Using Historical Experimental Information in the Bayesian Analysis of Reproduction Toxicological Experimental Results

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Outline

Introduction

What does aquatic toxicology experiments testing?

- Evaluating the potential (adverse) impact of chemicals in receiving waters, marine systems, and other aquatic ecosystems;
- Interesting endpoints: **survival**, **reproduction** and **growth** of organisms;
- In reproduction tests, the organisms are exposed to different levels of chemicals; the number of offspring are recorded.

Introduction

Statistical Methods for Reproductive Toxicology:

- ANOVA (Landis & Chapman, 2011)
  - NOEC: the no-observed-effect concentration, the greatest concentration level with responses that are not significantly different from the responses of the control group;
  - LOEC: the lowest-observed-effect concentration, the lowest concentration level with responses that differs from the control group responses
- Regression — relative inhibition concentration (RIp), the concentration level to some hazard, associated with a specified level (p) of change in the response relative to the control response.

Introduction

Why Bayesian?

Bayesian methods

- give flexible model outputs;
- are able to incorporate different levels of variability into a hierarchical framework;
- are able to incorporate expert knowledge/**historical information** into analysis.
- ...

Introduction

To utilize historical information, we can ...

- combine historical information and current data – analysis of the pooled data;
- use posterior distribution of parameters based on the historical data as the prior information (Zhang et al., 2012)
- use the historical data with a discount – power priors (Ibramhim and Chen, 2000; Chen et al., 2000)
- consider the similarity between current experiment and historical experiment – commensurate priors (Hobbs et al., 2012)

Introduction

Modeling reproduction outcomes

- Ideally, when organisms are alive until the end of the experiments, the number of young produced are often assumed to follow a Poisson distribution;
- When organisms are exposed to higher toxicant concentrations, the mortality rates usually increases and excess zeroes exists in the resulting number of total young due to death of organisms.
- When toxicity affects both fecundity and mortality, the reproduction outcomes can be modeled with zero-inflated Poisson.

Introduction

Motivating data

- Four experiments using Ceriodaphnia dubia conducted between August 29, 1989 and August 24, 1992;
- In each experiment, 9 to 10 organisms were assigned to each of 6 different exposure groups;
- The four experiments were carried out in 3 different labs.

