

Methods and software tools for design evaluation for population pharmacokinetics-pharmacodynamics studies.

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24 **Summary**

25 Population Pharmacokinetic (PK)-Pharmacodynamic (PD) (PKPD) models are increasingly used in drug
26 development and in academic research. Hence designing efficient studies is an important task.
27 Following the first theoretical work on optimal design for nonlinear mixed effect models, this
28 research theme has grown rapidly. There are now several different software tools that implement an
29 evaluation of the Fisher information matrix for population PKPD. We compared and evaluated five
30 software tools: PFIM, PkStaMP, PopDes, PopED, and POPT. The comparisons were performed using
31 two models: i) a simple one compartment warfarin PK model; ii) a more complex PKPD model for
32 Pegylated-interferon (peg-interferon) with both concentration and response of viral load of hepatitis
33 C virus (HCV) data. The results of the software were compared in terms of the standard error values
34 of the parameters (SE) predicted from the software and the empirical SE values obtained via
35 replicated clinical trial simulation and estimation. For the warfarin PK model and the peg-interferon
36 PKPD model all software gave similar results. Of interest it was seen, for all software, that the simpler
37 approximation to the Fisher information matrix, using the block diagonal matrix, provided predicted
38 SE values that were closer to the empirical SE values than when the more complicated approximation
39 was used (the full matrix). For most PKPD models, using any of the available software tools will
40 provide meaningful results, avoiding cumbersome simulation and allowing design optimisation.

41

42 Introduction

43 Estimation of pharmacokinetic (PK) parameters for an individual using nonlinear regression
44 techniques started in the 1960's, followed by estimation of dose-response and of pharmacodynamics
45 (PD) models. At around the same time mathematical approaches to defining the problem of optimal
46 design for parameter estimation in nonlinear regression was addressed (1-3). However this did not
47 reach the PK literature until some 20 years later (4). The problem was not only to draw inference
48 from data but also to define the best design(s) for estimation of parameters using maximum
49 likelihood or other estimation methods. For this purpose, the Fisher Information matrix (FIM) was
50 used to describe the informativeness of a design, i.e. how much information the design has in
51 relation to parameter estimation. Typically in PK the FIM is summarized by its determinant and
52 maximising the determinant, termed D-optimality, is equivalent to minimising the asymptotic
53 confidence region of the parameters, i.e. getting the most precise parameter estimates (5-9).
54 However, beyond theoretical developments, a limitation of individualised optimised designs of PKPD
55 studies is that those designs do not acknowledge population information and hence cannot have
56 fewer sampling times per individual than parameters to estimate. In addition, optimal designs with a
57 large number of observations per patient will have replicated optimal sampling times; which were
58 not favoured by pharmacologists interested in exploring complex PK models. Some later work also
59 explored Bayesian designs, where *a priori* distributions of the parameters were considered, and
60 individual parameters were estimated using maximum *a posteriori* probability (MAP). Optimal
61 designs for MAP estimation optimise individual designs given prior population information and are
62 suitable for e.g. therapeutic drug monitoring designs (10, 11). Since 1985, the software Adapt
63 (<https://bmsr.usc.edu/software/adapt/>) has included methods for optimal design in nonlinear
64 regression using several criteria for MAP estimation.

65 The population approach was introduced by Sheiner et al. (12) for PK analyses in the late 1970's and
66 since the 1980's there has been a large increase in the use of this approach as well as extensions to
67 PKPD. Estimation was mainly based on maximum likelihood using nonlinear mixed effects models
68 (NLMEM) thanks to the software NONMEM. To our knowledge the first article studying the impact of
69 a 'population design' on properties of estimates was performed in early 1990's by Al Banna et al. (13)
70 for a population PK and a population PKPD example. In this work the author used clinical trial
71 simulation (CTS) to explore possible designs. The authors studied the influence of the balance of
72 number of patients, number of sampling times and locations of the sampling times on the precision
73 of the parameter estimates. Several papers, all using CTS, were published (14-16) showing that some
74 designs could be rather poor, and that very sparse designs also performed poorly. The FDA's

75 Guidance for Industry Population Pharmacokinetics (17) from 1999 includes a specific section on
76 design, and suggests that simulation, based on preliminary information, should be performed to
77 “anticipate certain fatal study designs, and to recognize informative ones”.

78 Using CTS for design evaluation requires a large number of data sets to be simulated and then fitted
79 under each proposed design which is computationally expensive. However, since CTS is a user driven,
80 heuristic approach, then it can miss important regions of the design space because only a fixed
81 number of designs are investigated. Subsequently it was suggested to use the FIM in NLMEM to
82 predict asymptotic standard errors (SE) and define optimal designs without the need for intensive
83 simulations. Because the population likelihood has no closed-form expression the proposed
84 approach for defining the population FIM was to use a first-order linearisation of the model around
85 the random effects (which is the same as used for the first-order (FO) estimation methods). This
86 approximation results in a mixed effect model where the random effects enter the model linearly
87 (rather than nonlinearly) and hence has properties that are similar to linear mixed effects model. The
88 expression for the population FIM was first published in *Biometrika* in 1997 (18). In this work the FIM
89 was derived for a population PK example and an algorithm was proposed to optimise designs based
90 on the population FIM. This paper launched the new field of optimal design for nonlinear mixed
91 effects models. It has been quoted in the section ‘other influential papers of the 1990’s’ in a review
92 in *Biometrika* (19).

