Optimal designs for longitudinal studies with fractional polynomial models

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Joint work with Víctor Casero–Alonso & Weng Kee Wong

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A manifesto for reproducible science

Marcus R. Munafò[1,2*], Brian A. Nosek[3,4], Dorothy V. M. Bishop[5], Katherine S. Button[6], Christopher D. Chambers[7], Nathalie Percie du Sert[8], Uri Simonsohn[9], Eric-Jan Wagenmakers[10], Jennifer J. Ware[11] and John P. A. Ioannidis[12,13,14]

Improving the reliability and efficiency of scientific research will increase the credibility of the published scientific literature and accelerate discovery. Here we argue for the adoption of measures to optimize key elements of the scientific process: methods, reporting and dissemination, reproducibility, evaluation and incentives. There is some evidence from both simulations and empirical studies supporting the likely effectiveness of these measures, but their broad adoption by researchers, institutions, funders and journals will require iterative evaluation and improvement. We discuss the goals of these measures, and how they can be implemented, in the hope that this will facilitate action toward improving the transparency, reproducibility and efficiency of scientific research.

What proportion of published research is likely to be false? Low sample size, small effect sizes, data dredging (also known as *P*-hacking), conflicts of interest, large numbers of scientists working competitively in silos without combining their efforts, and so on, may conspire to dramatically increase

The problem

A hallmark of scientific creativity is the ability to see novel and unexpected patterns in data. John Snow's identification of links between cholera and water supply[17], Paul Broca's work on language lateralization[18] and Jocelyn Bell Burnell's discovery of pulsars[19] are

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Por una investigación de calidad (http://www.elespanol.com/opinion/tribunas/20170227/197100289_12.html)

Outline

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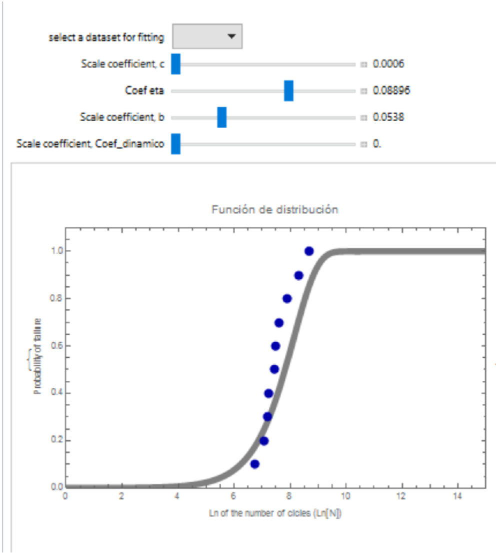
6. Conclusions.


select a dataset for fitting
Scale coefficient, c
0.0006
Coef eta
0.08896
Scale coefficient, b
0.0538
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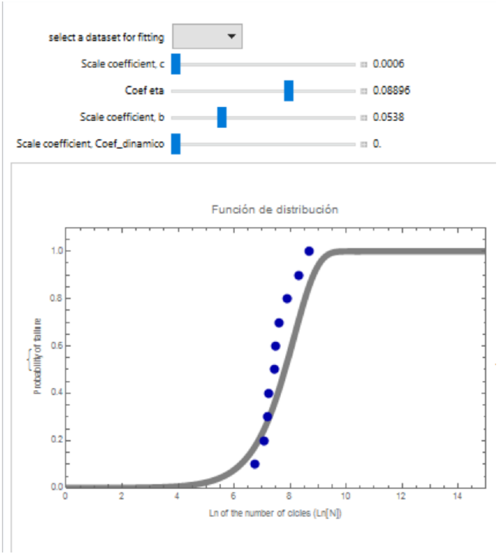
0.
Función de distribución
Probability of failure
Ln of the number of cicles (Ln[N])

