Supplementary Information for: A Digital Twin of Glimepiride for Personalized and Stratified Diabetes Treatment

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S1 Prisma Workflow (Fig. S1)

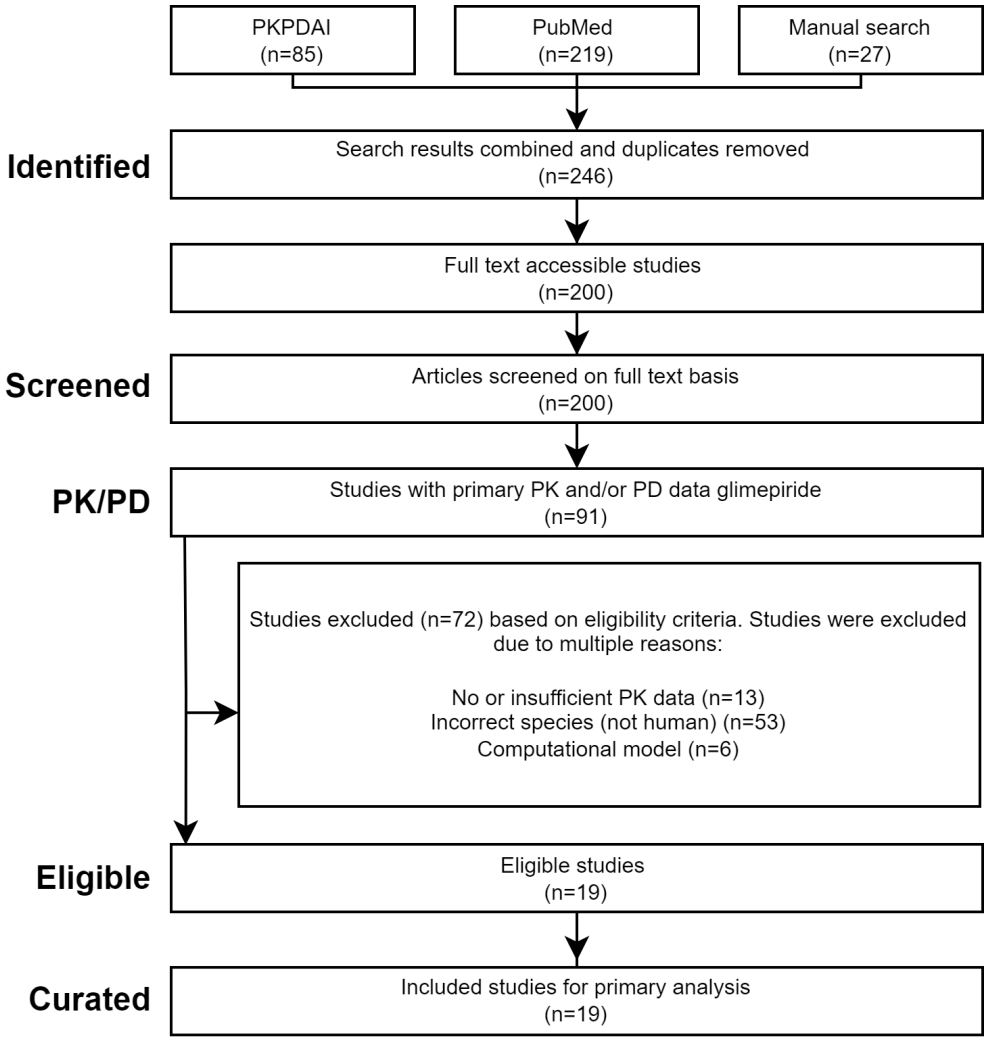

Fig. S1 PRISMA flow diagram. Overview of data selection for the pharmacokinetics dataset of glimepiride established in this work. PubMed, PKPDAI, and manual searches were used for the literature search on the pharmacokinetics of glimepiride. Application of the eligibility criteria resulted in 19 studies.

