M-101

Comparison of PK/PD simulations using ModViz POP, an R-Shiny based PK/PD interface and NONMEM

Hari Krishna Ananthula[1], Bhargava Kandala[1], Pavan Vaddady[1]

[1]Merck &Co. Inc., Kenilworth, NJ, USA

ABSTRACT

Objectives: ModViz POP is a user-friendly interface with built in PK/PD ODE library of models for simulating standard IV bolus, infusion and extravascular models along with user defined scenarios for handling complex QSP and PBPK models (1). The objective of the present work is to compare PK/PD simulations between ModViz POP and NONMEM.

Methods: Using both ModViz POP tool and NONMEM method, simulations were performed for different PK or PK/PD models as indicated in **Table 1**. Additionally, the effect of variability on simulations was assessed at two different levels of between subject variability in PK parameters (10% and 70%), and sample sizes (1000 and 10000). NCA parameters such as AUC_{last}, AUC_{inf}, C_{max} and T_{max} were summarized for NONMEM simulations using PKNCA package in R and compared against ModViz POP reported NCA parameters. PK/PD profiles were compared by plotting 2.5th, 50th and 97.5th percentiles of the simulated data against time.

Results: NCA PK parameters were similar between ModViz POP and NONMEM based PK simulations, with less than 1% fold difference between these two methods. For PK/PD models, PK profiles in central compartment and PD profiles in response compartment were superimposable between both the tools. ModViz simulations for both low and high inter subject variability were similar to corresponding NONMEM simulations as demonstrated by overlaid plots. Further, there was no significant effect of sample size on ModViz simulations in comparison to NONMEM.

Conclusions: ModViz POP simulations are easier to conduct with built-in plotting and NCA capabilities. The results from this analysis indicate that PK/PD simulations using ModViz POP are comparable to NONMEM.

Background

- **ModViz POP** is an interactive and dynamic visualization tool developed for simulating ordinary differential equation based pharmacokinetic and pharmacodynamic (PK/PD) models with variability. This platform has a wide array of library PK/PD models along with flexibility to simulate from any ODE based user defined model using a user-friendly interface.
- It is primarily programmed in R and uses key R packages such as **tidyverse**, **mrgsolve**, **PKNCA** and **xtable**. This tool utilizes R Shiny for the web application framework, LaTeX for PDF report generation, HTML and CSS for styling graphical interface.
- The present work was undertaken to compare PK/PD simulations between ModViz POP and NONMEM.

Methods

- Using both ModViz POP tool and NONMEM, simulations were performed for different PK or PK/PD models as indicated in **Table 1**.
- The sample size for simulations was set to 1000 subjects. Between subject variability on PK and PD parameters was set to 10%. The residual variability model for PK and PD simulations included both additive and proportional residual errors.
- The effect of variability on simulations was assessed at two different levels of between subject variability in PK parameters (10% and 70%). The effect of sample size was assessed by comparing simulations with 1000 and 10000 subjects.
- NCA parameters such as AUC_{last}, AUC_{inf}, C_{max} and T_{max} were summarized for NONMEM simulations using PKNCA package in R and compared against ModViz POP reported NCA parameters.
- PK/PD profiles were compared between the two tools by plotting 2.5th, 50th and 97.5th percentiles of the simulated data against time.

Results

- PK profiles in central compartment were superimposable between the tools, as shown in representative **figures 1 and 2** which correspond to a 2 compartment PK model with 1st order absorption and 1 compartment PK model with IV infusion, respectively.
- Similarly, PD profiles in response compartment were superimposable between the tools, as shown in representative **figures 3 and 4**, which correspond to Emax PK-PD model and Effect compartment PK-PD model, respectively.
- NCA PK parameters were similar between ModViz POP and NONMEM based PK simulations, with less than 1% fold difference between these two methods. **(Table 2)**
- Simulations between the tools were similar at a low BSV of 10% and high BSV of 70% (**Figure 5**).
- Simulations performed with ModViz POP were comparable to NONMEM at different sample sizes as tested with 1000 and 10000 subjects (**Figure 6**)

Table 1: Summary of PK/PD models simulated with ModViz POP & NONMEM

PK model	PD model	Key input PK parameters*	Key input PD Parameters*
IV bolus, 1 cmt	-	CL, V	-
IV infusion, 1 cmt	-	CL, V	-
Extravascular, 1 cmt	-	CL, V, KA, F	-
IV bolus, 2 cmt	-	CL, V1, V2, Q	-
IV infusion, 2 cmt	-	CL, V1, V2, Q	-
Extravascular, 2 cmt	-	CL, V1, V2, Q, KA, F	-
IV bolus, 1 cmt	E_{max} model	CL, V	E0, EC_{50}, E_{max}, n
IV bolus, 1 cmt	Effect cmt	CL, V	E0, EC_{50}, E_{max}, K_{E0}
IV bolus, 1 cmt	IDR-I & II	CL, V	K_{in}, K_{out}, IC_{50}, I_{max}, n
IV bolus, 1 cmt	IDR- III & IV	CL, V	K_{in}, K_{out}, EC_{50}, E_{max}, n

