

CONTEXT

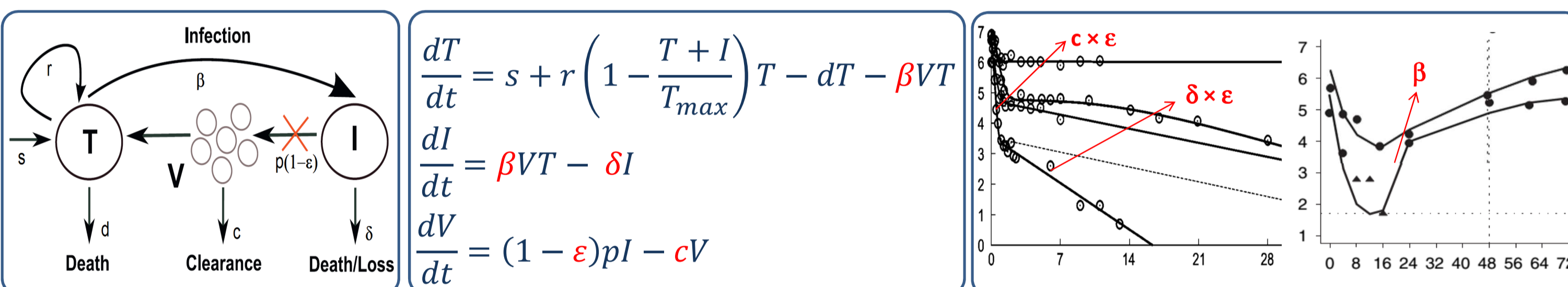
- Hepatitis C Virus (HCV):
 - infects 150 million people worldwide and causes 350000 deaths each year [1]
 - Peg-IFN + ribavirin is likely to remain the backbone treatment of HCV Genotype (GT)-2/3 [2]
 - Treatment individualization is recommended to reduce costs and adverse effects
- Parameters of viral kinetic models have a high predictive ability for treatment outcome [3]
- Bayesian estimation of individual parameters:
 - combines *a priori* information contained in population model and individual observations
 - can be used to predict treatment outcome and to individualize treatment
- Quality of parameter estimation and prediction depends on viral load sampling designs [4]
- Data below the detection limit (BDL):
 - Common issue in analyzing HCV viral load data
 - Methods for treating BDL data: omit, impute at an arbitrary value or taking into account in the likelihood function (LBA) [5-6]
 - LBA allow less biased population parameter estimates but how they impact individual parameter estimation was not studied [5-6]

OBJECTIVES

- Evaluate by simulation the influence on individual parameter estimation and treatment response prediction in the context of HCV-GT2/3 therapy of:
 - a priori* population model
 - viral load sampling designs
 - methods for handling BDL data

METHODS

VIRAL KINETIC MODEL [7-8]



STATISTICAL MODEL

$$y_{ij} = f(t_{ij}, \theta_i) \times \exp(\varepsilon_{ij})$$

f : nonlinear viral kinetic model identical for all individuals,

θ_i : individual parameters vector

- Log-distribution for β, δ, c (q^{th} parameter): $\theta_{iq} = \mu_q \exp(\eta_{iq})$

- Logit-distribution for $\varepsilon_i = \frac{\mu_\varepsilon}{\mu_\varepsilon + (1 - \mu_\varepsilon) \exp(-\eta_{i\varepsilon})}$

ε_{ij} : residual error supposed to follow normal distribution $N(0, \sigma^2)$

BAYESIAN INDIVIDUAL PARAMETER ESTIMATION

- Let $\Psi = \{\mu, \Omega, \sigma\}$ be the known population parameters vector and let $p(\eta_i | y_i, \Psi)$ be the conditional distribution of η_i . The MAP estimate of η_i is given by

$$\hat{\eta}_i = \operatorname{argmax}_{\eta_i} \left(\frac{p(y_i | \eta_i, \Psi) \times p(\eta_i | \Psi)}{p(y_i)} \right)$$

- As μ is known, once $\hat{\eta}_i$ is estimated, $\hat{\theta}_i$ can be easily calculated
- In presence of data below limit of detection (LOD), the distribution $p(y_i | \eta_i, \Psi)$ is calculated by:

$$p(y_i | \eta_i, \Psi) = \prod_{y_{ij} > LOD} \frac{1}{y_{ij}} \phi(\log(y_{ij}), \log(f(\eta_i, t_{ij})), \sigma^2) \mathbf{1}_{y_{ij} > LOD} \times \prod \Phi(\log(LOD), \log(f(\eta_i, t_{ij})), \sigma^2) \mathbf{1}_{y_{ij} \leq LOD}$$