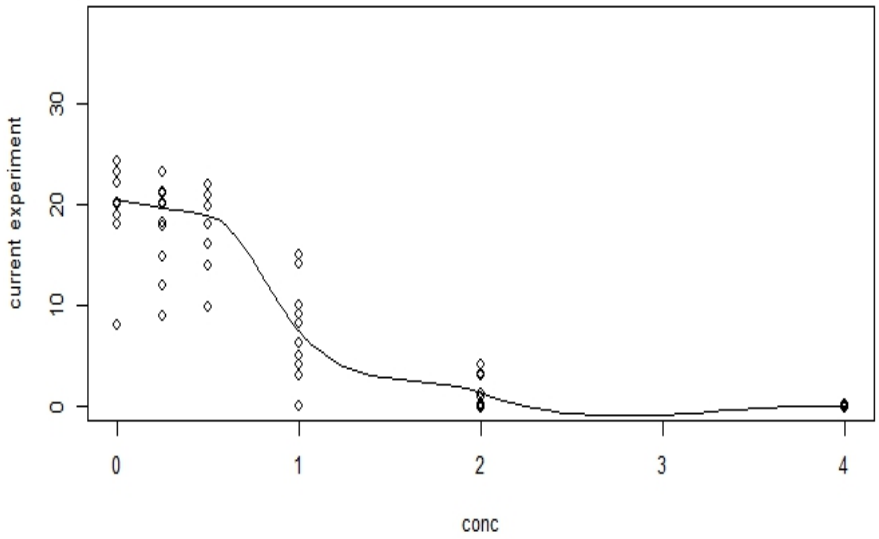
Introduction

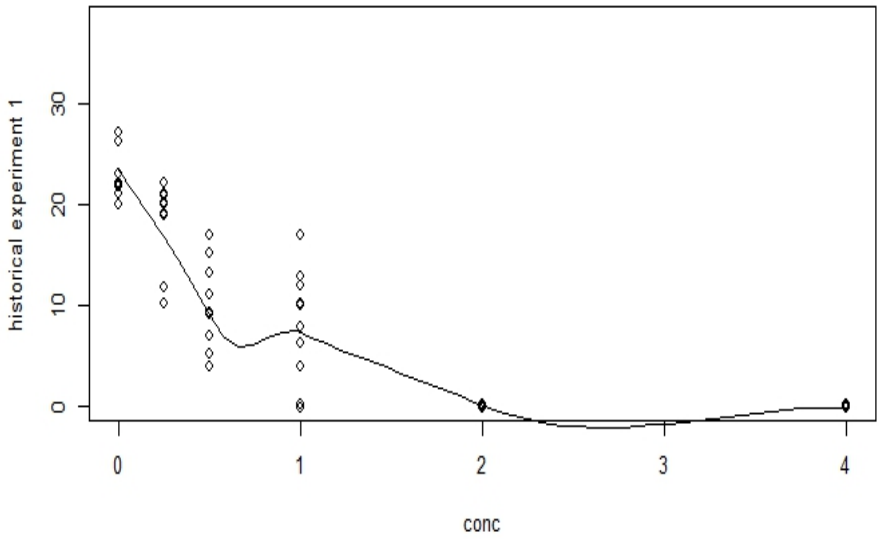
Motivating data

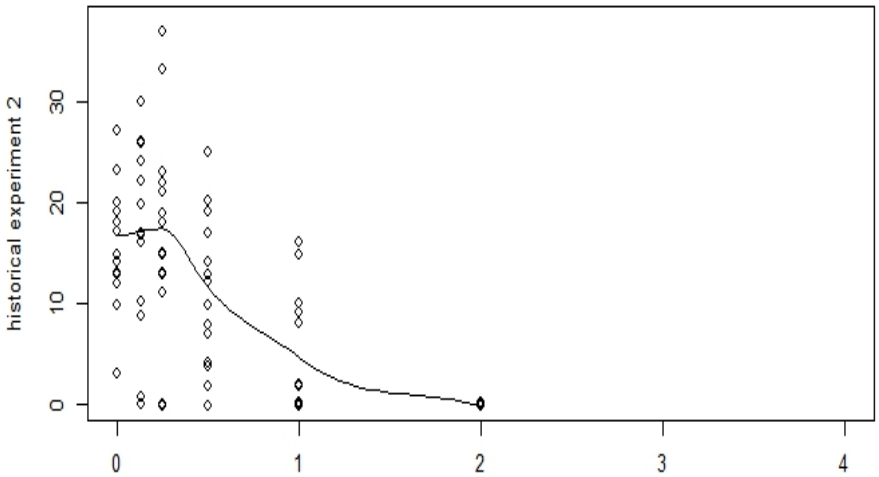
Experiment	Lab	Date	Exposures
current	1	Aug. 24, 92	$(0, 0.25, 0.5, 1, 2, 4\%)$
Historical 1	1	Aug. 4, 92	$(0, 0.25, 0.5, 1, 2, 4\%)$
Historical 2	2	Sep. 19, 90	$(0, 0.13, 0.25, 0.5, 1, 2\%)$
Historical 3	3	Aug. 29, 89	$(0, 0.25, 0.5, 1, 2, 4\%)$