*Between subject variability on all PK and PD parameters was included in simulations.
Abbreviations: cmt, compartment; IV, intravenous; CL, clearance; V1, central volume; V2, peripheral volume; Q, inter compartmental clearance; F, bioavailability; KA, absorption rate constant; E0, baseline effect; IC_{50} or EC_{50}, concentration at half-maximal effect; I_{max} or E_{max}, maximum effect; n, Sigmoidicity; K_{E0}, effect compartment rate constant; IDR, indirect response model; K_{in}, input rate constant, K_{out}, output rate constant

Figure 1: PK for 2 cmt extravascular route

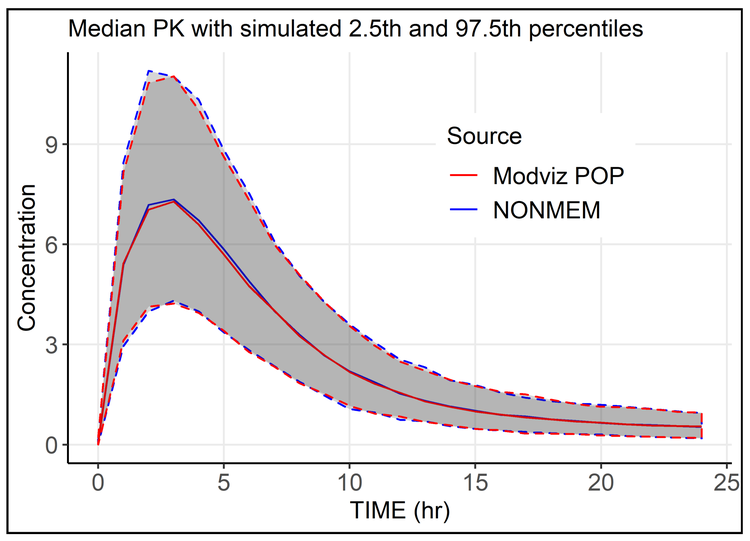


Figure 2: PK for 1 cmt IV infusion

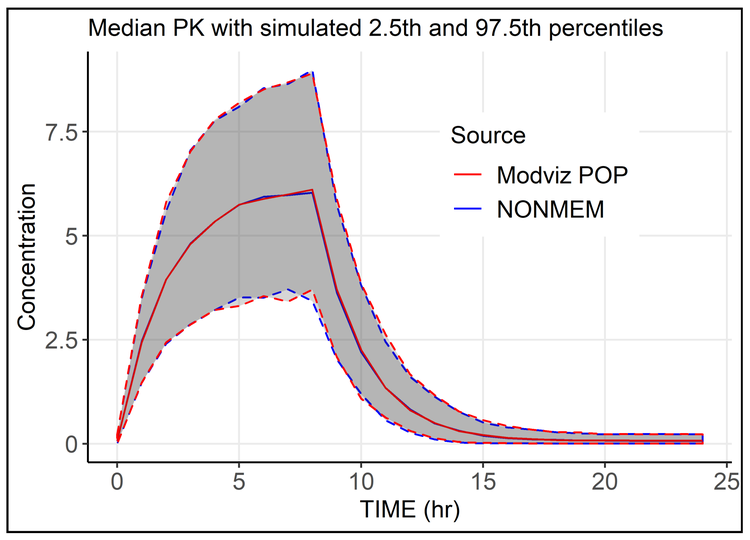


Figure 3: Emax PKPD Model

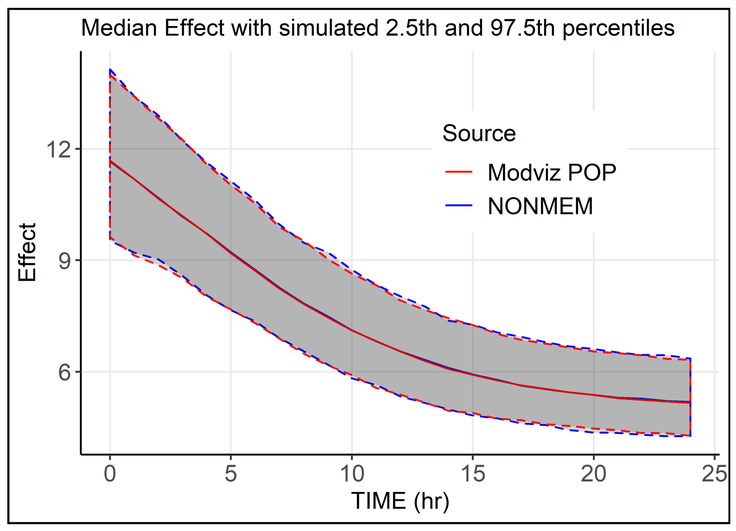


Figure 4: Effect compartment PKPD model

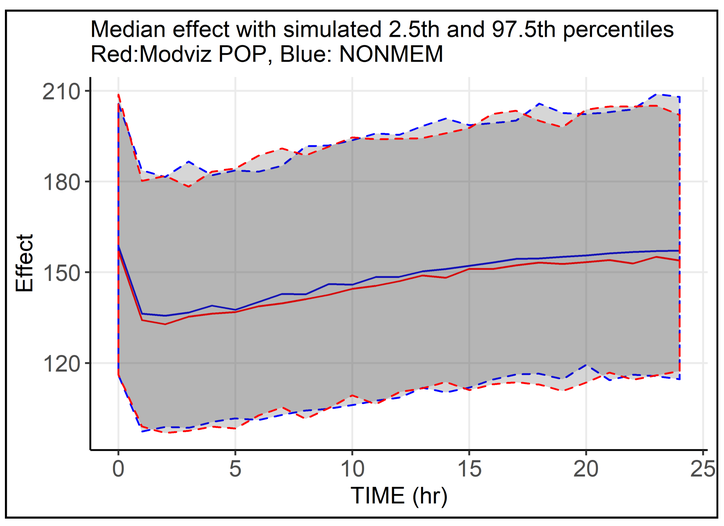


Figure 5: Simulations with low and high BSV for 1 cmt IV bolus PK model

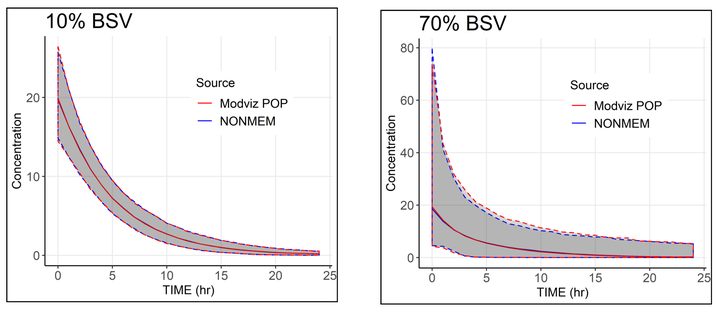
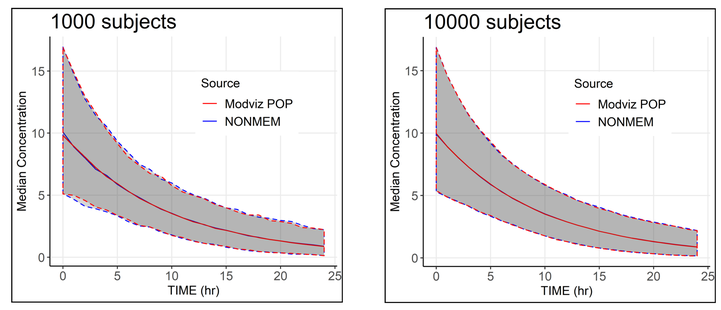


Table 2: Summary of NCA parameters for representative PK models

PK model	Tool	AUClast	Cmax	Tmax	AUCinf.pred
2 cmt extravascular	NONMEM	62.2 [14.2]	8.39 [18.0]	3 [1, 6]	65.2 [14.5]
	ModViz	61.8 [13.5]	8.32 [17.3]	3 [1, 7]	65.0 [14.1]
1 cmt IV infusion	NONMEM	50.0 [11.8]	7.21 [14.3]	6 [2, 9]	50.2 [12.0]
	ModViz	50.1 [11.7]	7.21 [13.7]	7 [2, 8]	50.4 [11.7]

1000 subjects are simulated at a dose of 500 mg. NCA parameters except Tmax are expressed as geometric mean [GCV]. Tmax is summarized as median[range]

Figure 6: Simulations with low and high sample size for 1 cmt IV bolus PK model



Conclusion

- ModViz POP simulations are easier to conduct with built-in plotting and NCA capabilities and the outputs for PK PD models are comparable to NONMEM.

1.Pavan Vaddady and Bhargava Kandala; ModViz Pop: R-Shiny Based PK/PD Interface for Empowering Teams to Perform Real-Time Simulations (M-079), J Pharmacokinet Pharmacodyn (2018) 45:S38

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