S2 Submodels (Fig. S2)

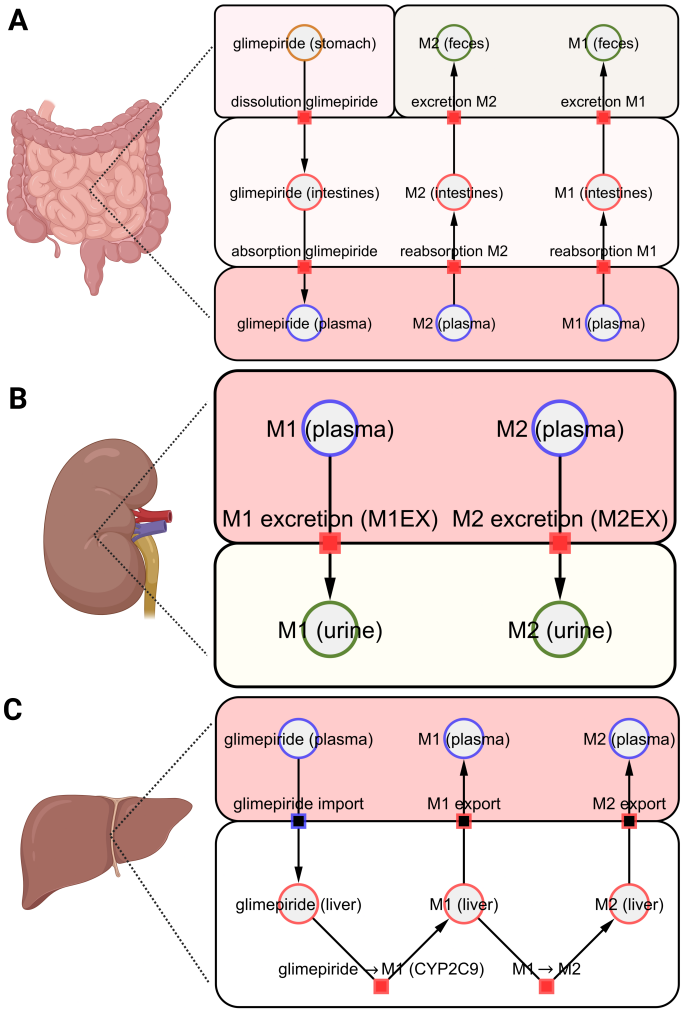

Fig. S2 Visualizations of the submodels. A) Intestine model: Glimepiride dissolves in the stomach, then transfers to the intestinal lumen, where it can be absorbed into plasma. Metabolites M1 and M2 undergo reabsorption into the intestinal lumen and excretion into feces. **B) Kidney model:** Metabolites M1 and M2 are transported from plasma to urine. **C) Liver model:** Glimepiride is transported from plasma to the liver, where it undergoes CYP2C9-mediated metabolism to form M1. This intermediate is further converted to M2. Both M1 and M2 are then exported back to plasma.

S3 Model Equations

The model and all associated materials (simulation scripts, parameters, and documentation) are publicly available in SBML format under a CC-BY 4.0 license at https://github.com/matthiaskoenig/glimepiride-model, version 0.6.1 [1], which also contains detailed model reports. The following sections provide an overview of the mathematical descriptions and ODEs for all submodels.

S3.1 Intestine Model

Dissolution of glimepiride ($\text{PODOSE}_{\text{gli}}$) (mass to amount):

$$\text{dissolution}_{gli} = \frac{\text{Ka}_{dis\_gli}}{60} \cdot \frac{\text{PODOSE}_{gli}}{\text{Mr}_{gli}}$$

where Ka_{dis_gli} [hr^{-1}] is scaled by $\frac{1}{60}$ to min^{-1}, PODOSE_{gli} is the oral dose [mg], and Mr_{gli} [g/mol] is the molecular weight of glimepiride.

The corresponding ODE is:

$$\frac{d\,PODOSE_{\text{gli}}}{dt} = -\text{dissolution}_{gli} \cdot \text{Mr}_{gli}$$

Absorption rate from intestinal lumen to systemic circulation:

$$\text{GLIABS} = f_{\text{absorption}} \cdot \text{GLIABS}_k \cdot V_{\text{lumen}} \cdot \text{gli}_{lumen}$$

where $f_{\text{absorption}}$ is a scaling factor for food effects, GLIABS_k [min^{-1}] is the first-order absorption rate constant, V_{lumen} [L] is the volume of the intestinal lumen, and gli_{lumen} [mmol/L] is the lumen concentration of glimepiride.

Net change in lumen glimepiride concentration:

$$\frac{d\,\text{gli}_{lumen}}{dt} = -\frac{\text{GLIABS}}{V_{\text{lumen}}} + \frac{\text{dissolution}_{gli}}{V_{\text{lumen}}}$$

Reabsorption rates for M1 (M1REABS) and M2 (M2REABS) from plasma to intestinal lumen:

$$\text{M1REABS} = \text{MREABS}_k \cdot \text{m1}_{ext} \cdot V_{\text{lumen}}$$

$$\text{M2REABS} = \text{MREABS}_k \cdot \text{m2}_{ext} \cdot V_{\text{lumen}}$$

where m1_{ext} and m2_{ext} [mmol/L] are the plasma concentrations of M1 and M2, respectively, and MREABS_k [min^{-1}] is the first-order reabsorption rate constant.