93 Since 1997 several methodological papers from various academic teams have published different
94 extensions, for instance robust designs, sampling windows, compound designs, multiple response
95 models, methods for discrete longitudinal data, and other approximations of the FIM, etc. Most
96 importantly, the derivation of the expression of the FIM was implemented in several software tools,
97 the first one PFIM (20) in 2001 appeared simultaneously in both R (<http://www.r-project.org/>) and
98 Matlab (<http://www.mathworks.fr/products/matlab/>). This was followed by POPT (21), and later to
99 incorporate an interface version WinPOPT, PopED (22), PopDes (23) and PkStaMp (24). There are
100 now five different software tools, all implementing the first-order approximation, with some tools
101 implementing one or several other approximations. These tools for designing population PKPD
102 studies are gaining popularity. In a recent study performed among European Federation of
103 Pharmaceutical Industries and Associations members’ (25), it was found that 9 out of 10
104 pharmaceutical companies are using one of these software tools for design evaluation or
105 optimisation, mainly in phases I and II.

106 The computation of the FIM is complex and depends on the numerical implementation. The purpose
107 of the present work was therefore to compare the results provided by those different software tools
108 in terms of FIM and predicted SE values. The same basic approximations were used in each software,
109 and the comparison was performed for two examples: (1) a simple PK example described by a one-
110 compartment model with first-order absorption and linear elimination and (2) a more complex PKPD
111 example where the PD component is defined by a system of nonlinear ordinary differential equations
112 (ODE). The objective was to explore the results from different software tools and to compare results
113 against those obtained using CTS. We wanted to show the user community that similar results would
114 be obtained with any software tool although programmed in different languages and by different
115 authors. This was also studied in the case of a multiple responses ODE model where the numerical
116 imbrication between ODE solver and numerical differentiation is complex. The results were provided
117 by the software developers, all authors of this article, who were given the equations of the models,
118 the values of the parameters and the designs to be evaluated. Results were compared to those
119 obtained by CTS.

120 The article is organized as follows: first the description of the population FIM for NLMEM, second a
121 description of the various software tools, and then an evaluation of the two examples. As no design
122 optimisation was performed in the present study, no optimisation characteristics or algorithms are
123 described.

124

125 **Statistical methods for design in NLMEM**

126 A design for a multi-response NLMEM is composed of N subjects each with an associated
127 elementary design ξ_i ($i = 1, \dots, N$). Hence a design for a population of N subjects can be described
128 as

$$129 \quad \Xi = (\xi_1, \dots, \xi_N) \quad (1)$$

130 Each elementary design ξ_i can be further divided into sub-designs

$$131 \quad \xi_i = (\xi_{i1}, \dots, \xi_{iK}) \quad (2)$$

132 with ξ_{ik} , $k = 1, \dots, K$ being the design associated with the k^{th} response. (e.g. drug concentration,
133 metabolite concentration, effect). It may thus be possible to have all responses measured at different
134 times, termed an unbalanced design.

135 A design for subject i at a response $k = 1, \dots, K$ often consists of several design variables which might
 136 be constant between observations, e.g. the drug dose, or vary between observations, e.g. the times
 137 at which the response variable is measured.

138 An elementary design ξ_l can be the same within a group l of N_l subjects ($l = 1, \dots, L$). Using a
 139 similar notation for the complete population design Ξ in a limited number of L groups of different
 140 elementary designs gives:

$$141 \quad \Xi = ([\xi_1, N_1], \dots, [\xi_L, N_L]) \quad (3)$$

142 where the total number of subjects in the design, N , is equal to the sum of the subjects in the L
 143 elementary designs. At the extreme, each subject may have a different design, $L = N$, or each subject
 144 may have the same design, $L = 1$.

145 In a NLMEM framework with multiple response, the vector of observations Y_i for the i^{th} subject is
 146 defined as the vector of K different responses:

$$147 \quad Y_i = [y_{i1}^T, y_{i1}^T, \dots, y_{iK}^T]^T \quad (4)$$

148 where y_{ik} , $k = 1, \dots, K$ is the vector of n_{ik} observations for subject i and response k modelled as

$$149 \quad y_{ik} = f_k(\theta_i, \xi_{ik}) + h_k(\theta_i, \xi_{ik}, \varepsilon_{ik}) \quad (5)$$

150 where $f_k(\cdot)$ is the structural model for the k^{th} response, θ_i is the i^{th} subject's parameter vector, $h_k(\cdot)$ is
 151 the residual error model for response k , often additive ($h = \varepsilon_{ik}$), proportional ($h = f_k(\cdot) \varepsilon_{ik}$) or a
 152 combination of both, ε_{ik} is the residual error vector for response k in subject i . In this paper additive
 153 (homoscedastic) or proportional (heteroscedastic) error models will be used in the examples so that
 154 only one residual variance parameter is defined for each response. To simplify notation we assume
 155 that ε_{ik} are normally distributed and independent between responses (which is not necessary, see
 156 e.g. (26, 27)) with mean zero and variance $\Sigma_k = \text{diag}(\sigma_k^2)$. The individual parameter vector θ_i , with
 157 parameter(s) that might be shared between responses, is described as

$$158 \quad \theta_i = g(\beta, b_i) \quad (6)$$

159 where β is the u -vector of fixed effects parameters, or typical subject parameter and b_i , the vector
 160 of the v random effects for the subject i defining the subject deviation from the typical value of the
 161 parameter. We assume that b_i is normally distributed with a mean of zero and a covariance matrix
 162 Ω of size $v \times v$. Again, to simplify notation we assume a diagonal (which is not necessary, see e.g.
 163 (18, 27-29)) interindividual covariance matrix (Ω) with diagonal elements ($\omega_1^2, \dots, \omega_v^2$). The vector of
 164 population parameters is thus defined as

$$165 \quad \psi = [\beta, \lambda] = [\beta, \omega_1^2, \dots, \omega_v^2, \sigma_1^2, \dots, \sigma_k^2] \quad (7)$$

166 where $\lambda = [\omega_1^2, \dots, \omega_v^2, \sigma_1^2, \dots, \sigma_k^2]$ is the vector of all variance components.

