

Reproducibility of a Digital Twin of Glimepiride for Personalized and Stratified Diabetes Treatment

Michelle Elias¹ and Matthias König^{1*}

¹Philippsstraße 13, 10115 Berlin, Germany, Humboldt-Universität zu Berlin, Faculty of Life Science, Institute for Biology, Systems Medicine of the Liver

ORIGINAL

Abstract

A digital twin in the form of a whole-body physiologically based pharmacokinetic (PBPK) model of glimepiride was developed to systematically evaluate the influence of patient-specific factors on drug disposition. Based on curated data from 20 clinical studies, the model simulates the absorption, distribution, metabolism and excretion (ADME) of the drug while accounting for variability in renal and hepatic function, CYP2C9 genetic variants and bodyweight. The model is implemented in the Systems Biology Markup Language (SBML) standard and simulations are performed using scripts that utilise the libRoadRunner library to run simulations and generate results. Here, we demonstrate the computational reproducibility of the key findings from the primary publication, thereby verifying the consistency and reproducibility of the model implementation with the published results.

Keywords: Glimepiride, PBPK, SBML, Pharmacokinetics, Computational Model

Curated Model Implementation

<https://doi.org/10.5281/zenodo.1731300>

Primary Publications

M. Elias and M. König. A digital twin of glimepiride for personalized and stratified diabetes treatment. *Frontiers in Pharmacology*, 16:1686415, Oct. 2025. ISSN 1663-9812. doi: 10.3389/fphar.2025.1686415.

1 Introduction

Glimepiride is a second-generation sulfonylurea whose pharmacokinetics are subject to pronounced inter-individual variability (McCall, 2001; Langtry and Balfour, 1998). The disposition of the drug is governed by its extensive metabolism in the liver, primarily by the cytochrome P450 2C9 (CYP2C9) enzyme, into its major metabolites M1 (partially active) and M2 (inactive) (Yoo et al., 2011; Suzuki et al., 2006). This metabolic pathway is a key determinant of the drug's safety and efficacy profile (Douras et al., 2017).

In the primary publication (Elias and König, 2025), a whole-body physiologically based pharmacokinetic (PBPK) model was developed to mechanistically integrate the key factors driving this variability. The model accounts for genetic polymorphisms in CYP2C9 (Yoo et al., 2011; Suzuki et al., 2006), as well as patient-specific renal function, hepatic function, and bodyweight (Rosenkranz, 1996; Rosenkranz et al., 1996; Shukla et al., 2004). The model's structure and parameters were derived from a comprehensive dataset that was curated from 20 published clinical studies which is available via the pharmacokinetics database PK-DB (Grzegorzewski et al., 2021). The model's development and scientific validation are described in detail in the primary paper.

OPEN ACCESS Reproducible Model

*Corresponding author
koenigmx@hu-berlin.de

Here, we present the original model, encoded in the Systems Biology Markup Language (SBML) (Hucka et al., 2019; Keating et al., 2020), and the accompanying simulation scripts required to run the simulations and reproduce the key results presented in the primary publication.

2 Model Description

The disposition of glimepiride is described using a whole-body physiologically based pharmacokinetic (PBPK) model. The model consists of interconnected compartments that simulate key organs involved in the drug's absorption, distribution, metabolism, and excretion (ADME). The mathematical framework of the model are ordinary differential equations (ODE). A schematic overview of the model structure is provided in Figure 1.

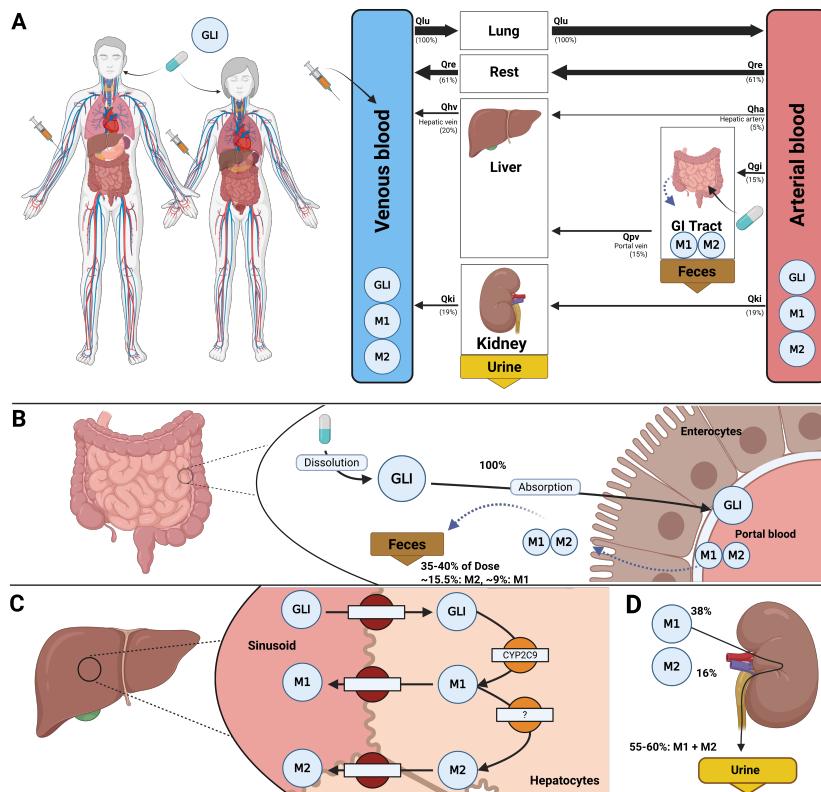


Figure 1. Whole-body PBPK model of glimepiride. A) Whole-body model illustrating glimepiride (GLI) administration (oral and intravenous), its systemic circulation via venous and arterial blood, and the key organs (liver, kidney, GI tract) involved in GLI metabolism, distribution, and excretion. B) Intestinal model showing dissolution and absorption of GLI by enterocytes. No enterohepatic circulation of M1 and M2 is assumed, but reverse transport via enterocytes is included. C) Hepatic model depicting CYP2C9-mediated metabolism of GLI to M1 and M2. D) Renal model highlighting the elimination of M1 and M2 via urine; unchanged GLI is not excreted renally.