Excretion from lumen to feces for M1 (M1EXC) and M2 (M2EXC):

$$\text{M1EXC} = \text{MEXC}_k \cdot \text{m1}_{lumen} \cdot V_{\text{lumen}}$$

$$\text{M2EXC} = MEXC_{\text{k}} \cdot m2_{\text{lumen}} \cdot V_{\text{lumen}}$$

where m1_{lumen} and m2_{lumen} [mmol/L] are lumen concentrations of M1 and M2, respectively, and MEXC_k [min^{-1}] is the excretion rate constant.

Net changes in lumen concentrations are:

$$\frac{d\,\text{m1}_{lumen}}{dt} = \frac{\text{M1REABS}}{V_{\text{lumen}}} - \frac{\text{M1EXC}}{V_{\text{lumen}}}$$

$$\frac{d\,\text{m2}_{lumen}}{dt} = \frac{\text{M2REABS}}{V_{\text{lumen}}} - \frac{\text{M2EXC}}{V_{\text{lumen}}}$$

Metabolite accumulation in feces(cumulative amounts m1_{feces}, m2_{feces} [mmol]):

$$\frac{d\,\text{m1}_{feces}}{dt} = \text{M1EXC}$$

$$\frac{d\,\text{m2}_{feces}}{dt} = \text{M2EXC}$$

Total fecal metabolites:

$$\text{mtot}_{feces} = \text{m1}_{feces} + \text{m2}_{feces}$$

Plasma concentration changes due to absorption/reabsorption are:

$$\frac{d\,\text{gli}_{ext}}{dt} = \frac{\text{GLIABS}}{V_{ext}}$$

where V_{ext} [L] is the plasma volume.

Plasma M1 and M2 concentration changes due to reabsorption from lumen:

$$\frac{d\,\mathrm{m1}_{ext}}{dt} = -\frac{\mathrm{M1REABS}}{V_{ext}}$$

$$\frac{d\,\mathrm{m2}_{ext}}{dt} = -\frac{\mathrm{M2REABS}}{V_{ext}}$$

Key parameters for the intestinal model:

- $\mathrm{Ka}_{\mathrm{dis\_gli}}$ [hr^{-1}]: Dissolution rate constant for glimepiride.
- $\mathrm{GLIABS}_{\mathrm{k}}$ [min^{-1}]: Absorption rate constant.
- $\mathrm{MREABS}_{\mathrm{k}}$, MEXC_k [min^{-1}]: Reabsorption and excretion rate constants for M1 and M2.
- V_{lumen} [L]: Volume of the intestinal lumen.
- $\mathrm{Mr}_{\mathrm{gli}}$ [g/mol]: Molecular weight of glimepiride.
- $\mathrm{f}_{\mathrm{absorption}}$ [-]: Scaling factor for food effects.
- $\mathrm{V}_{\mathrm{ext}}$ [L]: Plasma volume.

S3.2 Kidney Model

Renal excretion rates for M1 (M1EX) and M2 (M2EX):

$$\mathrm{M1EX} = f_{\mathrm{renal\_function}} \cdot V_{\mathrm{ki}} \cdot \mathrm{M1EX}_k \cdot m1_{\mathrm{ext}}$$

$$\mathrm{M2EX} = f_{\mathrm{renal\_function}} \cdot V_{\mathrm{ki}} \cdot \mathrm{M2EX}_k \cdot m2_{\mathrm{ext}}$$

where $f_{\mathrm{renal\_function}}$ is a scaling factor, V_{ki} [L] is the kidney compartment volume, $\mathrm{M1EX}_k$ and $\mathrm{M2EX}_k$ [min^{-1}] are excretion rate constants, and $m1_{\mathrm{ext}}$, $m2_{\mathrm{ext}}$ [mmol/L] are the plasma concentrations.

Estimated glomerular filtration rate (eGFR):

$$\mathrm{egfr} = f_{\mathrm{renal\_function}} \cdot \mathrm{egfr}_{healthy}$$

where $\mathrm{egfr}_{\mathrm{healthy}}$ [$\mathrm{ml/min/m}^2$] represents the typical eGFR value in a healthy individual.

