Handling data below the quantification limit in viral kinetic modelling for model evaluation and prediction of treatment outcome

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Outline

- Context
- Objectives
- 3 projects
  - Methods
  - Results
- Conclusions & Perspectives

Context: Viral kinetic (VK) models

- VK models
  - Better understanding of viral lifecycle (HCV, HIV) and mechanism of action of antiviral agents[1,2]
  - Improvement of the understanding of viral kinetics by including pharmacokinetic (PK) information [3,4]
- New effective anti-HCV treatments
  - Direct acting antivirals: telaprevir, boceprevir, sofosbuvir, daclatasvir,…
  - Host-targeting antivirals: alisporivir (Novartis)
  - Viral loads below the quantification limit (BQL) are indicators of treatment effectiveness

$\Rightarrow$ BQL data very frequent with new effective treatments

[1] Neumann et al, Science (1998)
[2] Guedj et al, PNAS (2013)
[3] Shudo et al, J Viral Hepat (2010)
[4] Talal et al, Hepatol (2006)

Context: Handling of BQL data

- Estimation of population parameters
  - Omitting BQL data often result in biased estimates[1-3]
  - Likelihood-based approaches (SAEM, M3 method in NONMEM, etc.) provide better parameter estimates [1-3]
- Model evaluation
  - Most evaluation methods omit or impute BQL data at the limit of quantification (LOQ) even though they were handled in estimation step

  ⇒ Trends in diagnostic graphs

  ⇒ Confuse model evaluation/selection
- Individual parameter estimation
  - Impact of handling BQL data is not yet studied

[1] Samson et al, Comput Stat Data An (2006)
[2] Bergstrand et al, AAPS J (2009)
[3] Yang et al, Pharm Stat (2010)

Objectives

- Extend prediction discrepancies (pd) and normalized prediction distribution errors (npde), to handle BQL data
- Build a PK-VK model for virologic response to alisporivir (ALV) and pegylated interferon (peg-IFN). Evaluate this PK-VK model with these metrics
- Evaluate the impact of BQL data, design and *a priori* information on individual parameter estimates and prediction of treatment outcome

Project 1

Extend prediction discrepancies (pd) and normalized prediction distribution errors (npde) to take into account BQL data

J Pharmacokinet Pharmacodyn (2012) 39:499–518
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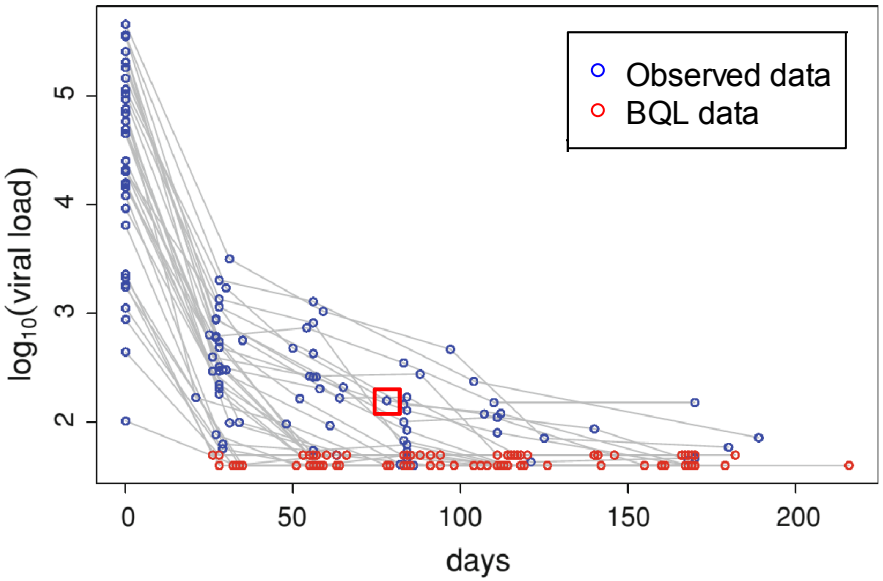
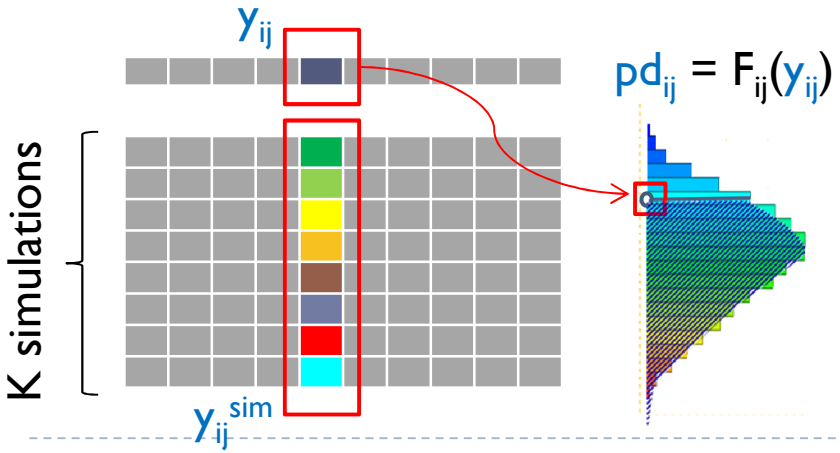
ORIGINAL PAPER

