Robust Designs for Toxicological Test

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Abstract

Toxicological tests are widely used to study toxicity in aquatic environments. Reproduction is a possible endpoint of this type of experiment, whose response variable is given by counts. There is literature about the suitable probability distribution to be used for analyzing these data. In the theory of optimal experimental design, the assumption of this probability distribution is essential, and when this assumption is not adequate, there may be a loss of efficiency in the design obtained. The main objective of this study is to propose robust designs when there is uncertainty about the probability distribution of the response variable. We introduce and compare three different strategies for attaining this goal and they are applied to *Ceriodaphnia Dubia* and *Lemna Minor* tests. In addition, a simulation study is performed to test the estimation properties of the robust designs obtained.

1. Optimal experimental design

Model

$$y = \eta(x;\theta) + \epsilon,\ x \in \mathcal{X}$$

Approximate design of q points

$$\xi = \begin{Bmatrix} x_1 & \dots & x_q \\ w_1 & \dots & w_q \end{Bmatrix} \in \Xi,\quad \sum_{i=1}^{q} w_i = 1$$

Likelihood function: exponential family distributions

$$l(y;\tau,\varphi) = \exp\left(\frac{y\tau - b(\tau)}{a(\varphi)} + c(y;\varphi)\right),$$

where τ and φ are the parameters of the probability distribution, and $a(\cdot)$, $b(\cdot)$ and $c(\cdot)$ are known functions.

Elemental information matrix

$$\nu(\eta) = -E\left[\frac{\partial^2 \log l(y;\eta)}{\partial \eta^2}\right]$$

Fisher information matrix (FIM)

$$M(\xi;\theta) = \sum_{i=1}^{q} I(x_i;\theta) w_i,$$

where

$$I(x;\theta) = -E\left[\frac{\partial^2 \log l(y;\eta(x;\theta))}{\partial\theta_j \partial\theta_k}\right] = \nu(\eta(x;\theta)) f(x;\theta) f^T(x;\theta),$$

and $f(x;\theta) = \partial\eta(x;\theta)/\partial\theta$.

D-optimality

$$\Phi_D(M(\xi;\theta)) = |M^{-1}(\xi;\theta)|^{(1/m)} \quad \text{(criterion)}$$
$$\xi^* = \arg\min_{\xi\in\Xi} \Phi_D(\xi) \quad (D\text{-optimal design})$$

D-efficiency

$$\text{eff}(\xi|\xi^*) = \left(\frac{|M(\xi;\theta)|}{|M(\xi^*;\theta)|}\right)^{1/m}$$

2. Strategies to obtain robust designs

I. Compound criterion

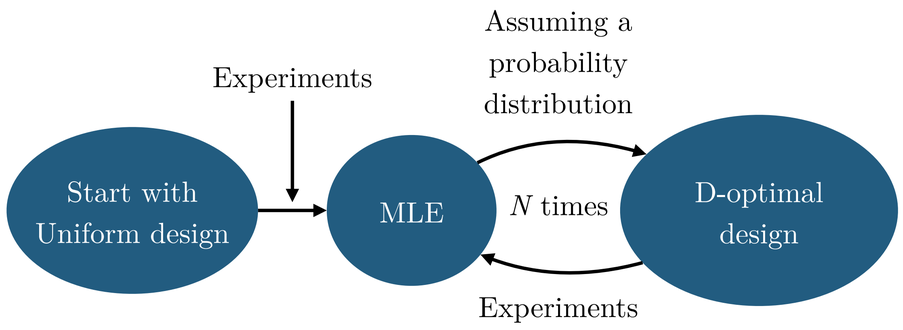
$$\Phi_C(\xi;\lambda) = \lambda \log \Phi_D(M_A(\xi;\theta)) + (1-\lambda)\log \Phi_D(M_B(\xi;\theta)),\quad \lambda \in [0,1],$$

where M_A and M_B are respectively the FIM's of each probability distribution considered.

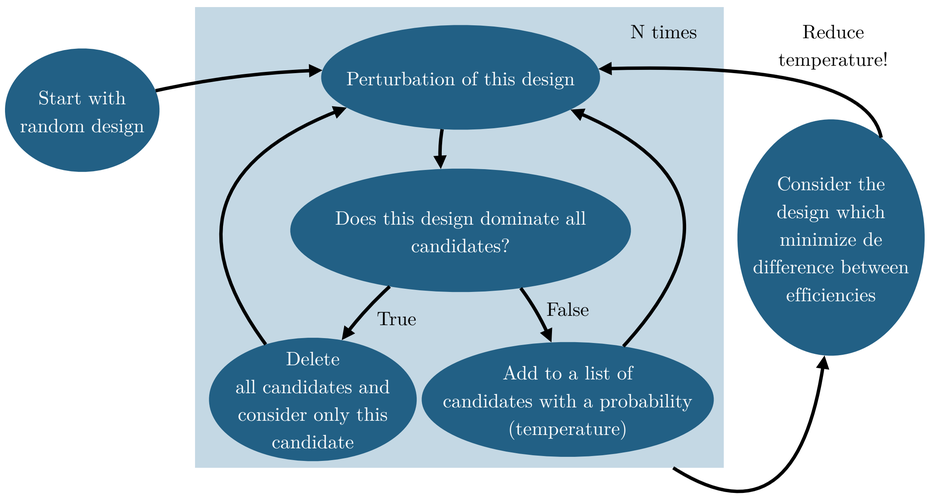
$$\xi^*_\lambda = \arg\max_{\xi\in\Xi} \Phi_C(\xi;\lambda).$$

The aim is to determine the value of λ whose ξ^*_λ satisfies $\text{eff}_A(\xi^*_\lambda|\xi^*_A) = \text{eff}_B(\xi^*_\lambda|\xi^*_B)$.

