Design evaluation and optimization for models of hepatitis C viral dynamics

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Context

- **Chronic hepatitis C virus (HCV) infection**
  - one of the most common causes of chronic liver disease
  - standard of care : weekly injections of pegylated interferon (PEG-IFN)+ daily oral ribavirin
- **Mathematical modeling of HCV RNA (viral load) decay after treatment initiation**
  - complex system of non-linear Ordinary Differential Equations (ODE)
  - critical insights for the understanding of the virus pathogenesis
  - parameters crucial for early predicting treatment outcome
- **Population designs evaluation and optimization for multiple response models**
  - methodology based on the Fisher Information matrix (M_F) [1]
  - implementation in PFIM 3.0 [2, 3]
- **Optimization with PFIM 3.0**
  - D-optimality criterion (det(M_F))
  - Federov-Wynn algorithm (statistical design optimization)
    - optimization of the sampling times in a given set specified by users

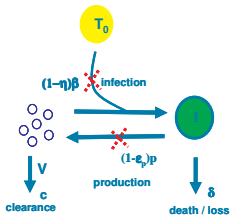
Objectives

- **To show the relevance of PFIM with model described by ODE system**
- **To evaluate and optimize designs for the estimation of viral parameters**

Viral dynamics modeling

- **Viral dynamics model with the drug effectiveness under PEG-IFN**
  - Neumann et al. viral dynamics model [4]
    - target cells (T), infected cells (I) and free virus (V)

Figure 1. HCV cells infection dynamics with the ODE system



$$\begin{cases} \frac{dX}{dt} = D - k_a X \\ \frac{dA}{dt} = k_a X - k_a A \\ C(t) = \frac{A(t)}{V_d} \\ \frac{dT}{dt} = s - \beta(1-\eta)VT - dT \\ \frac{dI}{dt} = \beta(1-\eta)VT - \delta I \\ \frac{dV}{dt} = p\left(1 - \frac{C(t)^{\alpha}}{C(t)^{\alpha} + EC_{50}^{\alpha}}\right)I - cV \end{cases}$$

  - pharmacokinetic model of concentrations of PEG-IFN [5]
    - first order absorption and elimination
    - D : dose of 180 µg of PEG-IFN by injection (weekly basis)
  - no closed-form solution to this system
  - as only concentrations of PEG-IFN and viral load are measured
    - some parameters are fixed [6] : p=10, s=20000 $mL^{-1}.d^{-1}$, d=0.001 d^{-1}, b=10^{-7} $mL.d^{-1}$, F=1, η= 0
- **Population model**
  - Population parameters
    - values of fixed effects
    - exponential model for random effects (CV =50%)
    - additive error model for concentrations and $\log_{10}$ (viral load)

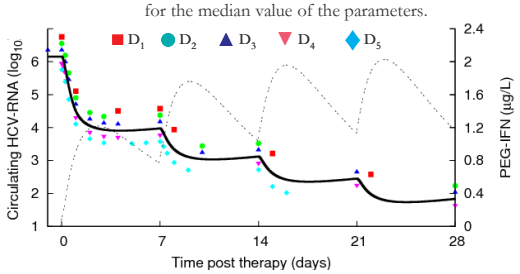
EC_{50}(µg. L^{-1})	n	δ (d^{-1})	C (d^{-1})	k_a (d^{-1})	k_c (d^{-1})	V_d (L)
0.20	0.12	0.10	0.13	0.12	0.10	0.10

- **Population designs**
  - five popular designs of the literature [7, 8, 9, 10, 5]

Table 1. Design used in the five studies of viral dynamics.

Design	Reference	Measurement times (in days after first injection)	Number of samples
D_1	Zeuzem (2005)	{0, 1, 4, 7, 8, 15, 22, 29}	8
D_2	Sherman (2005)	{0, 0.25, 0.5, 1, 2, 3, 7, 10, 14, 28}	10
D_3	Herrmann (2003)	{0, 0.25, 0.5, 1, 2, 3, 4, 7, 10, 14, 21, 28}	12
D_4	Zeuzem (2001)	{0, 0.040, 0.080, 0.12, 0.20, 0.33, 1, 2, 3, 4, 7, 14, 21, 28}	14
D_5	Talal (2006)	{0, 0.25, 0.5, 1, 2, 3, 5, 6, 7, 7.25, 7.5, 8, 9, 14, 15, 16}	16

Figure 2. Simulation of the viral dynamics (black) and PK profile (dashed) for the median value of the parameters.