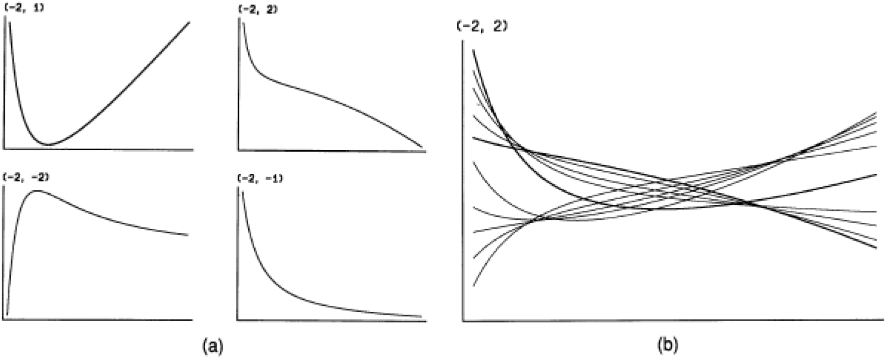
Robust estimation



Maximum Likely Look Estimator (MLLE)

FP models

$$\phi_2(x;\mathbf{p}) = \alpha_0 + \alpha_1 x^{(p_1)} + \alpha_2 x^{(p_2)}$$



$$\phi_m(x;\mathbf{p}) = \alpha_0 + \sum_{j=1}^{m} \alpha_j H_j(x)$$

- $H_1(x) = x^{(p_1)}$

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- $\mathbf{p} = (p_1, \ldots, p_m)$ with $p_j \in \mathcal{P} = \{-2, -1, -\frac{1}{2}, 0, \frac{1}{2}, 1, 2, 3\}$
  $(p_1 \leq \ldots \leq p_m)$

  $$\Downarrow$$

  $$x \neq 0 (> 0)$$

Design Theory

- Approximate designs: $\xi = \left\{ \begin{array}{cccc} x_1 & x_2 & \dots & x_k \\ w_1 & w_2 & \dots & w_k \end{array} \right\} \quad x_i \in \chi$

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    μ, user-selected weighting measure over S
  - $T_{21}(\xi) = \min_{\theta_2 \in \Theta_2} \left[\int_{\mathcal{X}} \{\eta(x, \theta_1) - \eta_2(x, \theta_2)\}^2 \xi(dx) \right]$.
    (assuming θ completely known).

- Equivalence Theorems:
  - $f(x)^T M^{-1}(\xi_D^\star) f(x) - (m+1) \ \leq \ 0$ for all $x \in X$.
  - $f(x)^T M^{-1}(\xi_I^\star) A M^{-1}(\xi_I^\star) f(x) - trAM^{-1}(\xi_I^\star) \leq \ 0$ for all $x \in X$.
  - $\max_x \psi(x, \xi_s) \leq \ 0$ for all $x \in X$, where $\psi(x, \xi_s) = [f^T(x)\theta - f_1^T(x)\hat{\theta}_1]^2 - \int_\chi [f^T(x)\theta - f_1^T(x)\hat{\theta}_1]^2 \xi(dx)$, and $\hat{\theta}_1 = \arg\min_{\theta_1} \int_\chi [f^T(x)\theta - f_1^T(x)\theta_1]^2 \xi(dx)$.

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- Efficiencies: $\left(\dfrac{|M(\xi)|}{|M(\xi_D^\star)|}\right)^{\dfrac{1}{m+1}}, \ \dfrac{\Phi_I(\xi_I^\star)}{\Phi_I(\xi)}, \ \dfrac{T_{21}(\xi)}{T_{21}(\xi_T^\star)}$.

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- A user-friendly **applet** Wolfram Mathematica

  `http://areaestadistica.uclm.es/oed/index.php/computer-tools/`

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- $c(x)$ is a linear combination of $1, x^p, x^{2p}$.
- They form a Tchebyshev system on the interval $[\epsilon, a]$ because

$$\begin{vmatrix} 1 & x_1^p & x_1^{2p} \\ 1 & x_2^p & x_2^{2p} \\ 1 & x_3^p & x_3^{2p} \end{vmatrix} = -(x_1^p - x_2^p)(x_1^p - x_3^p)(x_2^p - x_3^p),$$

  has the same sign for any $\epsilon \leq x_1 < x_2 < x_3 \leq a$.

... for FP1(p) models

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$$c(x) = 4\left(a^p - x^p\right)\left(\epsilon^p - x^p\right) / \left(a^p - \epsilon^p\right)^2 \leq 0, p \neq 0.$$

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- A similar argument applies when $p = 0$.

