

BACKGROUND

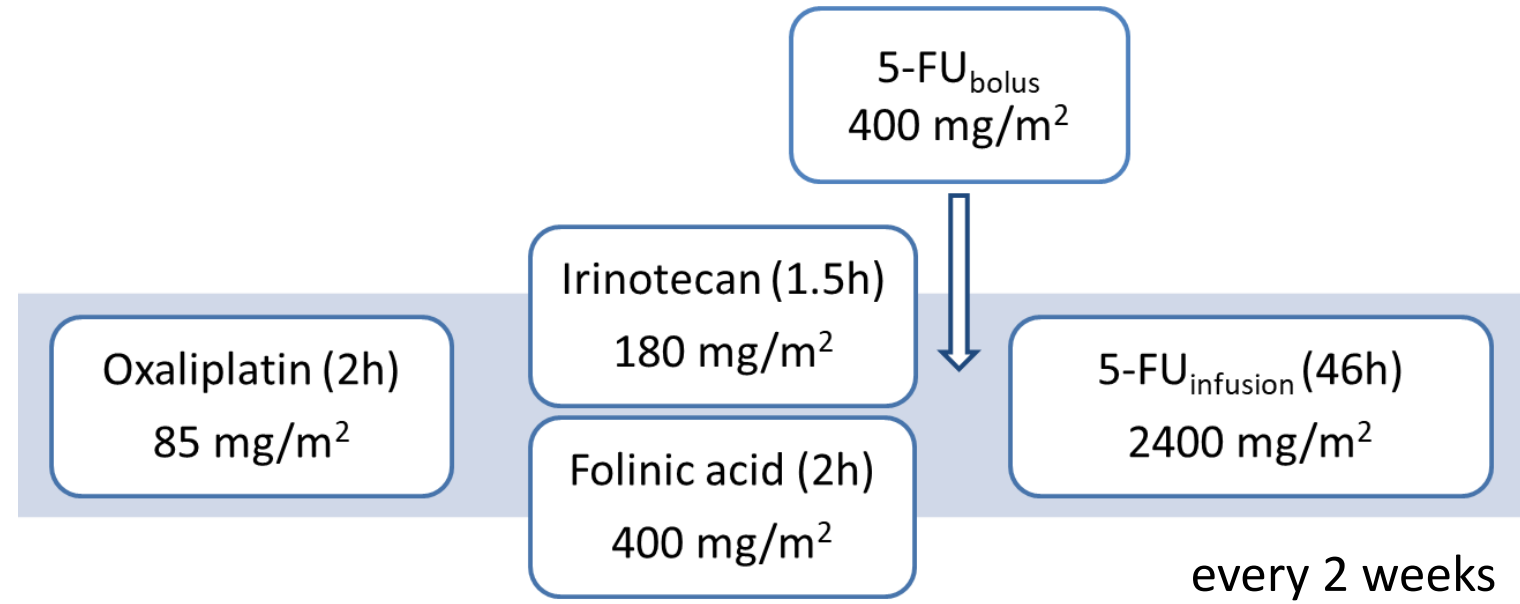
FOLFIRINOX

- The most efficient regimen in pancreatic cancer [1]
- Induces significant and dose-limiting toxic effects