167 The population Fisher information matrix $FIM(\psi, \Xi)$ for multiple response models with the
 168 population design Ξ is given by:

$$169 \quad FIM(\psi, \Xi) = E \left(- \frac{\partial^2 L(\psi, Y)}{\partial \psi \partial \psi^T} \right) \quad (8)$$

170 where $L(\psi, Y)$ is the log-likelihood of all the observations Y given the population parameters ψ .

171 Assuming independence across subjects, the log-likelihood can be defined as the sum of the
 172 individual contribution to the log-likelihood: $L(\psi, Y) = \sum_{i=1}^N L(\psi, Y_i)$. Therefore, the population
 173 Fisher information matrix (calculated using the second derivative of the log-likelihood) for N subjects
 174 can also be defined as the sum of the N elementary information matrices $FIM(\psi, \xi_i)$ computed for
 175 each subject i :

$$176 \quad FIM(\psi, \Xi) = \sum_{i=1}^N FIM(\psi, \xi_i) \quad (9)$$

177 In the case of a limited number of L groups (where each individual in a group share the same design),
 178 as in Equation (3), the population FIM is expressed by:

$$179 \quad FIM(\psi, \Xi) = \sum_{i=1}^L N_i FIM(\psi, \xi_i) \quad (10)$$

180

181 For one subject, given the design variables ξ_i and the NLMEM model, the FIM is a block matrix
182 defined as:

$$183 \quad FIM(\psi, \xi_i) = \frac{1}{2} \begin{bmatrix} A & C \\ C & B \end{bmatrix} \quad (11)$$

184 where $FIM(\beta, \xi_i) = \frac{1}{2} A$ is the block of the Fisher matrix for the fixed effects β and

185 $FIM(\lambda, \xi_i) = \frac{1}{2} B$ is the block of the Fisher matrix for the variance components λ .

186 When a standard FO approximation of the model is performed (see appendix), then the distribution
187 of the observations in patient i with design ξ_i is approximated by $Y_i \sim N(E_i, V_i)$. Expressions for the
188 population mean E_i and population variance V_i are given in the appendix. Then the following
189 expression for blocks A , B and C are obtained (18, 30, 31), ignoring indices i for simplicity :

$$190 \quad A_{pq} \cong 2 \frac{\partial E^T}{\partial \beta_p} V^{-1} \frac{\partial E}{\partial \beta_q} + \text{tr} \left(\frac{\partial V}{\partial \beta_p} V^{-1} \frac{\partial V}{\partial \beta_q} V^{-1} \right) \text{ with } p, q = 1.. \dim(\beta)$$

$$191 \quad B_{pq} \cong \frac{\partial V}{\partial \lambda_p} V^{-1} \frac{\partial V}{\partial \lambda_q} V^{-1} \text{ with } p, q = 1.. \dim(\lambda) \quad (12)$$

$$192 \quad C_{pq} \cong \text{tr} \left(\frac{\partial V}{\partial \lambda_p} V^{-1} \frac{\partial V}{\partial \beta_q} V^{-1} \right) \text{ with } p = 1.. \dim(\lambda), q = 1.. \dim(\beta)$$

193

194 This expression of the FIM (eq. 12) will be referred to as the full FIM in this paper.

195 If the approximated variance V is assumed independent of the typical population parameters β , the
196 matrix C will be zero and the matrices A and B will instead be defined as:

$$197 \quad A_{pq} \cong 2 \frac{\partial E^T}{\partial \beta_p} V^{-1} \frac{\partial E}{\partial \beta_q} \text{ with } p, q = 1.. \dim(\beta) \quad (13)$$

198
$$B_{pq} \cong \frac{\partial V}{\partial \lambda_p} V^{-1} \frac{\partial V}{\partial \lambda_q} V^{-1} \quad \text{with } p, q = 1.. \dim(\lambda)$$

199

200 which will be termed the block diagonal FIM in the following. The explicit formula for $FIM(\beta, \xi_i)$
201 using the block diagonal form is given in the appendix. More information about the derivation of the
202 FIM or other approximations are reported in (27, 28, 30, 32-34).

203

204 **Software description**

205 There are presently five software tools that implement experimental design evaluation and
206 optimisation of the FIM for multiple response population models. The five software tools are (in
207 alphabetical order) : PFIM (35), PkStaMp (24), PopDes (23), PopED (27, 31) and POPT (21). Four of
208 them have been developed by academic teams.

209 PFIM (Population Fisher Information Matrix) is the only tool that is using the software R, the other
210 software packages have been developed under the numerical computing environment MATLAB. The
211 first version of PFIM appeared in 2001 and since this date several releases have been issued. It is
212 available at www.pfim.biostat.fr. A graphical user interface (GUI) package using the R software
213 (PFIM Interface) is also available but does not include recent methodological developments.
214 Pk StaMP (Pharmacokinetic Sampling Times Allocation – Matlab Platform) is a library compiled as a
215 single executable file which does not require a MATLAB license. The developers can share the stand-
216 alone version with anyone interested. PopDes (Population Design) has been developed at the
217 University of Manchester and this application software is available at www.capkr.man.ac.uk/home
218 since 2007. PopED (Population optimal Experimental Design), freely available at poped.sf.net,
219 consists of two parts, a script version, responsible for all optimal design calculations, and a GUI. The
220 script version can use either MATLAB or FreeMat (<http://www.freemat.sf.net>)(a free alternative to
221 MATLAB) as an underlying engine. Some advanced PopED features such as automatic and symbolic
222 differentiation, Laplace approximation of Bayesian criteria and mode base linearisation are not
223 available in FreeMat, however all features presented in Table 1 are available in PopED using either
224 FreeMat or Matlab. POPT (Population OPTimal design) was developed from PFIM (MATLAB) in 2001
225 and is constructed as a set of MATLAB scripts. POPT requires MATLAB and can run on FreeMat. This
226 tool can be downloaded on the website www.winpopt.com. All the software tools run on any
227 common operating system platform (e.g. Windows, Linux, Mac).

