

Joint modelling of plasma and fecal moxifloxacin pharmacokinetics in healthy volunteers

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Introduction

Antibiotic administration has been associated to fecal microbiota disruption with emergence of antimicrobial resistance [1]. Fluoroquinolones such as moxifloxacin (MXF) have a profound impact on the gut microbiota. Most studies performed cross-sectional analyses of the prevalence of antimicrobial-resistant bacterial strains, without evaluating the time-varying pattern of resistance. However, animal data suggest that emergence of bacterial resistance can be predicted from fecal antibiotic exposure [2]. In order to link the individual exposure to antibiotic to the evolution microbiota disruption and antibiotic resistance, we developed a joint model of plasma and fecal pharmacokinetics of the fluoroquinolone antimicrobial MXF after oral administration in humans. This represents a first step for modelling the impact of individual dosing regimen on bacterial composition of the fecal microbiota.

Methods

Data

Fourteen healthy volunteers were recruited in a randomized clinical trial (sponsor Da Volterra) and received a 5-day course of MXF. None had previously received fluoroquinolone treatments. The MXF dosing regimen (400 mg OAD) was similar to that usually administered in infected patients. MXF plasma concentrations were determined at D₀ (H_{0.5}, H₁, H_{1.5}, H₂, H₃, H₄, H₆, H₁₂, H₂₄), at D₄ (H₀, H_{0.5}, H₁, H_{1.5}, H₂, H₃, H₄, H₆, H₁₂, H₂₄), at D₅ at H₈ and H₂₄, and at D₆ at H₈ and H₂₄. Eleven fecal samples were obtained from D₀ to D₁₅ for measures of MXF concentrations. MXF concentrations were determined by bioassay in plasma (limit of quantification LOQ 10 µg/L) and feces (LOQ 40 ng/g).

Structural model

Plasma MXF concentrations were analyzed using various compartmental models, parametrized in terms of first order absorption rate (k_a), volume of distribution (V) and first order elimination rate (k). Among the various models tested, the best structural model identified in the plasma modelling (2 compartments with first order absorption and lagtime) was used for the joint modelling.

Fecal MXF concentrations were modelled using a fecal compartment with first order elimination and assuming a daily weight of feces of 200g. The fecal compartment (Af) is either connected to the central (Ac) or peripheral (Ap) compartment of the plasma model (M1 and M2 vs M3 and M4, Figure 1). In M1 and M3, a transit compartment (At) is added between plasma and feces, assuming either different or equal entry and elimination rates for this compartment.