Empirical dose reduction

Postponement of the forthcoming courses

Treatment discontinuation

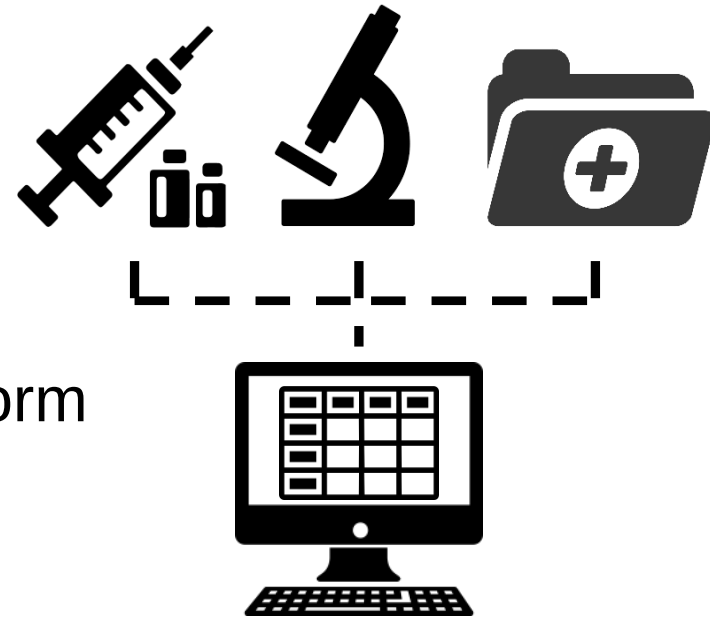


Model-based FOLFIRINOX regimen optimization might help improve patient outcome

MATERIAL & METHODS

Multicenter retrospective study in 3 centers :

- Data from 75 patients with pancreatic adenocarcinoma
- 596 neutrophils observations
- FOLFIRINOX regimen
- Granulocyte-Colony Stimulating Factor (G-CSF), pegylated form (PEG G-CSF)
- No pharmacokinetic (PK) data



5FU-PKPD model of neutropenia including G-CSF rescue

- 5FU PK simulated using the popPK model from Terret *et al.* [2]
- Pharmacodynamic (PD) model of neutropenia modified from Friberg *et al.* [3]
- PKPD model of G-CSF and PEG G-CSF added on the Friberg model (Pastor *et al.* [4])
- Effect of 5FU chemotherapy described with power function

$$E_{\text{drug}} = \text{slope} \times [\text{drug}]^{\beta}$$

Individual estimation of 5 PD parameters with Matlab 2018b

- slope, $E_{\text{max},1}$, $EC_{50,1}$, $E_{\text{max},2}$, $EC_{50,2}$

Simulation of alternative administration protocols of 5FU and G-CSF

- Increasing the duration of 5FU perfusion (120 hours)
- Decreasing the duration of 5FU perfusion (12 hours)
- Increasing the duration of 5FU perfusion (120 hours) and modifying the G-CSF protocol