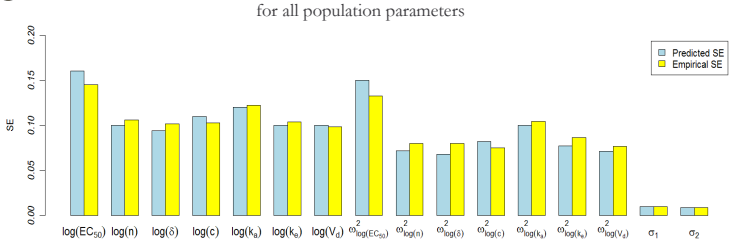
Methods

1. **Comparison between the standard error (SE) given by PFIM and the empirical SE**
   - simulation of 500 data sets (R software) using D3 design
   - estimation of the population parameters with MONOLIX (SAEM)
   - computation of the empirical SE defined as the standard deviation on the 1000 estimates of each parameter
2. **Evaluation of five designs [Table 1]**
   - 30 subjects
3. **Design optimisation using PFIM 3.0**
   - total number of samples : 240
   - potential sampling times are {D1-D5}
   - different number of sampling times per subject: 3, 4, 5 , 6, 7

Results

1

Figure 3. Barplot of the SE computed by PFIM and the empirical SE for all population parameters



→ **SE predicted by PFIM close to the empirical one**
→ **Relevance of PFIM for models described by ODE system**

2 Table 2. SE obtained for the fixed effects with the five designs included 30 patients

Design	Number of sampling times per patient	$log(EC_{50})$	log(n)	log(δ)	log(c)	$log(k_a)$	$log(k_c)$	$log(V_d)$
D_1	8	0.20	0.12	0.10	0.13	0.12	0.10	0.10
D_2	10	0.16	0.10	0.095	0.11	0.13	0.11	0.10
D_3	12	0.16	0.10	0.094	0.11	0.12	0.10	0.10
D_4	14	0.16	0.11	0.094	0.10	0.12	0.10	0.10
D_5	16	0.14	0.10	0.10	0.11	0.11	0.10	0.10

→ **Similar SE for all pharmacokinetic (PK) parameters**
→ **D_5 can precisely estimate IFN effectiveness (EC_{50} & n)**

3 Table 3. Optimal designs for N = 240 sampling times per response according to the number of samples per patient

Number of samples	N	Optimal Design {(sampling times), n}	$log(EC_{50})$	log(n)	log(δ)	log(c)	$log(k_a)$	$log(k_c)$	$log(V_d)$	Information criterion
3	80	{(0.7,9.), 3} {(0.10,.28.), 11} {(0.1,28.), 16} {(0.4,29.), 19} {(0.1,4.), 31}	0.21	0.12	0.081	0.096	0.14	0.11	0.084	193.2
4	60	{(0.1,4.28.), 38} {(0.1,10.,28.), 22}	0.17	0.090	0.070	0.090	0.12	0.083	0.08	230.2
5	48	{(0.1,4,16.,28.), 14} {(0.1,7,10.,29.), 34}	0.14	0.061	0.057	0.075	0.087	0.068	0.061	224.0
6	40	{(0.1,4,7,16.,28.), 40}	0.15	0.095	0.084	0.10	0.11	0.095	0.090	208.3
7	34	{(0.0.040.,1,4,7,9,29.), 4} {(0.1,4,7,9,28.,29.), 10} {(0.0.040.,1,4,7,16.,28.), 20}	0.15	0.070	0.065	0.081	0.094	0.075	0.070	193.0

→ **Best design with a number of samples per patient of four**
→ **Close SE as D_5 with a reduction by two of the number of samples**
→ **Importance of sampling times at four weeks**

Conclusion

- **Good approximation of M_F in PFIM for ODE systems**
  - negligible computation burden to evaluate / optimise designs
- **Total number of sampling measurements reduced by half with an appropriate design**
- **Design should not neglect long-term kinetics**

References

[1] Bazzoli et al. *Statistics in Medicine.* 2009, [2] Bazzoli et al. *Computer Methods and Program in Biomedicine.* 2009, [3] www.pfim.biostat.fr, [4] Neuman et al. *Science.* 1998, [5] Talal et al. *Hepatology.* 2006, [6] Gueidj et al. *Bulletin of Mathematical Biology. 2007,* [7] Zeuzem et al. *Journal of Hepatology.* 2005, [8] Sherman et al. *Gastroenterology.* 2005, [9] Herrmann et al. *Hepatology.* 2003, [10] Zeuzem et al. *Gastroenterology.* 2001.