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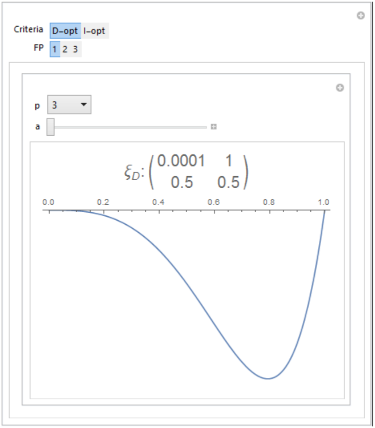
- They form a Tchebyshev system on $[\epsilon, a]$.
- The weights are found by finding the roots of the sensitivity function of the design supported at $x = \epsilon$ and $x = a$.

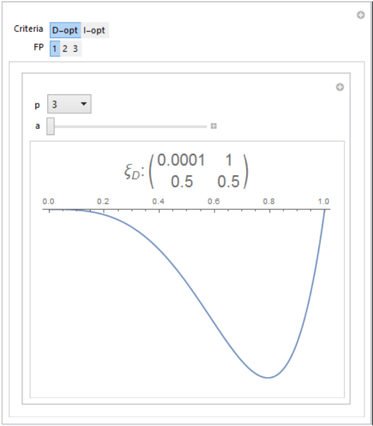
... for FP1(p) models

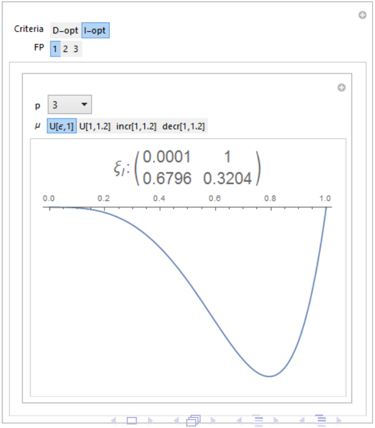
$$\xi_D^\star = \left\{ \begin{array}{cc} \epsilon & a \\ 1/2 & 1/2 \end{array} \right\}$$



$$\xi_D^\star = \left\{ \begin{array}{cc} \epsilon & a \\ 1/2 & 1/2 \end{array} \right\} \qquad \xi_I^\star = \left\{ \begin{array}{cc} \epsilon & a \\ w & 1-w \end{array} \right\}$$

$$\frac{1}{w} = 1 + \sqrt{\frac{(p+1)a^{2p+1} + a(2p+1)\left[(p+1)\epsilon^{2p} - 2(a\epsilon)^p\right] - 2p^2\epsilon^{2p+1}}{2p^2 a^{2p+1} - (p+1)(2p+1)\epsilon a^{2p} + \epsilon\left[2(2p+1)(a\epsilon)^p - (p+1)\epsilon^{2p}\right]}}$$





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- The Wronskians (Gasull et al., 2012) are positive for any p and q,

$$\begin{vmatrix} f_1(x) & f_2(x) & \cdots & f_k(x) \\ f_1'(x) & f_2'(x) & \cdots & f_k'(x) \\ \cdots & \cdots & \cdots & \cdots \\ f_1^{(k)}(x) & f_2^{(k)}(x) & \cdots & f_k^{(k)}(x) \end{vmatrix},$$

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- Thus, only three support points are possible: either 1 or 2 interior support points.

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- Thus, D is a decreasing function of s_1.
- Consequently, ϵ is a support point of the D–optimal design.

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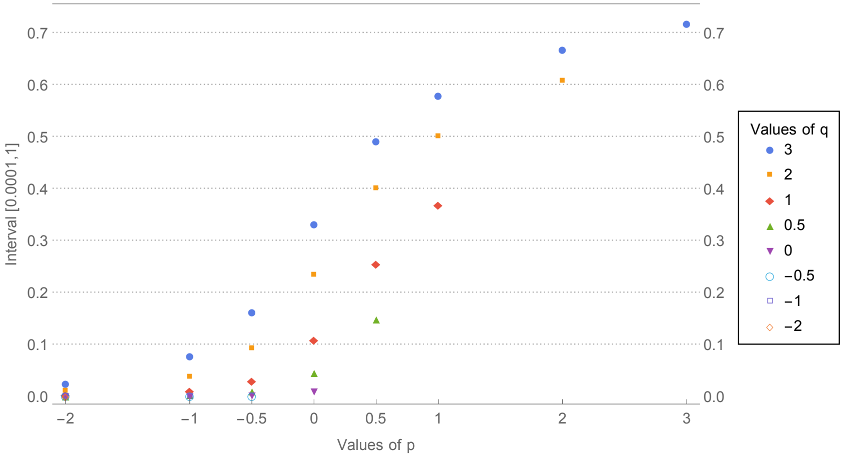
  - $p = q = 0$.
- The interior support point is the unique root of the derivative of the sensitivity function.