The model integrates the three main organ submodels which are interconnected via the systemic circulation. The gastrointestinal tract model simulates the dissolution of orally administered glimepiride, its subsequent first-order absorption, and the fecal excretion of metabolites. The liver model describes the primary metabolic pathway, where glimepiride is converted to its metabolites, M1 and M2. This biotransformation is modelled using Michaelis-Menten kinetics. The kidney model implements the renal excretion of the M1 and M2 metabolites from the plasma into urine via first-order clearance processes.

The model accounts for patient-specific factors through the corresponding scaling parameters. Genetic variability in CYP2C9 activity is controlled by the f_{cyp2c9} parameter, which modulates the

catalytic activity of the conversion of glimepiride via its maximal metabolic rate. The effect of renal impairment is implemented via the f_{renal} function parameter, which directly scales the renal excretion rates of the metabolites. Hepatic impairment is simulated using the $f_{\text{cirrhosis}}$ parameter, which modifies functional liver volume and liver blood flow. The influence of bodyweight is incorporated through allometric scaling of all relevant organ volumes and blood flows.

The PBPK model and its tissue-specific submodels were developed using the Systems Biology Markup Language (SBML) (Hucka et al., 2019; Keating et al., 2020). Programming and visualization of the models were performed using the sbmlutils (König, 2024) and cy3sbml (König et al., 2012) libraries. Numerical solutions for the ordinary differential equations (ODEs) underlying the model were computed using sbmlsim (König, 2021), which is powered by the high-performance SBML simulation engine libRoadRunner (Welsh et al., 2023; Somogyi et al., 2015). The tissue submodels were developed as SBML submodels and coupled with the whole-body model using the hierarchical model composition (comp) SBML extension (Smith et al., 2015). The complete model, submodels, reference simulations and visualisations are available as a COMBINE archive (OMEX) (Bergmann et al., 2014, 2015). The model is annotated with extensive metadata using the open modelling and exchange (OMEX) metadata specification (Neal et al., 2020, 2019). The model was validated using the SBML validator, with the model passing all validation tests including unit tests without errors or warnings. The FAIRness of the model was increased by following the FAIRification of computational models in biology workflow (Balaur et al., 2025).

The model and all associated materials (mathematical formulation, simulation scripts, parameters, and documentation) are publicly available in SBML format and OMEX archive under a CC-BY 4.0 license at <https://github.com/matthiaskoenig/glimepiride-model>, with version 0.6.2 used in the publication and for validation (Elias and König, 2025).

For interactive exploration of the model, a web application was developed. It is publicly accessible at <https://glimepiride.de>, and its source code is available at <https://github.com/matthiaskoenig/glimepiride-app>. As this application utilizes the identical underlying SBML model presented here, it reproduces the same pharmacokinetic profiles for a given set of patient parameters.

3 Computational Simulation

All simulations were performed using Python 3.13 together with the high-performance libRoadRunner simulation engine. The workflow was tested across multiple platforms, including Ubuntu 24.04/25.04 and Windows 11. For SBML model handling and simulation we relied on the sbmlutils and sbmlsim libraries, while data management and figure generation were carried out with standard scientific Python packages.

To ensure reproducibility, we provide two equivalent setups for regenerating all analyses and figures presented in Section 4: (1) a local Python installation using uv, and (2) a containerized workflow using Docker. Both approaches reproduce all results from the primary publication. Reproducibility is continuously validated through automated integration tests, with results available at <https://github.com/matthiaskoenig/glimepiride-model/actions>.

3.1 Python with uv (local install)

This workflow installs the package directly on your machine using uv.

Prerequisite: uv must be installed on your system (<https://docs.astral.sh/uv/getting-started/installation/>).

Clone the repository and move into its folder:

```
| git clone https://github.com/matthiaskoenig/glimepiride-model.git  
| cd glimepiride-model
```

Set up the uv virtual environment and install all dependencies:

```
| uv venv  
| uv sync
```

Run the full analysis:

```
| uv run run_glimepiride -a all -r results
```

All reproduced figures and outputs are written to `./results/` inside the repository.

Alternatively you can use any other way to setup a local python environment (e.g. conda) and install the package after cloning the repository via

```
| pip install -e .
```

or directly from the main branch via

```
| pip install git+https://github.com/matthiaskoenig/glimepiride-model.  
git@main
```

The full analysis can be run in the python environment via

```
| (env) run_glimepiride -a all -r results
```

3.2 Docker (containerized)

This workflow runs the analysis in a preconfigured Docker container.

Prerequisite: Docker must be installed on your system (<https://docs.docker.com/get-docker/>).

Start the container and mount a local `results/` directory:

```
| docker run -v "${PWD}/results:/results" -it matthiaskoenig/glimepiride:  
latest /bin/bash
```

Inside the container, run the analysis. Results will be written to the mounted folder:

```
| uv run run_glimepiride -a all -r /results
```

The reproduced figures and outputs are then accessible on the host system in `./results/`.

If file access is restricted on Linux due to permissions, adjust ownership and rights as follows:

```
| sudo chown $(id -u):$(id -g) -R "${PWD}/results"  
sudo chmod 775 "${PWD}/results"
```

3.3 Available Options

To run only specific parts of the analysis, see the available command-line options:

```
| uv run run_glimepiride --help
```

3.4 Outputs

The complete workflow reproduces all figures and results from the primary publication, including:

- Clinical study reproductions (Figure 2)
- Supplementary material simulations (Figure 3)
- Additional pharmacokinetic analyses (Figure 4)

All outputs are written to the `results/` directory. This folder contains the individual figure panels as PNG files as well as an automatically generated HTML report (`index.html`) that aggregates all figures in a single document. The contents correspond directly to Figures 2–4 of this manuscript.