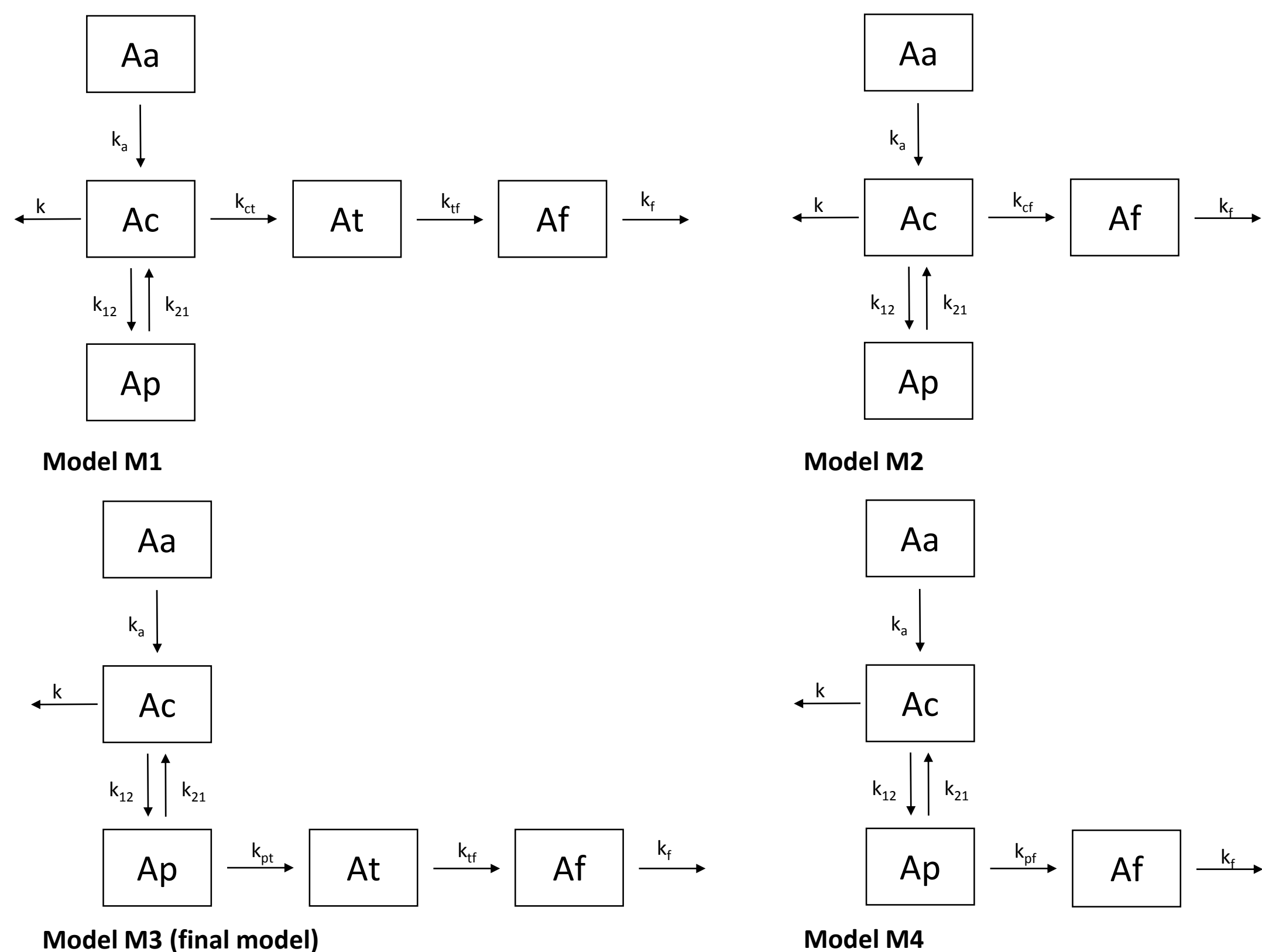


Figure 1: Schematic representation of the structural joint models studied for plasma and fecal MXF pharmacokinetics.

Population analysis

Nonlinear mixed-effects modelling was performed to jointly analyze plasma and fecal MXF concentrations in all subjects. Individual parameters were supposed to have a lognormal distribution. Proportional and combined models for the residual error were tested. Parameter were estimated using the SAEM algorithm in the Monolix software (Lixoft, France) [3], taking into account the information brought by data below the LOQ.

Model selection was performed by investigating various goodness of fit plots and the Bayesian Information Criteria.

Results

Five of the 14 volunteers (36%) were males. Median age and BMI were respectively 34.4 years (min-max, 23.3-59.5) and 23.3 kg/m² (min-max, 19.5-29.0). After the 1st and the 5th dose, respectively 126 and 196 plasma concentrations were available in plasma. 139 concentrations were available in feces.

The joint model M3 with equal entry and elimination rates from the transit compartment (k_{pt} = k_{tf} = k_{tr}) adequately described the data. The best residual error models were proportional for plasma and combined for fecal concentrations. Individual fits and normalised prediction distribution errors (NPDE) of the model are presented in the figures 3 and 4.