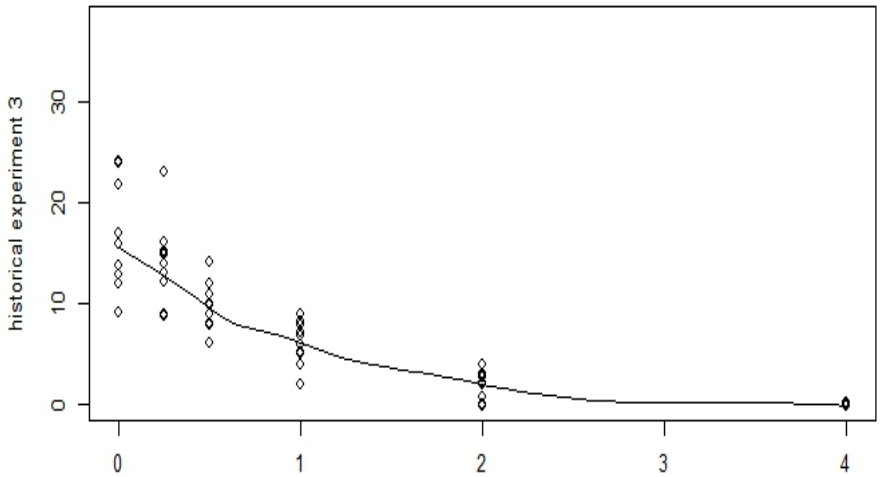
Introduction

Motivating data









Introduction

Data Notation

Concentration	c_0	c_1	c_2	c_3	c_4	c_5
Current	$Y_{01}, \ldots, Y_{0n_0}$	$Y_{11}, \ldots, Y_{1n_1}$	$\ldots$	$\ldots$	$\ldots$	$Y_{51}, \ldots, Y_{5n_5}$
H1	$Y^1_{01}, \ldots, Y^1_{0n^1_0}$	$Y^1_{11}, \ldots, Y^1_{1n^1_1}$	$\ldots$	$\ldots$	$\ldots$	$Y^1_{51}, \ldots, Y^1_{5n^1_5}$
H2	$Y^2_{01}, \ldots, Y^2_{0n^2_0}$	$Y^2_{11}, \ldots, Y^2_{1n^2_1}$	$\ldots$	$\ldots$	$\ldots$	$Y^2_{51}, \ldots, Y^2_{5n^2_5}$
H3	$Y^3_{01}, \ldots, Y^3_{0n^3_0}$	$Y^3_{11}, \ldots, Y^3_{1n^3_1}$	$\ldots$	$\ldots$	$\ldots$	$Y^3_{51}, \ldots, Y_{5n^3_5}$

- c_i: concentration levels
- Y_{ij}: number of total young produced in three broods by the jth organism exposed to concentration c_i,
- Y^k_{ij}: number of total young produced in three broods by the jth organism exposed to concentration c_i in the kth historical experiment,

Methods

Without excess zeroes:

$$\begin{aligned} Y_{ij} &\sim \textit{independent Poisson}(\mu_i), && (1) \\ log(\mu_i) &= \beta_0 + \beta_1 c_i + \beta_2 c_i^2 + \ldots + \beta_m c_i^m. && (2) \end{aligned}$$

- μ_i: mean total young produced in three broods of all organisms exposed to concentration c_i; $\mu_0 =$ the control group mean.
- β_k, $k = 0, 1, 2, \ldots, m$: coefficients associated with the (function of) exposure. ($m <$ number of concentration levels tested.)

Methods

With excess zeroes:

$$Y_{ij} = V_{ij} * (1 - B_{ij}). \quad (3)$$

$$V_{ij} \mid \mu_i \sim \textit{independent Poisson}(\mu_i), \quad (4)$$

$$log(\mu_i) = \beta_0 + \beta_1 c_i + \beta_2 c_i^2 + \ldots + \beta_m c_i^m. \quad (5)$$

$$B_{ij} \mid \pi_i \sim \textit{independent Bernoulli}(\pi_i), \quad (6)$$

$$logit(\pi_i) = \gamma_0 + \gamma_1 c_i + \gamma_2 c_i^2 + \ldots + \gamma_l c_i^l. \quad (7)$$

Methods

Model Notation

- $\mu_i^* = \mu_i(1 - \pi_i)$: mean total young produced in three broods of all organisms exposed to concentration c_i; μ_0^* = the control group mean.
- B_{ij}: latent variable indicating that zero young produced in three broods by the jth organism exposed to concentration c_i due to the death of organism, i.e., when $B_{ij} = 0$ the number of young are counts, while 0 might still be observed due to the chance of a discrete random variable equal to zero.