Extension of NPDE for evaluation of nonlinear mixed effect models in presence of data below the quantification limit with applications to HIV dynamic model

Thi Huyen Tram Nguyen · Emmanuelle Comets · France Mentré

Methods: pd and npde for observed data





- F_{ij}
  - Cumulative distribution function predicted by the model
  - Obtained by K Monte Carlo simulation
- $pd_{ij} = F_{ij}(y_{ij})$ [1]
- npde: normalized decorrelated pd [2]
- If the model is true (hypothesis H_0):

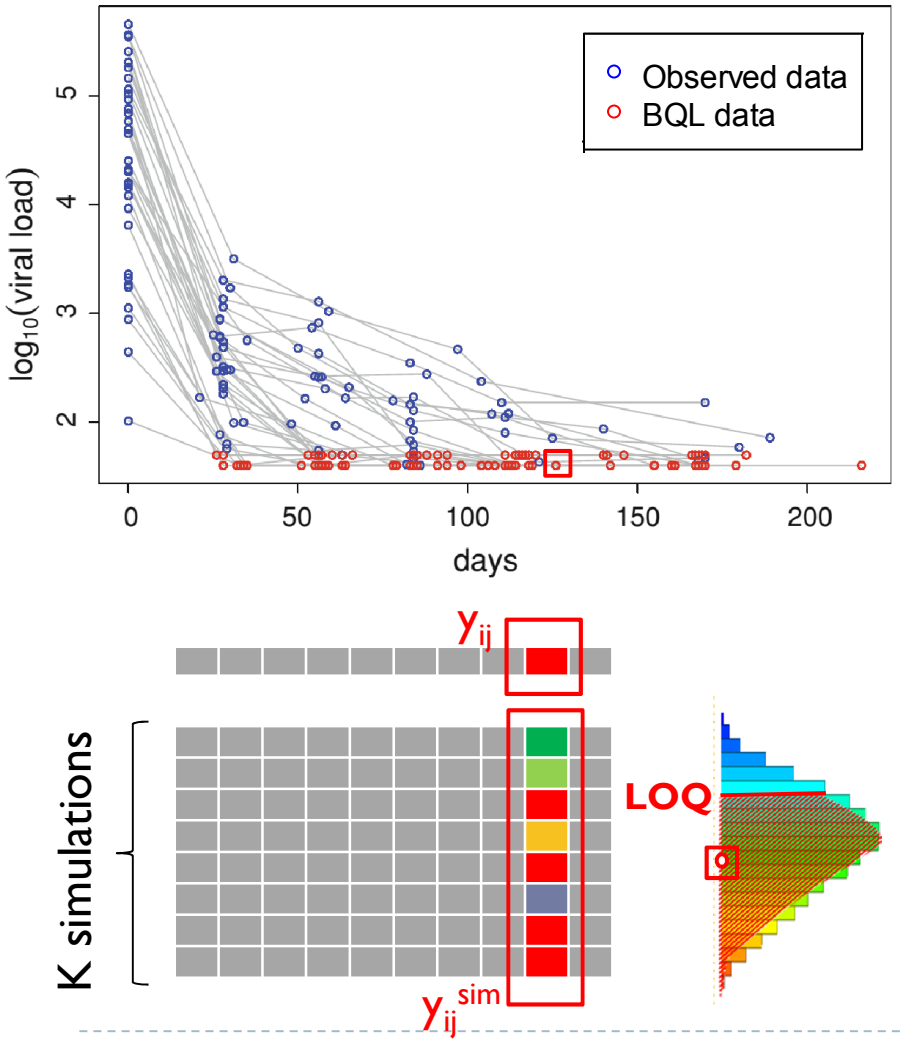
  $pd_{ij} \sim U[0,1]$

  $npde_{ij} \sim N(0,1)$

[1] Mentré et al, J Pharmacokinet Pharmacodyn (2000)

[2] Brendel et al, Pharm Res (2006)

Methods: pd and npde for BQL data



- pd_{ij} for a BQL observation y_{ij}
  - $F_{ij}(LOQ)$: probability of being under LOQ
  - pd_{ij} is randomly chosen in $U[0,F_{ij}(LOQ)]$
- $npde_{ij}$ for a BQL observation y_{ij}
  - Impute observed and simulated BQL data
  - Calculate $npde_{ij}$ from imputed data