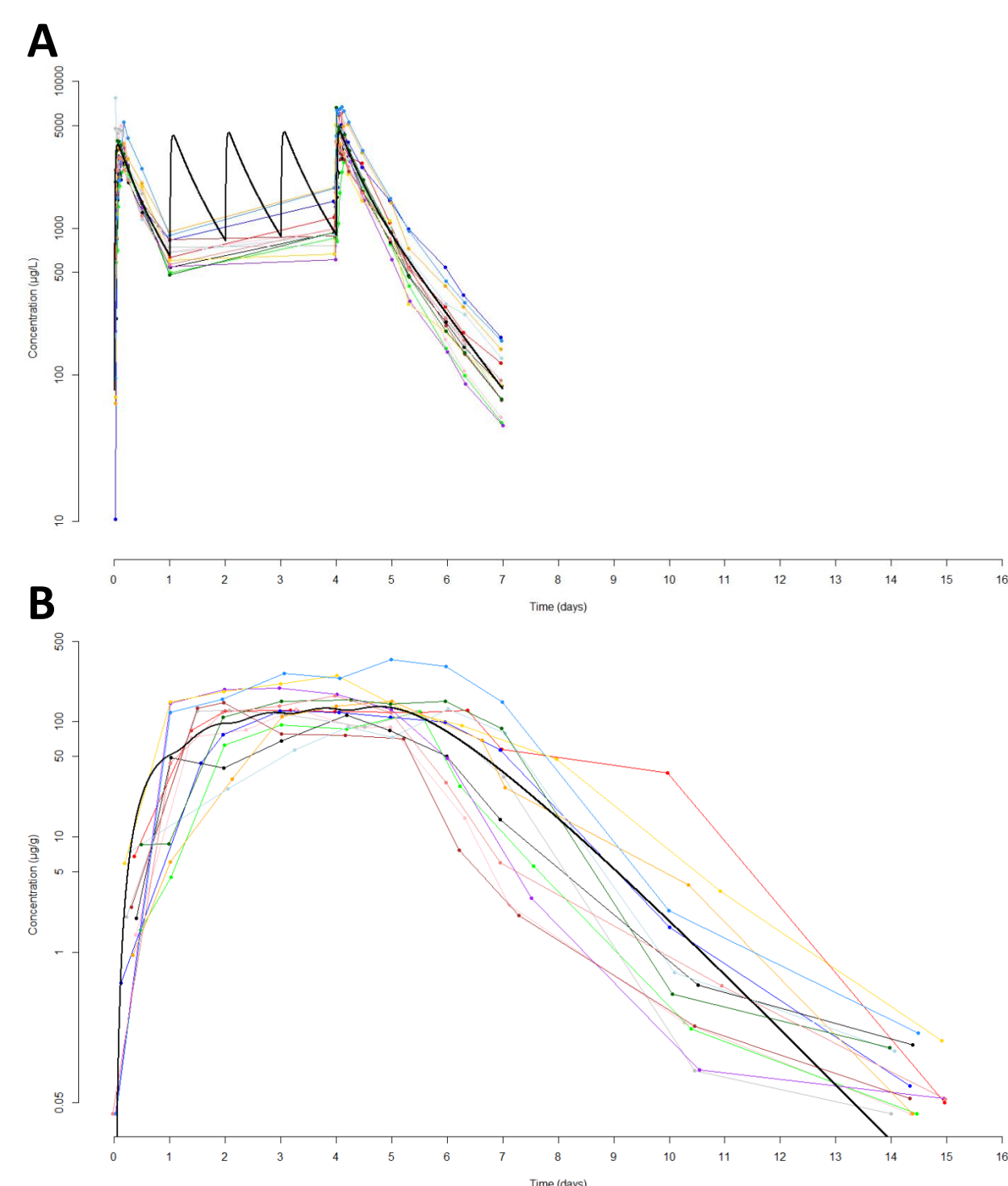


Figure 2: Spaghetti plots of observed plasma (A) and fecal (B) concentrations. Black thick lines represent the model prediction curves using the fixed effects of the final joint model (M3).

Parameter	Estimate (rse%)	Inter-individual variability	Estimate (rse%)	Residual error	Estimate (rse%)
Tlag (h)	0.26 (24)			σ _{slope_plasma}	0.23 (4)
k _a (h ⁻¹)	2.6 (46)	ω _{Tlag}	0.63 (29)	σ _{add_fecal} (µg/g)	0.07 (35)
V (L)	94.5 (5)	ω _{ka}	1.6 (21)	σ _{slope_fecal}	0.52 (7)
k (h ⁻¹)	0.03 (7)	ω _v	0.17 (23)		
k ₁₂ (h ⁻¹)	0.07 (6)	ω _k	0.22 (26)		
k ₂₁ (h ⁻¹)	0.03 (13)	ω _{k12}	0.06 (194)		
k _{tr} (h ⁻¹)	0.06 (7)	ω _{k21}	0.42 (23)		
k _f (h ⁻¹)	0.35 (12)	ω _{ktr}	0.25 (23)		
		ω _{kf}	0.36 (25)		

Table: Estimated population parameters and relative standard errors (rse) in the final joint model (M3).