3.5 Available Options

Specific parts of the analysis can be executed by providing command-line arguments. A full overview of the available options is obtained via:

```
| uv run run_glimepiride --help
```

3.6 Outputs

The workflow reproduces all figures and results from the primary publication, including:

- Clinical study reproductions (Figure 2)
- Supplementary simulations (Figure 3)
- Additional pharmacokinetic analyses (Figure 4)

All results are stored in the `results/` directory. This directory contains the individual figure panels in PNG format as well as an automatically generated HTML report (`index.html`) that consolidates all figures into a single document. The content of this report directly corresponds to Figures 2–4 in the manuscript.

4 Reproducibility Goals

The reproducibility of the glimepiride PBPK model was confirmed by reproducing key figures from the original publication and its supplementary material. The figures presented here are a selection chosen to demonstrate consistent reproduction of results across different dose levels, pathophysiological states and genotypes. Table 1 and Table 2 provide an overview of the simulation observables and the parameter changes specific to each study or experiment. The model and simulation scripts can be used to reproduce the full set of results from the original study and its supplements, including the parameter scan (pharmacokinetic parameter plots), as these are based on the results of the time-course profiles.

Table 1. Plotted observables and parameter changes per study.

StudyID	Plotted (sid)	Changes
Ahmed2016	Cve_gli	BW = 75 kg PODOSE_gli = 1 mg
Badian1994	Cve_gli, Cve_m1, Cve_m2, Cve_m1_m2, Aurine_m1, Aurine_m2, Aurine_m1_m2	BW = 78 kg PODOSE_gli = 1 mg Ri_gli = 1 mg/min (IV start)
Badian1996	Cve_m1, Cve_m2, Aurine_m1, Aurine_m2, Aurine_m1_m2	BW = 75 kg Ri_m1 = 1.5 mg/min (IV start)
Choi2014	Cve_gli, Cve_m1	BW = 70.8 kg PODOSE_gli = 4 mg
FDA1995	Cve_gli, Cve_m1, Cve_m2, Cve_m1_m2, Aurine_m1_m2, Afeces_gli, Afeces_m1, Afeces_m2, Afeces_m1_m2	PODOSE_gli = 1 mg Ri_gli = 1 mg/min (IV start)
Helmy2013	Cve_gli	BW = 72.75 kg PODOSE_gli = 1, 2, 3, 4, 6 mg
Kasichayanula2011c	Cve_gli	PODOSE_gli = 4 mg
Kim2017	Cve_gli	BW = 69.6 kg PODOSE_gli = 4 mg
Lee2012	Cve_gli	BW = 71.8 kg PODOSE_gli = 2 mg LI_f_cyp2c9 = *1/*1, *1/*3, *3/*3
Lehr1990	Cve_gli, Cve_m1, Cve_m2, Cve_m1_m2	PODOSE_gli = 3 mg
Liu2010	Cve_gli, Cve_m1	BW = 64 kg PODOSE_gli = 2 mg
Malerczyk1994	Cve_gli, Aurine_m1_m2	BW = 78 kg PODOSE_gli = 1, 2, 4, 8 mg
Matsuki2007	Cve_gli	PODOSE_gli = 2 mg (single), 1 mg (multiple)
Niemi2002	Cve_gli	BW = 68 kg PODOSE_gli = 0.5 mg LI_f_cyp2c9 = *1/*1, *1/*2, *1/*3
Ratheiser1993	Cve_gli, Aurine_m1_m2	Ri_gli = 0.25, 0.5, 0.75, 1, 1.25, 1.5 mg/min (IV start)
Rosenkranz1996a	Cve_gli, Cve_m1, Cve_m2, Cve_m1_m2, Aurine_m1_m2	PODOSE_gli = 3 mg KI_f_renal_function = normal, mild, moderate, severe
Shukla2004	Cve_gli, Cve_m1, Cve_m2, Cve_m1_m2, Aurine_m1, Aurine_m2, Aurine_m1_m2	BW = 72 kg (normal), 130 kg (obese) PODOSE_gli = 8 mg
Suzuki2006	Cve_gli	PODOSE_gli = 1 mg LI_f_cyp2c9 = *1/*1, *1/*3
Wang2005	Cve_gli	PODOSE_gli = 4 mg LI_f_cyp2c9 = *1/*1, *1/*3, *3/*3
Yoo2011	Cve_gli	BW = 67.6 kg PODOSE_gli = 2 mg LI_f_cyp2c9 = *1/*1, *1/*3

Table 2. Plotted observables and parameter changes per experiment.

StudyID	Plotted (sid)	Changes
BodyweightExperiment	Cve_gli, Cve_m1, Cve_m2, Aurine_m1_m2	PODOSE_gli = 8 mg BW = 45, 70, 95, 120, 145, 170 kg
DoseDependencyExperiment	Cve_gli, Cve_m1, Cve_m2, Aurine_m1_m2	PODOSE_gli = 0, 1, 2, 3, 4, 5, 6, 7, 8 mg
GeneticVariantExperiment	Cve_gli, Cve_m1, Cve_m2, Aurine_m1_m2	PODOSE_gli = 4 mg LI_f_cyp2c9 = *1/*1 (1.00), *1/*2 (0.84), *1/*3 (0.62), *3/*3 (0.23)
RenalImpairmentExperiment	Cve_gli, Cve_m1, Cve_m2, Aurine_m1_m2	PODOSE_gli = 3 mg KI_f_renal_function = Nor- mal (1.00), Mild (0.50), Moderate (0.35), Severe (0.20)
HepaticImpairmentExperiment	Cve_gli, Cve_m1, Cve_m2, Aurine_m1_m2	PODOSE_gli = 3 mg f_cirrhosis = Control (0.00), Mild (0.399), Moder- ate (0.698), Severe (0.813)