II. Multistage designs



III. Multiple Objective Annealing Algorithm



3. Application to toxicological tests

Lemna Minor

$$\eta(x;\theta) = \theta_0 + \theta_1 x + \theta_2 x^2$$

Poisson vs homoscedastic normal

Ceriodaphnia Dubia

$$\eta(x;\theta) = \frac{\theta_0 + \theta_1 x}{1 + e^{-\theta_2 x^{\theta_3}}}$$

Poisson vs heteroscedastic normal

Model	Test	True dist.	eff($\xi_\mathcal{N}$)	eff($\xi_\mathcal{P}$)	eff(ξ_C)	I. CC	II. MSD	III.MOAA
Quad	*Lem.*	N. Homo.	1	0.580	0.763	**0.885**	-	0.882
		Poisson	0.316	1	0.276		-	0.878
Log	*Cer.*	N. Hetero.	1	0.536	0.644	0.874	**0.971**	0.861
		Poisson	0.035	1	0.023		**0.957**	0.862

Table 1. Efficiencies of the designs assuming normal distribution (homoscedastic or heteroscedastic) $\xi_\mathcal{N}$, Poisson $\xi_\mathcal{P}$, and the conventional designs ξ_C (described in the protocols), with respect to the optimal for each scenario. The last three columns show the efficiencies, for each scenario, of the strategies described in the work. Best values are in **bold**.

4. Simulation study

		Linear quadratic model			Linear logistic model			
		θ_0	θ_1	θ_2	θ_0	θ_1	θ_2	θ_3
Bias	I. CC	0.0564	-0.1105	0.1100	**0.0017**	0.1420	-0.1675	0.2357
	II. MSD	-	-	-	0.0349	0.0710	-0.6754	0.9468
	III. MOAA	**0.0220**	**-0.0229**	0.0531	0.0201	**0.0433**	-0.1250	0.1772
	$\xi_\mathcal{N}$	0.0514	0.0830	**0.0139**	0.0931	-0.2159	**-0.0642**	**0.1371**
	ξ_C	0.0999	0.0585	0.0622	0.0040	0.2668	-0.1122	0.1593
	$\xi_\mathcal{P}$	*0.0343*	*-0.0449*	*0.0528*	*0.0346*	*0.0376*	*-0.1169*	*0.1610*
MSE	I. CC	**2.5994**	**16.8003**	**8.5340**	1.5806	26.7912	3.2674	6.6377
	II. MSD	-	-	-	1.4445	**24.1075**	74.9387	149.4130
	III. MOAA	2.7391	17.4507	8.7216	1.6828	27.9434	**3.1227**	6.3107
	$\xi_\mathcal{N}$	3.5566	42.5683	25.1961	17.3698	97.7235	5.3251	**1.2492**
	ξ_C	2.8420	34.1900	20.6127	**1.3048**	66.8872	7.3087	15.1987
	$\xi_\mathcal{P}$	*2.6753*	*14.4189*	*6.7637*	*1.5424*	*25.2558*	*2.0853*	*4.3009*
CV	I. CC	**0.0102**	**0.0119**	**0.0150**	0.0512	0.1340	0.0857	0.0899
	II. MSD	-	-	-	0.0489	**0.1274**	0.4011	0.4167
	III. MOAA	0.0110	0.0122	0.0151	0.0553	0.1373	**0.0841**	0.0880
	$\xi_\mathcal{N}$	0.0125	0.0190	0.0257	0.1691	0.2585	0.1103	**0.0390**
	ξ_C	0.0111	0.0170	0.0233	**0.0465**	0.2112	0.1290	0.1370
	$\xi_\mathcal{P}$	*0.0108*	*0.0111*	*0.0133*	*0.0505*	*0.1305*	*0.0687*	*0.0726*

Table 2. Bias, mean square error and coefficient of variation of the estimators of the parameters of the models considered. The simulation study was done by performing 10 000 repetitions of simulated experiments with 60 observations each using the designs calculated in this work and the conventional designs, *assuming that the Poisson distribution is the true one*. Best values are in **bold**.

Conclusions

The strategies proposed are robust in terms of efficiency when misspecification in the probability distribution of the response occurs. In general the three strategies present similar values of bias, MSE and CV in almost all cases, comparing to the obtained with the reference design $\xi_\mathcal{P}$.

Bibliography

1. Atkinson, A. C., Fedorov, V. V., Herzberg, A. M., and Zang, R. (2014). Elemental information matrices and optimal experimental design for generalized regression models. *Journal of Statistical Planning and Inference*, 144:81–91.
2. Lehmann, R., Bachmann, J., Maletzki, D., Polleichtner, C., Ratte, H. T., and Ratte, M. (2016). A new approach to overcome shortcomings with multiple testing of reproduction data in ecotoxicology. *Stochastic Environmental Research and Risk Assessment*, 30:871–882.
3. Lewis, P., Klemm, D., Lazorchak, J., Norberg-King, T., and Peltier, W. (2002). *Short-term methods for estimating the chronic toxicity of effluents and receiving water to freshwater organisms*. Fourth edition.

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