Methods

Model Notation

- V_{ij}: latent variable representing that total young produced in three broods by the jth organism exposed to concentration c_i assuming the organism survive.
- π_i: mortality rate of organisms exposed to concentration c_i before having the first brood.
- β_k, $k = 0, 1, 2, \ldots, m$: coefficients associated with the (function of) exposure. ($m <$ number of concentration levels tested.)
- γ_k, $k = 0, 1, 2, \ldots, l$: coefficients concerning relationship between the mortality and exposure.

Methods

Potency Estimation

- Mean (excess zeroes case): $E(Y_{ij}) = \mu_i^* = \mu_i(1-\pi_i) = e^{\beta_0+\beta_1 c_i+\ldots+\beta_m c_i^m}(1 - \frac{exp(\gamma_0+\gamma_1 c_i+\ldots+\gamma_l c_i^l)}{1+exp(\gamma_0+\gamma_1 c_i+\ldots+\gamma_l c_i^l)})$.
- Often $m \leq 2$ and $l \leq 2$ is sufficiently flexible.
- RIp is the concentration level that satisfies

$$1 - p = \mu^*_{RIp}/\mu^*_0, \tag{8}$$

where p is the proportion of inhibition and $0 < p < 1$.

Methods

Popular choice of priors

- Normal priors for regression coefficients (Wheeler and Bailer, 2009; Zhang et al., 2012)
- $\beta_i \sim N(\beta_i^0, \sigma_i^2)$,
- $\gamma_i \sim N(\gamma_i^0, \delta_i^2)$;
- Uniform distributions used for standard deviation parameters (Gelman, 2006)

Methods

Utilizing historical information in priors

- Fix the shape of distribution (normal), hyperparameters needed:

  Normal prior means, β_0^0 and γ_0^0, can be specified based on the sample mean and sample proportion of observed zeroes in previous reproductive control tests;

- Use the historical data likelihood directly – power priors and commensurate priors.

Methods

Power priors

- The power prior is defined to be the likelihood function based on the historical data raised to a power, a (Ibrahim and Chen, 2000).
- Historical data $\mathbf{D}_0 = (Y_{ij}^{hk},\ all\ i, j, k)$ be the historical data and $\pi_0(\boldsymbol{\theta})$ be the initial prior distribution for $\boldsymbol{\theta} = (\boldsymbol{\beta}, \boldsymbol{\gamma})$.
- The power prior distribution of $\boldsymbol{\theta}$ for the current study is

$$\pi(\boldsymbol{\theta}|\mathbf{D}_0, a) \propto L(\boldsymbol{\theta}|\mathbf{D}_0)^a \pi_0(\boldsymbol{\theta})$$

Methods

Power priors

- "Effective Sample Size": an_0
- It is reasonable to restrict $0 \leq a \leq 1$ where higher a indicates an increased impact of the historical data which implies a strong similarity between the historical and current study.
- If $a = 1$, then historical data and current data are treated equally.
- $a = 0$ indicates no inclusion of the historical data.

Methods

Power priors

- Conditional power prior: assuming fixed values of a;
- Joint power prior: assuming $a \sim \pi(a)$;
- Modified power prior: joint power prior divided by a normalizing constant. (Duan et al., 2006a, 2006b)

Methods

Commensurate priors

- initially derived to utilize historical **control** information (Hobbs et al., 2011; Hobbs et al., 2012).
- Historical data $\mathbf{D}_0$ is conditional on parameters $\boldsymbol{\theta}_0$;
- $\boldsymbol{\theta} \mid \boldsymbol{\theta}_0 \sim \pi(\boldsymbol{\theta}_0, \tau)$, where $\boldsymbol{\theta}$ is mean and τ is precision.
- The commensurate prior distribution of $\boldsymbol{\theta}$ for the current study is

$$\pi(\boldsymbol{\theta}|\mathbf{D}_0, \boldsymbol{\theta}_0, \tau) \propto L(\boldsymbol{\theta}_0|\mathbf{D}_0)\pi(\boldsymbol{\theta} \mid \boldsymbol{\theta}_0, \tau)\pi_0(\boldsymbol{\theta}),$$

where $\pi_0(\boldsymbol{\theta})$ is a vague initial prior for $\boldsymbol{\theta}$.