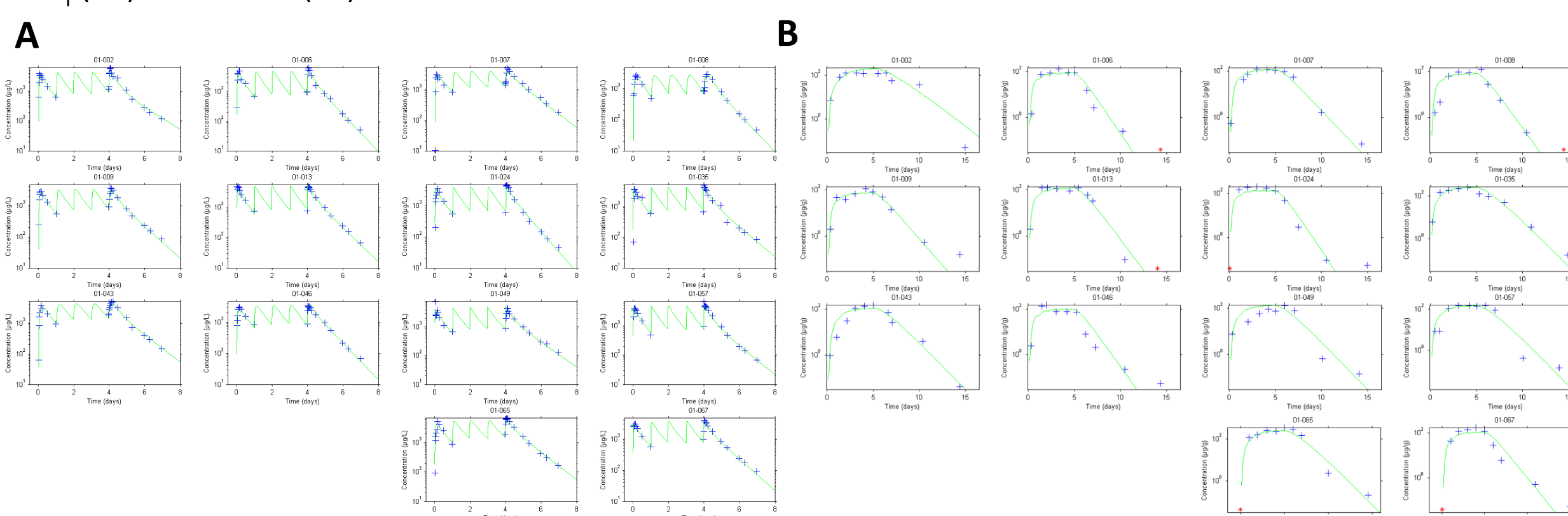


Figure 3: Individual fits for the plasma (panel A) and fecal (panel B) concentrations for the final joint model (M3). Observed MXF concentrations are represented in blue, and data below the limit of quantification are represented in red. Green lines represent the individual predictions.

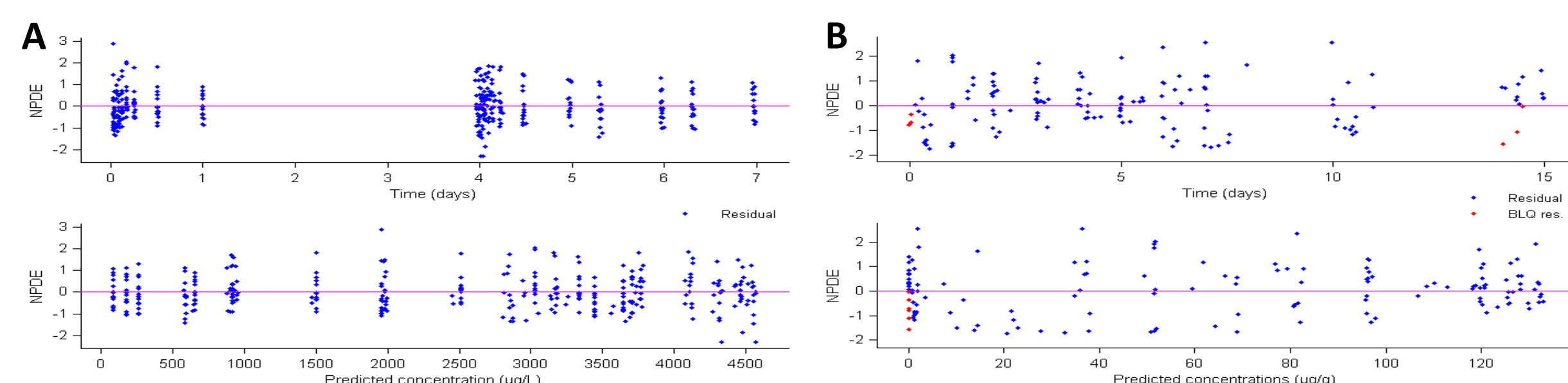


Figure 4: Plots of NPDE vs time and vs predicted concentrations for the plasma (panel A) and fecal (panel B) concentrations for the final joint model (M3). NPDE are represented in blue, and NPDE below the limit of quantification are represented in red.

Conclusion

We developed here the first joint model of plasma and fecal MXF pharmacokinetics in humans. Estimated plasma pharmacokinetic parameters were similar to those previously published [4]. MXF was still detectable in feces 9 days after the end of treatment. This long-term persistence probably explains the impact of fluoroquinolones on the gut microbiota. Our analysis represent a first-step toward a physiological model of the impact of MXF on the fecal microbiota. Further work include the analysis of the within microbiota diversity, as previous works reported alterations of its composition after administration of other antimicrobials [5,6].

References

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