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Objectives

This study aimed to develop a K-PD model characterizing CA 125 and tumor size kinetics, using a population nonlinear mixed-effects modeling approach.

Methods

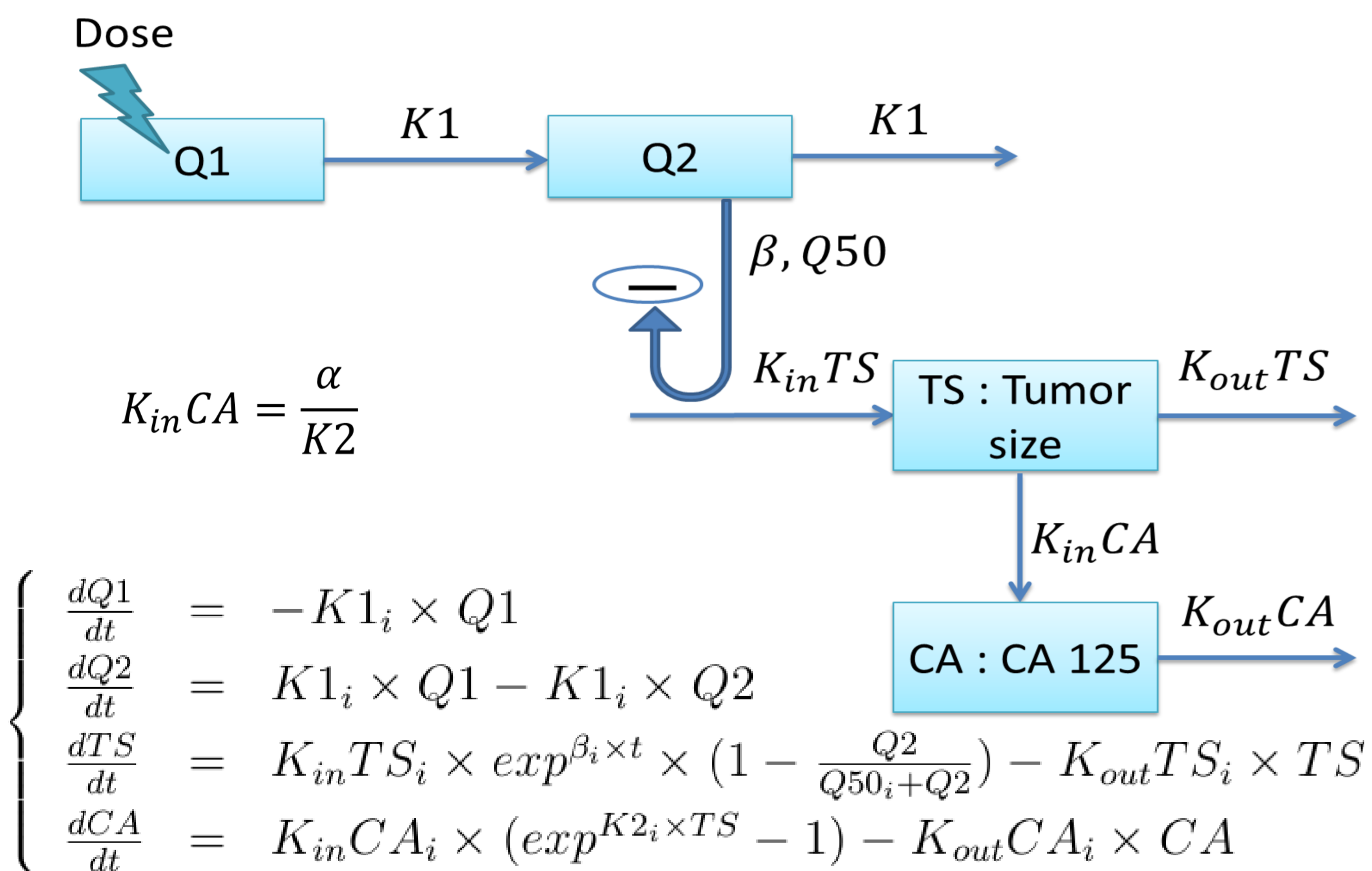
- Data:**
 - 533 patients: medians of 10 CA 125 values (U/ml), 4 tumor sizes observations (mm) and 17 covariates per subject
 - CA 125 : Box Cox transformation. Tumor size : Log transformation
- Model:**
 - Absence of PK data → K-PD model
 - Population analysis (NLME) with Monolix 3.2
 - Criterion for model selection and covariates inclusion: Objective Function (nested models) and AIC (non-nested models)
 - Model evaluation: GOF, simulation-based diagnostic (VPC ...)

