Experience with `nlmixr(2)` at UCL

Joe Standing

j.standing@ucl.ac.uk

Professor of Pharmacometrics: UCL School of Pharmacy / ICH
Honorary Research Pharmacist: Great Ormond Street Hospital for Children
Visiting Professor of Clinical Pharmacology, University of Stellenbosch

2 September 2025

London Pharmacometrics Interest Group, Mondays at 1pm

UCL

- Prof Joe Standing (Paediatrics)
- Dr Frank Kloprogge (Infectious Diseases)
- Prof Suzanne Reeves (Psychiatry)

SGUL

- Dr Dagan Lonsdale (ICU)

RVC

- Prof Ludo Pelligand (Anaesthesia, infection)
- Dr Andrew Mead (Infectious Diseases)

KCL

- Dr Jig Patel (Haematology)
- Dr Charlotte Barker (Pharmacogenomics/Paediatrics)

Others

- Stellenbosch Pharmacometrics Group
- Dr Jan-Stefan van der Walt, Occams
- Dr Martin Johnson, Merck
- Dr Jugal Suthar, Vesynta
- Dr Sue Cole, MHRA

Everyone welcome!

History of `nlmixr` use at UCL

- **2018:** Started to explore `nlmixr` with existing datasets, went on course at ACoP in San Diego
- **2019:** Re-wrote UCL pharmacometrics course to run with `nlmixr`
- **2020:** Fitted SARS-CoV-2 viral dynamic models with `nlmixr`
- **2021 - present:** `nlmixr2` now the default tool used for things like:
  - PK modelling
  - PD modelling
  - PKPD modelling
  - Bayesian TDM
  - Automating pharmacometrics

Overview

- PK modelling
- PD modelling
- PKPD modelling
- Bayesian TDM
- Automating pharmacometrics

CASE 1: SAEM *vs* FOCEI in `nlmixr`

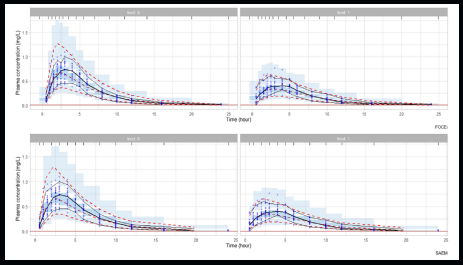
DOI: 10.1111/bcp.15496

ORIGINAL ARTICLE

Assessment of the *nlmixr* R package for population pharmacokinetic modeling: A metformin case study

Wen Yao Mak[1,2] | Qing Xi Ooi[3] | Cintia Valeria Cruz[4] | Irene Looi[5] | Kah Hay Yuen[6] | Joseph F. Standing[7,8]

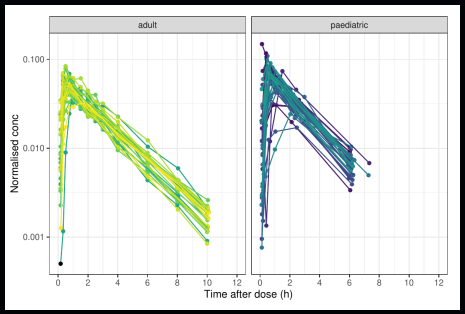
- Compared performance of SAEM and FOCEI on metformin fed/fasted
- Very similar fits/parameter estimates

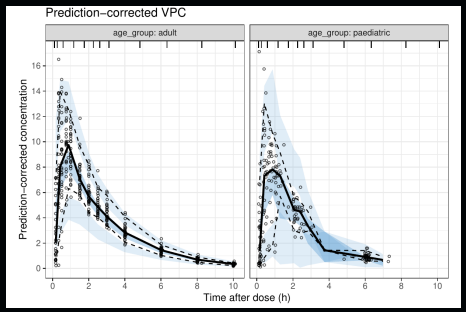


- Simulation/estimation $\rightarrow$ SAEM more robust than FOCEI
- Unclear if still true with `nlmixr2`

CASE 2: Temozolomide paediatric formulation, regulatory submission

- Joint model of volunteer and paediatric patient PK
- Report submitted to FDA and EMA
- Parameter estimates very similar in `NONMEM` (sponsor request not regulator!)