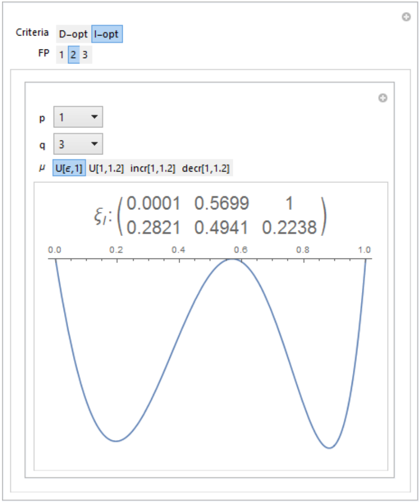
$$\xi_D^\star = \left\{ \begin{array}{ccc} \epsilon & s & a \\ 1/3 & 1/3 & 1/3 \end{array} \right\} \quad \ldots$$

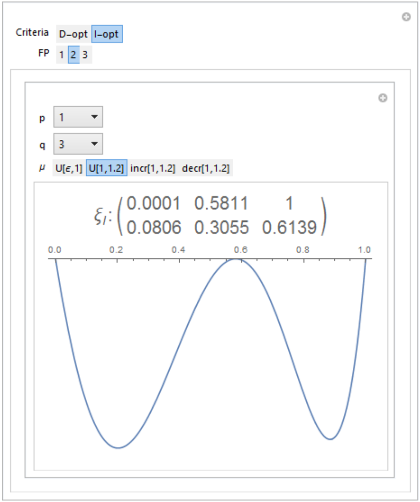
... for FP2(p,q)

$$\xi_D^\star = \left\{ \begin{array}{ccc} \epsilon & s & a \\ 1/3 & 1/3 & 1/3 \end{array} \right\} \quad \ldots \quad s = \left(\frac{(a^q - \epsilon^q)\, p}{(a^p - \epsilon^p)\, q} \right)^{1/(-p+q)}$$



$$\xi_I^\star = \left\{ \begin{array}{ccc} \epsilon & s & a \\ w_1 & w_2 & 1 - w_1 - w_2 \end{array} \right\}$$

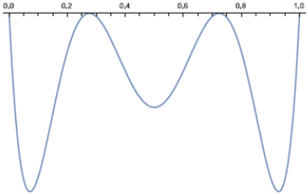




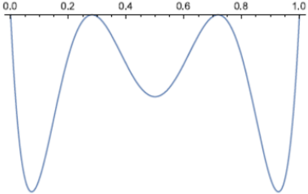
$$\xi_D^\star = \left\{ \begin{array}{cccc} \epsilon & s_1 & s_2 & a \\ 1/4 & 1/4 & 1/4 & 1/4 \end{array} \right\} \quad \xi_I^\star = \left\{ \begin{array}{cccc} \epsilon & s_1 & s_2 & a \\ w_1 & w_2 & w_3 & 1-\sum_i w_i \end{array} \right\}$$

FP3(1,2,3)

$$\xi_D: \begin{pmatrix} 0.0001 & 0.2765 & 0.7236 & 1 \\ 0.25 & 0.25 & 0.25 & 0.25 \end{pmatrix}$$

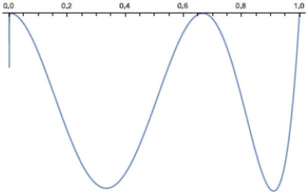


$$\xi_I: \begin{pmatrix} 0.0001 & 0.2818 & 0.7183 & 1 \\ 0.1549 & 0.3451 & 0.3451 & 0.1549 \end{pmatrix}$$

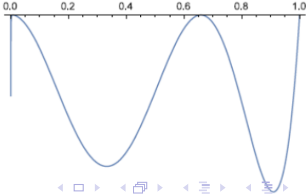


FP3(-2,2,3)