4.1 Reproduction of Key Clinical Study Simulations

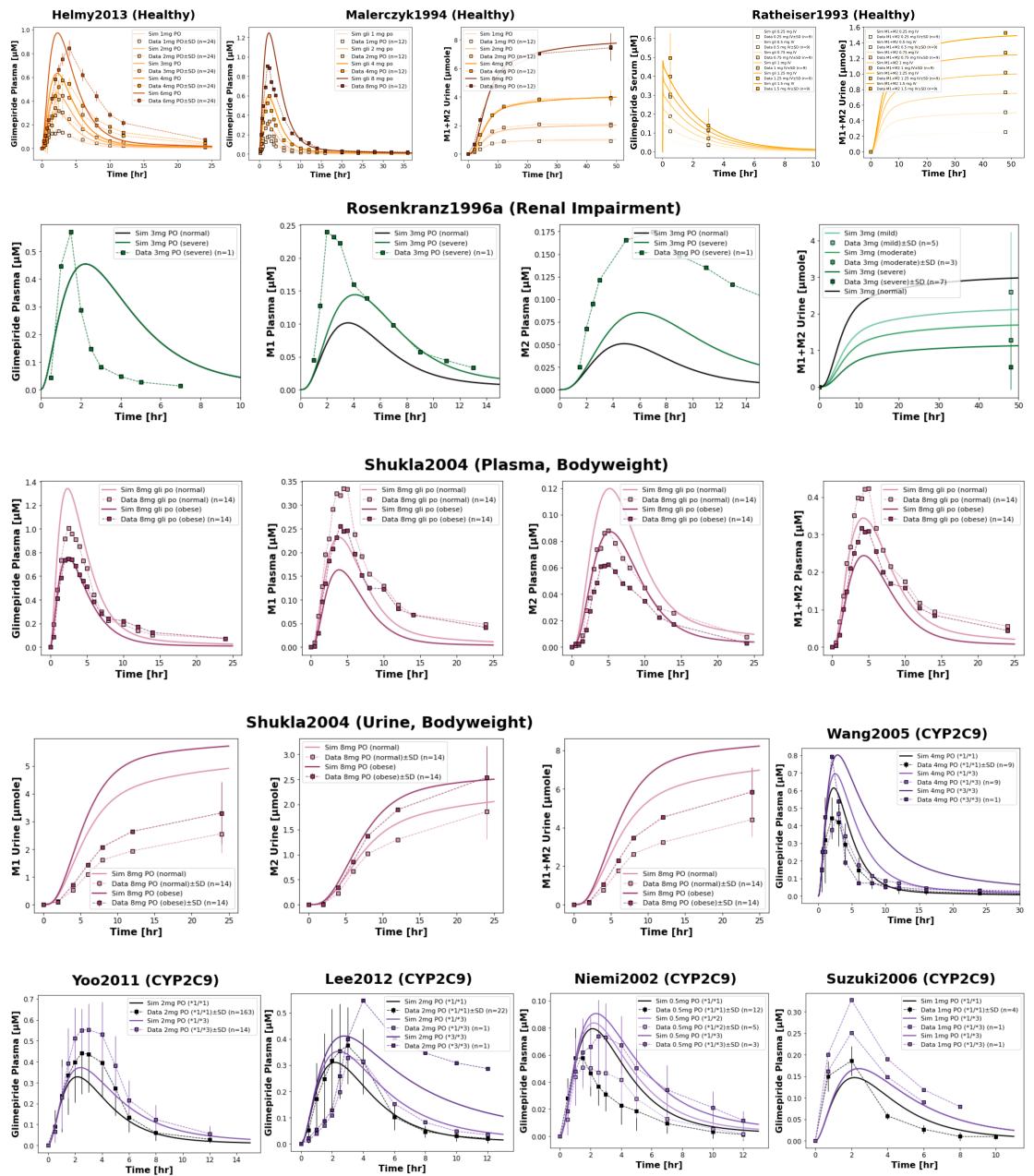


Figure 2. Reproduction of key clinical studies from the primary publication. The model successfully reproduces the influence of renal impairment (Rosenkranz1996a (Rosenkranz et al., 1996)), bodyweight (Shukla2004 (Shukla et al., 2004)), CYP2C9 genetic variants (Wang2005 (Wang et al., 2005), Yoo2011 (Yoo et al., 2011), Lee2012 (Lee et al., 2012), Niemi2002 (Niemi et al., 2002), Suzuki2006 (Suzuki et al., 2006)), and dose dependency (Helmy2013 (Helmy et al., 2013), Malerczyk1994 (Malerczyk et al., 1994), Rattheiser1993 (Rattheiser et al., 1993)) on glimepiride and metabolite pharmacokinetics. Simulated profiles (lines) are compared with observed clinical data (squares connected by dashed lines, with SD shown where available).