Creatinine clearance (crcl) derivation:

$$\text{crcl} = \frac{\text{egfr} \cdot \text{BSA}}{1.73} \cdot 1.1$$

where BSA [m^2] is the body surface area, crcl is expressed in [mL/min], 1.73 [m^2] is the standard adult BSA used for normalization, and the factor 1.1 is a correction factor that accounts for the systematic overestimation of creatinine clearance compared to the actual GFR.

ODEs for plasma concentrations and urine amounts:

For M1:

$$\frac{d\, m1_{\text{ext}}}{dt} = -\frac{\text{M1EX}}{V_{\text{ext}}}$$

$$\frac{d\, m1_{\text{urine}}}{dt} = \text{M1EX}$$

For M2:

$$\frac{d\, m2_{\text{ext}}}{dt} = -\frac{\text{M2EX}}{V_{\text{ext}}}$$

$$\frac{d\, m2_{\text{urine}}}{dt} = \text{M2EX}$$

where V_{ext} [L] is the plasma volume.

Key parameters for the kidney model:

- M1EX_k, M2EX_k [min^{-1}]: First-order excretion rate constants for M1 and M2.
- V_{ki} [L]: Kidney compartment volume.
- V_{ext} [L]: Plasma volume in the kidney.
- $f_{\text{renal\_function}}$ [-]: Scaling factor to account for normal or impaired renal function.

S3.3 Liver Model

Glimepiride import rate from plasma to liver (GLIIM):

$$\text{GLIIM} = \text{GLIIM}_k \cdot V_{\text{li}} \cdot \left(\text{gli}_{ext} - \text{gli}\right)$$

where GLIIM_k [min^{-1}] is the import rate constant, V_{li} [L] is the liver volume, and gli_{ext}, gli [mmol/L] are the glimepiride concentrations in plasma and liver, respectively.

Glimepiride conversion to M1:

$$\text{GLI2M1} = f_{\text{cyp2c9}} \cdot \text{GLI2M1}_{Vmax} \cdot V_{\text{li}} \cdot \frac{\text{gli}}{\text{gli} + \text{GLI2M1}_{Km\_gli}}$$

where f_{cyp2c9} is a scaling factor for CYP2C9 activity, GLI2M1_{Vmax} [mmol min^{-1} L^{-1}] is the maximum rate of conversion of GLI to M1, and GLI2M1_Km_gli [mmol/L] is the Michaelis constant.

M1 export to plasma (M1EX):

$$\text{M1EX} = \text{M1EX}_k \cdot V_{\text{li}} \cdot \left(\text{m1} - \text{m1}_{ext}\right)$$

M1 conversion to M2 (M12M2):

$$\text{M12M2} = \text{M12M2}_k \cdot V_{\text{li}} \cdot \text{m1}$$

where M12M2_k [min^{-1}] is the rate constant, and m1 [mmol/L] is the M1 concentration in the liver.

M2 export rate to plasma (M2EX):

$$\text{M2EX} = \text{M2EX}_k \cdot V_{\text{li}} \cdot \left(\text{m2} - \text{m2}_{ext}\right)$$

where m2 and m2_{ext} are liver and plasma concentration, and M2EX_k [min^{-1}] is the M2 export rate constant.

ODEs for liver concentrations:

$$\begin{aligned}
\frac{d\,\text{gli}}{dt} &= \frac{\text{GLIIM}}{V_{\text{li}}} - \frac{\text{GLI2M1}}{V_{\text{li}}} \\
\frac{d\,\text{m1}}{dt} &= \frac{\text{GLI2M1}}{V_{\text{li}}} - \frac{\text{M1EX}}{V_{\text{li}}} - \frac{\text{M12M2}}{V_{\text{li}}} \\
\frac{d\,\text{m2}}{dt} &= \frac{\text{M12M2}}{V_{\text{li}}} - \frac{\text{M2EX}}{V_{\text{li}}}
\end{aligned}$$

ODEs for plasma concentration changes due to liver exchange/metabolism:

$$\begin{aligned}
\frac{d\,\text{gli}_{\text{ext}}}{dt} &= -\frac{\text{GLIIM}}{V_{\text{ext}}} \\
\frac{d\,\text{m1}_{\text{ext}}}{dt} &= \frac{\text{M1EX}}{V_{\text{ext}}}
\end{aligned}$$

$$\frac{d\,\mathrm{m2_{ext}}}{dt} = \frac{\mathrm{M2EX}}{V_{\mathrm{ext}}}$$

This model assumes glimepiride is fully metabolized by the liver. CYP2C9 enzyme activity is varied by f_{cyp2c9}. Glimepiride to M1 conversion follows Michaelis-Menten kinetics, while M1 to M2 conversion follows mass-action kinetics. Metabolite exports are modeled as first-order processes driven by concentration gradients.