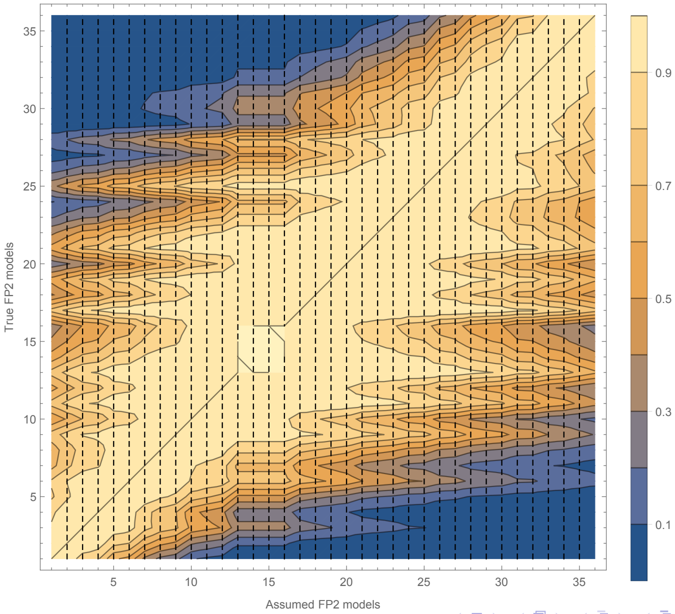
$$\xi_D: \begin{pmatrix} 0.0001 & 0.0068 & 0.6667 & 1 \\ 0.25 & 0.25 & 0.25 & 0.25 \end{pmatrix}$$



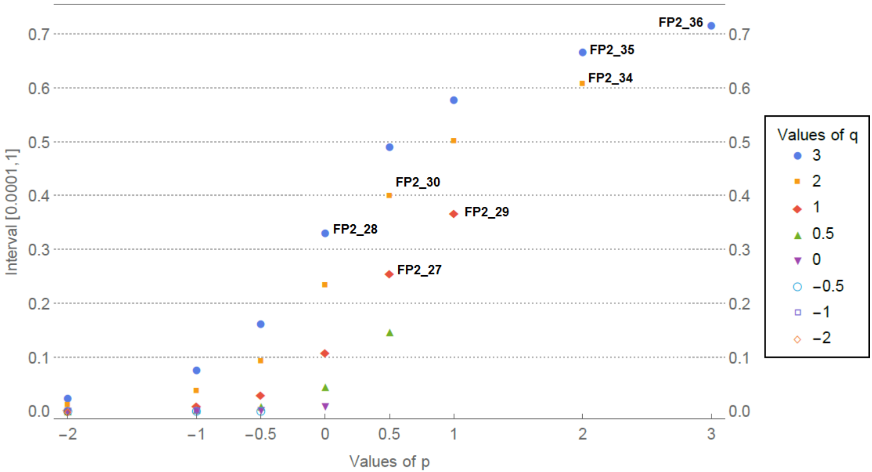
$$\xi_I: \begin{pmatrix} 0.0001 & 0.0078 & 0.6582 & 1 \\ 0.0039 & 0.3597 & 0.4401 & 0.1963 \end{pmatrix}$$

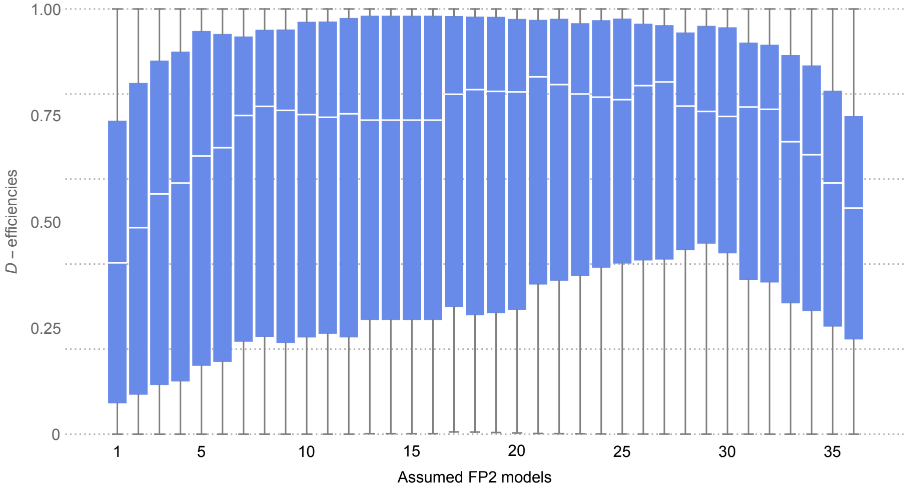


Model Uncertainty (FP2)