4.2 Reproduction of Supplementary Clinical Study Simulations

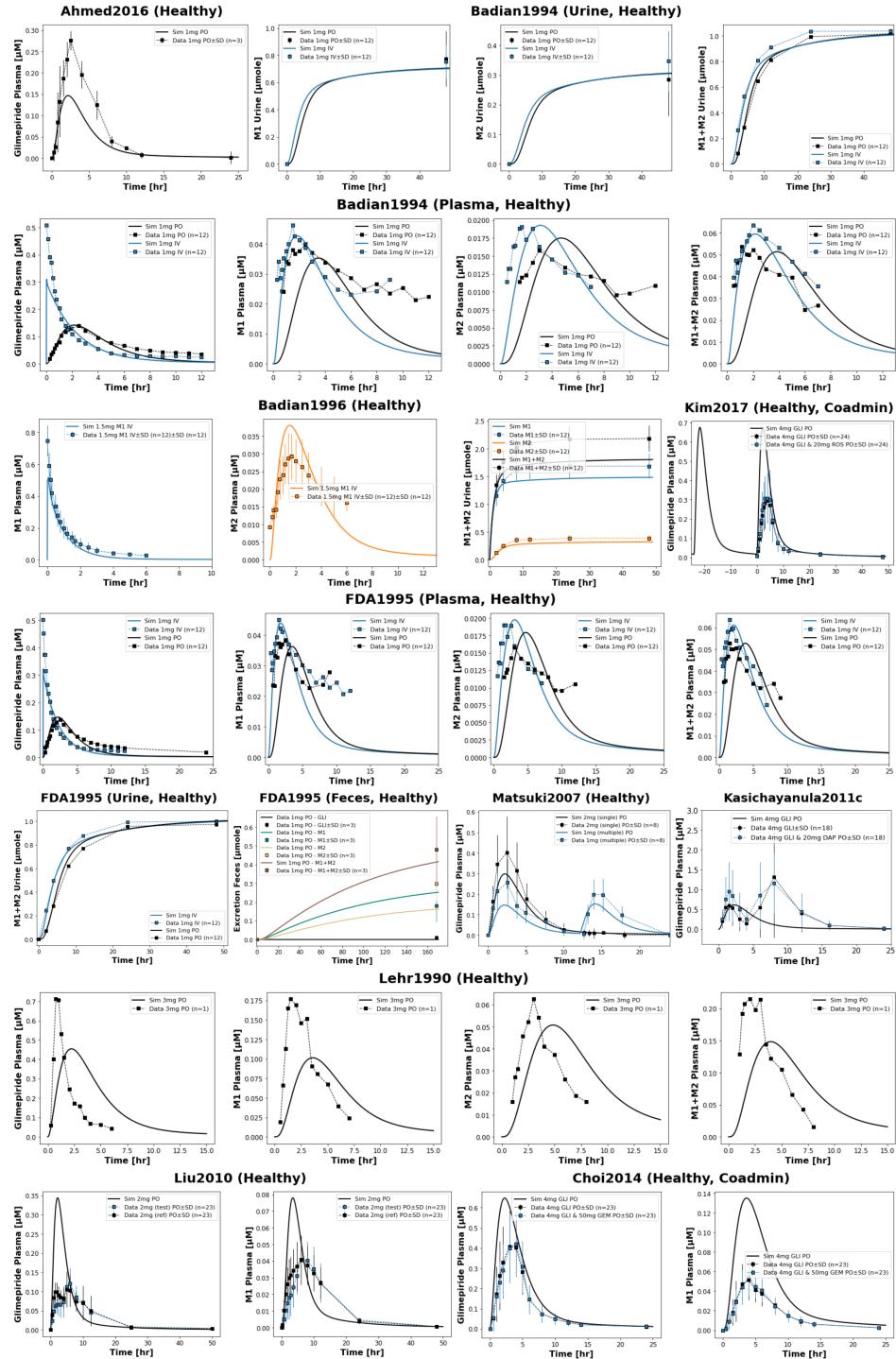


Figure 3. Reproduction of clinical study simulations from the primary publication's supplementary material. The model accurately reproduces pharmacokinetic profiles across various study scenarios (Ahmed2016 (Ahmed et al., 2016), Badian1994 (Badian et al., 1994), Badian1996 (Badian et al., 1996), Choi2014 (Choi et al., 2014), FDA1995 (U.S. Food and Drug Administration (FDA), 1995), Kasichayanula2011c (Kasichayanula et al., 2011), Kim2017 (Kim et al., 2017), Lehr1990 (Lehr and Damm, 1990), Liu2010 (Liu et al., 2010), Matsuki2007 (Matsuki et al., 2007)). Simulated profiles (lines) are compared with observed clinical data squares connected by dashed lines, with SD shown where available).