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CASE 3: SARS-CoV-2 viral dynamics

DOI: 10.1002/psp4.13022

ARTICLE

SARS-CoV-2 viral dynamic modeling to inform model selection and timing and efficacy of antiviral therapy

Shengyuan Zhang[1] | Akosua A. Agyeman[2] | Christoforos Hadjichrysanthou[3,4] | Joseph F. Standing[2]

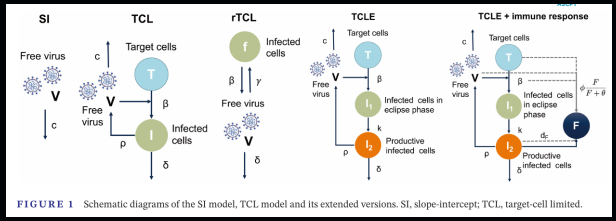
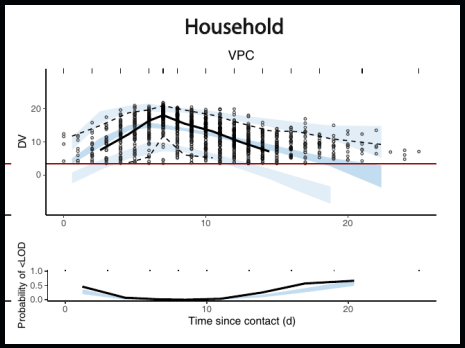
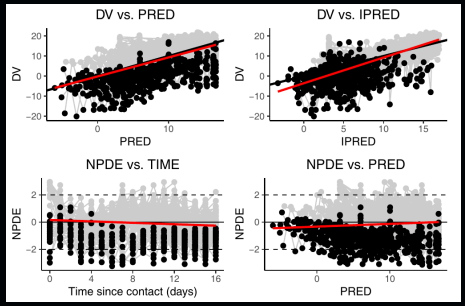


FIGURE 1 Schematic diagrams of the SI model, TCL model and its extended versions. SI, slope-intercept; TCL, target-cell limited.





CASE 4: SARS-CoV-2 viral and antibody dynamics

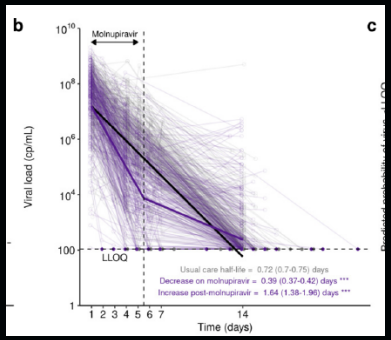
nature communications

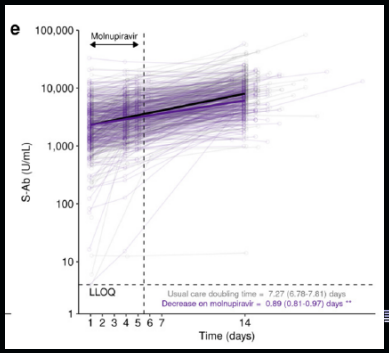
Article

https://doi.org/10.1038/s41467-024-45641-0

Randomized controlled trial of molnupiravir SARS-CoV-2 viral and antibody response in at-risk adult outpatients

- Modelled viral load and spike antibody increase
- Time varying drug effect
- M3 BLQ handling





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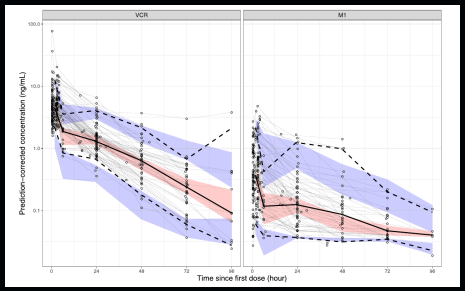
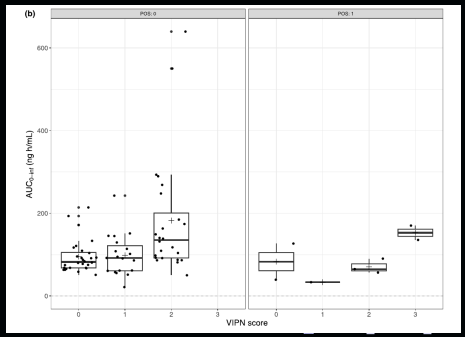
CASE 5: Vincristine PKPD in children with ALL