$\phi(x, m, v)$: pdf of normal distribution with mean m , variance v , evaluated at x

$\Phi(x, m, v)$: cdf of normal distribution with mean m , variance v , evaluated at x

SIMULATION STUDY

Data simulation

- Four nested designs were considered (Table 1)
- Simulate $N = 1000$ vectors of η_i using values of M_{true} model (Table 2)
- Calculate θ_i and predict viral loads for 1000 patients
- Select viral loads at the sampling times of the design of interest to obtain other datasets
- Assume: sustained virological response (SVR) is attained if infected cell number $< 1/15L$ [3]
- $LOD = 45$ IU/mL. Viral loads below LOD or after SVR is attained are consider BDL.

Table 2: Parameter values of the different viral kinetic models ($M_{true}, M_{\delta\varepsilon}, M_{\beta}$)

	Unit	M_{true}	$M_{\delta\varepsilon}$	M_{β}
s	cells/mL/day	60000	60000	60000
d	1/day	0.001	0.001	0.001
δ	1/day	0.32	0.14	0.32
c	1/day	9	9	9
β	virions/day	50	50	50
p	mL/virions/day	10^{-7}	10^{-7}	10^{-6}
ε		0.996	0.900	0.996
r	1/day	0.006	0.006	0.006
T_{max}	cells/mL	1.3×10^7	1.3×10^7	1.3×10^7
ω_b		0.5	0.5	0.5
ω_c		0.5	0.5	0.5
ω_β		0.5	0.5	0.5
ω_ε		2.5	2.5	2.5
σ		0.461	0.461	0.461

Table 1: Sampling timepoints for four studied designs

	D0	D1	D4	W1	W2	W4	W6	W8	W12	W16	W20	W24
D24w	x	x	x	x	x	x	x	x	x	x	x	x
D4w	x	x	x	x	x	x						
D4w_sparse	x			x	x	x						
D4w_challenge	x					x						

Individual parameter estimation

- Fix Ψ at *a priori* values corresponding to true (M_{true}) and false models ($M_{\delta\varepsilon}, M_{\beta}$) (Table 2) to perform MAP
- BDL data are omitted (OMIT) or taken into account by LBA
- Evaluation criteria: mean relative error (MRE), relative RMSE and Shrinkage

Prediction of treatment outcome

- Simulate the individual predicted infected profile using estimated individual parameters
- If predicted infected cells < 1 cell/15L, predicted response is SVR
- Compare with the simulated response to calculate Misclassification rate (sum of False Positive and False Negative rates)

RESULTS

DESCRIPTION OF SIMULATED DATA

- SVR rate: 78.4%, consistent with the rate of 80% reported in the literature for HCV GT-2/3 [9]
- % rebounders (HCV RNA declines $> 1 \log_{10}$ then rebounds under treatment): 11.7%
- % BDL data: 57.4, 27.8, 37.7 and 38.5% in designs $D_{24w}, D_{4w}, D_{4w_sparse}, D_{4w_challenge}$ respectively

INDIVIDUAL PARAMETER ESTIMATION

MRE, RMSE and Shrinkage of the four parameters in 6 selected scenario	Model Design Method	MRE (%)				RRMSE (%)				Shrinkage (%)			
		β	δ	c	$\log_{10}(1-\varepsilon)$	β	δ	c	$\log_{10}(1-\varepsilon)$	β	δ	c	ε
$M_{true}-D_{24w}-LBA$		12.1	4.9	-3.5	3.9	55.2	26.0	27.9	46.4	89.8	22.1	27.5	7.8
$M_{true}-D_{4w}-LBA$		12.4	5.3	-3.6	4.3	57.6	27.9	28.0	41.2	95.1	26.0	29.1	8.9
$M_{true}-D_{4w_sparse}-LBA$		12.2	5.8	6.0	3.9	57.5	36.7	45.4	47.2	96.3	45.8	55.6	26.5
$M_{\delta\varepsilon}-D_{4w_sparse}-LBA$		11.4	-14.3	27.6	12.2	56.7	32.1	63.0	55.9	97.6	46.1	54.8	21.9
$M_{\delta\varepsilon}-D_{4w_sparse}-OMIT$		11.9	-24.6	35.3	-2.2	57.3	38.1	70.2	64.8	97.8	56.9	53.5	22.1
$M_{\beta}-D_{4w_sparse}-LBA$		1013.6	95.9	27.6	103.8	1156.0	116.3	63.1	229.6	97.6	46.1	54.8	21.9

