
- $\eta_0, \eta_{\beta_i} \sim N(0, 10^6)$
- $\sigma_0^2, \sigma_{\beta_i}^2 \sim i\Gamma(10^{-3}, 10^{-3})$

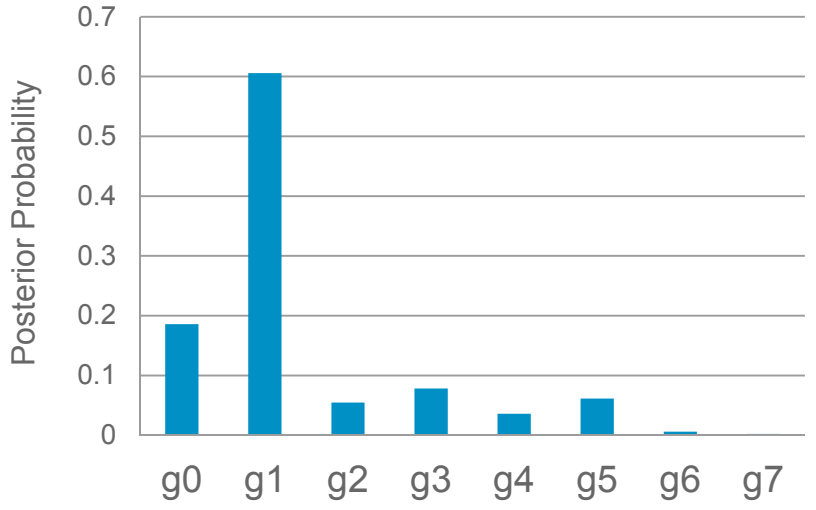
If we now define $g = \sum_{i=1}^{K} I_i 2^{i-1}$, the posterior distribution of ***g*** **describes the distribution of the monotone dose-response shapes.**

