Joint modeling of moxifloxacin pharmacokinetics and fecal microbiota disruption in healthy volunteers

Charles Burdet[1,2], Thu Thuy Nguyen[1], Jean de Gunzburg[3], Stéphanie Ferreira[4], Annie Ducher[3], Xavier Duval[1,2], Marina Varastet[3], Antoine Andremont[1,2], France Mentré[1,2]

[1]INSERM, IAME, UMR 1137, F-75018 Paris, France; Université Paris Diderot, Sorbonne Paris Cité, Paris, France
[2] AP-HP, Bichat Hospital, Paris, France; [3] Da Volterra, Paris, France; [4] Genoscreen, Lille, France

Introduction

- Metagenomic analysis provides a detailed picture of the intestinal microbiota. Antibiotic administration has a major disrupting impact [1].
- We developed a joint model of plasma and free fecal concentration of moxifloxacin (ffMXF), a fluoroquinolone antibiotic, after oral administration in humans, and their impact on fecal microbiota.

Methods

Data

- 14 healthy volunteers (HVs) treated by 400 mg MXF OAD for 5 days & 8 control HVs not treated included in a clinical trial (sponsor Da Volterra, PI X. Duval). Multiple plasma and fecal sampling for ffMXF measurement and microbiota analysis (Fig 1 & 2).

Figure 1: Design of the trial.
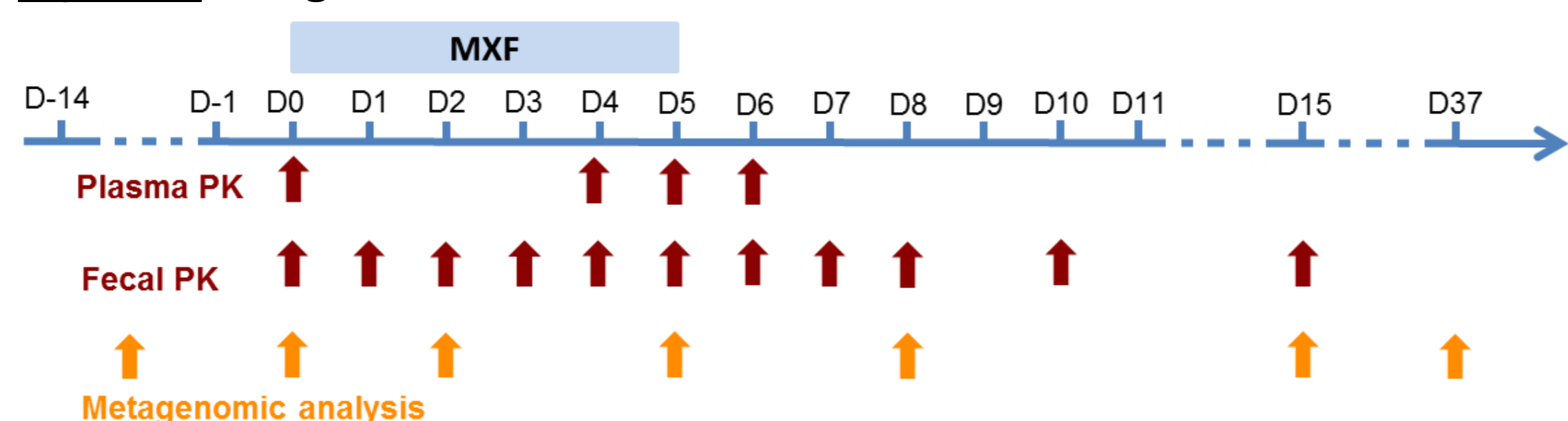
- ffMXF measured by bioassay, metagenomic analysis by sequencing of the V3-V4 16S rDNA region (Genoscreen, Lille, France). Bacterial α-diversity estimated using the number of different Operational Taxonomic Units (OTUs) in each sample.