Key parameters for the liver model:

- GLIIM_k [min^{-1}]: Glimepiride import rate constant (plasma $\rightarrow$ liver).
- $\mathrm{GLI2M1}_{Vmax}$ [$\mathrm{mmol\,min}^{-1}\,\mathrm{L}^{-1}$], GLI2M1_Km_gli [mmol/L]: Michaelis-Menten parameters for glimepiride $\rightarrow$ M1 conversion.
- $\mathrm{M12M2}_k$ [min^{-1}]: First-order rate constant for M1 $\rightarrow$ M2.
- $\mathrm{M1EX}_k, \mathrm{M2EX}_k$ [min^{-1}]: Rate constants for M1 and M2 export.
- f_{cyp2c9} [-]: Scaling factor for CYP2C9 activity.
- V_{li}, V_{ext} [L]: Volumes of liver and plasma compartments, respectively.

S4 Parameter Optimization

S4.1 Optimal Parameters (Tab. S1)

Table S1 Optimized parameters for the glimepiride PBPK model.

Parameter	Value	Unit	Description
$\texttt{GU\_\_GLIABS}_{\texttt{k}}$	0.01590	min^{-1}	Absorption rate constant of glimepiride into plasma.
$\texttt{GU\_\_MREABS}_{\texttt{k}}$	0.01592	min^{-1}	Reabsorption rate constant of metabolites into the intestines.
$\texttt{GU\_\_MEXC}_{\texttt{k}}$	0.00017	min^{-1}	Fecal excretion rate constant of metabolites.
$\texttt{LI\_\_GLI2M1}_{\texttt{Vmax}}$	0.00005	mmole/min/L	Maximum velocity of glimepiride to M1 conversion in the liver.
$\texttt{LI\_\_M1EX}_{\texttt{k}}$	0.07774	min^{-1}	Transport rate constant of M1 from the liver to plasma.
$\texttt{LI\_\_M12M2}_{\texttt{k}}$	0.01485	min^{-1}	Rate constant of M1 to M2 conversion in the liver.
$\texttt{LI\_\_M2EX}_{\texttt{k}}$ [1]	99.99817	min^{-1}	Transport rate constant of M2 from the liver to plasma.
$\texttt{KI\_\_M1EX}_{\texttt{k}}$	0.14801	min^{-1}	Renal excretion rate constant of M1 into urine.
$\texttt{KI\_\_M2EX}_{\texttt{k}}$	0.09849	min^{-1}	Renal excretion rate constant of M2 into urine.
$\texttt{ftissue}_{\texttt{gli}}$	0.00071	L/min	Tissue-to-plasma partition coefficient of glimepiride.
$\texttt{Kp}_{\texttt{gli}}$ [2]	10.02060	-	Partition coefficient for glimepiride distribution.

A total of 100 optimization runs were performed.
[1] Reached upper bound during parameter optimization.
[2] Reached lower bound during parameter optimization.

S4.2 Parameter Optimization Results (Fig. S3)

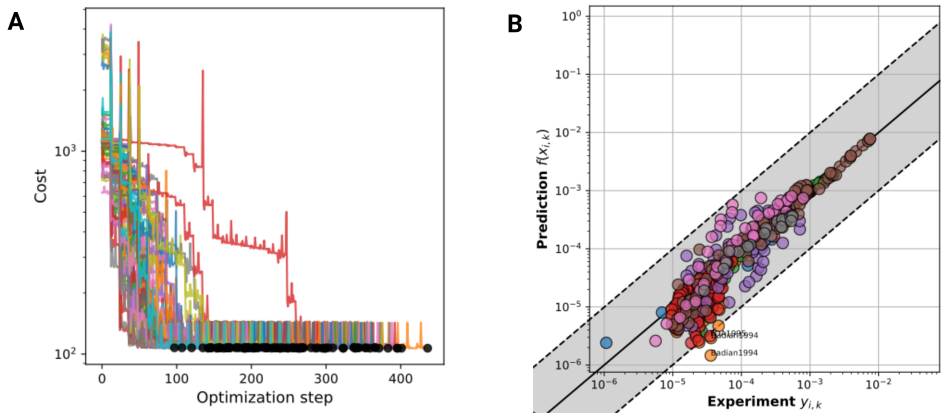

Fig. S3 Results of the parameter fitting. A) Cost reduction over optimization steps. **B)** Goodness-of-fit plot comparing model predictions to experimental data.