Pharmacokinetic, Pharmacodynamic and Pharmacogenetic Studies Related to Vincristine-Induced Peripheral Neuropathy in Chinese Pediatric ALL Patients

Yawen Yuan[1,2,*], Wenting Hu[3], Changcheng Chen[3], Ruen Yao[4], Shunguo Zhang[1], Xiao Zhu[5], Bulong Xu[1], Zhonghui Huang[2], Shengyuan Zhang[2], Xuexian Wang[1], Mei Zheng[1], Xiaohui Huang[6,*,†] and Joseph F. Standing[2,*,†]

- Parent/metabolite model
- Quantified probability of toxicity



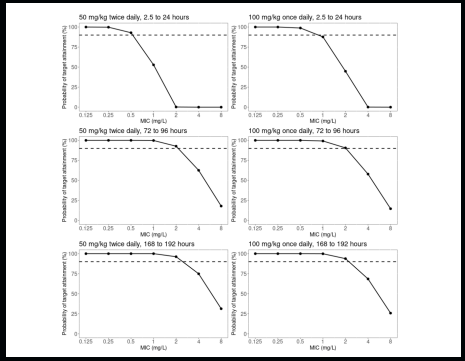


CASE 6: Ceftriaxone CSF PKPD

Population pharmacokinetic modeling of ceftriaxone in cerebrospinal fluid in children: should we be using once- or twice-daily dosing for meningitis?

A. Boast,[1,2,3] W. Zhang,[4] H. Soeorg,[4] G. Gonis,[1] A. Di Carlo,[1] A. Daley,[1,3] N. Curtis,[1,2,3] B. McWhinney,[5] J. P. J. Ungerer,[5,6] A. Lei,[2] J. F. Standing,[4,7] A. Gwee[1,2,3]

- Very sparse plasma data
- PK mainly in CSF
- Simulated probability of target attainment (PTA)



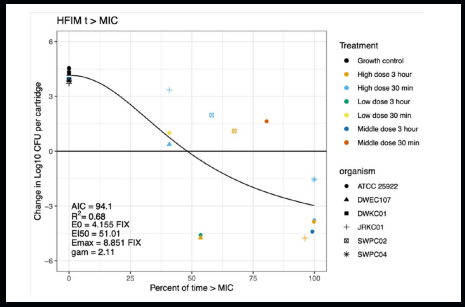
CASE 7: Piperacillin/tazobactam PKPD

https://doi.org/10.1093/jacamr/dlae036

Defining the pharmacokinetic/pharmacodynamic index of piperacillin/tazobactam within a hollow-fibre infection model to determine target attainment in intensive care patients

Suzanne A. M. Wenker[1,2]*, Najla Alabdulkarim[1,3], John B. Readman[1], Elise M. A. Slob[2,4], Giovanni Satta[5], Shanom Ali[6], Nishma Gadher[7], Rob Shulman[7] and Joseph F. Standing[1,8]

- Hollow fibre infection model
- Developed/fitted PK model
- Dose fractionaltion study to define PKPD index
- Simulated PTA

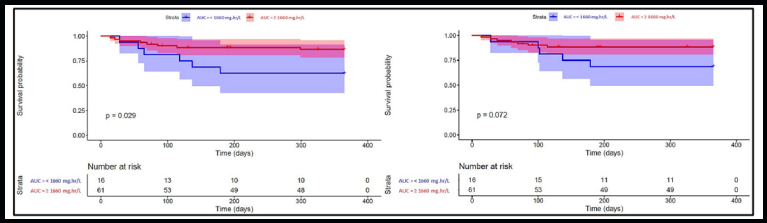


CASE 8: Treosulfan PKPD in haematopoietic stem cell transplant

Treosulfan Exposure Predicts Thalassemia-Free Survival in Patients with Beta Thalassemia Major Undergoing Allogeneic Hematopoietic Cell Transplantation

Aswin Anand Pai[1,2], Ezhilpavai Mohanan[1], John C. Panetta[3], Uday P. Kulkarni[1], Raveen Stephen Stallon Illangeswaran[1], Balaji Balakrishnan[1,6], Agila Jayaraman[1], Eunice S. Edison[1], Kavitha M. Lakshmi[1], Anup J. Devasia[1], Nambiathayil Aboobacker Fouzia[1], Anu Korula[1], Aby Abraham[1], Biju George[1], Alok Srivastava[1], Vikram Mathews[1], Joseph F. Standing[4,5] and Poonkuzhali Balasubramanian[1,*]