Sorted by “s” (interior support point)





1.00
0.75
0.50
0.25
0
D − efficiencies
1
5
10
15
20
25
30
35
Assumed FP2 models

Introduced by Atkinson and Fedorov (1975a, b) for discriminating between two rival linear models

$$T_{21}(\xi) = \min_{\theta_2 \in \Theta_2} \left[\int_{\mathcal{X}} \{\eta(x, \theta_1) - \eta_2(x, \theta_2)\}^2 \xi(dx) \right].$$

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KL–optimality for any distribution (López-Fidalgo, Tommasi and Trandafir, 2007):

$$I_{21}(\xi) = \min_{\theta_2 \in \Theta_2} \left\{ \int_{\mathcal{X}} \mathcal{I}(f, f_2, x, \theta_2) \xi(dx) \right\}$$

where $\mathcal{I}(f, f_2, x, \theta_2) = \int f(y, x, \tau) \log \left\{ \frac{f(y, x, \tau)}{f_2(y, x, \theta_2, \tau)} \right\}$ is the Kullback–Leibler (KL) distance.

1. Given a design ξ_s at step s, compute

$$\theta_{2,s} = \arg\min_{\theta_2 \in \Theta_2} \left\{ \int_{\mathcal{X}} \mathcal{I}(f, f_2, x, \theta_2) \xi(dx) \right\}$$

$$x_s = \arg\max_{x \in \mathcal{X}} \{ \mathcal{I}(f, f_2, x, \theta_{2,s}) \}.$$

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2. Then

$$\xi_{s+1} = (1 - \alpha_s)\xi_s + \alpha_s \xi_{x_s}$$

$(0 \leq \alpha_s \leq 1, \lim_{s \to \infty} \alpha_s = 0, \sum_{s=0}^{\infty} \alpha_s = \infty, \sum_{s=0}^{\infty} \alpha_s^2 < \infty)$.

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3. The stopping rule for the algorithm is based on the GET

$$\left[1 + \frac{max_{x\in\mathcal{X}} \psi(x, \xi_s)}{I_{21}(\xi_s)}\right]^{-1} > \delta(= 0.999)$$

$$\text{f=FP1(0); f}_2\text{=FP1(1/2)} \quad \left\{ \begin{array}{ccc} 0.01 & 0.153269 & 1 \\ \frac{73}{216} & \frac{1}{2} & \frac{35}{216} \end{array} \right\}$$

$$\text{f=FP1(1/2); f}_2\text{=FP1(0)} \quad \left\{ \begin{array}{ccc} 0.01 & 0.152248 & 1 \\ \frac{19}{93} & \frac{1}{2} & \frac{55}{186} \end{array} \right\}$$

$$\text{f=FP1(0); f}_2\text{=FP1(3)} \quad \left\{ \begin{array}{ccc} 0.01 & 0.417462 & 1 \\ \frac{89}{192} & \frac{1}{2} & \frac{7}{192} \end{array} \right\}$$

$$\text{f=FP1(-2); f}_2\text{=FP1(3)} \quad \left\{ \begin{array}{ccc} 0.01 & 0.148491 & 1 \\ \frac{263}{528} & \frac{1}{2} & \frac{1}{528} \end{array} \right\}$$

Efficiencies for FP1(p)

	D-eff (0)	D-eff (1/2)	I-eff (0)	I-eff (1/2)	T-eff (0, 1/2)	T-eff (1/2, 0)
$\xi_D(0,1/2)$	100	100	80.9	95.6	0.0	0.0
$\xi_I(0)$	87.4	87.4	100	91.2	0.0	0.0
$\xi_I(1/2)$	97.7	97.7	92.8	100	0.0	0.0
$\xi_T(0,1/2)$	71.4	66.2	55.7	51.4	100	85.9
$\xi_T(1/2,0)$	69.6	74.5	73.5	75.1	87.0	100

The value of p is between parentheses.