- β , a rebound-related parameter, is poorly estimated in all scenario
- Data within the 1st week allow good estimation of δ, c, ε
- Using $M_{\delta\varepsilon}$: underestimated δ & overestimated c with increasing MRE & RRMSE
- Using M_{β} : highly estimation errors for all parameters
- Methods for handling BDL data: not much impact on individual parameter estimation if true *a priori* information is used (results not shown, see [10])

PREDICTION OF TREATMENT OUTCOME

- True *a priori* information allows good prediction, regardless of designs, methods for handling BDL data
- False *a priori* information about δ and ε still gives good prediction if BDL data are correctly handled as they are estimable
- False *a priori* information about β results in high prediction errors
- Modeling approach allows better results than basing on empirical rules used in clinics (rapid virologic response) (results not shown, see [10])

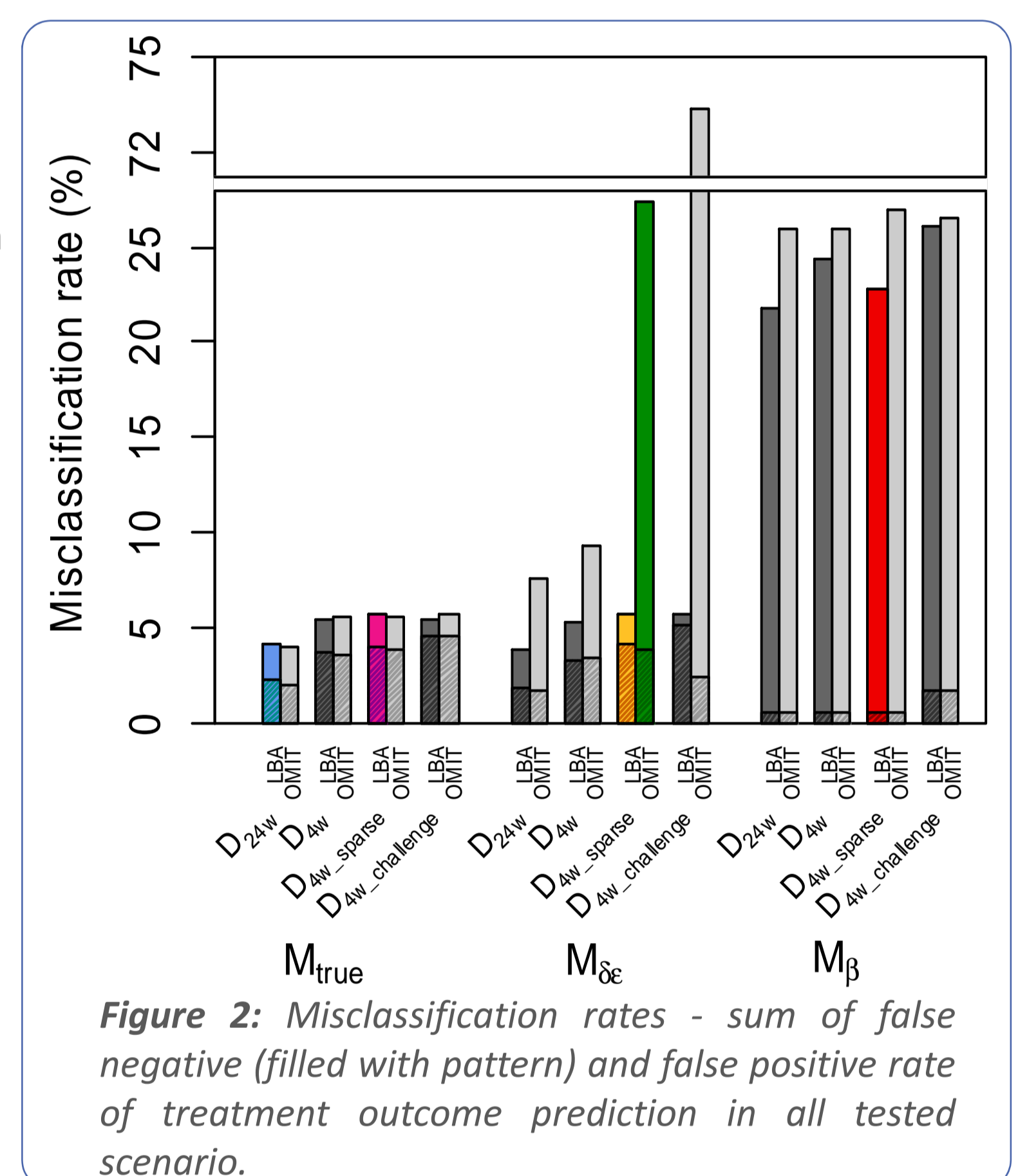


Figure 2: Misclassification rates - sum of false negative (filled with pattern) and false positive rate of treatment outcome prediction in all tested scenario.