Figure 2: Plasma (left) and fecal (right) ffMXF (red), and number of OTUs (bottom, orange) in MXF-treated (plain lines) and control (dashed lines) HVs; Blue arrows represent MXF administration.
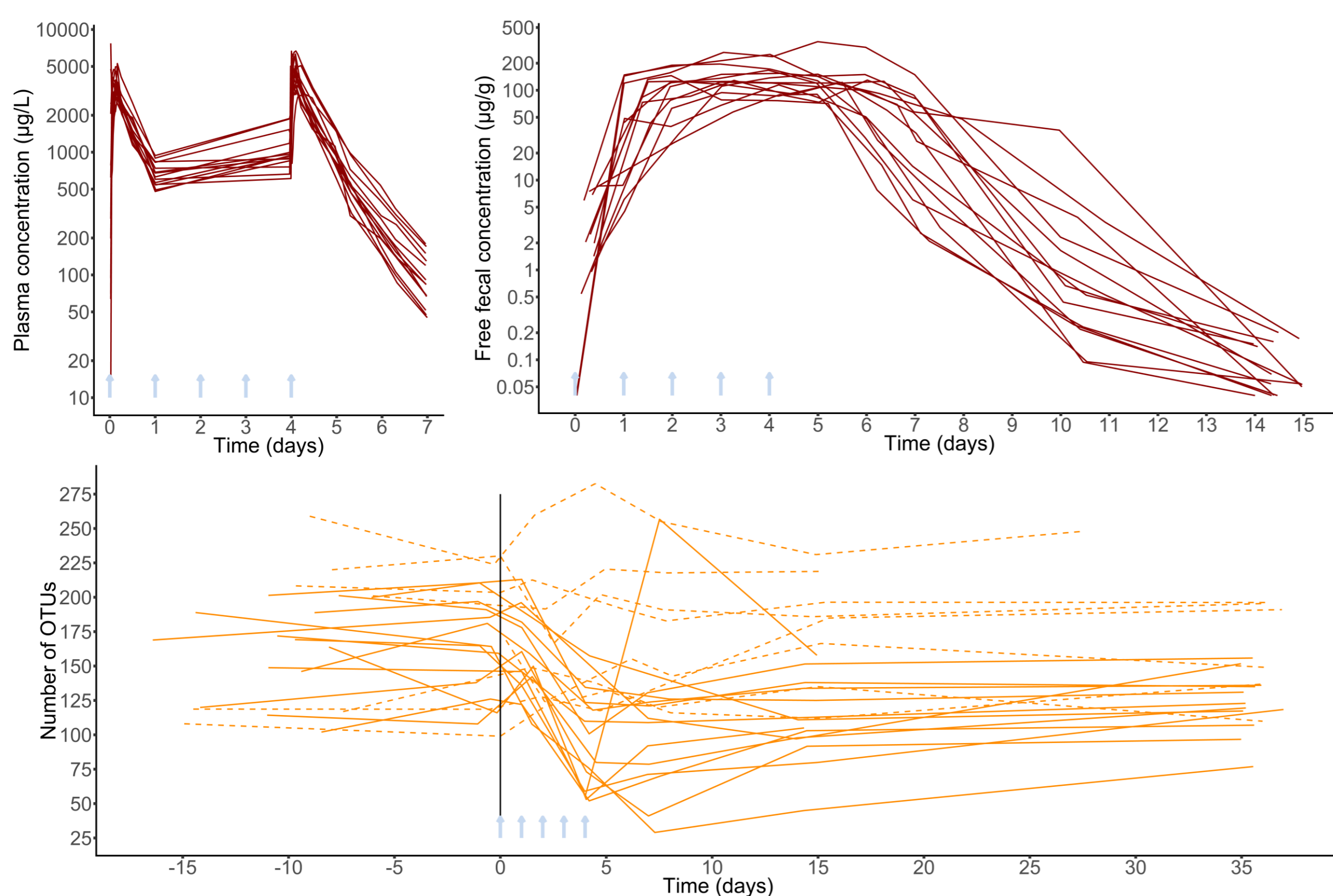
Modelling

- 2-step analysis: first joint plasma and fecal PK modelling in MXF-treated subjects (Fig 3), then PKPD modelling using all subjects.
- Turn-over models tested to model the impact of ffMXF on bacterial diversity [2].
- Parameter estimation performed using non-linear mixed-effects modelling with SAEM algorithm in the Monolix software.

Conclusion

- First PKPD model that joins the plasma and fecal PK profiles of an antibiotic to its deleterious effects on the intestinal microbiota.
- MXF is still detectable in feces 10 days after the end of treatment, with highly variable impact on number of OTUs. Return to pre-treatment state is incomplete 30 days after the end of treatment.
- The characterization of other indices of microbiota disruption by MXF is ongoing.

References

[1] Dethlefsen, L. & Relman, D. A. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. Proc Natl Acad Sci U A 108 Suppl 1, 4554–4561 (2011).
[2] Nguyen TT, Guedj J, Chachaty E, de Gunzburg J, Andremont A, Mentre F. Mathematical modeling of bacterial kinetics to predict the impact of antibiotic colonic exposure and treatment duration on the amount of resistant enterobacteria excreted. PLoS Comput Biol 2014; 10(9): e1003840.