Methods

Commensurate priors

- τ: positive value reflecting belief of the commensurability of historical and current control responses;
- The bigger τ is, the more similar between $\boldsymbol{\theta}$ and $\boldsymbol{\theta}_0$;
- When τ is close to zero, the historical and current data are not compatible at all;
- When τ approaches infinity, the two data sets are from the same population and we can analyze a pooled data set;
- Fully Bayesian analysis: $\tau \sim \pi(\tau)$; $\boldsymbol{\theta}_0 \sim \pi(\boldsymbol{\theta}_0)$

Methods

Different scenarios of incorporating historical information:

- Single historical data, control information only;
- Single historical data, all information;
- Multiple historical data, control information only;
- Multiple historical data, all information;

Methods

Multiple historical experiments available

- When power prior is used, different historical data sets may have differing values of "a_0" with the current data of interest.

$$p(\boldsymbol{\theta}|\mathbf{D}_1, \ldots \mathbf{D}_H, \mathbf{a}) \propto L(\boldsymbol{\theta}|\mathbf{D}_1)^{a_1} \ldots L(\boldsymbol{\theta}|\mathbf{D}_H)^{a_H} p_0(\boldsymbol{\theta}).$$

- When commensurate prior is used to incorporate multiple historical control data sets,

$$p(\boldsymbol{\theta}|\mathbf{D}_1^0, \ldots \mathbf{D}_H^0, \boldsymbol{\theta}_0, \tau) \propto L(\boldsymbol{\theta}_0|\mathbf{D}_1^0) \ldots L(\boldsymbol{\theta}_0|\mathbf{D}_H^0) \pi(\boldsymbol{\theta}|\boldsymbol{\theta}_0, \tau) p_0(\boldsymbol{\theta}_0).$$

Application

Incorporating single historical data

- Consider two experiments first: current and historical 1;
- Experiments conducted in the same lab during the same month;
- Conditional power priors with different a's;
- Commensurate prior with $\tau \sim \Gamma(4, 0.5)$.

Application

Incorporating single historical control data, Poisson distributed assumed

	Power Priors							Commensurate priors
	$a = 0$	$a = 0.1$	$a = 0.3$	$a = 0.5$	$a = 0.7$	$a = 0.9$	$a = 1$	$\hat{\tau}$ =8.02
β_0								
PE	2.99	3.00	3.03	3.05	3.06	3.08	3.08	2.99
SD	0.07	0.06	0.06	0.05	0.05	0.05	0.05	0.07
95% CI	[2.85,3.11]	[2.88,3.12]	[2.91,3.14]	[2.94,3.15]	[2.97,3.16]	[2.98,3.17]	[2.99,3.17]	[2.86,3.12]
β_1								
PE	-0.18	-0.22	-0.30	-0.35	-0.39	-0.42	-0.43	-0.21
SD	0.23	0.22	0.22	0.21	0.20	0.20	0.19	0.23
95% CI	[-0.63, 0.26]	[-0.66, 0.22]	[-0.71, 0.14]	[-0.75, 0.07]	[-0.77, 0.01]	[-0.80, -0.03]	[-0.80, -0.05]	[-0.64, 0.24]
β_2								
PE	-0.61	-0.59	-0.55	-0.53	-0.51	-0.50	-0.49	-0.60
SD	0.15	0.15	0.14	0.14	0.13	0.13	0.13	0.15
95% CI	[-0.90, -0.33]	[-0.89, -0.31]	[-0.85, -0.30]	[-0.82, -0.28]	[-0.79, -0.27]	[-0.77, -0.25]	[-0.77, -0.25]	[-0.89, -0.32]

