Physiologically based pharmacokinetic modelling of Mercury Distribution

September 18, 2025

Introduction

- Development of a predictive model for mercury distribution in the human body.
- Mercury distributes to multiple organs, with significant accumulation in the kidneys, liver, and nervous system, depending on its chemical form.
- Human exposure occurs mainly through ingestion, followed by transport via the bloodstream and diffusion into tissues.
- Compartmental modeling is used to describe uptake, redistribution, and elimination processes.

Original Model

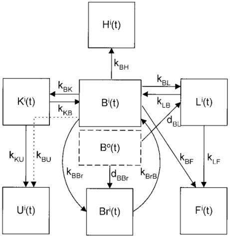


Figure: Conceptual representation of inorganic mercury kinetics

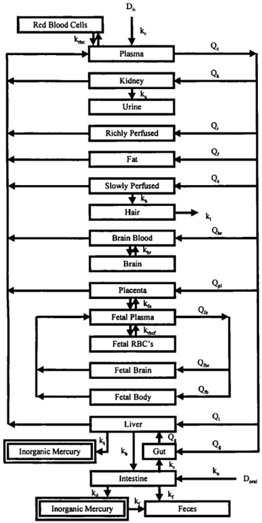


Fig. 1. Physiologically based pharmacokinetic model for MeHg used in this analysis. Abbreviations are defined in Table I.

Original Model

- Linear time-dependent ODE system:

$$\frac{dy}{dt} = M(t)y + u(t)$$

- $y(t) \in \mathbb{R}^n$: state vector (compartment concentrations).
- $M(t) \in \mathbb{R}^{n \times n}$: flow matrix.
- $u(t) \in \mathbb{R}^n$: external input vector.

Sensitivity Equations

- Sensitivity matrix $S(t)$ with entries:

$$S_{i,p}(t) = \frac{\partial y_i(t)}{\partial \theta_p}, \quad i = 1, \dots, n, \; p = 1, \dots, m$$

- Differentiating the system with respect to each parameter θ_p:

$$\frac{d}{dt} S_{:,p} = \frac{\partial M(t)}{\partial \theta_p} y + M(t) S_{:,p} + \frac{\partial u(t)}{\partial \theta_p}$$

  where $S_{:,p}$ is the p-th column of $S(t)$.
- Compact matrix form for all parameters:

$$\dot{S}(t) = M(t)S(t) + \frac{\partial M(t)}{\partial \theta} y(t) + \frac{\partial u(t)}{\partial \theta}$$

- Full block-matrix formulation of the combined system:

$$\frac{d}{dt} \begin{bmatrix} y \\ S \end{bmatrix} = \begin{bmatrix} M & 0 \\ \nabla_p M & M \end{bmatrix} \begin{bmatrix} y \\ S \end{bmatrix} + \begin{bmatrix} u \\ \nabla_p u \end{bmatrix}$$

Solution Strategy

- Start with linear system:

$$\frac{dy}{dt} = M(t)y + u(t), \quad y(0) = y_0$$

- At $t = 0$, set $A = M(0)$ and diagonalize:

$$A = PDP^{-1}, \quad D = \mathrm{diag}(\lambda_1, \ldots, \lambda_n)$$

- Homogeneous solution:

$$y_h(t) = Pe^{Dt}P^{-1}y_0$$

- Inhomogeneous solution (variation of constants):

$$y(t) = e^{At}y_0 + \int_0^t e^{A(t-s)}u(s)\,ds$$

Integral Matrices

- Define exponential and integral matrices:

$$W(t) = e^{Dt}, \quad Q = \frac{e^{Dt} - I}{D}$$

- For piecewise constant $u(t)$:

$$\int_0^t e^{D(t-s)} u(s)\, ds \;\approx\; H(t)u$$

- Entries of $H(t)$:

$$H_{ij}(t) = \begin{cases} te^{\lambda_i t}, & i = j \\ \dfrac{e^{\lambda_j t} - e^{\lambda_i t}}{\lambda_j - \lambda_i}, & i \neq j \end{cases}$$

Full Solution in Matrix Form

- General solution:

$$y(t) = PW(t)P^{-1}y_0 + PH(t)P^{-1}u$$

- For a discrete time grid $t_0, t_1, \ldots, t_N$:

$$W_1[i,j] = \theta(t_i - t_j)e^{\lambda_k(t_i - t_j)}$$

$$y(t_i) = P\left[W(t_i)P^{-1}y_0 + \sum_{j=0}^{i} W_1[i,j]P^{-1}u(t_j)\,\Delta t_j\right]$$

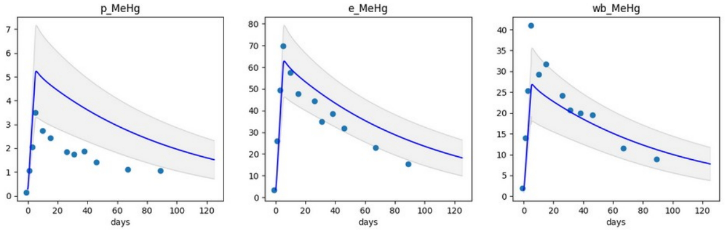
Roles of matrices:

- $W = e^{Dt}$: homogeneous exponential growth
- $Q = (e^{Dt} - I)/D$: diagonal integral
- H: analytic convolution integral
- W_1: discrete Green's function
- $P^{-1}y_0$: initial conditions