Methods: Simulation study

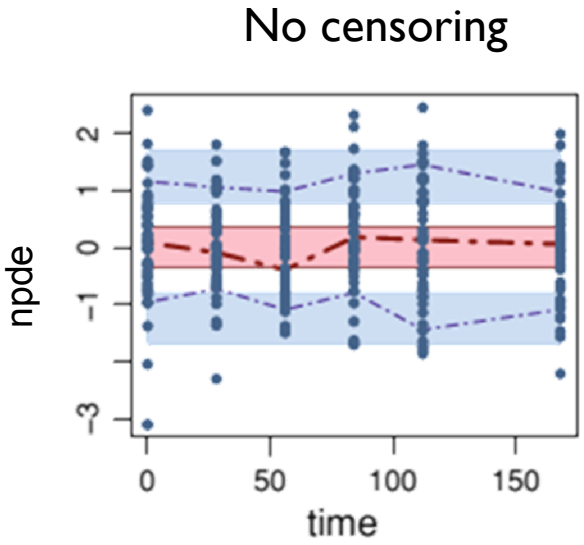
- Results under H_0 are presented
- Model: inspired from a model built for real data[1]
  - Observed dataset
  - Monte Carlo samples to approximate F_{ij}
- 2 censoring levels: LOQ = 0 (no censoring), 50 copies/mL
- Evaluation of new metrics
  - Graphical evaluation
  - Type I error of the global test[1] to test if npde ~ N(0,1)

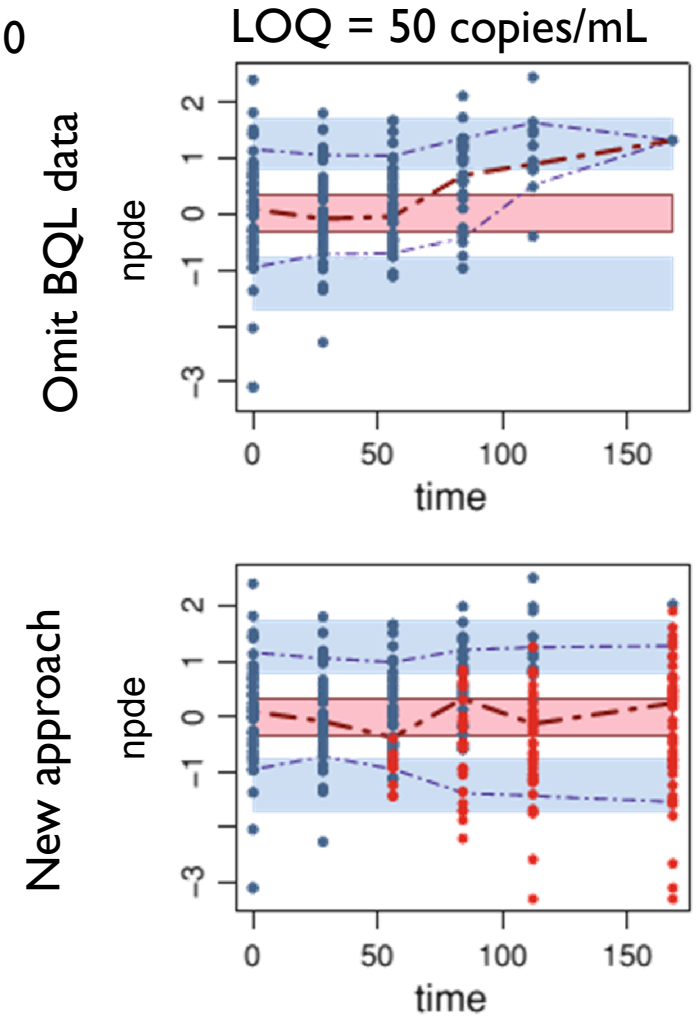
(Powers also evaluated but results not shown)

[1] Brendel et al, Pharm Res (2006)