Application

Incorporating single historical control data, Poisson distributed assumed

	Power Priors							Commensurate priors
	$a = 0$	$a = 0.1$	$a = 0.3$	$a = 0.5$	$a = 0.7$	$a = 0.9$	$a = 1$	$\hat{\tau}$ =8.02
RI_{25}								
PE	0.55	0.53	0.50	0.48	0.46	0.45	0.44	0.54
SD	0.10	0.10	0.09	0.08	0.08	0.07	0.07	0.10
95% CI	[0.37,0.76]	[0.37,0.74]	[0.35,0.70]	[0.34,0.66]	[0.33,0.63]	[0.32,0.61]	[0.32,0.60]	[0.37, 0.75]
RI_{50}								
PE	0.93	0.91	0.88	0.86	0.84	0.83	0.83	0.92
SD	0.09	0.08	0.08	0.08	0.07	0.07	0.07	0.09
95% CI	[0.76,1.10]	[0.75,1.07]	[0.72,1.04]	[0.71,1.02]	[0.70,0.99]	[0.69,0.97]	[0.69,0.97]	[0.75, 1.09]

Application

Incorporating single historical control data, ZI-Poisson distributed assumed

	Power Priors							Commensurate priors
	$a = 0$	$a = 0.1$	$a = 0.3$	$a = 0.5$	$a = 0.7$	$a = 0.9$	$a = 1$	$\widehat{\tau_{\beta_0}}$ =8.00 $\widehat{\tau_{\gamma_0}}$ =7.36
β_0								
PE	2.98	3.00	3.03	3.04	3.06	3.07	3.08	2.99
SD	0.07	0.06	0.06	0.05	0.05	0.05	0.05	0.07
95% CI	[2.85, 3.11]	[2.87, 3.12]	[2.91, 3.14]	[2.94, 3.15]	[2.96, 3.16]	[2.98, 3.17]	[2.99, 3.17]	[2.86, 3.11]
β_1								
PE	-0.16	-0.21	-0.28	-0.34	-0.39	-0.41	-0.43	-0.18
SD	0.24	0.23	0.22	0.22	0.21	0.21	0.20	0.24
95% CI	[-0.63, 0.31]	[-0.67, 0.26]	[-0.71, 0.15]	[-0.76, 0.09]	[-0.80, 0.03]	[-0.81, 0.00]	[-0.83, -0.03]	[-0.63, 0.28]
β_2								
PE	-0.55	-0.53	-0.49	-0.47	-0.44	-0.43	-0.42	-0.54
SD	0.16	0.16	0.15	0.16	0.15	0.15	0.15	0.16
95% CI	[-0.87, -0.23]	[-0.85, -0.22]	[-0.80, -0.20]	[-0.78, -0.17]	[-0.74, -0.15]	[-0.74, -0.15]	[-0.72, -0.13]	[-0.86, -0.23]

Application

Incorporating single historical control data, ZI-Poisson distributed assumed

	Power Priors							Commensurate priors
	$a = 0$	$a = 0.1$	$a = 0.3$	$a = 0.5$	$a = 0.7$	$a = 0.9$	$a = 1$	$\widehat{\tau_{\beta_0}}$ =8.00 $\widehat{\tau_{\gamma_0}}$ =7.36
γ_0								
PE	-5.63	-5.47	-5.53	-5.61	-5.66	-5.77	-5.79	-5.71
SD	2.61	2.93	2.50	2.84	2.56	2.90	2.55	3.06
95% CI	[-12.45, -2.76]	[-13.64, -2.55]	[-12.11, -2.70]	[-13.08, -2.77]	[-12.44, -2.84]	[-14.27, -2.89]	[-12.51. -3.00]	[-13.21, -2.90]
γ_1								
PE	2.03	1.91	2.00	2.02	2.07	2.12	2.18	2.05
SD	2.59	2.92	2.59	2.81	2.81	2.86	2.85	2.72
95% CI	[-4.74, 4.97]	[-5.93, 5.23]	[-4.04, 4.89]	[-5.40, 5.05]	[-5.17, 5.09]	[-5.98, 5.11]	[-5.46, 5.19]	[-4.96, 4.94]