Introduction

- Ovarian cancer:**
 - The leading cause of death among cases of gynecologic cancer
 - The majority of patients present an advanced stage of disease at the time of diagnosis, and 70% of them relapse → Poor prognosis
- CA 125:** tumor marker for epithelial ovarian cancer (90% of all ovarian cancers) [1]
- CALYPSO trial:**
 - Carboplatin-Paclitaxel (C-P) vs Carboplatin-Pegylated Liposomal Doxorubicin (C-PLD) in relapsed ovarian cancer
 - Results: superiority in PFS and better therapeutic index of C-PLD over standard C-P [2]

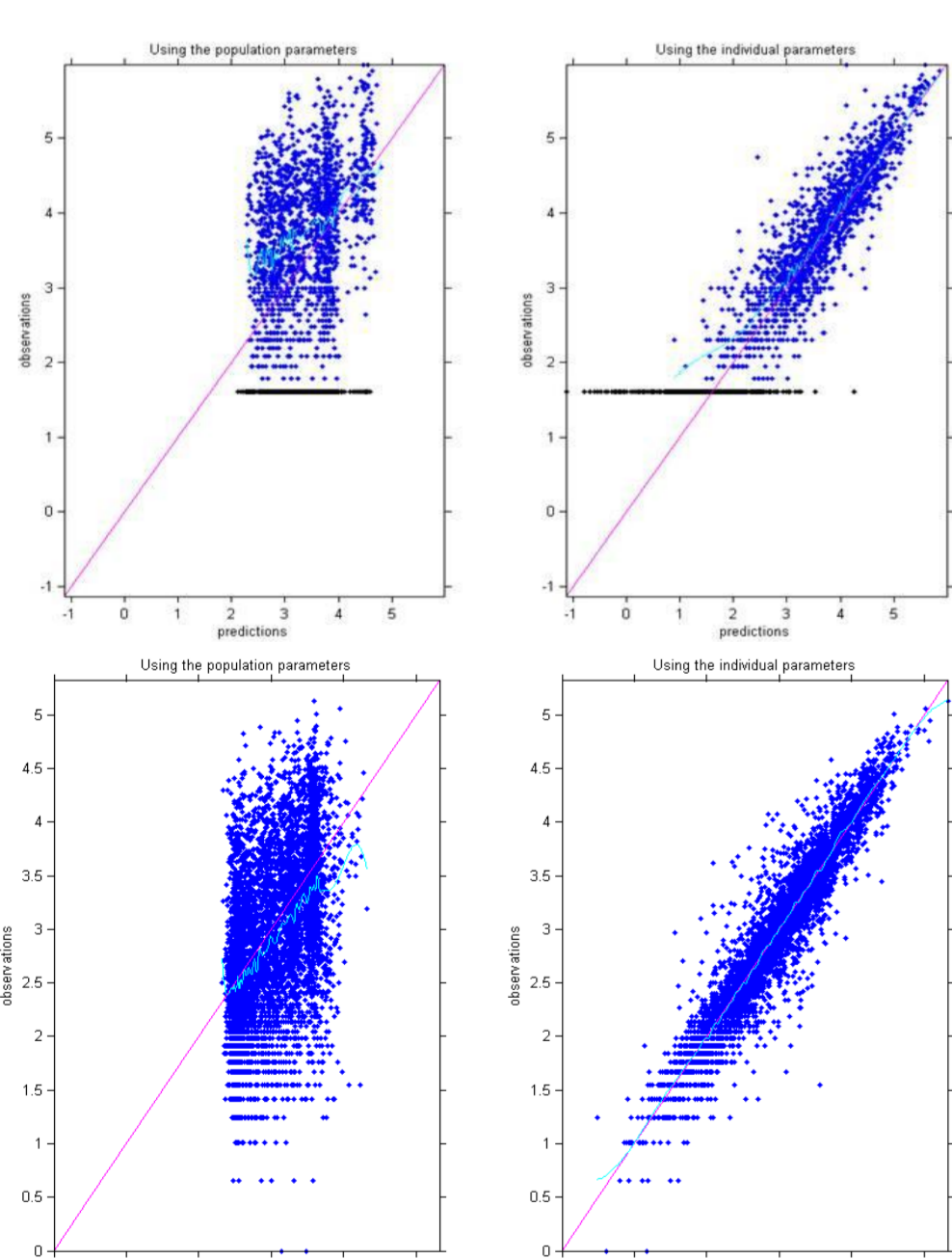
Results

K-PD model :