Applications to biomedical studies

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  - The best were FP1(-1) and FP2(-2,1).

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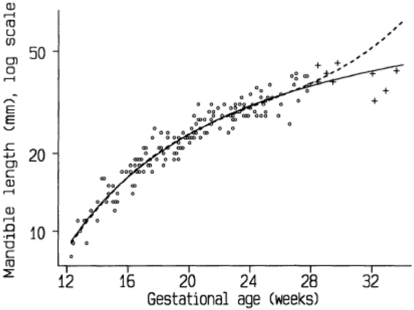

Fig. 3. Extrapolated fit for the mandible data (shown on a log-scale) using two models: ———, fractional polynomial $\phi_1(X; -1)$; --------, cubic polynomial

$$\xi_D^\star = \left\{ \begin{array}{cc} 12 & 28 \\ 1/2 & 1/2 \end{array} \right\} \qquad \xi_I^\star = \left\{ \begin{array}{cc} 12 & 28 \\ 0.4226 & 0.5774 \end{array} \right\}$$

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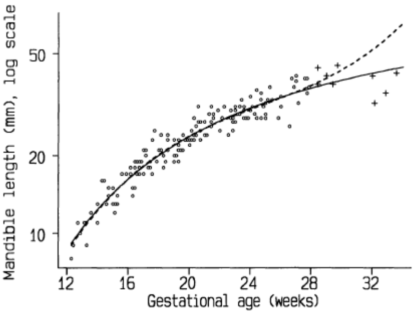

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- Question was how best predict the IgG levels for this age group.

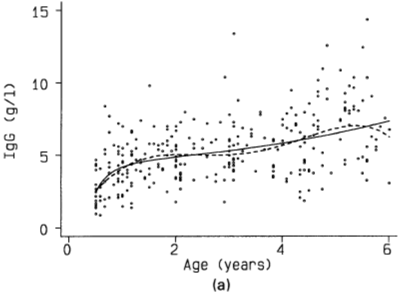
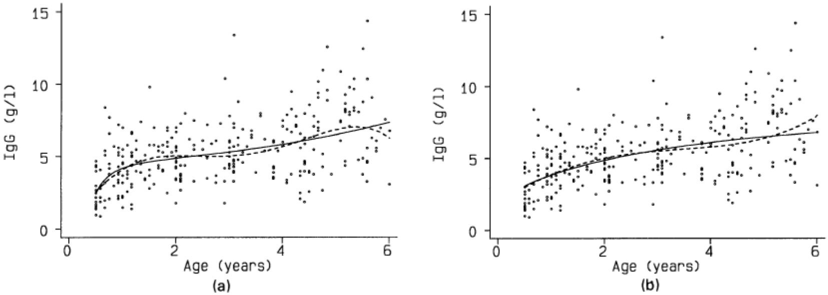


Fig. 5. Fits for IgG data: (a) $\phi_2(X;\ -2, 2)$ (———), quartic (-------); (b) $\phi_2(X;\ \frac{1}{2}, 1)$ (———), cubic (-------)

$$\xi_D^\star = \begin{Bmatrix} 0.5 & 1.7321 & 6 \\ 1/3 & 1/3 & 1/3 \end{Bmatrix}$$



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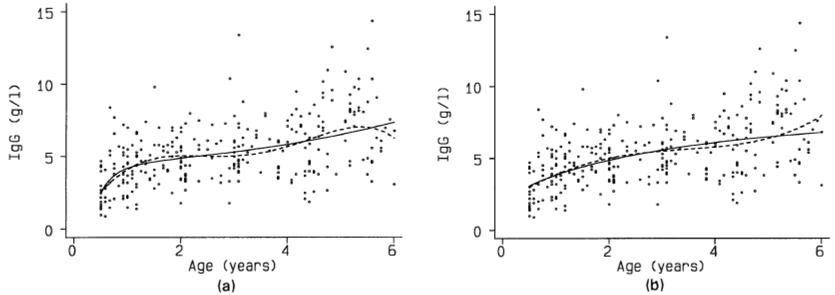