228

229 **Comparison of software for design evaluation**

230 As we focus on design evaluation and not design optimisation, we first compared the software tools
231 with respect to a) required programming language, b) availability, c) library of PK and PD models, and
232 ability to deal with: d) multiple response models, e) models defined by differential equations, e)
233 unbalanced multiple response designs, f) correlations between random effects and/or residuals, g)
234 models including inter-occasion variability, h) models including fixed effects for the influence of
235 discrete covariates on the parameters, i) computation of the predicted power. Table 1 is a summary
236 of the comparison of the software with respect to these different aspects. Globally, for all software
237 tools, the library of PK models includes one, two and three compartment models, with bolus,
238 infusion and first-order (e.g. oral) administration, after a single dose, multiple doses and at steady
239 state. PK models with first-order elimination and models Michaelis-Menten elimination are available.
240 Regarding PD models, immediate linear and Emax models and turnover response models are
241 available.

242 Over recent years, those tools have included various improvements in terms of model specification
243 and calculations of the FIM. For all of them, design evaluation can be performed for single or multiple
244 response models either using libraries of standard PK and PD models or using a user-defined model.
245 For the latter, regardless of the software used, the model can be written using an analytical form or
246 using a differential equation system. In the case of multiple response models, population designs can
247 be different across the responses for all the software. Regarding the calculations of the information
248 matrix, the majority of the software can handle either a block diagonal Fisher information matrix
249 (block FIM) or the full matrix (full FIM). Otherwise, only PopDes and PopED allow for calculations for
250 a model with both correlation between random effects (full covariance matrix Ω) and correlation
251 between residuals (full covariance matrix Σ), PKStamp allows full covariance matrix Ω . It is possible in
252 PFIM, PopDes and PopED to use models with inter-occasion variability (IOV) and models including
253 fixed effects for the influence of discrete covariates on the parameters. The computation of the
254 predicted power of the Wald test (30, 36) for a given distribution of a discrete covariate can be
255 evaluated in PFIM, PopDES and PopED frameworks.

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261 **Examples**

262 Two different examples were used to illustrate the performance of the five population design
263 software tools. Note that the examples evaluated the prediction for a given design, by evaluating the
264 FIM and the predicted asymptotic SEs, without design optimisation. This was done to evaluate the
265 core calculations of the FIM. The FIM is evaluated with the full and the block diagonal derivation (eq.
266 12, 13) with the different software tools.

267 In the first example a one compartment PK model (based on a warfarin PK model) with first-order
268 absorption was used (35). The design of that study consisted of 32 subjects with a single dose of 70
269 mg (a dose of 1mg/kg and a weight of 70 kg), and with 8 sampling times post-dose (in hours):

270
$$\Xi = ([\xi_1, N_1]) = (\xi_1, 32)$$

271
$$\xi_1 = (t_i) = (0.5, 1, 2, 6, 24, 36, 72, 120)$$

272 The residual error model was proportional ($h = f \cdot \varepsilon$) with a coefficient of variation of 10% (
273 $\sigma^2 = 0.01$) and exponential random effects were assumed for all parameters ($g = \beta e^{b_i}$). Table 2
274 reports the model parameters and their values. The dose and design are based on (34, 37).

275 For the second example a multiple response PKPD model with repeated dosing was selected with the
276 same design across responses (38). The model describes hepatitis C virus (HCV) kinetics, or more
277 specifically, the effect of peg-interferon dose of 180 $\mu\text{g}/\text{week}$ administered as a 24 hour infusion
278 once a week for 4 weeks. The same sequence of 12 sampling times for both PK and PD
279 measurements (in days, post-first-dose) was used for 30 subjects:

280
$$\Xi = ([\{\xi_{PK}, \xi_{PD}\}, N_{PKPD}]) = (\xi_{PK}, \xi_{PD}, 30)$$

281
$$\xi_{PK} = \xi_{PD} = (t_i) = (0, 0.25, 0.5, 1, 2, 3, 4, 7, 10, 14, 21, 28)$$

282 The HCV model is described by the following system of ODEs:

$$\begin{aligned}
\frac{dX}{dt} &= -k_a X(t) + r(t), & X(0) &= 0 \\
\frac{dA}{dt} &= k_a X(t) - k_e A(t), & A(0) &= 0 \\
\frac{dT}{dt} &= s - T(t)(eW(t) + d), & T(0) &= \frac{c\delta}{pe} \\
\frac{dI}{dt} &= eW(t)T(t) - \delta I(t), & I(0) &= \frac{sep - dc\delta}{p\delta e} \\
\frac{dW}{dt} &= p \left(1 - \frac{C(t)^n}{C(t)^n + EC_{50}^n} \right) I(t) - cW(t), & W(0) &= \frac{sep - dc\delta}{c\delta e}
\end{aligned}$$