Results

- Graphical evaluation under H_0





Results

- Type I errors*

No censoring	LOQ = 50 copies/mL	
5.4	Omit BQL data	46.9
	New approach	6.2

*Type I errors evaluated on 1000 datasets

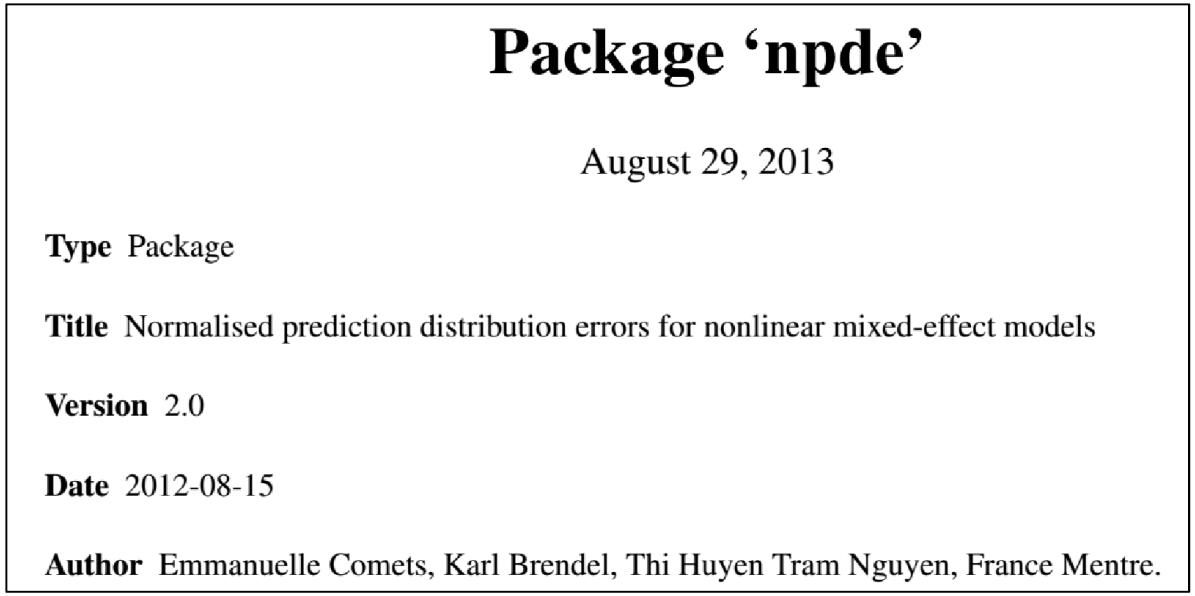
Prediction interval for 5%: [3.6 – 6.4]

Results

- New pd, npde and other graphical improvements were implemented in the package npde 2.0 for R

www.npde.biostat.fr

cran.r-project.org/web/packages/npde



Package 'npde'

August 29, 2013

Type Package

Title Normalised prediction distribution errors for nonlinear mixed-effect models

Version 2.0

Date 2012-08-15

Author Emmanuelle Comets, Karl Brendel, Thi Huyen Tram Nguyen, France Mentre.

Project 2

PK-VK model to characterize virologic response to alisporivir (ALV) and pegylated interferon (peg-IFN)

A pharmacokinetic – viral kinetic model describes the effect of alisporivir monotherapy or in combination with peg-IFN on hepatitis C virologic response

Thi Huyen Tram Nguyen[1,2], France Mentré[1,2], Micha Levi[3], Jing Yu[4], Jérémie Guedj[1,2]

(Submitted)

Methods

- Alisporivir (Novartis):
  - Cyclophillin inhibitor
  - Currently in phase 3
- Study DEB025-A2203[1]
  - Phase 2a clinical study: 4-week treatment & 3-week wash-out
  - 90 naïve patients
    - Infected with various HCV genotypes (GT)
    - Randomized into 5 treatment arms
- Data
  - PK concentrations of ALV, peg-IFN
  - Viral load data

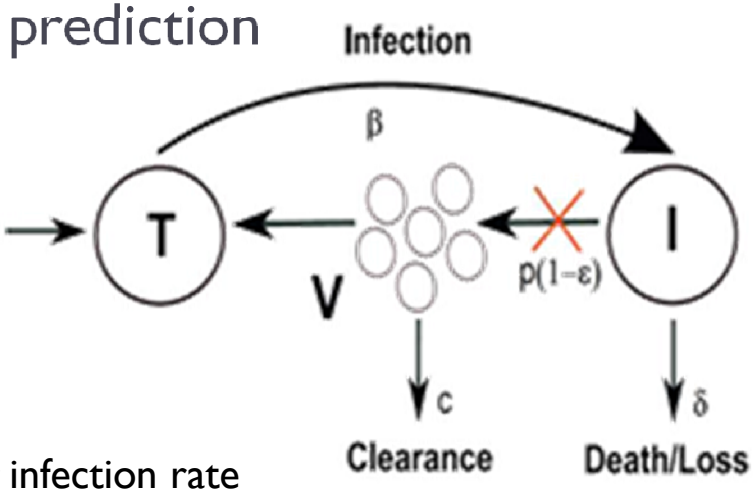
5 treatment arms

ALV Dose (mg)	Peg-IFN (µg)
200	180
600	180
1000	180
1000	0
0	180

[1] Flisiak et al, Hepatol (2009)

Methods

- Modeling strategy
  - Build PK models for ALV and peg-IFN
  - Build viral kinetic model[1] by incorporating individual PK prediction