Results

- Two phases:
  1. Ingestion phase (5 days)
  2. Elimination phase (no intake)
- Initial steady state used for realistic concentrations
- Model output:

$$y(t) = PW(t)P^{-1}y_0 + PH(t)P^{-1}u$$



Parameter Optimization

- Experimental data $\{(t_i, y_i)\}_{i=1}^{N}$, $y_i \in \mathbb{R}^3$.
- Residuals normalized:

$$r_{i,j}(\theta_f) = \frac{\hat{y}_j(t_i; \theta_f, \theta_c) - y_{i,j}}{\sigma_{i,j}}$$

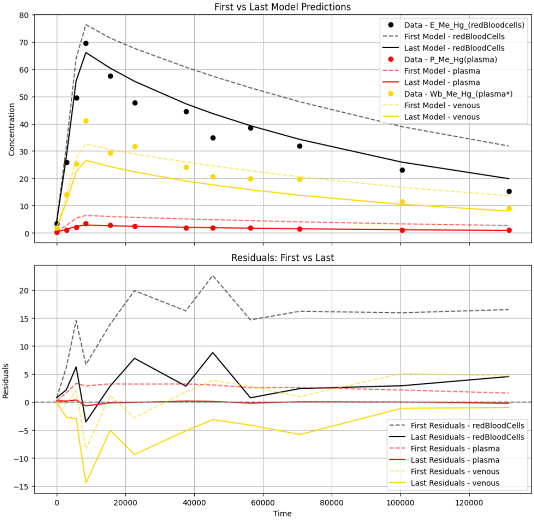
- Robust soft-L1 loss:

$$\rho(u) = 2\left(\sqrt{1+u} - 1\right), \quad u \geq 0$$

- Objective function:

$$C(\theta_f) = \sum_{k=1}^{3N} \rho(r_k(\theta_f)^2)$$

Original Model



Example of the parameter optimization

Parameter Uncertainty Estimation

Jacobian of residuals:

$$J \in \mathbb{R}^{N_r \times q}, \quad J_{ij} = \frac{\partial r_i}{\partial \theta_{f,j}}\Big|_{\theta_f^*}$$

Residual variance:

$$s^2 = \frac{\|\mathbf{r}(\theta_f^*)\|_2^2}{N_r - q}$$

Parameter covariance (Gauss–Newton):

$$\mathrm{Cov}(\theta_f^*) \approx s^2 (J^\top J)^{-1}, \quad E_j = \sqrt{[\mathrm{Cov}(\theta_f^*)]_{jj}}$$

Remark: Hessian neglects second derivatives; accurate for small or nearly linear residuals.

Prediction Uncertainty and Confidence Intervals

Prediction uncertainty propagation

For a model output $y(t;\theta)$, the sensitivity to parameters is

$$g_j(t) \approx \frac{y(t;\theta_f^* + \varepsilon e_j) - y(t;\theta_f^*)}{\varepsilon}, \quad \mathbf{g}(t) = \begin{pmatrix} g_1(t) & \cdots & g_q(t) \end{pmatrix}.$$

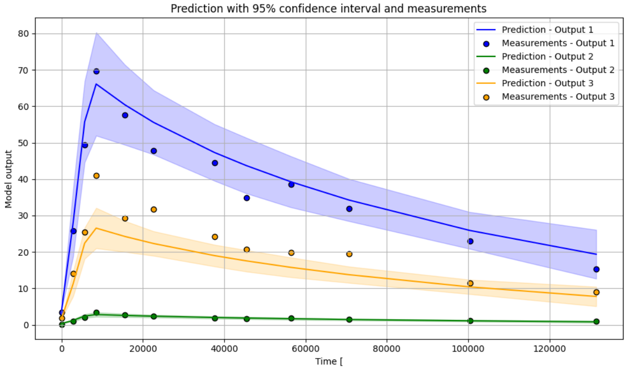
The prediction variance and standard error are

$$\mathrm{Var}(y(t;\theta_f^*)) \approx \mathbf{g}(t)\,\mathrm{Cov}(\theta_f^*)\,\mathbf{g}(t)^\top, \quad \mathrm{SE}(t) = \sqrt{\mathrm{Var}(y(t;\theta_f^*))}.$$

Quick summary

- Residual variance: $s^2 = \frac{\|r(\theta_f^*)\|_2^2}{N_r - q}$
- Parameter covariance: $\mathrm{Cov}(\theta_f^*) \approx s^2(J^\top J)^{-1}$
- Prediction variance: $\mathrm{Var}(y(t;\theta_f^*)) \approx g(t)\,\mathrm{Cov}(\theta_f^*)\,g(t)^\top$
- 95% confidence interval: $y(t;\theta_f^*) \pm 1.96 \cdot SE(t)$

Original Model



Example of the parameter optimization with SE.

Conclusion and Future Work

- PBPK model successfully describes mercury distribution in humans.
- Predicts compartment concentrations under ingestion and elimination scenarios.
- Parameter optimization improves model fit to experimental data.
- Framework supports uncertainty quantification and risk assessment.
- Future work / next steps:
  - Put Jacobi matrix from model in the least squares instead of default Jacobi.
  - Find the parameters that add more to uncertainty.
  - Incorporate population variability to refine risk assessment.