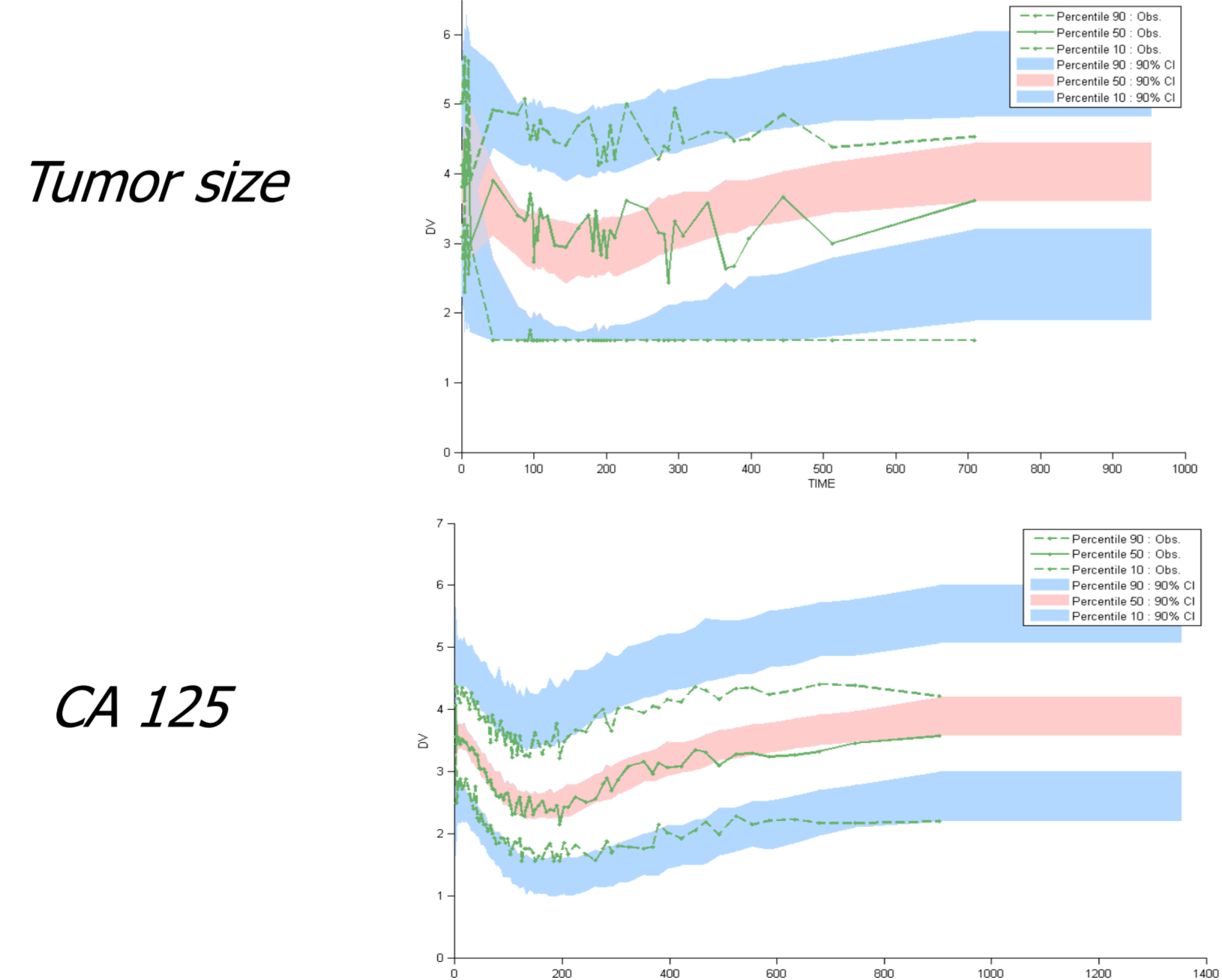


Model evaluation :

