Population PKPD analysis using nlmixr and NONMEM

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Objectives

With the aim of making resources required for pharmacometric analysis more easily available, a free R package nlmixr has been developed.[1] It has been reported that its pharmacokinetic (PK) results are similar to those in NONMEM.[2] We wished to evaluate pharmacokinetic and pharmacodynamic (PKPD) performance by comparing nlmixr with NONMEM.

Methods

A turnover (TO) model and an effect compartment (CE) model were selected as examples of delayed effect models. Simultaneous fits of PK and PD data were done. Stochastic approximation expectation maximization (SAEM) and first-order conditional estimation with interaction (FOCEi) were used with nlmixr 1.0.0-7 and NONMEM 7.43.

Logit transform of E_{max} in SAEM estimation of poplogit:

```
logit=poplogit+eta.emax
emax = 1/(1+exp(-logit))
```

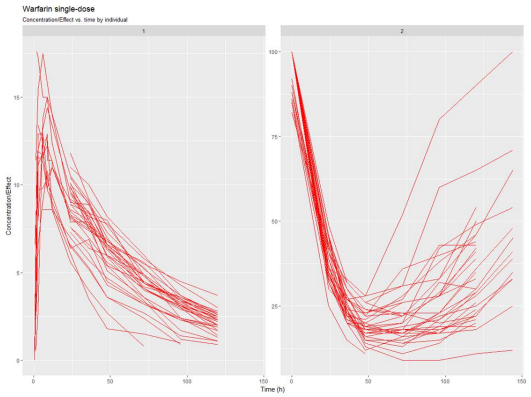
Logit transform of E_{max} in FOCEi estimation of popemax:

```
poplogit = log(popemax/(1-popemax))
logit=poplogit + eta.emax
emax = 1/(1+exp(-logit))
```

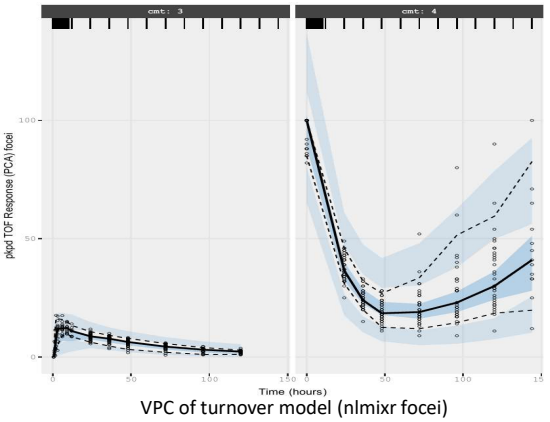
Warfarin plasma concentrations[3,4] were fitted to one-compartment distribution, first order absorption with a single transit compartment and first order elimination model. The prothrombin complex activity (PCA)[3,4] was used as a measure of warfarin effect. The maximum extent of inhibition of PCA by warfarin, E_{max} was logit transformed in the PD models so that E_{max} was in the range of 0 - 1.

Results

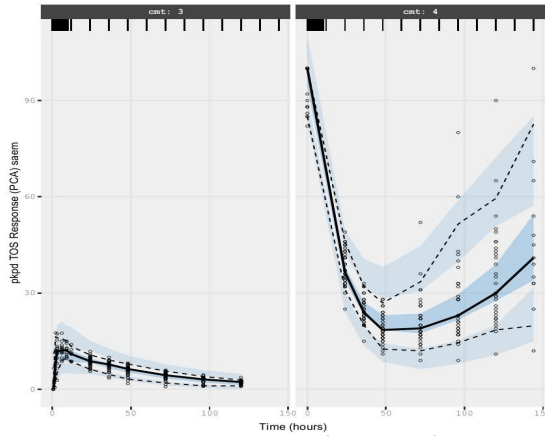
The objective function value (Obj) and parameter estimates from NONMEM and nlmixr are shown in the table. The turnover model using nlmixr saem was better than focei as shown by the Obj but the VPC for warfarin effect was better using focei. NONMEM obtained a better fit (lower Obj) compared to nlmixr for TO models with both focei and saem methods.



Individual time-course plots of PK and PK data



VPC of turnover model (nlmixr focei)



VPC turnover model (nlmixr saem)

Comparison of nlmixr vs. NONMEM

Model	Program	Meth	Obj	POP KTR	POP KA	POP CL	POP V	ETA KTR	ETA KA	ETA CL	ETA V	EPS PKPROP	EPS PKADD	POP EMAX	POP EC50	POP KOUT	POP E0	ETA EMAX	ETA EC50	ETA KOUT	ETA E0	EPS ADD	Total minutes
TO	NM	FOCEI	1326.43	1.10	1.10	0.135	7.78	0.753	0.754	0.281	0.224	0.099	0.474	0.999	1.16	0.0521	96.6	0.01	0.429	0.091	0.052	3.72	8.68
TO	nlmixr	FOCEI	1440.72	1.00	1.00	0.144	8.08	1.11	4.03	0.356	0.203	0.139	0.211	0.976	0.85	0.0529	95.1	1.01	0.523	0.193	0.177	3.90	221
TO	NM	SAEM	1341.14	1.13	1.22	0.134	7.71	0.637	0.638	0.285	0.230	0.101	0.485	0.977	1.04	0.0536	96.6	0	0.459	0.084	0.052	3.82	1.49
TO	nlmixr	SAEM	1374.16	1.51	0.95	0.134	7.74	1.19	0.403	0.279	0.227	0.106	0.280	1.000	1.17	0.0524	96.6	0.565	0.448	0.081	0.052	3.76	1.07
CE	NM	FOCEI	2053.49	1.16	1.16	0.133	7.90	0.802	0.803	0.288	0.224	0.098	0.513	0.536	0.102	0.0072	98.5	0.01	0.327	9.63	0.007	25.2	22.3
CE	nlmixr	FOCEI	1518.18	1.00	1.00	0.134	7.96	0.903	0.851	0.292	0.234	0.106	0.405	0.999	1.71	0.0213	96.9.		0.281	0.293	0.071	6.54	199
CE	NM	SAEM	2067.24	1.17	1.19	0.133	7.86	0.714	0.557	0.293	0.228	0.099	0.527	0.725	0.107	0.0055	130.0	0	0.002	2.59	0.000	25.4	1.48
CE	nlmixr	SAEM	1623.61	1.29	0.96	0.133	8.05	1.06	0.569	0.275	0.214	0.185	0.091	1.000	1.69	0.0219	96.5	0.844	0.306	0.340	0.027	6.60	0.976

Pop emax for nlmixr saem models was estimated as the logit of E_{max}. The expit of the estimate is shown in the table.

Conclusion

The usefulness of nlmixr for simple PKPD phamacometric analysis is shown in this study since it obtained similar results to NONMEM. Simultaneous PKPD analysis is possible using nlmixr in the R environment.

Acknowledgements

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References

1. https://nlmixrdevelopment.github.io/nlmixr_bookdown/index.html
2. https://github.com/nlmixrdevelopment/nlmixr/files/1579013/SpareUUI_171221.pdf
3. O'Reilly RA, Aggeler PM, Leong LS. Studies of the coumarin anticoagulant drugs: The pharmacodynamics of warfarin in man. Journal of Clinical Investigation 1963; 42(10): 1542-1551.
4. O'Reilly RA, Aggeler PM. Studies on coumarin anticoagulant drugs Initiation of warfarin therapy without a loading dose. Circulation 1968; 38: 169-177.