Application

Incorporating single historical control data, ZI-Poisson distributed assumed

	Power Priors							Commensurate priors
	$a = 0$	$a = 0.1$	$a = 0.3$	$a = 0.5$	$a = 0.7$	$a = 0.9$	$a = 1$	$\widehat{\tau_{\beta_0}}$ =8.00 $\widehat{\tau_{\gamma_0}}$ =7.36
RI_{25}								
PE	0.58	0.56	0.52	0.50	0.47	0.46	0.45	0.57
SD	0.11	0.11	0.10	0.10	0.09	0.09	0.08	0.11
95% CI	[0.38, 0.81]	[0.37, 0.78]	[0.35, 0.73]	[0.34, 0.70]	[0.33, 0.67]	[0.33, 0.65]	[0.32, 0.63]	[0.38, 0.79]
RI_{50}								
PE	0.97	0.95	0.92	0.89	0.87	0.86	0.85	0.96
SD	0.09	0.10	0.09	0.09	0.08	0.08	0.08	0.09
95% CI	[0.78, 1.15]	[0.77, 1.13]	[0.75, 1.09]	[0.73, 1.06]	[0.71, 1.04]	[0.71, 1.02]	[0.70, 1.01]	[0.77, 1.14]

Application

Incorporating all information from single historical data, Poisson distributed assumed

	Power Priors							Commensurate priors
	$a = 0$	$a = 0.1$	$a = 0.3$	$a = 0.5$	$a = 0.7$	$a = 0.9$	$a = 1$	$\widehat{\tau_{\beta_0}} = 4.22$ $\widehat{\tau_{\beta_1}} = 0.66$ $\widehat{\tau_{\beta_2}} = 0.57$
RI_{25}								
PE	0.55	0.56	0.60	0.62	0.64	0.65	0.65	0.58
SD	0.10	0.10	0.08	0.08	0.07	0.06	0.06	0.10
95% CI	[0.37,0.76]	[0.40,0.76]	[0.44,0.76]	[0.47,0.77]	[0.50,0.77]	[0.52,0.76]	[0.54,0.77]	[0.40,0.79]
RI_{50}								
PE	0.93	0.93	0.93	0.94	0.94	0.94	0.94	0.95
SD	0.09	0.08	0.07	0.06	0.05	0.05	0.04	0.08
95% CI	[0.76,1.10]	[0.77,1.08]	[0.80,1.06]	[0.82,1.05]	[0.84,1.04]	[0.84,1.03]	[0.85,1.02]	[0.78,1.11]

Application

Incorporating all information from single historical data, ZI-Poisson distributed assumed

	Power Priors							Commensurate priors
	$a = 0$	$a = 0.1$	$a = 0.3$	$a = 0.5$	$a = 0.7$	$a = 0.9$	$a = 1$	$\widehat{\tau_{\beta_0}} = 7.79$ $\widehat{\tau_{\beta_1}}$=7.02 $\widehat{\tau_{\beta_2}}$=7.85 $\widehat{\tau_{\gamma_0}}$=6.54 $\widehat{\tau_{\gamma_1}}$=4.97
RI_{25}								
PE	0.58	0.60	0.63	0.65	0.67	0.67	0.69	0.62
SD	0.11	0.13	0.12	0.11	0.08	0.07	0.07	0.10
95% CI	[0.38,0.81]	[0.41,0.81]	[0.45,0.82]	[0.49,0.82]	[0.51,0.82]	[0.53,0.81]	[0.55,0.82]	[0.42, 0.81]
RI_{50}								
PE	0.97	0.97	0.99	0.99	0.98	0.98	0.99	0.98
SD	0.09	0.11	0.08	0.07	0.06	0.06	0.06	0.08
95% CI	[0.78,1.15]	[0.80,1.14]	[0.83,1.13]	[0.85,1.12]	[0.87,1.10]	[0.87,1.10]	[0.88,1.10]	[0.81, 1.14]