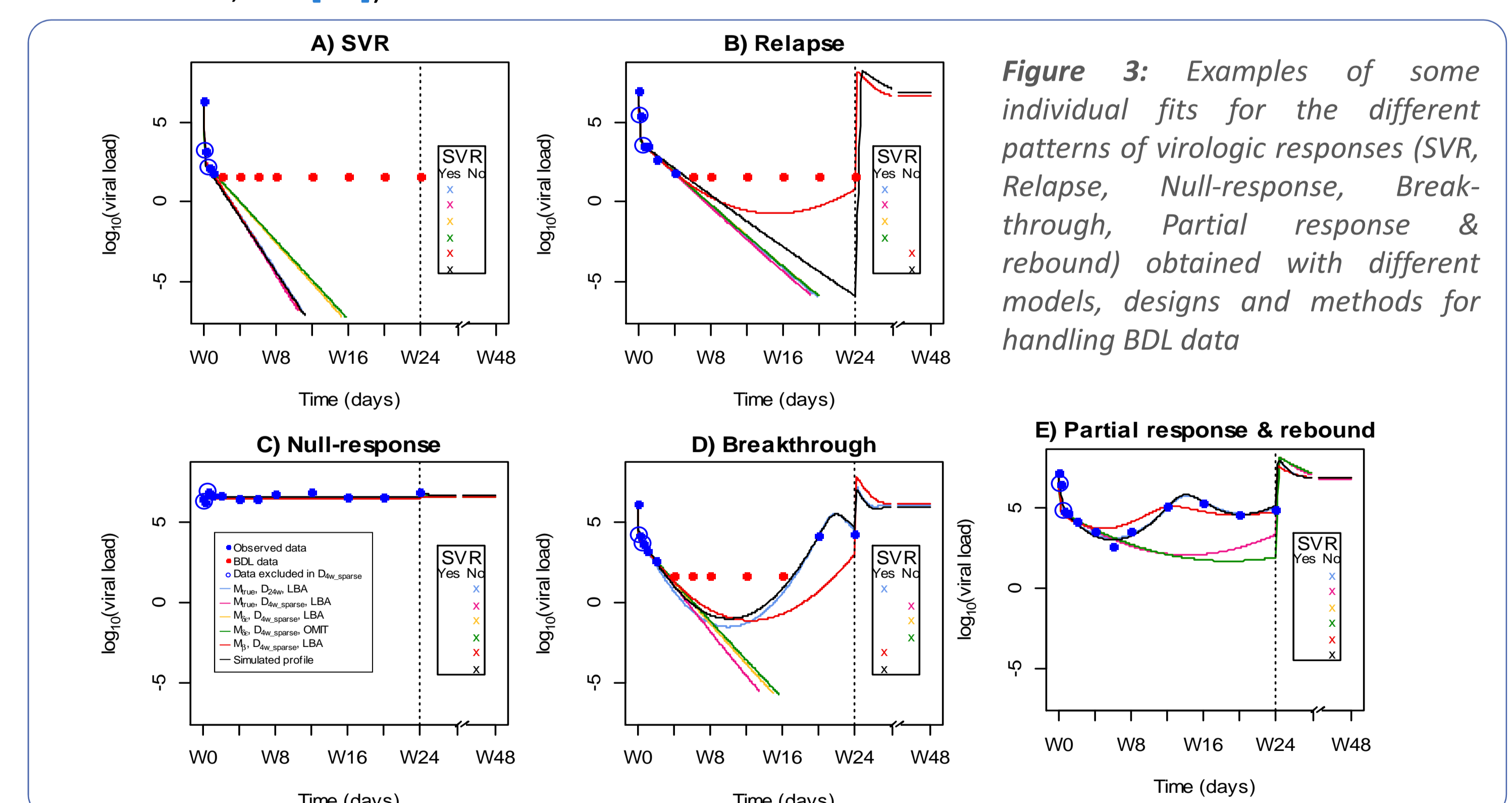


Figure 3: Examples of some individual fits for the different patterns of virologic responses (SVR, Relapse, Null-response, Breakthrough, Partial response & rebound) obtained with different models, designs and methods for handling BDL data

CONCLUSIONS

- Using correct *a priori* information, good individual parameter estimation and treatment outcome prediction are obtained with only six viral load measurements in four weeks after treatment initiation
- The results remained satisfactory if wrong *a priori* values on identifiable parameters were used unless BDL data were omitted
- Bayesian individual estimation could provide rapid and reliable treatment outcome prediction to guide future therapy
- This approach needs *a priori* population model, which is not always available and not valid for other populations

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