- Fitted PK
- Investigated relationship of PK to long-term outcome



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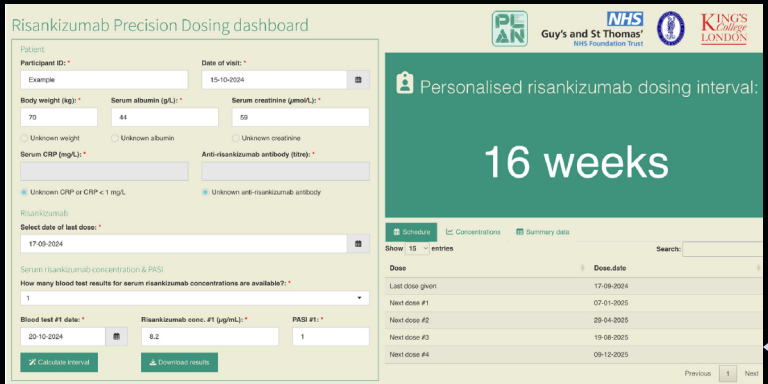
CASE 9: Personalising biologic dosing in Psoriasis

Personalizing Biologic Therapy in Psoriasis: Development, Validation, and User Testing of a Precision-Dosing Dashboard

JID Open

Charlotte M. Thomas[1], David Baudry[1], Zehra Arkir[2], Bola Coker[3], Tejus Dasandi[3], Kingsley Powell[1], Monica Arenas-Hernandez[1], Jenny Leung[3], Krystal Rawstron[3], Chioma Nwaogu[3], Sarah Chapman[1], Richard Woolf[3], Andrew Pink[1], Jonathan Barker[1], Joseph F. Standing[5,6], Catherine H. Smith[1,6] and Satveer K. Mahil[1,6]

- Implemented Bayesian model predictions using `est = "posthoc"`
- Wrote interface with RShiny, installed on secure server
- Currently being tested in clinical trial



CASE 10: Vancomycin model-based TDM in children

Development and Evaluation of Multi-Model Informed Precision Dosing Tool for Optimizing Vancomycin Therapy in Pediatric Patients

Yawen Yuan[1†], Li Xu[2], Yueling Xi[3], Zhonghui Huang[4], Jing Cao[1], Zhiling Li[1†], Joseph F Standing[2†]

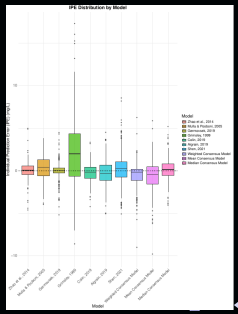
Manuscript *in press*, Therapeutic Drug Monitoring

- Systematic literature review to identify previous models
- Evaluate predictive performance of each model along with consensus (mean, median, consensus)
- Shiny interface code in supplement

$$w_i = \frac{1}{|IPE_i|}$$

$$\widetilde{w}_i = \frac{w_i}{\sum_i w_i}$$

$$\theta_{weighted} = \sum_i \widetilde{w}_i \times \theta_i$$



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CASE 11: Automation of Pharmacometrics

- `nlmixr2autoinit`
  - Manuscript *in press* JPKPD
  - Automated algorithms require an automated way to set initial estimates
  - `PKNCA` fine for rich data, `nlmixr2autoinit` also handles sparse data
  - `devtools::install_github("ucl-pharmacometrics/nlmixr2autoinit")`
- `nlmixr2auto`
  - Automated structural and statistical model building
  - Different algorithms (stepwise, ACO, GA, Tabu) benchmarked against exhaustive search
  - `devtools::install_github("ucl-pharmacometrics/nlmixr2auto")`

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Conclusion

- `nlmixr2` is:
  - A powerful and flexible tool for all areas of pharmacometrics
  - Accepted by major journals and regulators
  - Developing rapidly (?more rapidly than other tools?)

- Acknowledgement:
  - Postdocs: Akosua Agyeman, Yawen Yuan, Hiie Soeorg
  - PhD students: Zhonghui Huang, Aswin Anand Pai
  - **PRE-PhD students**: Wenyao Mak, Cintia Cruz, Shengyuan Zhang, Charlotte Thomas, Suzanne Wenker, Floyd Zhang