RESULTS

5FU-PKPD model of neutropenia including G-CSF rescue

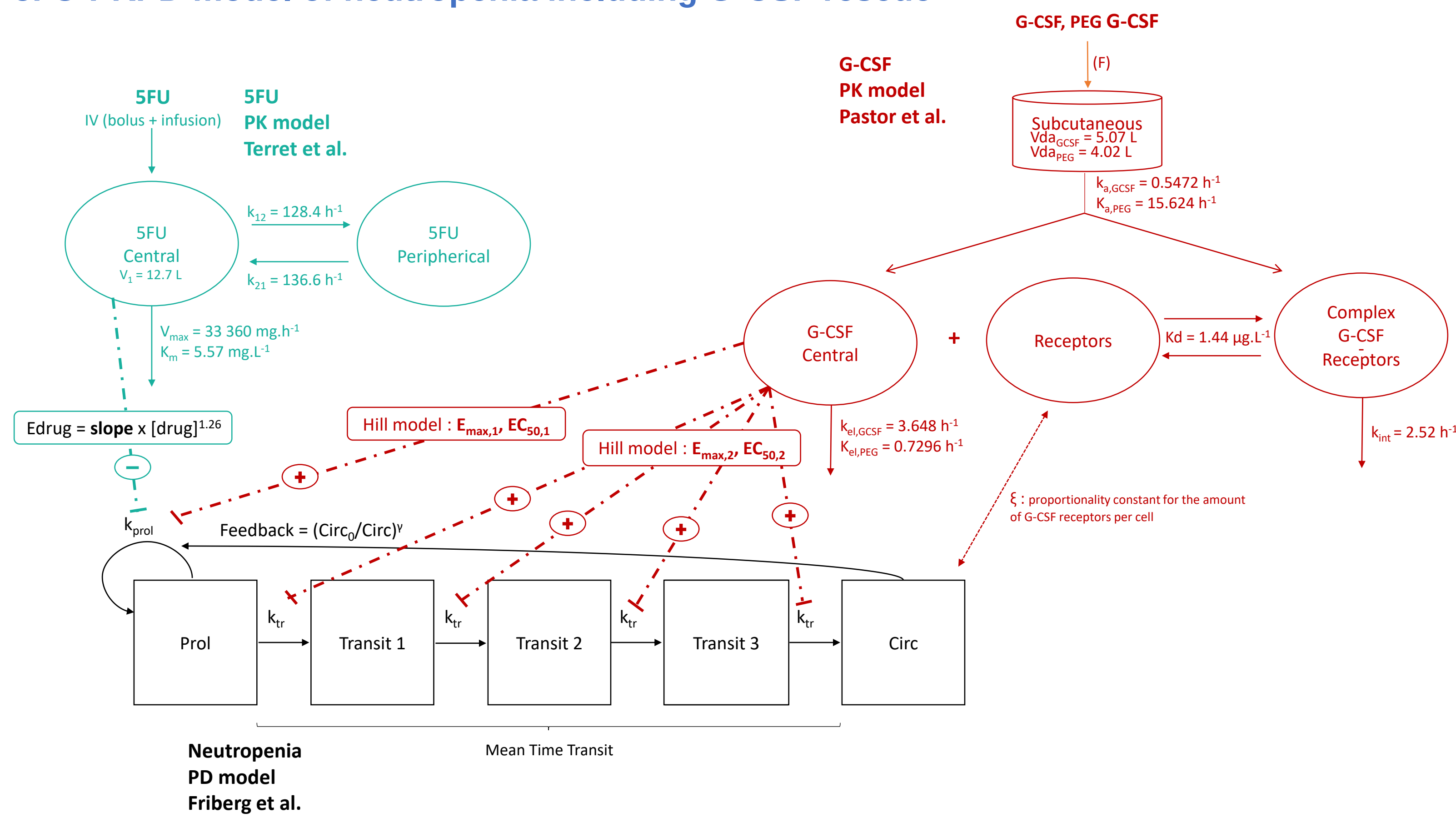


Figure 1 : PKPD model describing the neutropenic effect of 5FU including G-CSF rescue (pegylated, PEG G-CSF or non pegylated form, G-CSF).

Estimation of individual PD parameters

- Example for ID 22 :
 - 8 courses of FOLFIRINOX without 5FU bolus
 - 5FU dose decreased by 30% after the 1st course
 - 2 delays of one week after 6th and 7th courses
 - Administration of 4 to 5 doses of G-CSF from the 2nd course

	slope (L/μg)	$E_{\text{max},1}$	$EC_{50,1}$ (μg/L)	$E_{\text{max},2}$	$EC_{50,2}$ (μg/L)	MSE
Estimate (RSE%)	1.17 (12%)	11.85 (1.75%)	0.15 (0.71%)	11.71 (0.34%)	0.15 (1.75%)	0.52