β: infection rate
p: production rate per infected cell
c: clearance rate of free virus
δ: loss rate of infected cells
ε: treatment effectiveness

$$\frac{dI}{dt} = \beta VT - \delta I$$

$$\frac{dV}{dt} = (1-\varepsilon)pI - cV$$

$$\varepsilon_{ALV}(t) = \frac{C_{ALV}(t)}{IC50_{ALV} + C_{ALV}(t)}$$

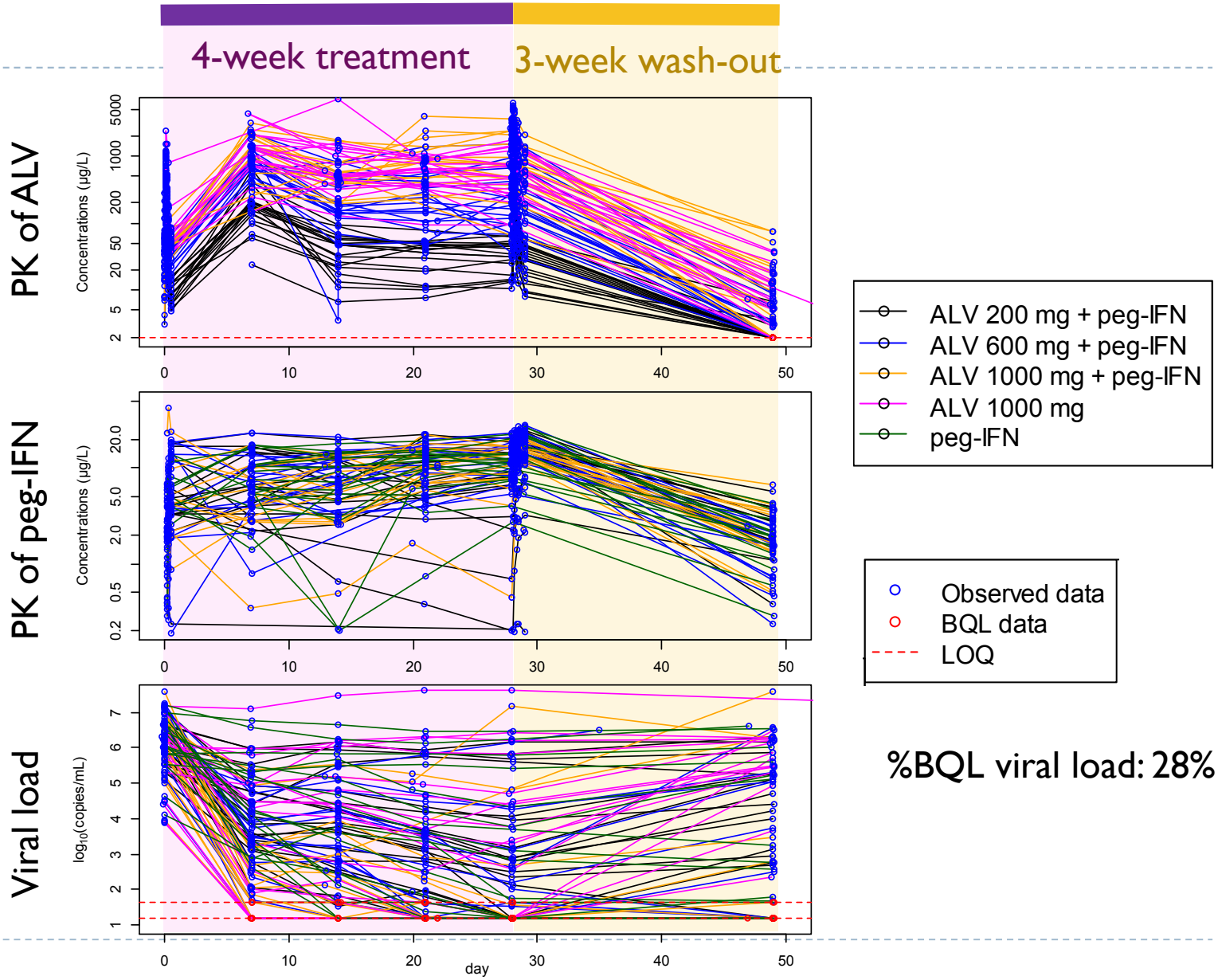
$$\varepsilon_{peg}(t) = \frac{C_{peg}(t)}{IC50_{peg} + C_{peg}(t)}$$

$$\varepsilon = 1 - (1 - \varepsilon_{peg})(1 - \varepsilon_{ALV})$$

- Parameter estimation: SAEM (MONOLIX 4.2)