S5 Simulations

S5.1 Dose Dependency (Fig. S4)

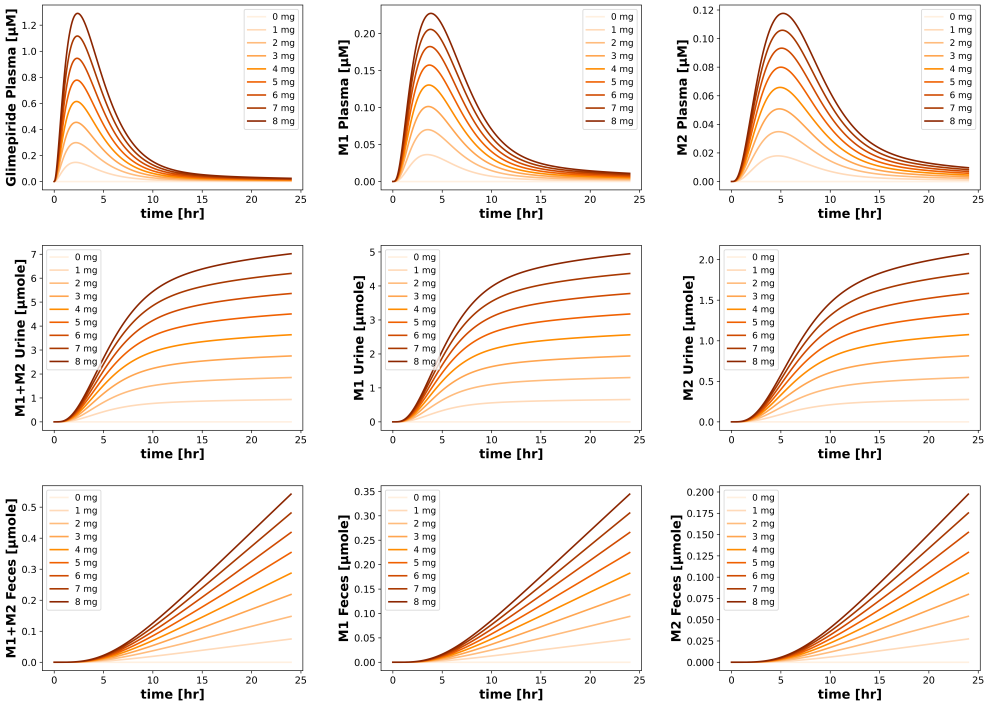

Fig. S4 Simulated concentration-time and cumulative excretion-time profiles of glimepiride and its primary metabolites following various oral doses. Profiles were generated for multiple glimepiride doses to demonstrate dose dependency in absorption, metabolism, and excretion.

S5.2 Renal Impairment (Fig. S5)

