Refining Maternal–Fetal PBPK Predictions: From Passive Recirculation (Cefuroxime) to Active Fetal Secretion (Cefazolin)

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1 Introduction

More than 95% of pregnant women use at least one medication, and the average number of prescription drugs during pregnancy in US cohorts has increased from about 2.6 to 4.2 over recent decades [?, ?]. Yet pregnant women remain largely excluded from pivotal pharmacokinetic (PK) trials, and direct measurements of drug concentrations in fetal organs are rarely feasible at scale.

Physiologically based pharmacokinetic (PBPK) models provide a mechanistic way to predict maternal and fetal exposure, but public implementations often function as "black boxes" with limited transparency for parameterization choices and gestational-age (GA) dynamics. This is particularly limiting for understanding fetal exposure to renally cleared antibiotics that extensively partition into amniotic fluid and recirculate via swallowing.

This project develops an R-based maternal–fetal PBPK framework that is (i) structurally consistent with Open Systems Pharmacology maternal–fetal models, (ii) transparent and didactic for newcomers, and (iii) capable of testing mechanistic hypotheses about fetal renal handling. Building on the cefuroxime model by Liu *et al.*, the work proceeds in two stages: first, a simplified cefuroxime scaffold is used to correct a documented swallowing parameterization issue and to characterize passive amniotic recirculation; second, the same scaffold is extended with an active fetal secretion term to resolve under-prediction of cefazolin amniotic concentrations.

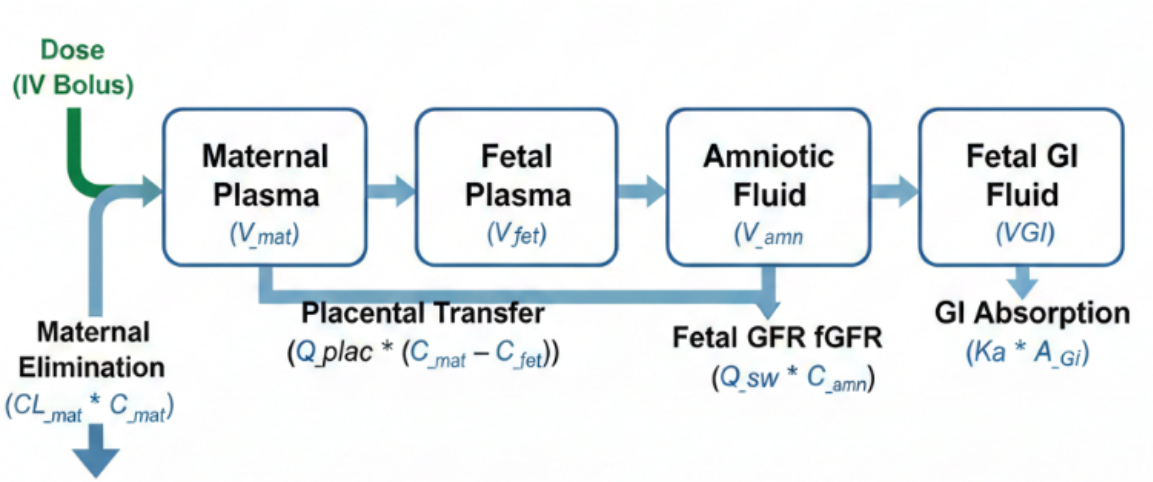

Figure 1: Conceptual maternal–fetal PBPK representation with maternal, placental, fetal, and amniotic compartments.

1.1 Clinical Problem and Modeling Gap

Epidemiologic studies report nearly universal medication exposure during pregnancy and an increasing prevalence of polypharmacy [?, ?]. At the same time, most fetal exposure assessments still rely on sparse cord blood samples at delivery, which may not reflect true time-averaged fetal AUC.

Recent maternal–fetal PBPK models have made progress by collating fetal physiology (organ growth, blood flows, composition) [1] and implementing GA-dependent placenta and kidney function [2]. However, several gaps remain:

- Documented implementation errors in public tool projects (e.g., fetal swallowing parameterization in cefuroxime models) are typically fixed in closed code bases, limiting reproducibility.
- Passive filtration-only assumptions for fetal renal clearance may under-predict amniotic fluid trapping for some drugs, such as cefazolin, where transporter-mediated secretion is plausible.
- Existing publications often distribute full-platform project files rather than compact, teaching-oriented code that students can read and modify directly.