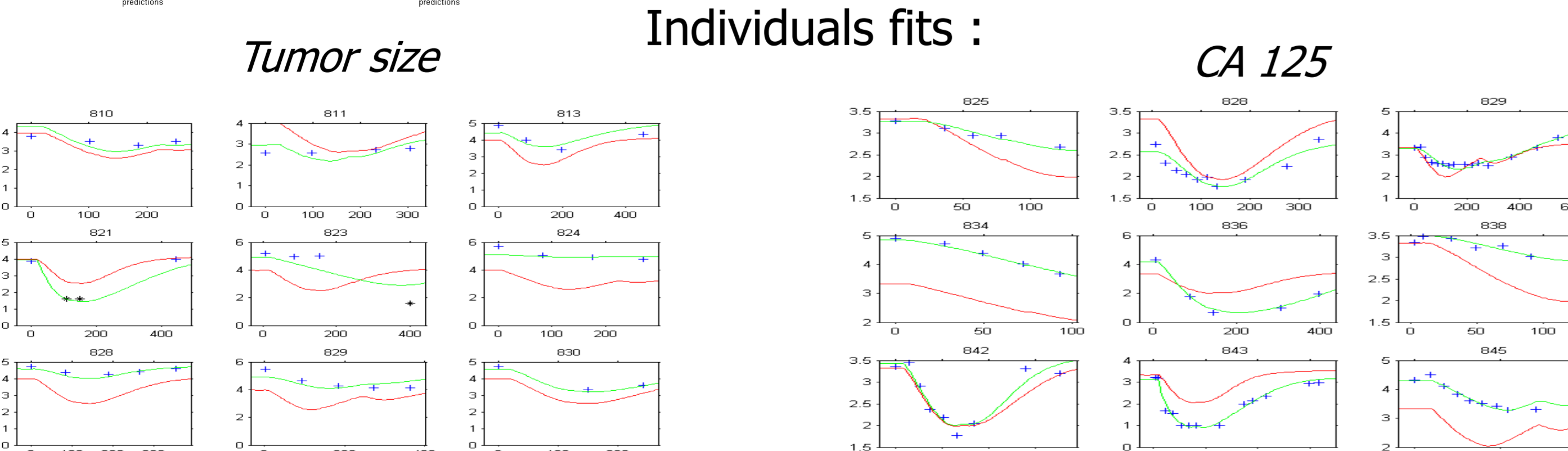
Predictions vs Observations :



VPC :