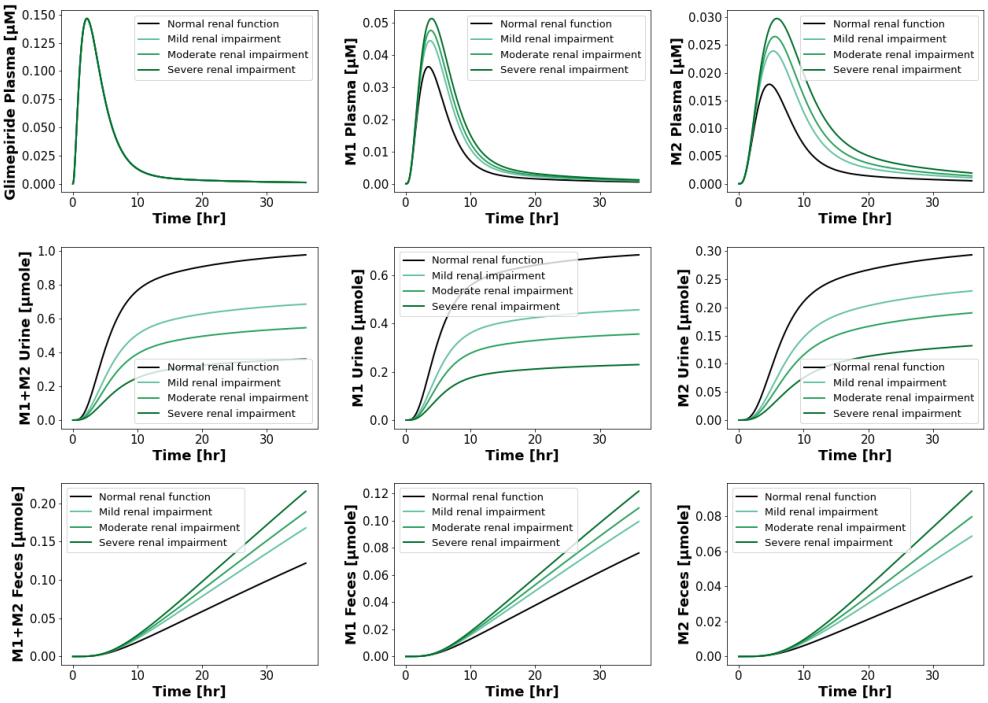

Fig. S5 Simulated pharmacokinetic profiles of glimepiride (3 mg dose) and its metabolites across varying degrees of renal impairment. Concentration-time curves and cumulative excretion patterns are compared to normal renal function.

S5.3 Hepatic Impairment (Fig. S6)

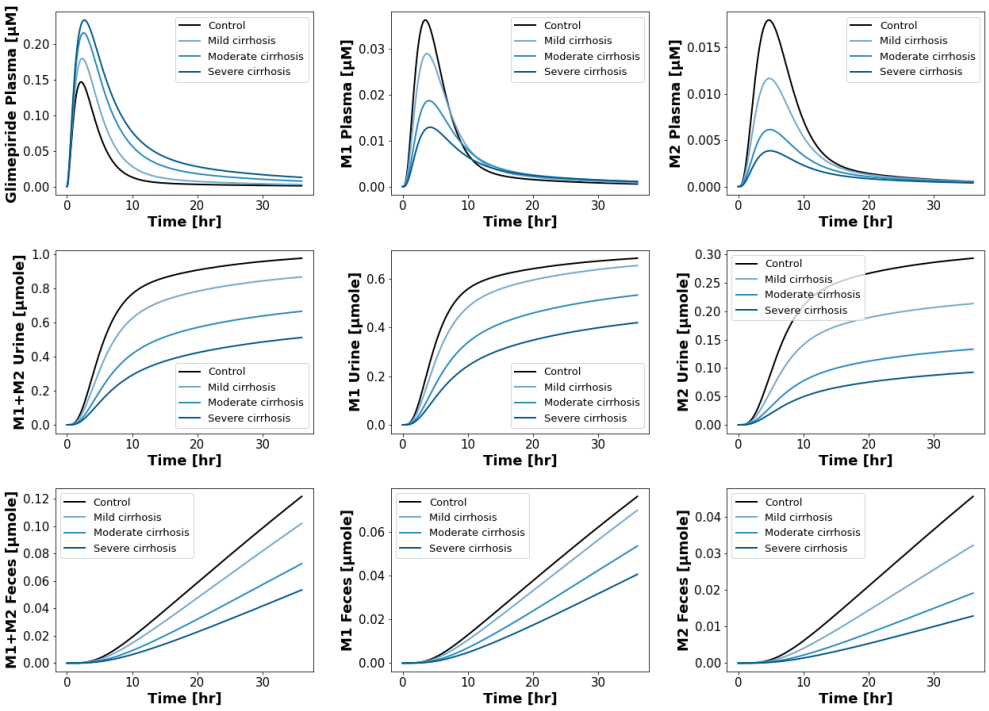

Fig. S6 Simulated pharmacokinetic profiles of glimepiride (1 mg dose) and its metabolites across varying degrees of cirrhosis. Concentration-time curves and cumulative excretion patterns are compared to normal (control) hepatic function.

S5.4 Bodyweight Dependency (Fig. S7)