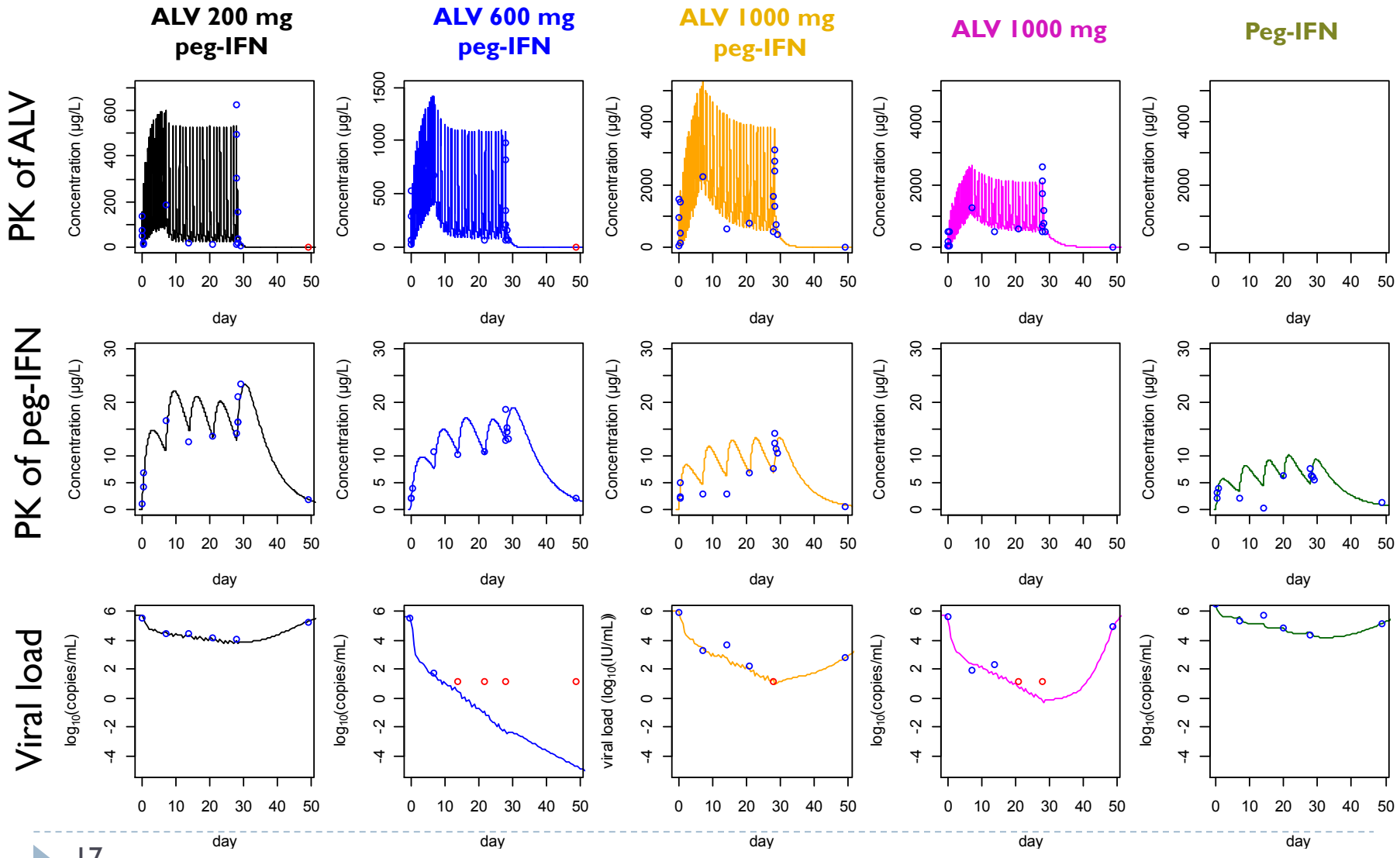
[1] Neumann et al, Science (1998)