Results

- In the best model, ffMXF increased the elimination of the number of OTUs by via an E_{max} model (Fig 3).
- Goodness of fit of the model were satisfactory. Individual fits of ffMXF and number of OTUs presented in Fig 4.

Figure 3: Compartmental model obtained for plasma and fecal MXF PK (red) and for bacterial diversity (orange). Compartments are a, transit, Aa, absorption, Ac, central, Ap, peripheral, At1 & At2, transit, Af, fecal
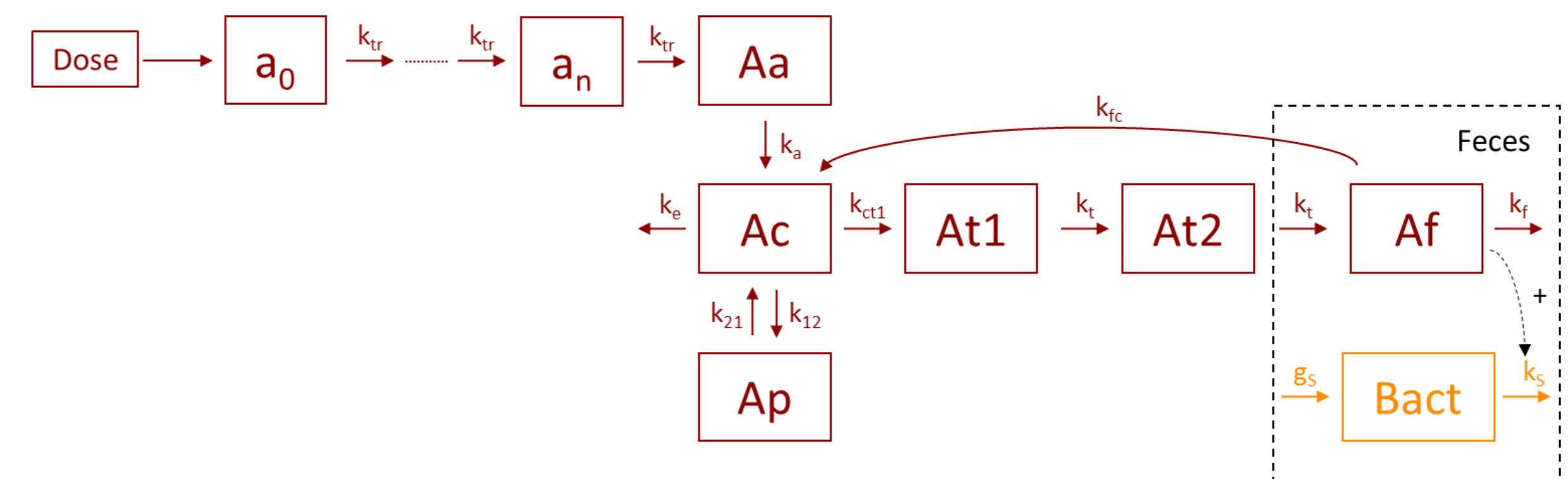
Parameter	Estimate (rse%)	Inter-individual variability (rse)
Mtt (d)	0.0144 (30)	0.917 (24)
k_{tr} (d^{-1})	152 (57)	1.74 (26)
k_a (d^{-1})	136 (65)	1.81 (28)
V (L)	101 (5)	0.164 (24)
k (d^{-1})	1.58 (4)	0.133 (24)
k_{12} (d^{-1})	0.118 (18)	0 (fixed)
k_{21} (d^{-1})	0.967 (1)	0 (fixed)
k_{cb} (d^{-1})	0.217 (13)	0.224 (52)
k_{fc} (d^{-1})	0.319 (36)	0.63 (41)
k_t (d^{-1})	3.17 (16)	0.472 (26)
k_f (d^{-1})	1.47 (16)	0.447 (25)
P_f (g)	200 (fixed)	0 (fixed)
g_s	5.03 (16)	0 (fixed)
k_s (OTU.d^{-1})	0.0305 (17)	0.188 (17)
E_{max}	7.77 (35)	0.392 (65)
EC_{50} (μg/g)	127 (74)	1.05 (42)

Residual error	Estimate (rse%)
σ_{slope_plasma}	0.217 (4)
σ_{inter_fecal} (μg/g)	0.0495 (37)
σ_{slope_fecal}	0.492 (8)
σ_{inter_OTUs}	23.4 (9)

Table 1: Estimated population parameters and relative standard errors (rse) in the final joint model.

Figure 4: Top : individual fits of ffMXF (red). Bottom: number of OTUs (orange) in MXF-treated HVs, and spaghetti plot (dotted black line) and population prediction (plain line) in control HVs.