284

285 where $C(t) = A(t)/V_d$ is the drug concentration at time t and $r(t)$ is the constant infusion rate. The
286 viral dynamics model considers target cells, T , productively infected cells, I and viral particles, W .
287 Target cells are produced at a rate s and die at a rate d . Cells become infected with de-novo infection
288 rate e . After infection, these cells are lost with rate δ . In the absence of treatment, virus is produced
289 by infected cells at a rate p and cleared at a rate c , for more details see (38, 39). The model for each
290 response in subject i is defined as

$$\begin{aligned}
y_{i,PK} &= C(t_i) + \varepsilon_{iPK} \\
\log_{10}(y_{i,PD}) &= \log_{10}(W(t_i)) + \varepsilon_{iPD}
\end{aligned}$$

292 An additive error model was assumed for both PK and PD (log viral load) compartments from which
293 observations were drawn with a standard deviation of 0.2. Some of the parameters in the model are
294 fixed (p, d, e, s). For the other seven parameters ($k_a, k_e, V_d, EC_{50}, n, \delta, c$), log transformation was
295 made with additive random effects on the log fixed effect with a variance ω^2 of 0.25. All parameters
296 and their values are listed in Table 3.

297

298 **Methods**

299

300 For each example using each software tool, we computed the FIM based on the FO linearisation,
301 given the parameters and the design. We used both the block-diagonal and the full FIM (not available
302 in POPT). From the FIM, we computed the predicted SE values for each parameter and the

303 information D-criterion which is defined as the determinant of the FIM to the power of one over the
304 number of parameters: $|\text{FIM}|^{1/\text{dim}(\psi)}$.

305 To investigate the FIM predictive performance, the empirical SE values were also estimated using
306 CTS. More precisely, for each example, multiple data sets were simulated and then fitted using the
307 Stochastic Approximation Expectation Maximisation (SAEM) algorithm in MONOLIX 2.4
308 (www.lixoft.eu) and, for the PK example also with the FOCEI algorithm in NONMEM 7
309 (<http://www.iconplc.com/technology/products/nonmem/>). Empirical standard errors were derived
310 from the estimated parameters. The empirical D-criterion was computed from the normalized
311 empirical variance-covariance matrix of all estimated parameters, $|\text{cov}(\psi)^{-1}|^{1/\text{dim}(\psi)}$. Because the
312 CTS was much more time consuming for the HCV PKPD model, we did not perform the estimation
313 with NONMEM and we did only 500 replicates, whereas we simulated 1000 replicates for the
314 warfarin PK model.

315 For the CTS, to compute the empirical covariance matrix, the full variance-covariance matrix of all the
316 estimated vectors was computed, not as two separate blocks for fixed effects and random
317 components.

318

319 **Results**

320

321 For the PK model, the results show no differences between the optimal design software tools when
322 evaluating the FIM using the block diagonal and full form. In the same way, all software reported the
323 same expected D-criterion (Figure 1), and the same expected relative standard errors (RSE) values
324 expressed in % (Table 4).

325 In this example, the block diagonal FIM calculations gave an expected D-criterion that was very
326 similar to the observed D-criterion based on the inverse of the empirical covariance matrix (Figure 1).
327 However, for all software, the block diagonal D-criterion is slightly smaller than the NONMEM FOCEI
328 based criterion. Note that the result from MONOLIX is lower than the expected D-criterions, in line
329 with theoretical expectations the Cramer-Rao inequality (FIM is an asymptotic upper bound on the
330 information). The full FIM predicts considerably more information compared to the simulations
331 (expected D-criterions are larger than the observed values), and predicts total information that is
332 farther from the empirical values than the block diagonal calculations. The same trends are evident
333 when looking at the RSE values, reported in Table 4. Good agreement between the CTS and the block

334 diagonal FIM was found, while the full FIM predicted considerably higher precision in β_{Ka} and $\beta_{CL/F}$

335 .

336 For the more complicated PKPD model, results are summarized In Figure 2 and Table 5 where RSE (%)
337 are reported. The D-criterion reveals negligible differences between any of the software (Figure 2)
338 and also almost no difference between predicted SE values (Table 5). In this example, as in the PK
339 example, using the block diagonal FIM gave D-criterion predicted values that were very similar to the
340 D-criterion based on the inverse of the empirical covariance matrix (Figure 2). The full FIM predicts
341 considerably more information compared to the simulations (expected D-criterions larger than the
342 observed values) and predicts total information (D-criterion) that is farther from the empirical values
343 than the block diagonal calculations. The same trends are evident when looking at SE values for each
344 parameter (Table 5). We found good agreement between CTS and the block diagonal FIM, while the
345 full FIM predicted higher precision in numerous parameters than observed.

346

347

348 **Discussion**

349 The first statistical developments for the evaluation of the FIM for NLMEM to compare and evaluate
350 population designs without simulation were performed in the late 90's. Since then, five different
351 software tools have been developed. We have compared these tools in terms of design evaluation.
352 Optimisation was not considered in the present work. It should be noted that most software are
353 under active development with regular addition of new features.

354 We compared the expression of the FIM computed by the five different optimal design software
355 packages for two examples. The first example was a simple PK model for which the algebraic
356 solution could be written analytically. When using the same approximation, all optimal design
357 software packages achieved the same D-efficiency criterion and predicted RSE values (%). The second
358 example was more complex, had two responses (both PK and PD measurements) and the model was
359 written as a series of five differential equations. For this example, the D-criterion and RSE
360 comparisons revealed negligible differences between software. The differences could potentially be
361 explained by the use of different differential equation solvers, methods of implementing multiple
362 response calculations, methods for computing numerical derivatives, tolerance levels for ODEs and
363 numerical implementations of e.g. matrix inverses and solving of linear systems, etc. These small
364 differences could be seen even across the MATLAB computations of the FIM. In this work we did not
365 impose the same implementation of the various steps across software, hence the importance of the
366 present comparison.