4.3 Reproduction of Additional Simulations

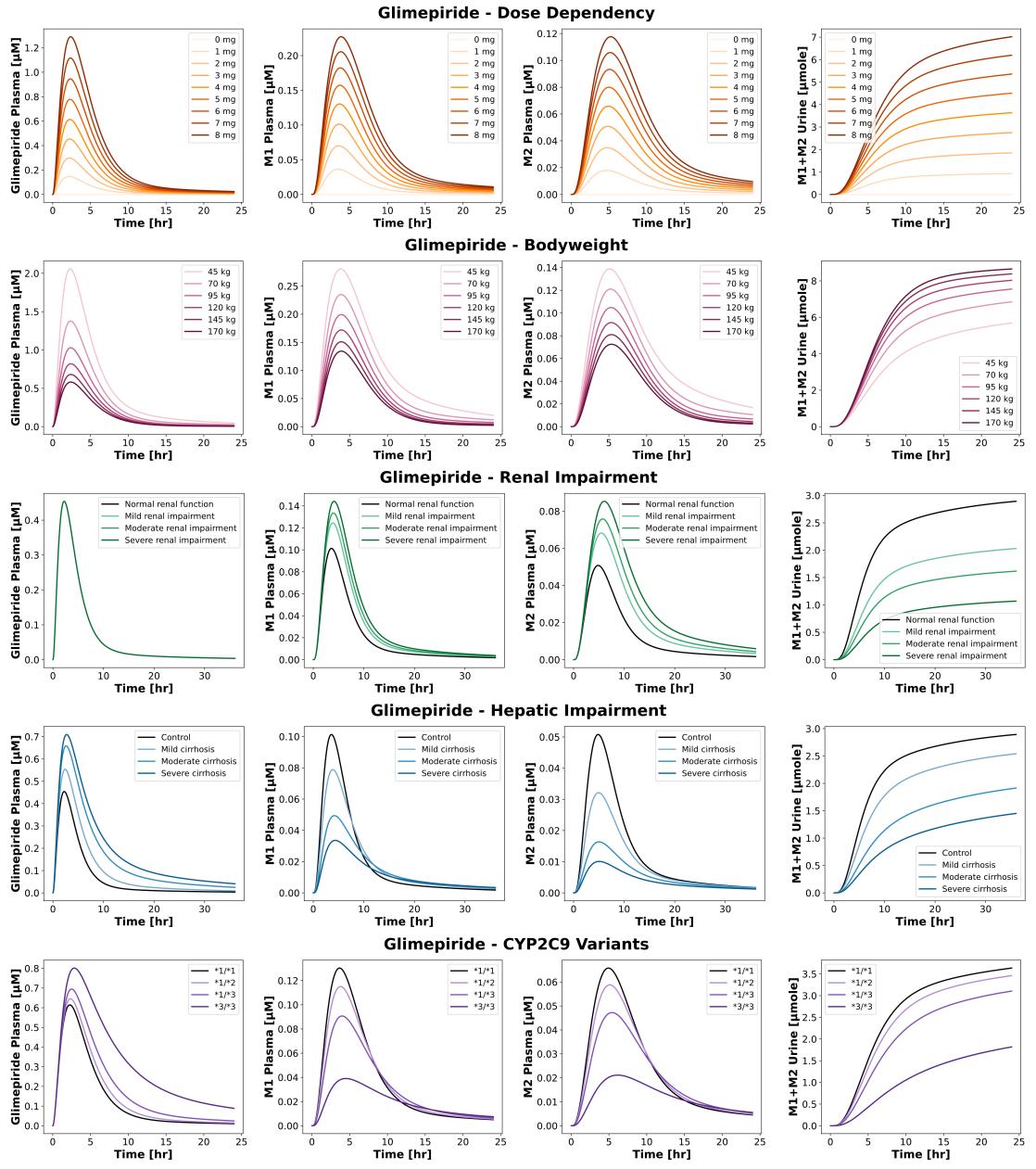


Figure 4. Reproduction of simulations from the primary publication and its supplementary material. The model accurately reproduces pharmacokinetic profiles in various scenarios, including dose dependency, bodyweight dependence, renal impairment, hepatic impairment and CYP2C9 polymorphisms.

5 Discussion

We have demonstrated the computational reproducibility of the key findings from the glimepiride PBPK model presented in the primary publication. Using the provided simulation scripts, all figures were regenerated without modifying parameters or structure, verifying the consistency of the model. Reproducibility was confirmed across different operating systems using both a local installation with uv and a Dockerized workflow. The uv-based approach allows users to install the package and dependencies natively, while the containerized workflow provides a fully preconfigured environment and ensures consistent results independent of the local setup. Encoding the model in SBML with hierarchical composition removes ambiguity and allows modular reuse of the tissue submodels. Together with the use of community standards and FAIR practices, this provides a transparent and reusable resource that can be applied or extended in future pharmacokinetic modelling work.

Author Contributions

M.E. and M.K. contributed to conceptualization, methodology, data curation, development of the PBPK model, analyses, web application, and reproducibility of the computational workflow. M.E. wrote the original draft. M.K. provided supervision throughout the project and contributed to manuscript review and editing. Both authors approved the final manuscript.

Funding

Matthias König (MK) was supported by the Federal Ministry of Education and Research (BMBF, Germany) within ATLAS by grant number 031L0304B and by the German Research Foundation (DFG) within the Research Unit Program FOR 5151 "QuaLiPerF (Quantifying Liver Perfusion-Function Relationship in Complex Resection - A Systems Medicine Approach)" by grant number 436883643 and by grant number 465194077 (Priority Programme SPP 2311, Subproject SimLivA). This work was supported by the BMBF-funded de.NBI Cloud within the German Network for Bioinformatics Infrastructure (de.NBI) (031A537B, 031A533A, 031A538A, 031A533B, 031A535A, 031A537C, 031A534A, 031A532B).

Acknowledgments

Figures were created in BioRender. König, M. (2025) <https://BioRender.com/l01pcwd>.

References

- T. A. Ahmed, K. M. El-Say, B. M. Aljaeid, U. A. Fahmy, and F. I. Abd-Allah. Transdermal glimepiride delivery system based on optimized ethosomal nano-vesicles: Preparation, characterization, in vitro, ex vivo and clinical evaluation. *International journal of pharmaceutics*, 500(1-2):245–254, Mar. 2016. ISSN 1873-3476 0378-5173. doi: 10.1016/j.ijpharm.2016.01.017.
- M. Badian, A. Korn, K. H. Lehr, V. Malerczyk, and W. Waldhäusl. Absolute bioavailability of glimepiride (Amaryl) after oral administration. *Drug metabolism and drug interactions*, 11(4): 331–339, 1994. ISSN 0792-5077. doi: 10.1515/dmdi.1994.11.4.331.
- M. Badian, A. Korn, K. H. Lehr, V. Malerczyk, and W. Waldhäusl. Pharmacokinetics and pharmacodynamics of the hydroxymetabolite of glimepiride (Amaryl) after intravenous administration. *Drug metabolism and drug interactions*, 13(1):69–85, 1996. ISSN 0792-5077. doi: 10.1515/dmdi.1996.13.1.69.
- I. Balaur, D. P. Nickerson, D. Welter, J. A. Wodke, F. Ancien, T. Gebhardt, V. Grouès, H. Hermjakob, M. König, N. Radde, A. Rougny, R. Schneider, R. S. Malik-Sheriff, K. B. Shiferaw, M. Stefan, V. Satagopam, and D. Waltemath. FAIRification of computational models in biology, Mar. 2025.
- F. T. Bergmann, R. Adams, S. Moodie, J. Cooper, M. Glont, M. Golebiewski, M. Hucka, C. Laibe, A. K. Miller, D. P. Nickerson, B. G. Olivier, N. Rodriguez, H. M. Sauro, M. Scharm, S. Soiland-Reyes, D. Waltemath, F. Yvon, and N. Le Novère. COMBINE archive and OMEX format: One file to share all information to reproduce a modeling project. *BMC bioinformatics*, 15(1):369, Dec. 2014. ISSN 1471-2105. doi: 10.1186/s12859-014-0369-z.
- F. T. Bergmann, N. Rodriguez, and N. Le Novère. COMBINE Archive Specification Version 1. *Journal of Integrative Bioinformatics*, 12(2):261, Sept. 2015. ISSN 1613-4516. doi: 10.2390/biecoll-jib-2015-261.
- H. Y. Choi, Y. H. Kim, M. J. Kim, S. H. Lee, K. Bang, S. Han, H.-S. Lim, and K.-S. Bae. Evaluation of pharmacokinetic drug interactions between gemigliptin (dipeptidylpeptidase-4 inhibitor) and glimepiride (sulfonylurea) in healthy volunteers. *Drugs in R&D*, 14(3):165–176, Sept. 2014. ISSN 1179-6901 1174-5886. doi: 10.1007/s40268-014-0054-8.
- A. Douros, H. Yin, O. H. Y. Yu, K. B. Filion, L. Azoulay, and S. Suissa. Pharmacologic Differences of Sulfonylureas and the Risk of Adverse Cardiovascular and Hypoglycemic Events. *Diabetes Care*, 40(11):1506–1513, Nov. 2017. ISSN 0149-5992, 1935-5548. doi: 10.2337/dc17-0595.
- M. Elias and M. König. Physiologically based pharmacokinetic (PBPK) model of glimepiride. Zenodo, Oct. 2025.
- J. Grzegorzewski, J. Brandhorst, K. Green, D. Eleftheriadou, Y. Duport, F. Barthorscht, A. Köller, D. Y. J. Ke, S. De Angelis, and M. König. PK-DB: Pharmacokinetics database for individualized and stratified computational modeling. *Nucleic Acids Research*, 49(D1):D1358–D1364, Jan. 2021. ISSN 1362-4962. doi: 10.1093/nar/gkaa990.
- S. A. Helmy, H. M. El Bedaiwy, and N. O. Mansour. Dose Linearity of Glimepiride in Healthy Human Egyptian Volunteers. *Clinical pharmacology in drug development*, 2(3):264–269, July 2013. ISSN 2160-763X. doi: 10.1002/cpdd.20.
- M. Hucka, F. T. Bergmann, C. Chaouiya, A. Dräger, S. Hoops, S. M. Keating, M. König, N. L. Novère, C. J. Myers, B. G. Olivier, S. Sahle, J. C. Schaff, R. Sheriff, L. P. Smith, D. Waltemath, D. J. Wilkinson, and F. Zhang. The Systems Biology Markup Language (SBML): Language Specification for Level 3 Version 2 Core Release 2. *Journal of Integrative Bioinformatics*, 16(2), June 2019. ISSN 1613-4516. doi: 10.1515/jib-2019-0021.
- S. Kasichayanula, X. Liu, W. C. Shyu, W. Zhang, M. Pfister, S. C. Griffen, T. Li, F. P. LaCreta, and D. W. Boulton. Lack of pharmacokinetic interaction between dapagliflozin, a novel sodium-glucose transporter 2 inhibitor, and metformin, pioglitazone, glimepiride or sitagliptin in healthy subjects. *Diabetes, obesity & metabolism*, 13(1):47–54, Jan. 2011. ISSN 1463-1326 1462-8902. doi: 10.1111/j.1463-1326.2010.01314.x.