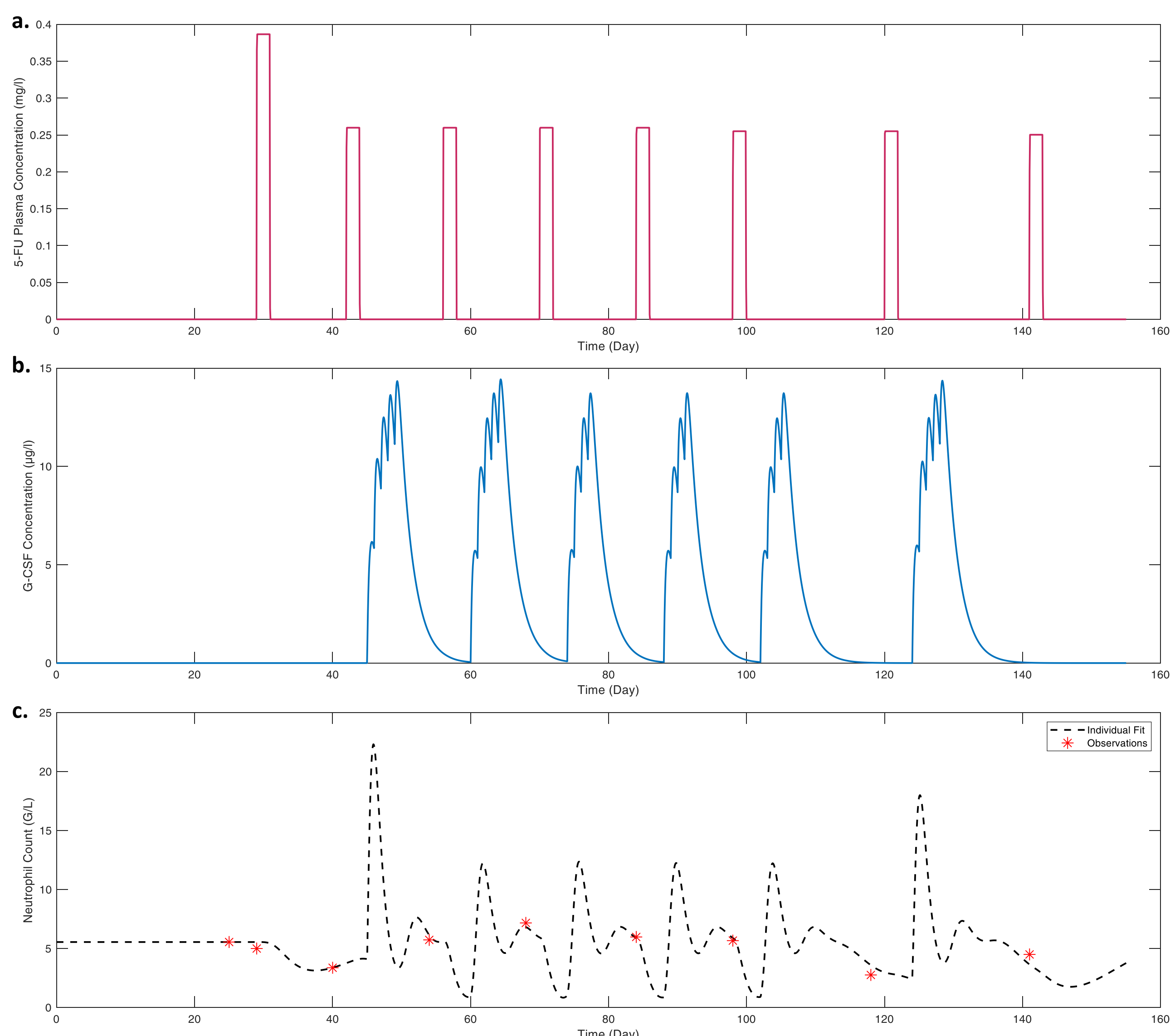


Figure 2 : Example of pharmacokinetics and pharmacodynamics profiles for ID 22

a. 5FU pharmacokinetics b. Total (free and bound) G-CSF pharmacokinetics c. Individual predicted neutrophil profiles (---) and observations (*)

REFERENCES

- Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011;364(19):1817–1825.
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- Pastor ML, Laffont CM, Gladieff L, Schmitt A, Chatelut E, Concorde D. Model-based approach to describe G-CSF effects in carboplatin-treated cancer patients. *Pharm Res.* 2013 Nov;30(11):2795–807.