Results: Spaghetti plots



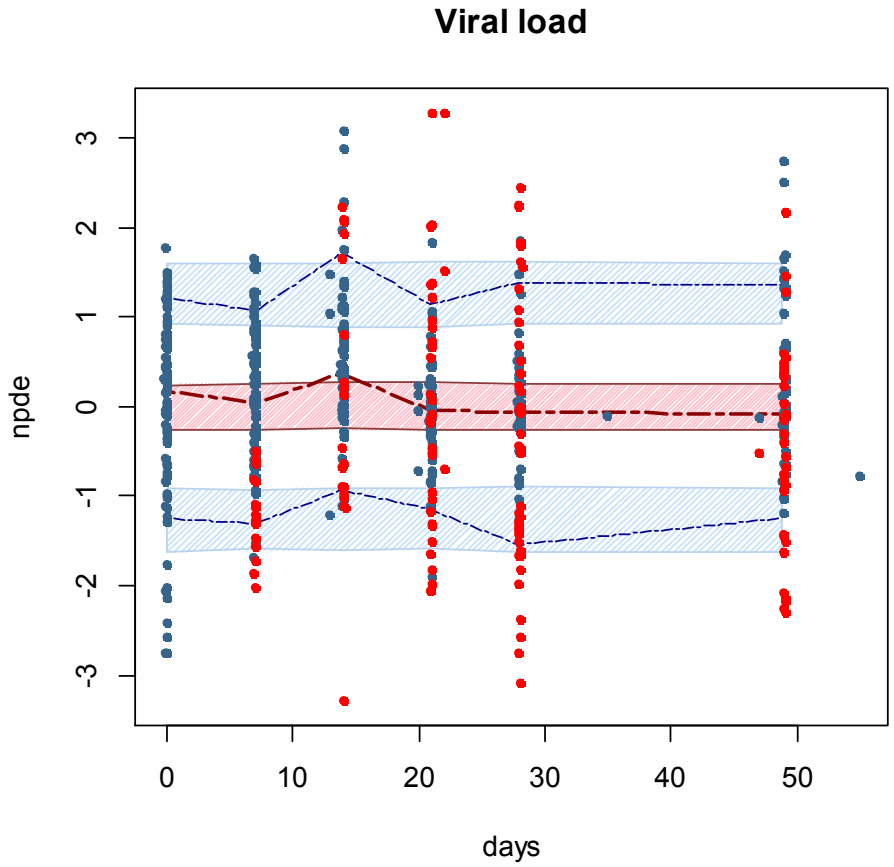
%BQL viral load: 28%

Results: Individual fits



Results

- Scatterplot of npde vs time for final PK-VK model

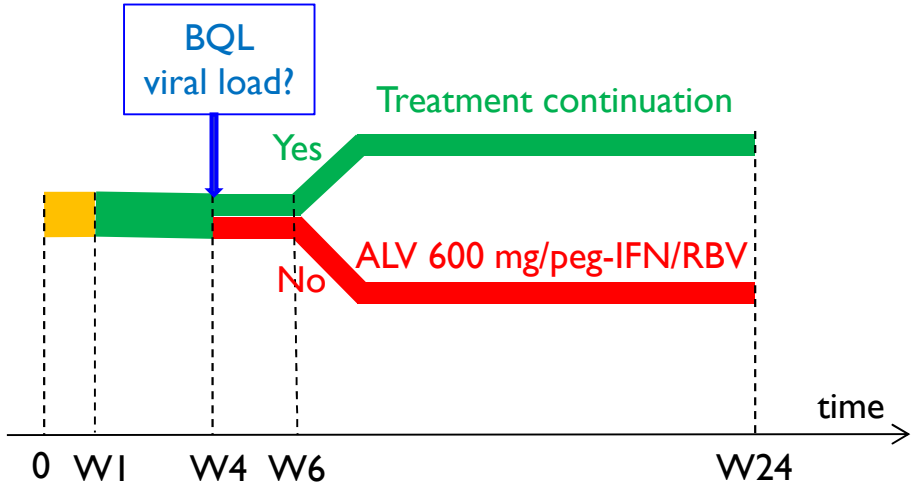


⇒PK-VK model is adequate to describe viral kinetics in the 203 study

⇒Will it be able to predict virologic response in another study?

External validation - Simulation

- VITAL-1 study (phase 2b)
  - Different dosing regimens and different combinations of ALV
    - ALV 600 mg/Ribavirin (RBV)
    - ALV 800 mg/Ribavirin
    - ALV 600 mg/peg-IFN
  - Complex design: response-guided therapy



- Compare model predictions and virologic response of VITAL-1 study
  - Sustained virologic response (SVR): undetectable viral load 24 weeks after stop of treatment
  - Prediction of SVR: SVR achieved if the "cure boundary" is reached during treatment (<1 predicted infected cell in the whole body fluids)[1,2]

(1) Dixit et al, Nature (2004)
(2) Snoeck et al, Clin Pharmacol Ther (2011)

External validation - Results

Treatment arms	% BQL data at week 4		% BQL data at week 12		% SVR	
	Observed	Predicted*	Observed	Predicted*	Observed	Predicted*
ALV 600 mg/RBV (N=77)	37.0	44.0 (33.8 – 51.9)	99.0	92.9 (88.3 - 96.8)	91	91.7 (85.7 – 96.1)
ALV 800 mg/RBV (N=80)	42.0	46.8 (36.3 – 58.4)	98.0	93.6 (88.1 – 97.5)	91	92.6 (86.3 – 97.5)
ALV 600 mg/peg-IFN (N=35)	85.0	87.2 (74.3 – 95.8)	96.0	96.2 (89.9 - 100.0)	91	94.9 (87.1 – 100.0)

*Median (95% prediction interval obtained from 100 simulations)

Project 3

Impact of BQL data, design and *a priori* information of population parameters on individual parameter estimates and prediction of treatment outcome

Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e56; doi:10.1038/psp.2013.31

www.nature.com/psp

ORIGINAL ARTICLE

Influence of *a priori* Information, Designs, and Undetectable Data on Individual Parameters Estimation and Prediction of Hepatitis C Treatment Outcome