- S. M. Keating, D. Waltemath, M. König, F. Zhang, A. Dräger, C. Chaouiya, F. T. Bergmann, A. Finney, C. S. Gillespie, T. Helikar, S. Hoops, R. S. Malik-Sheriff, S. L. Moodie, I. I. Moraru, C. J. Myers, A. Naldi, B. G. Olivier, S. Sahle, J. C. Schaff, L. P. Smith, M. J. Swat, D. Thieffry, L. Watanabe, D. J. Wilkinson, M. L. Blinov, K. Begley, J. R. Faeder, H. F. Gómez, T. M. Hamm, Y. Inagaki, W. Liebermeister, A. L. Lister, D. Lucio, E. Mjolsness, C. J. Proctor, K. Raman, N. Rodriguez, C. A. Shaffer, B. E. Shapiro, J. Stelling, N. Swainston, N. Tanimura, J. Wagner, M. Meier-Schellersheim, H. M. Sauro, B. Palsson, H. Bolouri, H. Kitano, A. Funahashi, H. Hermjakob, J. C. Doyle, M. Hucka, and SBML Level 3 Community members. *SBML Level 3: An extensible format for the exchange and reuse of biological models*. *Molecular Systems Biology*, 16(8):e9110, Aug. 2020. ISSN 1744-4292. doi: 10.1525/msb.20199110.
- C. O. Kim, E. S. Oh, H. Kim, and M. S. Park. Pharmacokinetic interactions between glimepiride and rosuvastatin in healthy Korean subjects: Does the SLCO1B1 or CYP2C9 genetic polymorphism affect these drug interactions? *Drug design, development and therapy*, 11:503–512, 2017. ISSN 1177-8881. doi: 10.2147/DDDT.S129586.
- M. König. Sbmlsim: SBML simulation made easy, Sept. 2021.
- M. König. Sbmlutils: Python utilities for SBML. Zenodo, Aug. 2024.
- M. König, A. Dräger, and H.-G. Holzhütter. CySBML: A Cytoscape plugin for SBML. *Bioinformatics*, 28(18):2402–2403, Sept. 2012. ISSN 1367-4811, 1367-4803. doi: 10.1093/bioinformatics/bts432.
- H. D. Langtry and J. A. Balfour. Glimepiride. A review of its use in the management of type 2 diabetes mellitus. *Drugs*, 55(4):563–584, Apr. 1998. ISSN 0012-6667. doi: 10.2165/00003495-199855040-00007.
- H. W. Lee, M.-s. Lim, J. Lee, M.-Y. Jegal, D.-W. Kim, W.-K. Lee, I.-J. Jang, J.-G. Shin, and Y.-R. Yoon. Frequency of CYP2C9 variant alleles, including CYP2C9*13 in a Korean population and effect on glimepiride pharmacokinetics. *Journal of clinical pharmacy and therapeutics*, 37(1):105–111, Feb. 2012. ISSN 1365-2710 0269-4727. doi: 10.1111/j.1365-2710.2010.01238.x.
- K. H. Lehr and P. Damm. Simultaneous determination of the sulphonylurea glimepiride and its metabolites in human serum and urine by high-performance liquid chromatography after pre-column derivatization. *Journal of chromatography*, 526(2):497–505, Apr. 1990. doi: 10.1016/s0378-4347(00)82531-1.
- Y. Liu, M.-q. Zhang, J.-m. Zhu, J.-y. Jia, Y.-m. Liu, G.-y. Liu, S. Li, L.-p. Weng, and C. Yu. Bioequivalence and pharmacokinetic evaluation of two formulations of glimepiride 2 mg: A single-dose, randomized-sequence, open-label, two-way crossover study in healthy Chinese male volunteers. *Clinical therapeutics*, 32(5):986–995, May 2010. ISSN 1879-114X 0149-2918. doi: 10.1016/j.clinthera.2010.04.016.
- V. Malerczyk, M. Badian, A. Korn, K. H. Lehr, and W. Waldhäusl. Dose linearity assessment of glimepiride (Amaryl) tablets in healthy volunteers. *Drug metabolism and drug interactions*, 11(4):341–357, 1994. ISSN 0792-5077. doi: 10.1515/dmdi.1994.11.4.341.
- M. Matsuki, M. Matsuda, K. Kohara, M. Shimoda, Y. Kanda, K. Tawaramoto, M. Shigetoh, F. Kawasaki, K. Kotani, and K. Kaku. Pharmacokinetics and pharmacodynamics of glimepiride in type 2 diabetic patients: Compared effects of once- versus twice-daily dosing. *Endocrine journal*, 54(4):571–576, Aug. 2007. ISSN 0918-8959. doi: 10.1507/endocrj.k06-052.
- A. L. McCall. Clinical review of glimepiride. *Expert Opinion on Pharmacotherapy*, 2(4):699–713, Apr. 2001. ISSN 1465-6566. doi: 10.1517/14656566.2.4.699.
- M. L. Neal, M. König, D. Nickerson, G. Mısırlı, R. Kalbasi, A. Dräger, K. Atalag, V. Chelliah, M. T. Cooling, D. L. Cook, S. Crook, M. de Alba, S. H. Friedman, A. Garny, J. H. Gennari, P. Gleeson, M. Golebiewski, M. Hucka, N. Juty, C. Myers, B. G. Olivier, H. M. Sauro, M. Scharm, J. L. Snoep, V. Touré, A. Wipat, O. Wolkenhauer, and D. Waltemath. Harmonizing semantic annotations for