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$$\xi_D^\star = \begin{Bmatrix} 0.5 & 1.7321 & 6 \\ 1/3 & 1/3 & 1/3 \end{Bmatrix} \qquad \xi_I^\star = \begin{Bmatrix} 0.5 & 1.8491 & 6 \\ 0.1194 & 0.5511 & 0.3295 \end{Bmatrix},\ U[.5, 6]$$

$$\text{D–eff}(\xi_{implem.}) = 53.2\% \qquad \xi_I^\star = \begin{Bmatrix} 0.5 & 1.7391 & 6 \\ 0.0135 & 0.1881 & 0.7984 \end{Bmatrix},\ \underbrace{incr[6, 7]}_{\mu}$$

$$\ldots$$

Application 3: longitudinal studies (growth curve with FP)

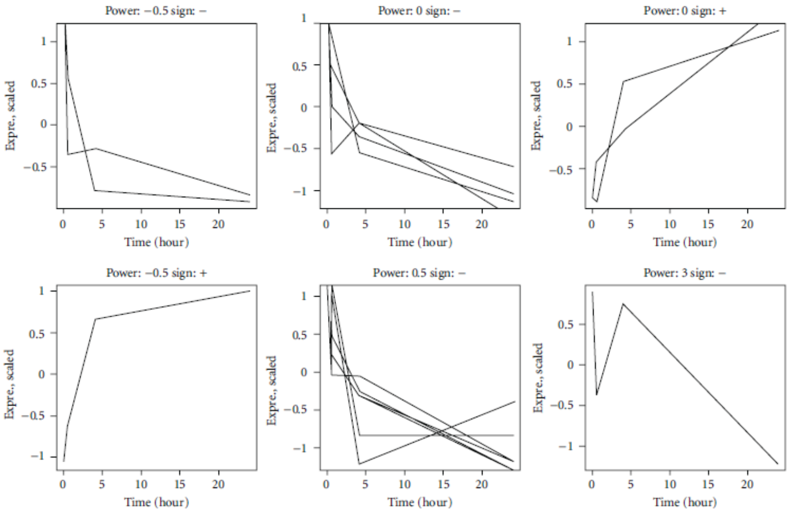

FIGURE 2: Time-course expression patterns for the 15 significant genes plotted according to the estimated power for transformation and sign of the regression coefficient.

- Longitudinal study (gene expression data).

... using appropriate OED theory

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...

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Obs: For $\xi_I^\star$:

$$\frac{1}{w} = 1 + \sqrt{\frac{(p+1)a^{2p+1} + a(2p+1)\left[(p+1)\epsilon^{2p} - 2(a\epsilon)^p\right] - 2p^2\epsilon^{2p+1}}{2p^2a^{2p+1} - (p+1)(2p+1)\epsilon a^{2p} + \epsilon\left[2(2p+1)(a\epsilon)^p - (p+1)\right.}}$$

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More covariates... Multi-factor FP models

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Computer Tools

- BiokmodWeb, applications to pharmacokinetic, internal dosimetry and nuclear medicine, by Dr. Guillermo Sánchez León. (web link)
- Computer tool based on webMathematica for Mathematics and Statistics, by Dr. Guillermo Sánchez León. (web link)
- Computer tool based on webMathematica for Optimal Desing, by Dr. Juan Manuel Rodríguez-Díaz. (web link)
- OEDforFPmodels: Interactive Applet (developed using Mathematica) to generate Optimal Experimental Design for Fractional Polynomial models up to degree 3, by Víctor Casero-Alonso, Jesús López-Fidalgo and Weng Kee Wong (with the help of Diego Urruchi).
  The free CDF Player from wolfram.com is needed (or a version 8 or higher of Mathematica software).
- MVbinary: Interactive Applet (developed using Mathematica) to generate Optimal Designs for the minimax criterion MV in binary response and heteroscedastic simple regression models, by Víctor Casero-Alonso, Jesús López-Fidalgo and Ben Torsney (with the help of Diego Urruchi).
  The free CDF Player from wolfram.com is needed (or a version 8 or higher of Mathematica software).
  Based on paper: *Casero-Alonso, López-Fidalgo and Torsney (2017)*
  In: *Computer Methods and Programs in Biomedicine*
  DOI: http://dx.doi.org/10.1016/j.cmpb.2016.10.009
- OED_Hormesis: Interactive web App (based on R-Shiny) to generate Optimal Experimental Design for detecting Hormesis by Víctor Casero-Alonso, Andrey Pepelyshev and Weng Kee Wong.

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