367

368 In both examples the expected SE values from the block diagonal FIM were close to the empirical SE
369 values obtained from CTS. The runtimes for all software tools were a few seconds compared to
370 minutes (warfarin example) or days (HCV example) for the CTS evaluation. Although computational
371 speed has increased dramatically since the 1990's, a significant speed advantage is seen with the
372 developed software tools even without considering design optimisation. For instance for the HCV
373 PKPD model the CTS took several days for one design, so that optimization of doses and sampling
374 times would be difficult.

375 In both examples investigated, the block diagonal FIM calculations give an expected D-criterion that
376 is very similar to the observed D-criterion based on the inverse of the empirical covariance matrix
377 and RSE(%) values for parameter match well. In contrast, the full FIM predicts more information
378 compared to the simulations (expected D-criterions larger than the observed values). More
379 discussion on the assumptions beyond the block or full matrix can be found in (33) together with

380 suggestions of other stochastic approaches. It seems that when using a FO approximation for
381 computation of the FIM, linearisation around some fixed values for the fixed effects which are then
382 no longer considered as estimable parameters and therefore corresponds to the block diagonal
383 matrix, provides the best approach. Also higher order approximations to the FIM are available that
384 may give better prediction of RSE(%) values (27).

385 Results using the simple FO approximation and the block diagonal FIM are very close to those
386 obtained by CTS using both FOCEI and SAEM estimation methods in the two examples. However,
387 since the expected FIM calculation is computing an asymptotically lower bound of the covariance of
388 the parameters, and the calculations are based on approximations, the authors suggest that a CTS
389 study of the proposed final design be performed in order to evaluate the likely performance of the
390 design in the setting in which it is proposed to be used. Since this would be a single CTS at a specified
391 design then this should not be computationally onerous compared to attempting to “optimise”
392 designs using CTS. In addition, using a CTS study of the final design makes it possible to assess the
393 bias which is not evaluated by the FIM.

394 In this first comparison between the software, we did only design evaluation for continuous data and
395 using the simpler FO approximation of the FIM. This first step was necessary before the next work
396 where we will compare results of design optimisation. Indeed now that we know that similar
397 criterion across software are obtained, we can compare the rather different optimisation algorithms
398 implemented. In principle any design variable that is present in the model can be optimised within an
399 optimal design framework. Examples of design variables that can be optimised are measurement
400 sampling times, doses, distribution of subjects between elementary designs, number of
401 measurement samples in an elementary design, etc. How this is done and which design variables can
402 be optimised varies between software, but the independent variable (e.g. measurement sampling
403 times) and the group assignment can be optimised in all software presented in this paper. Results will
404 depend on the assumptions about the model and the parameter values, so that sensitivity studies
405 should be performed to implement ‘robust’ designs, i.e. designs that are robust to the assumed *a*
406 *priori* values of the parameters. Approaches for design optimisation using a priori distribution of the
407 parameters were suggested and implemented for standard nonlinear regression and extended to
408 population approaches and should also be compared in further studies.

409 In conclusion, optimal design software tools allow for direct evaluation of population PKPD designs
410 and are now widely used in industry (25). Choice of software can depend on what platform the user
411 has available and what features they are looking since the FIM calculation in the different software

412 gives similar results. Population approaches are increasingly used and for more complex/
 413 physiological PD models. It is very difficult to guess, without using one of these tools, what are the
 414 good designs for those complex ODE models and whether the study will be reliable. We suggest that
 415 before performing any population PKPD study, the design should be evaluated with a good balance
 416 between the approach based on the Fisher Matrix (for optimising the design) and CTS (for evaluating
 417 the final design).

418

419 **Appendix : Development of the FIM in NLMEM for multiple responses using FO approximation**

420 For each subject i with design ξ_i , the elementary Fisher information matrix is defined as

$$421 \quad FIM(\psi, \xi_i) = E \left(- \frac{\partial^2 L_i(\psi; Y_i)}{\partial \psi \partial \psi^T} \right) \quad (14)$$

422 where $L_i(\psi; Y_i)$ is the log likelihood of the vector of observations Y_i given the population
 423 parameters ψ .

424 Let $F(\theta_i, \xi_i) = F(g(\beta, b_i), \xi_i)$, and $H(\theta_i, \xi_i, \varepsilon_i) = H(g(\beta, b_i), \xi_i, \varepsilon_i)$, be the vector composed
 425 of the K vectors of n_{ik} predicted responses $f_k(\theta_i, \xi_{ik})$, and error $h_k(\theta_i, \xi_{ik}, \varepsilon_{ik})$ respectively. Then
 426 equation (5) can be written

$$427 \quad Y_i = F(g(\beta, b_i), \xi_i) + H(g(\beta, b_i), \xi_i, \varepsilon_i). \quad (15)$$

428 As there is no analytical expression for the log-likelihood $L_i(\psi; Y_i)$ for nonlinear models, a first-order
 429 Taylor expansion around the expectation of b_i is used:

$$430 \quad F(g(\beta, b_i), \xi_i) \cong F(g(\beta, 0), \xi_i) + \left(\frac{\partial F(g(\beta, b_i), \xi_i)}{\partial b^T} \Big|_{b_i=0} \right) b. \quad (16)$$

431 Then equation (16) can be approximated as:

$$432 \quad Y_i \cong F(g(\beta, 0), \xi_i) + \left(\frac{\partial F(g(\beta, b_i), \xi_i)}{\partial b^T} \Big|_{b_i=0} \right) b + H(g(\beta, 0), \xi_i, \varepsilon_i), \quad (17)$$

433 Therefore, $Y_i \sim N(E_i, V_i)$ approximately, with marginal expectation E_i and variance V_i given by:

434 $E(Y_i) \cong E_i = F(g(\beta, 0), \xi_i)$ (18)

435 $Var(Y_i) \cong V_i = \left(\frac{\partial F(g(\beta, b_i), \xi_i)}{\partial b^T} \Big|_{b_i=0} \right) \Omega \left(\frac{\partial F(g(\beta, b_i), \xi_i)}{\partial b^T} \Big|_{b_i=0} \right)^T + \Sigma(\beta, \xi_i)$ (19)

436 where $\Sigma(\beta, \xi_i)$ is the variance of $H(g(\beta, 0), \xi_i, \varepsilon_i)$. $\Sigma(\beta, \xi_i)$ has a simple expression for usual
 437 error models where ε_i enters linearly, otherwise it can be computed using a first-order linearisation
 438 of H around the expectation of ε_i .