SAS PROC MCMC

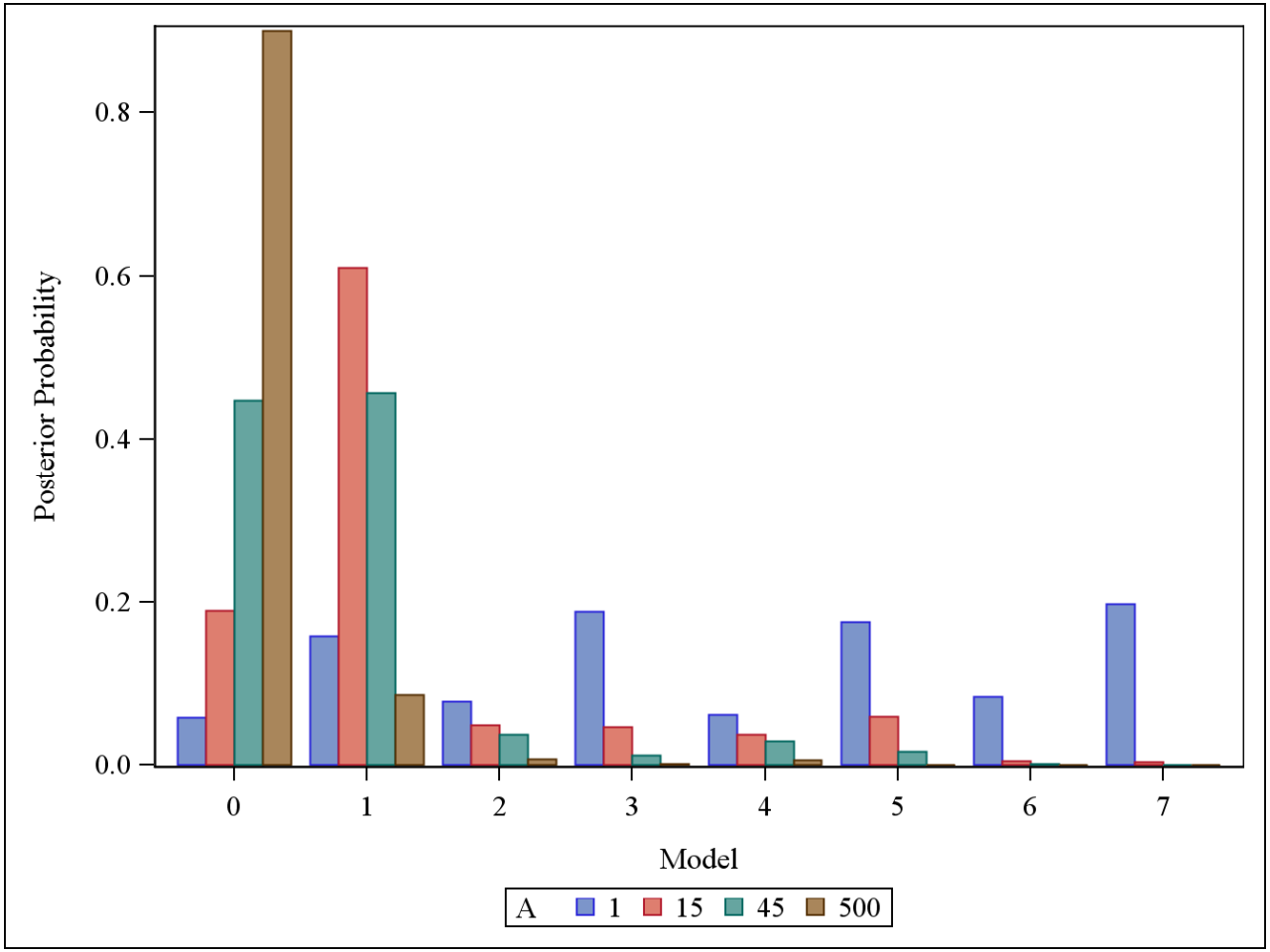
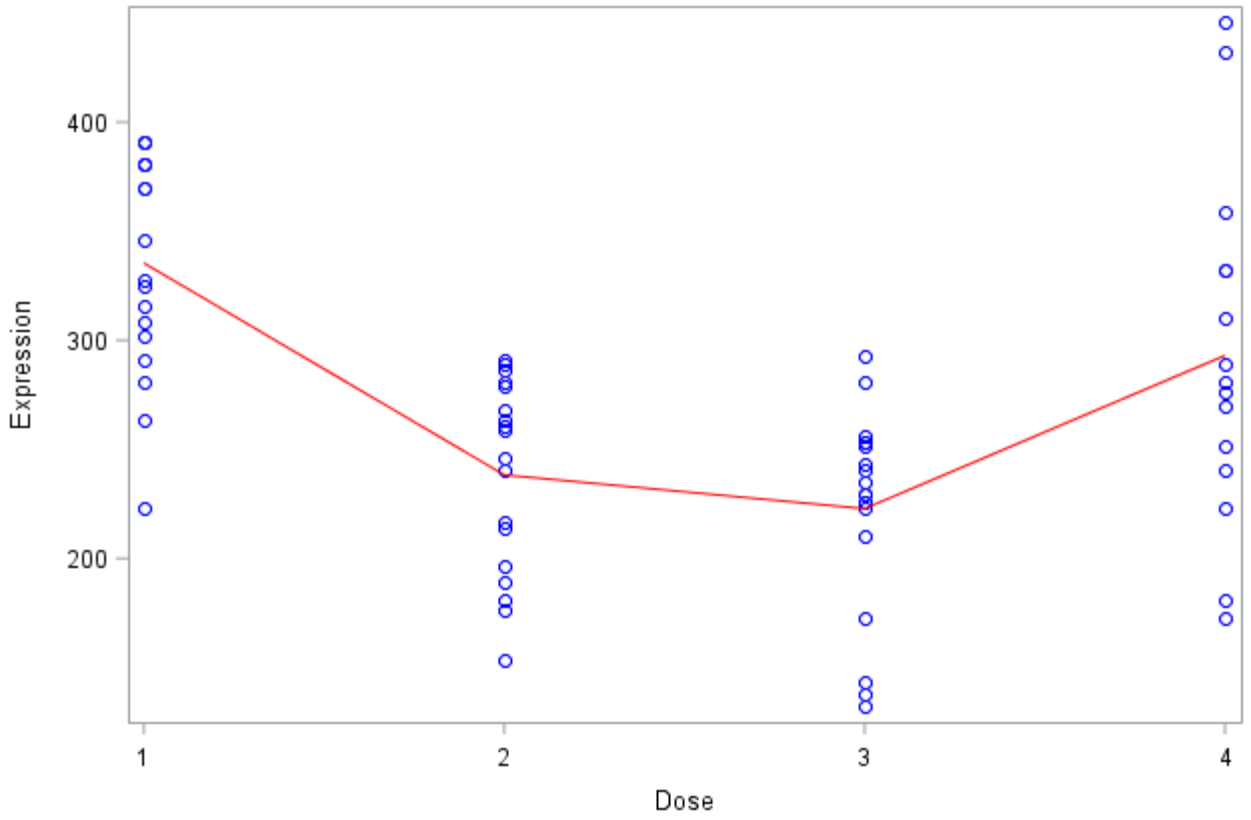
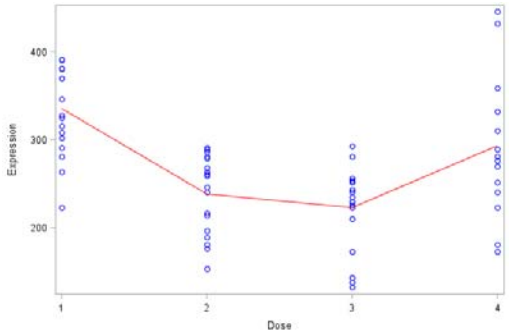
```
PROC MCMC data=marker220
          nbi=10000
          nmc=100000
          thin=50
          seed=712015
          monitor=(mu0 I1 I2 I3 beta1 beta2 beta3 g)
          ...
          ...


         prior beta1 ~ normal(eta1,var=s2_beta1,lower=0,upper=15);
         ...

         mu = mu0 - I1*beta1*(dose in (5,50,500))
                  - I2*beta2*(dose in (50,500))
                  - I3*beta3*(dose in (500));

         model expression ~ normal(mu, var=s2);

  beginnodata;
    g=I1+2*I2+4*I3;
  endnodata;

run;
```