Application

Values of a_0's used in power priors when 3 sets of historical control are used

Experiment	Current	Historical 1	Historical 2	Historical 3
Lab	1	1	2	3
Power parameters a_1	/	0	0	0
a_2	/	0.5	0.5	0.5
a_3	/	0.9	0.1	0.2
a_4	/	0.9	0.1	0.1
a_5	/	0.9	0.1	0.5
a_6	/	0.8	0.2	0.5
a_7	/	0.7	0.3	0.5
a_8	/	0.6	0.4	0.5

Application

Incorporating multiple historical control data, Poisson distributed assumed

	Power Priors $\boldsymbol{a} = (a_1, a_2, a_3)$								Commensu rate priors
	(0,0,0)	(0.5,0.5,0.5)	(0.9,0.1,0.2)	(0.9,0.1,0.1)	(0.9,0.1,0.5)	(0.8,0.2,0.5)	(0.7,0.3,0.5)	(0.6,0.4,0.5)	$\hat{t}$ =4.29
RI_{25}									
PE	0.55	0.61	0.52	0.51	0.54	0.56	0.58	0.60	0.55
SD	0.10	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.10
95 % CI	[0.37,0.76]	[0.45, 0.78]	[0.37, 0.69]	[0.37, 0.68]	[0.39, 0.71]	[0.41, 0.73]	[0.42, 0.74]	[0.44, 0.76]	[0.37,0.76]
RI_{50}									
PE	0.93	0.97	0.89	0.89	0.92	0.93	0.95	0.96	0.93
SD	0.09	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.09
95 % CI	[0.76,1.10]	[0.84, 1.11]	[0.75, 1.04]	[0.75, 1.03]	[0.78, 1.05]	[0.80, 1.07]	[0.81, 1.08]	[0.82, 1.09]	[0.76,1.10]

Application

Incorporating multiple historical control data, ZI-Poisson distributed assumed

	Power Priors $\boldsymbol{a} = (a_1, a_2, a_3)$								Commensurate priors
	(0,0,0)	(0.5,0.5,0.5)	(0.9,0.1,0.2)	(0.9,0.1,0.1)	(0.9,0.1,0.5)	(0.8,0.2,0.5)	(0.7,0.3,0.5)	(0.6,0.4,0.5)	$\widehat{\tau_{\beta_0}} = 8.28$ $\widehat{\tau_{\gamma_0}} = 7.37$
RI_{25}									
PE	0.58	0.63	0.53	0.53	0.56	0.58	0.60	0.62	0.58
SD	0.11	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.11
95% CI	[0.38, 0.81]	[0.45, 0.82]	[0.38, 0.71]	[0.37, 0.71]	[0.40, 0.74]	[0.41, 0.76]	[0.43, 0.78]	[0.45, 0.80]	[0.39, 0.81]
RI_{50}									
PE	0.97	1.01	0.93	0.92	0.95	0.97	0.98	1.00	0.97
SD	0.09	0.08	0.08	0.08	0.08	0.08	0.08	0.07	0.09
95% CI	[0.78, 1.15]	[0.86, 1.16]	[0.78, 1.08]	[0.77, 1.08]	[0.80, 1.10]	[0.82, 1.12]	[0.83, 1.13]	[0.85, 1.14]	[0.79, 1.15]

Discussion

- This study serves as a template of Bayesian potency estimation when historical information are available.
- Extend the Bayesian method to incorporate historical information about multiple endpoints jointly (hatching success, survival, growth and reproduction).
- Applications in design? Sample size determination?

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