439 Then the elementary FIM for the fixed effects using the block diagonal form (equation 13), has the
 440 following expression:

441 $FIM(\beta, \xi_i) \cong J(\beta, \xi_i)^T V_i^{-1} J(\beta, \xi_i)$ (20)

442 where $J(\beta, \xi_i) = \frac{\partial F(g(\beta, 0), \xi_i)}{\partial \beta^T}$

443 Of note, when $\Omega = 0$, $FIM(\beta, \xi_i)$ reduces to the FIM for individual nonlinear regression with
 444 parameters β .

445

446

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541

542

Table 1. Available features in the software tools available for population design evaluation

	Software				
	PFIM	PkStaMp	PopDes	PopED	POPT
Language	R	Matlab	Matlab	Matlab FreeMat	Matlab FreeMat
Available on website	✓		✓	✓	✓
Library of PKPD models	✓	✓	✓	✓	✓
User defined models	✓	✓	✓	✓	✓
Multi-response models	✓	✓	✓	✓	✓
Designs differ across responses	✓	✓	✓	✓	✓
ODE models	✓	✓	✓	✓	✓
Full FIM	✓	✓	✓	✓	
Full covariance matrix for Ω		✓	✓	✓	
Full covariance matrix for Σ			✓	✓	
IOV	✓		✓	✓	
Discrete covariates/ power	✓/✓		✓/	✓/✓	✓/

FIM: Fisher Information matrix; GUI: Graphical User Interface; IOV: Inter-Occasion Variability; ODE: Ordinary Differential Equation; Ω : interindividual covariance matrix ; Σ : residual covariance matrix ;

Table 2 - Model parameters of warfarin PK model

Parameter	Value
$\beta_{CL/F}$ (L/h)	0.15
$\beta_{V/F}$ (L)	8.00
β_{ka} (1/h)	1.00
$\omega_{CL/F}^2$	0.07
$\omega_{V/F}^2$	0.02
ω_{ka}^2	0.60
σ^2	0.01

CL/F : apparent clearance of the warfarin; V/F : apparent volume of the warfarin; ka : constant of absorption of the warfarin;
 β : fixed effects ; ω^2 : interindividual variance; σ^2 : residual variance.

Table 3 - Model parameters for HCV PK/VK model

Parameter	Value
p (fixed) ¹	100
d (1/d) (fixed) ¹	0.001
e (mL/d) (fixed) ¹	1E-07
s (mL ⁻¹ /d) (fixed) ¹	20 000
β_{ka} (1/d)	0.80
β_{ke} (1/d)	0.15
β_{Vd} (mL)	100 000
$\beta_{EC_{50}}$ ($\mu\text{g/mL}$)	0.00012
β_n	2
β_δ (1/d)	0.20
β_c (1/d)	7
ω_{ka}^2	0.25
ω_{ke}^2	0.25
ω_{Vd}^2	0.25
$\omega_{EC_{50}}^2$	0.25
ω_n^2	0.25
ω_δ^2	0.25
ω_c^2	0.25
σ_{PK}^2	0.04
σ_{PD}^2	0.04

¹ Parameters defined in the section 3.

ka : rate constant of absorption; ke : rate constant of elimination; Vd : volume of distribution; EC_{50} : drug concentration in the blood at which the drug is 50% effective; n : Hill coefficient; δ : rate constant of elimination of infected cells; c : rate constant of elimination of viral particles; β : fixed effects; ω^2 : interindividual variance; σ_{PK}^2 : residual variance for the PK response; σ_{PD}^2 : residual variance for the PD response.

Table 4 - Fisher Information Matrix (FIM) predicted RSEs (%) for warfarin PK model with the various software tools compared to empirical RSEs (%)

Parameter	Block diagonal FIM	Full FIM	Simulations	
	PFIM/PkStaMp/PopDes/PopED/POPT	PFIM/PkStaMp/PopDes/PopED	NONMEM	MONOLIX
β_{ka}	13.9	4.8	13.6	13.8
$\beta_{CL/F}$	4.7	3.6	4.9	4.8
$\beta_{V/F}$	2.8	2.6	2.7	2.8
ω_{ka}^2	25.8	26.5	26.6	28.1
$\omega_{CL/F}^2$	25.6	26.3	26.1	26.6
$\omega_{V/F}^2$	30.3	30.9	32.4	30.8
σ^2	11.2	12.4	10.9	11.0

CL/F : apparent clearance of the warfarin; V/F : apparent volume of the warfarin; ka : constant of absorption of the warfarin; β : fixed effects; ω^2 : interindividual variance; σ^2 : residual variance.