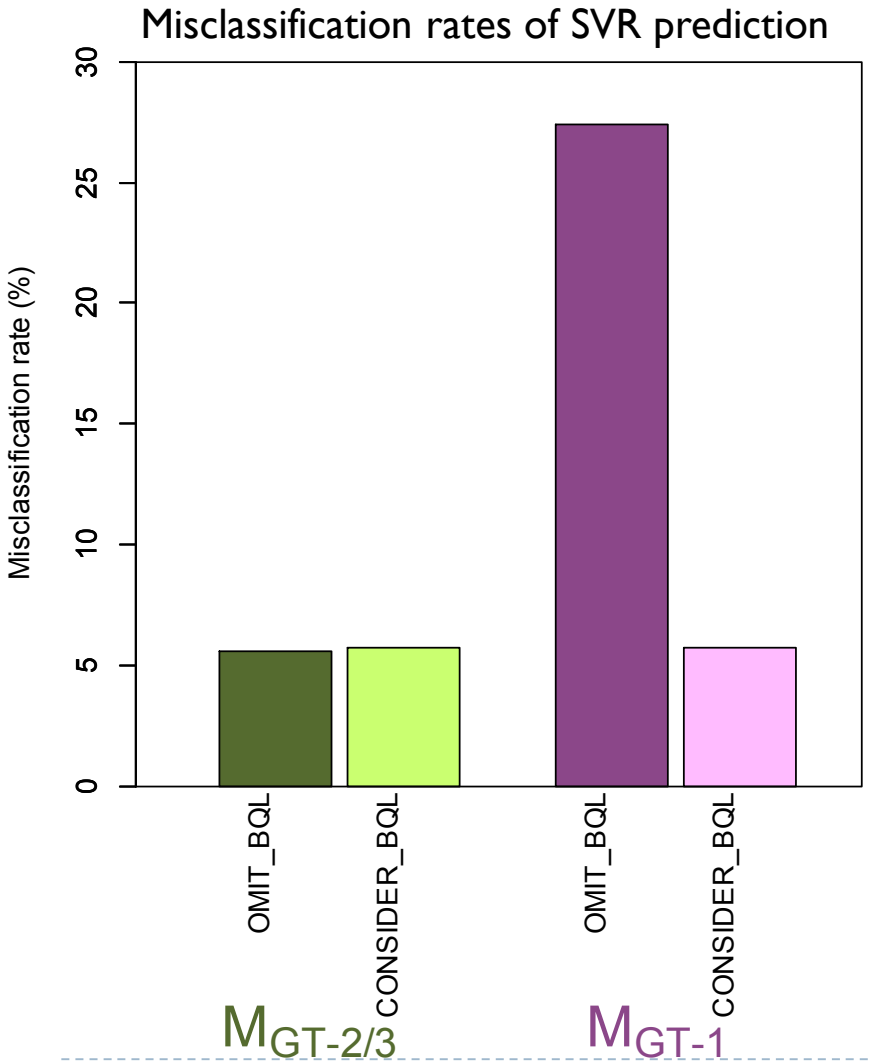
THT Nguyen,[1,2] J Guedj,[1,2] J Yu,[3] M Levi[4] and F Mentré[1,5]

Methods: Simulation study

- Data simulation
  - Virologic response in 1000 patients using typical parameters found in HCV GT-2/3 patients receiving peg-IFN/RBV for 24 weeks[1]
- Individual parameter estimation & SVR prediction
  - Bayesian approach
  - *A priori* information
    - True model ($M_{GT-2/3}$)
    - False model (M_{GT-1}): typical viral kinetic parameters of HCV GT-1 patients[2]
  - Design: Day 0, Week 1, Week 2, Week 4 (influence of design not shown)
  - Methods for handling BQL data
    - OMIT_BQL: omitting all BQL data
    - CONSIDER_BQL: taking into account BQL data
  - Comparison of predicted and simulated SVR for each patient

[1] Bochud et al, J Hepatol (2011)
[2] Dahari et al. , Hepatol (2007)

Results



- Good prediction with the true model $M_{GT-2/3}$ regardless of methods for handling BQL data
- Good prediction with the false model M_{GT-1} if BQL data correctly handled

Conclusions

- Extended pd/npde for handling BQL data show better behaviors than naïve evaluation methods
- These metrics were implemented in npde 2.0
- The new metrics were used to evaluate a model of HCV kinetics during a short term treatment with alisporivir
- This model provided good predictions for both early viral kinetics and treatment outcome in a subsequent phase 2 study
- Bayesian estimation of individual parameters could provide good prediction of treatment outcome from only few early responses if BQL data are correctly handled

Perspectives

- Extension of other evaluation metrics to handle BQL data
- Comparison with other approaches that handle BQL data (e.g., IPRED method in MONOLIX)
- Prediction of individual treatment outcome with uncertainty using *a posteriori* distribution of individual parameters
- Optimal design which accounts for BQL data to obtain precise individual estimation/prediction
- Evaluation of viral kinetic prediction for HCV treatment individualization

Thank you for your attention!

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