- computational models in biology. *Briefings in Bioinformatics*, 20(2):540–550, Mar. 2019. ISSN 1477-4054. doi: 10.1093/bib/bby087.
- M. L. Neal, J. H. Gennari, D. Waltemath, D. P. Nickerson, and M. König. Open modeling and exchange (OMEX) metadata specification version 1.0. June 2020. doi: 10.18452/32800.
- M. Niemi, I. Cascorbi, R. Timm, H. K. Kroemer, P. J. Neuvonen, and K. T. Kivistö. Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. *Clinical pharmacology and therapeutics*, 72(3):326–332, Sept. 2002. ISSN 0009-9236. doi: 10.1067/mcp.2002.127495.
- K. Ratheiser, A. Korn, W. Waldhäusl, M. Komjati, H. Vierhapper, M. Badian, and V. Malerczyk. Dose relationship of stimulated insulin production following intravenous application of glimepiride in healthy man. *Arzneimittel-Forschung*, 43(8):856–858, Aug. 1993. ISSN 0004-4172.
- B. Rosenkranz. Pharmacokinetic basis for the safety of glimepiride in risk groups of NIDDM patients. *Hormone and Metabolic Research = Hormon- Und Stoffwechselforschung = Hormones Et Métabolisme*, 28(9):434–439, Sept. 1996. ISSN 0018-5043. doi: 10.1055/s-2007-979833.
- B. Rosenkranz, V. Profozic, Z. Metelko, V. Mrzljak, C. Lange, and V. Malerczyk. Pharmacokinetics and safety of glimepiride at clinically effective doses in diabetic patients with renal impairment. *Diabetologia*, 39(12):1617–1624, Dec. 1996. ISSN 0012-186X. doi: 10.1007/s001250050624.
- U. A. Shukla, E. M. Chi, and K.-H. Lehr. Glimepiride pharmacokinetics in obese versus non-obese diabetic patients. *The Annals of pharmacotherapy*, 38(1):30–35, Jan. 2004. ISSN 1060-0280. doi: 10.1345/aph.1C397.
- L. P. Smith, M. Hucka, S. Hoops, A. Finney, M. Ginkel, C. J. Myers, I. Moraru, and W. Liebermeister. SBML Level 3 package: Hierarchical Model Composition, Version 1 Release 3. *Journal of Integrative Bioinformatics*, 12(2):268, Sept. 2015. ISSN 1613-4516. doi: 10.2390/biecoll-jib-2015-268.
- E. T. Somogyi, J.-M. Bouteiller, J. A. Glazier, M. König, J. K. Medley, M. H. Swat, and H. M. Sauro. libRoadRunner: A high performance SBML simulation and analysis library. *Bioinformatics*, 31(20):3315–3321, Oct. 2015. ISSN 1367-4811, 1367-4803. doi: 10.1093/bioinformatics/btv363.
- K. Suzuki, T. Yanagawa, T. Shibasaki, N. Kaniwa, R. Hasegawa, and M. Tohkin. Effect of CYP2C9 genetic polymorphisms on the efficacy and pharmacokinetics of glimepiride in subjects with type 2 diabetes. *Diabetes research and clinical practice*, 72(2):148–154, May 2006. ISSN 0168-8227. doi: 10.1016/j.diabres.2005.09.019.
- U.S. Food and Drug Administration (FDA). Glimepiride Drug Label – FDA Approved Information. Technical report, U.S. Food and Drug Administration (FDA), 1995.
- R. Wang, K. Chen, S.-y. Wen, J. Li, and S.-q. Wang. Pharmacokinetics of glimepiride and cytochrome P450 2C9 genetic polymorphisms. *Clinical pharmacology and therapeutics*, 78(1):90–92, July 2005. ISSN 0009-9236. doi: 10.1016/j.clpt.2005.03.008.
- C. Welsh, J. Xu, L. Smith, M. König, K. Choi, and H. M. Sauro. libRoadRunner 2.0: A high performance SBML simulation and analysis library. *Bioinformatics*, 39(1):btac770, Jan. 2023. ISSN 1367-4811. doi: 10.1093/bioinformatics/btac770.
- H.-D. Yoo, M.-S. Kim, H.-Y. Cho, and Y.-B. Lee. Population pharmacokinetic analysis of glimepiride with CYP2C9 genetic polymorphism in healthy Korean subjects. *European journal of clinical pharmacology*, 67(9):889–898, Sept. 2011. ISSN 1432-1041 0031-6970. doi: 10.1007/s00228-011-1035-2.