Simulation of alternative administration protocols of 5FU and G-CSF

Simulation with increasing/decreasing of 5FU infusion duration

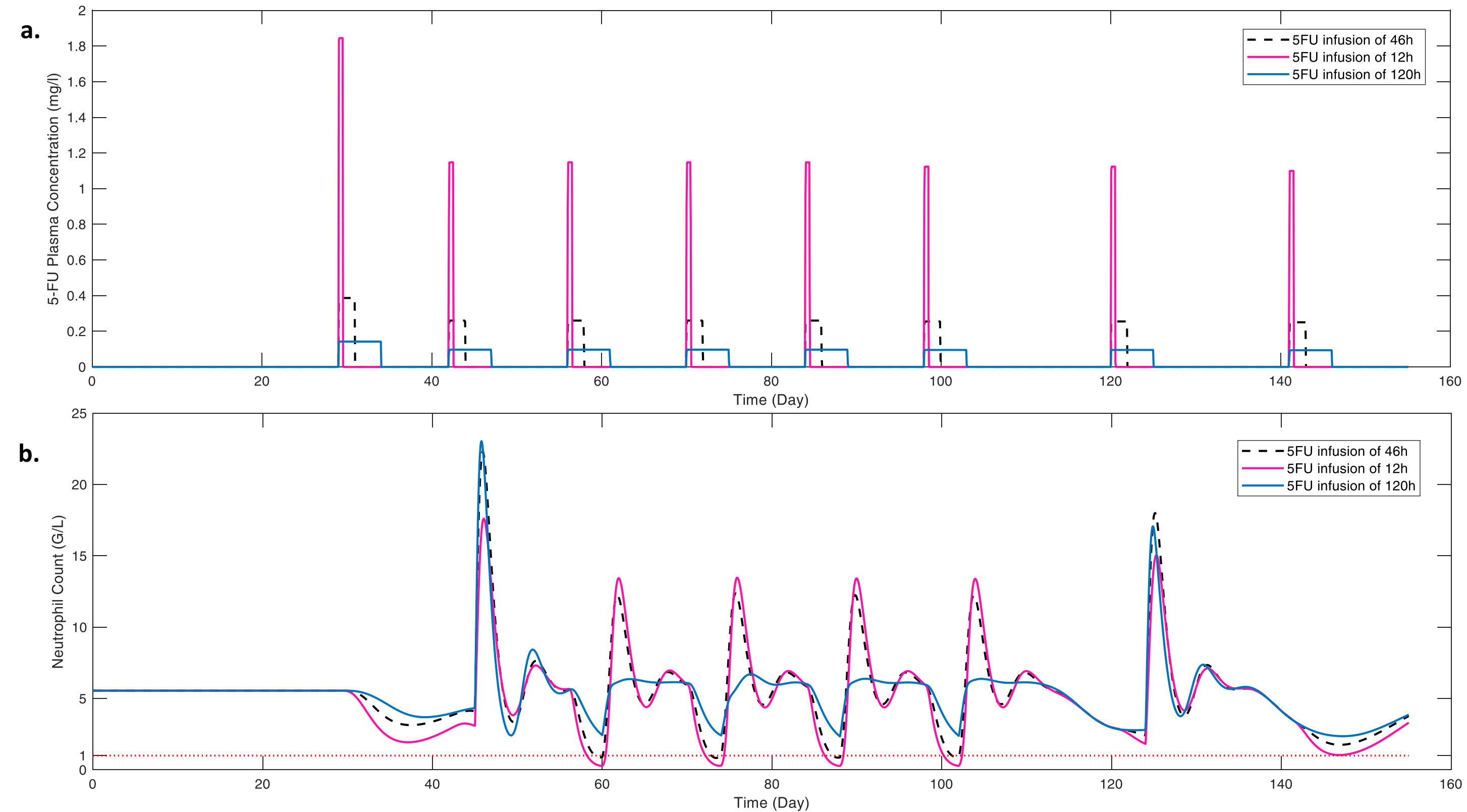


Figure 3 : Simulation of PKPD model with variation on the duration of 5FU infusion. a. 5FU pharmacokinetics. b. Simulated neutrophil profiles.

The PKPD model seems to show the following trends:

- The fluctuations of neutrophil count are reduced with a longer duration of 5FU infusion (120 hours).
- A shorter duration of 5FU infusion (12 hours) involves severe neutropenia and large fluctuations of neutrophils.

Simulation with 5FU infusion of 120 hours and substituting 4 or 5 administrations of G-CSF by one administration of PEG G-CSF at different times after two, four and six days. (D+2, D+4 or D+6)