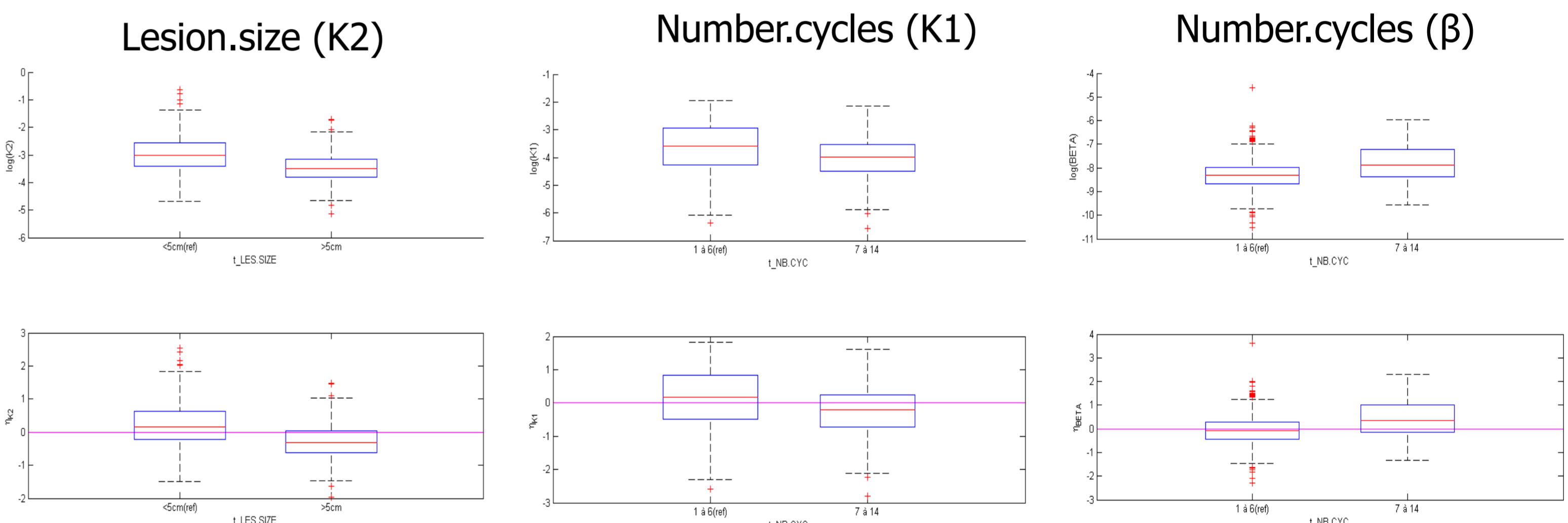
Individuals fits :



Estimated parameters:

Parameter	Unit	Estimate	R.S.E (%)	IIV (%)	R.S.E (%)
K1 (nb. cycles < 6)	day ⁻¹	0.0262	5	98.2	4
K1 (nb. cycles > 6)	day ⁻¹	0.0135	5		
K_{inTS}	mm · day ⁻¹	2.85	7	144	4
β (nb. cycles < 6)	day ⁻¹	0.000204	15	107	10
β (nb. cycles > 6)	day ⁻¹	0.00054			
Q50	AU	0.375	6	107	4
K_{outTS}	day ⁻¹	0.0536	7	147	4
K_{inCA}	U · ml ⁻¹ · day ⁻¹ · mm ⁻¹	0.368	7	133	4
K2 (lesion.size < 5cm)	mm ⁻¹	0.0437	5	78.7	5
K2 (lesion.size > 5cm)	mm ⁻¹	0.0413			
K_{outCA}	day ⁻¹	0.6	3	56.3	6

Covariates:



Discussion

- β increases with the number of cycles → Chemoresistance

Medians estimated parameter \ Treatment	C - P	C - PLD
K1	0.024	0.033
K_{inTS}	3.242	2.463
β	0.0002	0.0002
Q50	0.388	0.456
K_{outTS}	0.057	0.047
α	0.357	0.289
K2	0.044	0.040
K_{outCA}	0.599	0.608

- Q50 (C-P) > Q50 (C-PLD) :

contrary to Pujade and al.'s results:

- VPC for CA 125 : the model seems to overestimate the variability
- Tumor size values : not match the total tumor, but a target lesion
- CA 125 : lack of sensitivity and specificity = possible discrepancy with tumor size

Conclusions and Perspectives

- First combined model characterizing CA 125 and tumor size kinetics in relapsed ovarian cancer patients receiving chemotherapy
- Leads to better understanding of CA 125 as biomarker and its use for treatment monitoring and/or evaluation

References

- [1] R. C. Bast, R. C. Knapp. Reactivity of a monoclonal antibody with human ovarian carcinoma. J Clin Invest, 68(5) :13311337, Nov 1981.
[2] E. Pujade-Lauraine. Protocol : Calypso a multi-national, randomized, phase iii, gcig intergroup study comparing pegylated liposomal doxorubicin (caelyx R) and carboplatin vs. paclitaxel and carboplatin in patients with epithelial ovarian cancer in late relapse (>6 months). 2005.