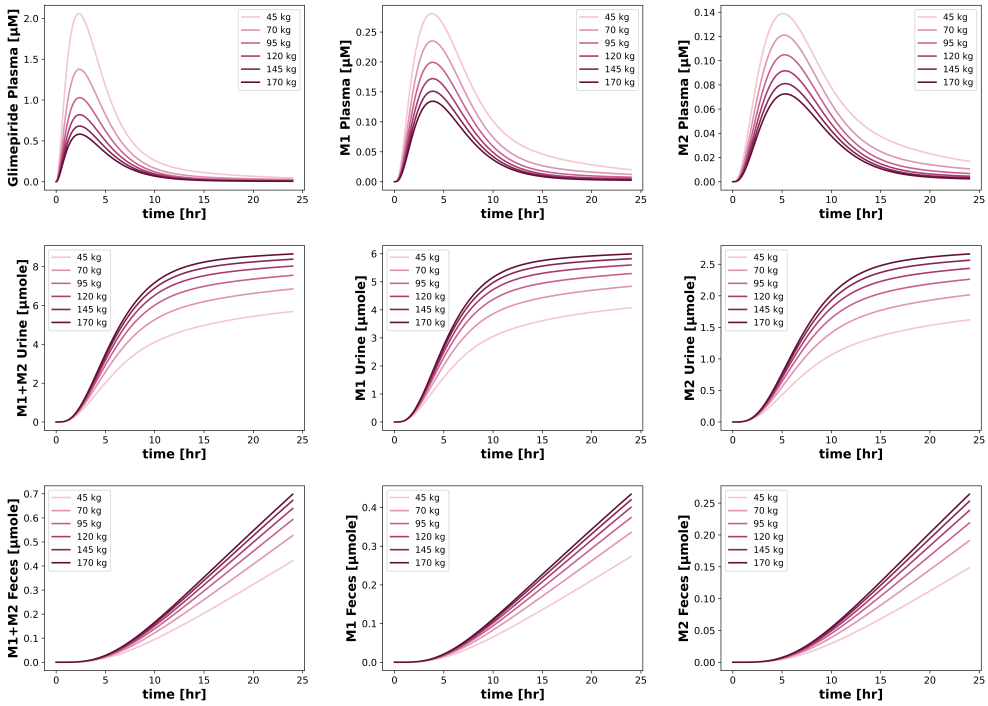

Fig. S7 Simulated pharmacokinetic profiles of glimepiride (8 mg dose) and its metabolites across different bodyweights. Concentration-time curves and cumulative excretion patterns illustrate the impact of bodyweight on drug disposition.

S5.5 CYP2C9 Polymorphisms (Fig. S8)

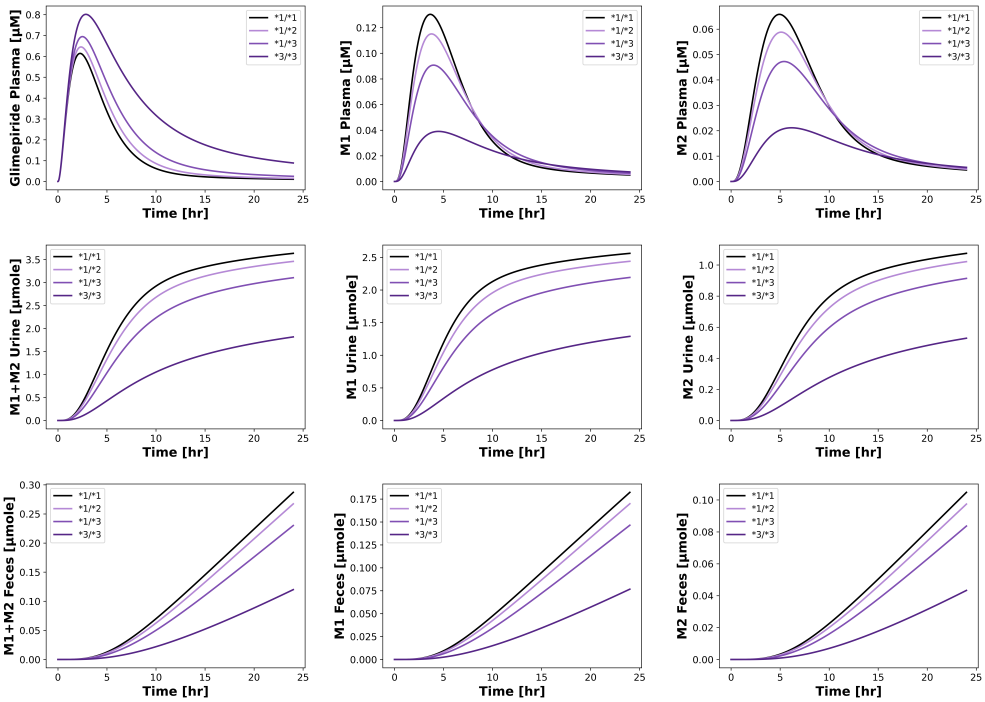

Fig. S8 Simulated pharmacokinetic profiles of glimepiride (4 mg dose) and its metabolites across the main CYP2C9 genotypes. Concentration-time curves and cumulative excretion patterns demonstrate the impact of genetic polymorphisms on drug metabolism.

References

[1] Elias, M. & König, M. Physiologically based pharmacokinetic (PBPK) model of glimepiride. Zenodo (2025).