Results

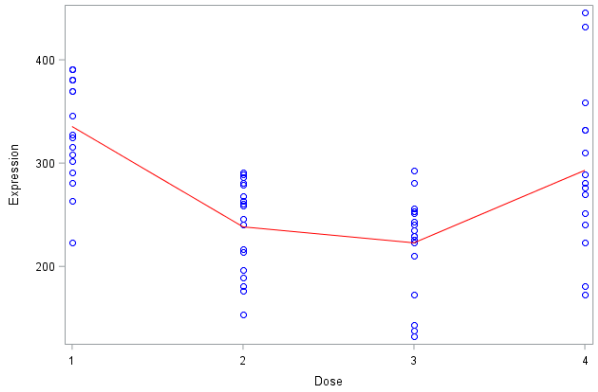
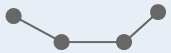

35
30
25
20
0
1
2
3
Dose
(0 – null model) 0.1859
(1) 0.6058
(2) 0.0546
(3) 0.0483
(4) 0.0359
(5) 0.0614
(6) 0.0059
(7) 0.0022


Posterior Probability
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
g0
g1
g2
g3
g4
g5
g6
g7

Discussion of Methods

- Can (easily) be extended to be used with correlated data:
  - ```
    prior s2_r ~igamma (shape=0.001 , scale=0.001);  #define variance for random effect

    random r ~ normal (0, var=s2_r) subject=id monitor=(r);  # random effect to account within subj corr

    mu=mu0 -I1*beta1 *(dose in (5, 50, 500))
        -I2*beta2 *(dose in (50, 500))
        -I3*beta3*(dose in (500)) +r;
    ```
  - Only compound symmetry
- Effect of truncation:
  - $\beta_i \sim N\left(\eta_{\beta_i}, \sigma^2_{\beta_i}\right) I(0, A)$; *A* denotes the expected difference in the response
- Down-turn / Up-turn protection may be needed
    ```

Truncation

- Effect of truncation:
  $\beta_i \sim N\left(\eta_{\beta_i}, \sigma^2_{\beta_i}\right) I(0, A)$; A denotes the expected difference in the response
  - To complete the specification of the hierarchical model, we assume the following prior distributions for the unknown model parameters,

$$\mu_0 \sim \mathrm{TN}(\eta_{\mu_0}, \tau_{\mu_0}^{-1}, 0, \infty),$$
$$\delta_i \sim \mathrm{TN}(\eta_{\delta_i}, \tau_{\delta_i}^{-1}, 0, A) \quad k =, 1, \ldots, K-1. \qquad (11)$$

Here $\mathrm{TN}(\mu, \sigma^2, a, b)$ is a truncated normal distribution and A is a positive constant. The truncated distribution improves properties of the MCMC chains and it is a priori constrained to lie between zero and the difference in the range of the response vector. We assume noninformative distributions for the hyperparameters in the model

Otava M., Shkedy Z., Lin D., Göhlmann H.W.H., Bijnens L., Talloen W., Kasim A. (2014). Dose–Response Modeling Under Simple Order Restrictions Using Bayesian Variable Selection Methods. *Statistics in Biopharmaceutical Research*, 6:3, 252-262.

  - Derive from data? Empirical Bayes approach?

Effect of Truncation



Effect of Truncation (2)

The results are highly sensitive to the specification of the truncation factor.

- It is essential to include a sensible value of A, which should reflect an upper limit of the expected results.
- This was investigated by O'Hara and Sillanpää (2009), who describe '*The MCMC algorithm to fit the model does not require any tuning, but when Ij = 0, the updated value of βj is sampled from the full conditional distribution, which is its prior distribution. Mixing will be poor if this is too vague, as the sampled values of βj will only rarely be in the region where θj has high posterior support, so the sampler will only rarely flip from Ij = 0 to Ij = 1.*'
- The truncation factor A can (should?) be estimated from the data
  - Empirical Bayes approach (?)
  - 2 x range?

Up-Turn Protection - Example

Consider the following marker, with a possible up-turn effect at the last dose:



Up-Turn Protection – Results (1)

Result:



g		A=350	A=400
0		1 (0.15%)	
1		1899 (94.95%)	197 (95.85%)
3		68 (3.40%)	55 (2.75%)
5		30 (1.50%)	28 (1.40%)
7		2 (0.10%)	

```
NOTE: Starting optimization.
NOTE: Tuning the proposal distribution.
NOTE: Generating the burn-in samples.
NOTE: Beginning sample generation.
NOTE: Generating diagnostic plots.
ERROR: Unable to compute correlation statistics for variable l1.
WARNING: Unable to compute correlation statistics for variable l1. Results are set to missing.
WARNING: There is insufficient variation in the data to create a density plot.
NOTE: The data set WORK.POSTDATA has 2000 observations and 25 variables.
NOTE: PROCEDURE MCMC used (Total process time):
      real time           1:39.60
      cpu time            1:38.12
```

Up-Turn Protection

- Introduce additional parameters I4, beta4, … to reflect up-turn:
  - ```
    mu = mu0 - I1*beta1*(dose in (2,3,4)) - I2*beta2*(dose in (3,4)) - I3*beta3*(dose in (4))
          + I4*beta4*(I3=0)*(dose in (4)) ;

    model weight ~ normal(mu, var=s2);

    beginnodata;
      g=I1+2*I2+4*I3 +8*I4;
    endnodata;
    ```



  - Results:

g		A=350
1		26 (1.30%)
9		1701 (85.05%)
11		273 (13.65%)
    ```

Discussion

- Method enables to address multiple perspectives simultaneously
  - Compare with max-t tests
- Implement general down-turn / up-turn protection for the method to be useful for biomarker selection
- (Implement permutation test)
- Computationally intensive!

Implementation

- Rather high acceptance of Bayesian methods in Early Clinical Development
  - Build on this also for early biomarker development / biomarker detection
- Standard “displays” / methods to ensure understanding
- High level of interaction needed
  (specification of questions, determination of priors, …)

Literature

Carter, RE 2004. Application of stochastic processes to participant recruitment in clinical trials. Controlled Clinical Trials, 25: 429-436

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