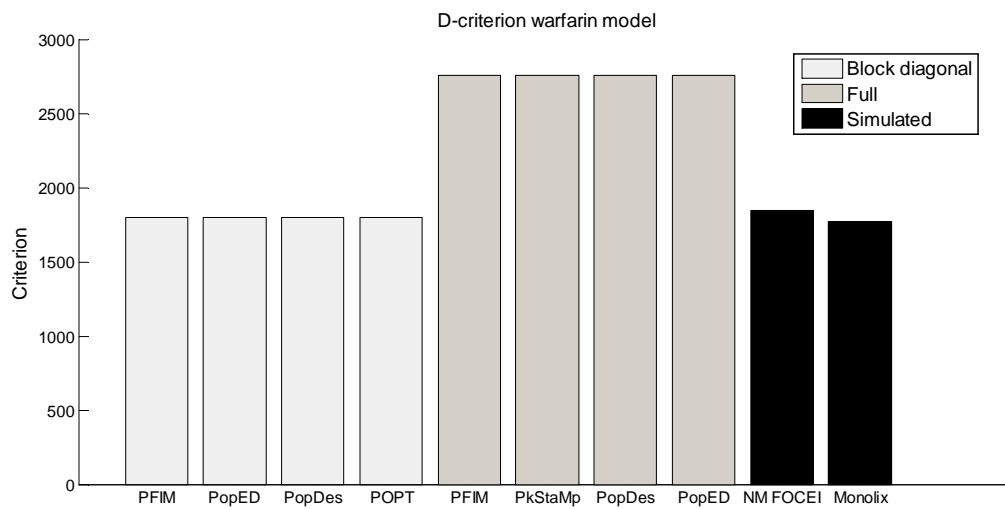
Table 5 – Fisher Information Matrix (FIM) predicted RSEs (%) for the HCV model parameters with the various software tools compared to empirical RSEs

Parameter	Block diagonal FIM			Full FIM		Simulations
	PFIM	PkStaMp/PopDes/PopED	POPT	PFIM	PkStaMp/PopDes/PopED	MONOLIX
β_{ka}	12.0	12.1	13.2	8.6	8.6	12.2
β_{ke}	10.4	10.5	11.1	6.8	6.9	10.4
β_{Vd}	9.9	10.0	11.2	8.3	8.4	9.9
$\beta_{EC_{50}}$	15.8	15.8	15.7	13.6	13.5	14.5
β_n	10.5	10.4	10.4	7.4	7.5	10.6
β_δ	9.5	9.4	9.4	8.7	8.5	10.1
β_c	11.1	11.0	11.0	8.8	8.7	10.3
ω_{ka}^2	39.6	40.0	42.0	42.8	43.2	41.6
ω_{ke}^2	30.4	30.8	31.6	36.4	37.2	34.4
ω_{Vd}^2	28.4	28.8	31.6	32.8	33.2	30.4
$\omega_{EC_{50}}^2$	60.8	60.4	60.0	66.4	66.4	53.2
ω_n^2	28.8	28.8	28.8	32.8	32.8	31.6
ω_δ^2	27.2	27.2	27.2	32.4	31.6	31.6
ω_c^2	32.8	32.8	32.4	34.0	33.6	30.0
σ_{PK}^2	9.0	8.5	8.3	9.3	8.5	10.0
σ_{PD}^2	8.0	9.0	9.0	8.5	9.3	9.0

ka : rate constant of absorption; ke : rate constant of elimination; Vd : volume of distribution; EC_{50} : drug concentration in the blood at which the drug is 50% effective; n : Hill coefficient; δ : rate constant of elimination of infected cells; c : rate constant of elimination of viral particles; β : fixed effects; ω^2 : interindividual variance; σ_{PK}^2 : residual variance for the PK response; σ_{PD}^2 : residual variance for the PD response.

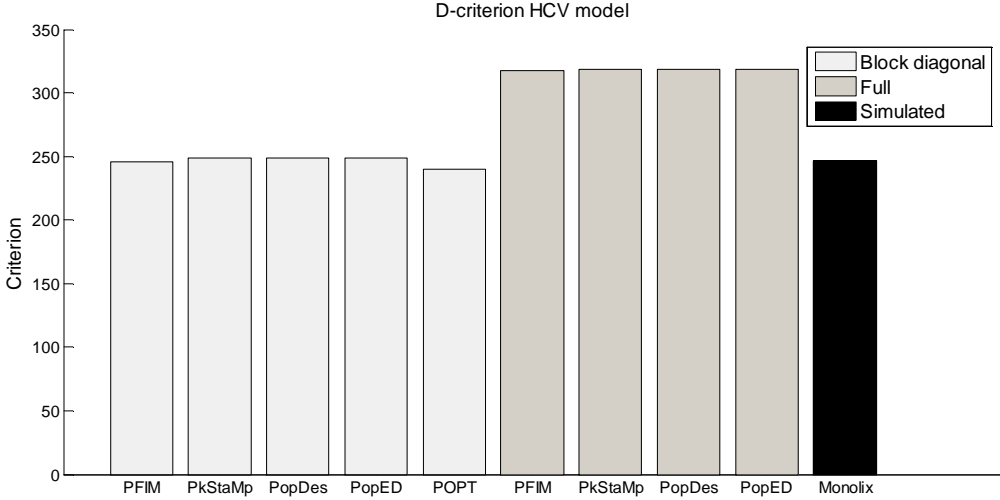
Figures

Figure 1. D-criterion predicted by the different software tools for the warfarin PK model compared to simulated D-criterion calculated from the inverse of the empirical covariance matrix.



NM FOCEI is calculated from the estimates using the first-order conditional estimation method with interaction in NONMEM. The Monolix criterion is calculated from the estimates using the SAEM algorithm in Monolix.

Figure 2. D-criterion predicted by the different software tools for the HCV model. Simulated D-criterion calculated from the inverse of the empirical covariance matrix.



The Monolix criterion is calculated from the estimates using the SAEM algorithm in Monolix.