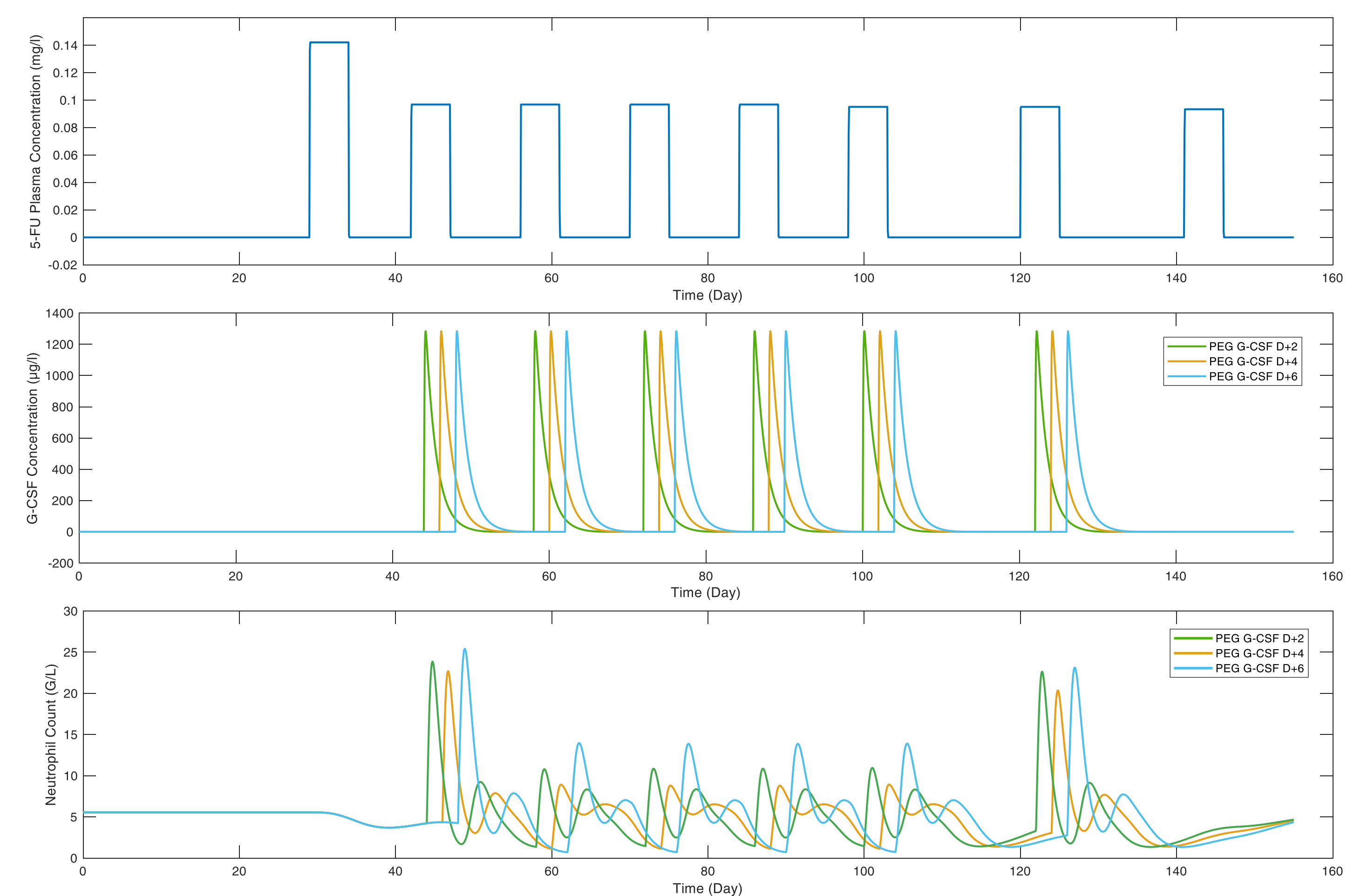


Figure 4 : Simulation of PKPD model with variation on the form of granulocyte-colony stimulating factors. a. 5FU pharmacokinetics. b. PEG G-CSF pharmacokinetics. c. Simulated neutrophil profiles.

The PKPD model seems to show that:

- The fluctuations of neutrophil count are reduced and the nadir level is slightly higher with an administration of PEG G-CSF at D+4 after the start of the 120 hours 5FU infusion duration when compared to D+2 or D+6.

CONCLUSION

- This preliminary modelling work is a proof of concept. PKPD modelling can be a useful tool to improve administration protocol of chemotherapy and G-CSF in FOLFIRINOX regimen (i.e., dosing, scheduling, sequencing).
- To model FOLFIRINOX regimen, effects of oxaliplatin and SN38 (active metabolite of irinotecan) will be considered and PD parameters will be re-estimated in this new context. PD parameters and their variability will be further studied using a population approach.
- Furthermore, to design a new FOLFIRINOX regimen both efficient and clinical feasible, we need to take into account the major categorical adverse effects (such as peripheral neuropathy and digestive toxicities). To this aim, we are developing a model using Hidden Markov Chains to select the administration protocol minimizing the occurrence probabilities of main limiting adverse effects.