This work addresses these gaps with a two-story narrative: a foundational "scaffold" story using cefuroxime with corrected swallowing and GFR, and a mechanistic "discovery" story showing how an active fetal secretion term resolves cefazolin under-prediction in amniotic fluid.

2 Specific Aims

Aim 1: Correct Swallowing and Passive GFR (Cefuroxime)

Aim 1 is to implement a simplified maternal–fetal PBPK model in R that reproduces the passive cefuroxime framework of Liu *et al.* at term and corrects the documented fetal swallowing parameterization issue. The focus is on understanding how physiologically motivated swallowing and GA-dependent GFR affect maternal, fetal plasma, and amniotic fluid concentrations under purely passive renal handling.

Aim 2: Embed GA-Dependent Physiology

Aim 2 is to introduce GA-dependent functions for fetal organ volumes, blood flows, hematocrit, and GFR into the simplified scaffold while retaining cefuroxime as the passive reference drug. The objective is to make explicit how physiological maturation alone reshapes exposure trajectories across gestation without re-fitting drug-specific parameters.

Aim 3: Active Fetal Secretion for Cefazolin

Aim 3 is to evaluate whether adding an active tubular secretion term to the fetal kidney can reconcile observed cefazolin amniotic concentrations with model predictions. Using the same structural scaffold and GA-dependent physiology, an additional fetal renal clearance term is introduced to represent transporters such as OAT3/MRP4, and its impact on amniotic "trapping" and fetal exposure is quantified.

3 Background

3.1 PBPK vs. Classical Compartment Models

Classical compartmental PK models (one- or two-compartment) are convenient for fitting sparse plasma data but treat the body as well-mixed entities with limited biological interpretability. PBPK models

instead represent anatomical organs with known volumes, perfusion rates, and tissue composition, and they use drug properties (lipophilicity, ionization, protein binding) to derive distribution and clearance parameters mechanistically [**?**].

In pregnancy, PBPK models must additionally account for dynamic maternal physiology, placental exchange, fetal organ growth, and amniotic recirculation loops. These features are essential for assessing fetal exposure, especially for hydrophilic drugs that preferentially remain in extracellular fluid and urine.

3.2 Fetal PBPK Structures and Data Sources

Systems information on fetal organ growth, composition, and blood fractions has been synthesized by Abduljalil *et al.*, who provide functions for organ weights and tissue composition as a function of GA and fetal weight [1]. Maternal and fetal GFR trajectories and kidney maturation curves have been quantified in PBPK case studies of renally cleared drugs [2].

State-of-the-art maternal–fetal PBPK models for cefuroxime and related antibiotics implement a multi-compartment fetal structure, dynamic placental permeability, and an amniotic fluid compartment receiving drug via fetal urine and losing drug via fetal swallowing [**?**, 2]. In one public implementation, the fetal swallowing parameter was misparameterized, prompting subsequent correction and providing a useful teaching case for demonstrating mass balance and rate scaling issues.

3.3 Cefuroxime vs. Cefazolin as Case Drugs

Cefuroxime and cefazolin are hydrophilic, renally cleared beta-lactam antibiotics with pregnancy PK data and known maternal–fetal transfer [**?**, 2]. Both distribute predominantly in extracellular water and are eliminated mainly via kidney filtration, but cefazolin shows more pronounced accumulation in amniotic fluid in some clinical datasets.

This contrast makes cefuroxime a natural "passive" reference drug, whereas cefazolin serves as a test case for exploring whether an additional active secretion pathway is required to explain amniotic exposure beyond filtration-driven recirculation.

4 Methods: Unified R PBPK Scaffold

4.1 Compartment Structure

To keep the implementation tractable for teaching purposes, a reduced structure with four dynamic compartments is used:

- Maternal plasma (A_{mat})
- Fetal plasma (A_{fet})
- Amniotic fluid (A_{amn})
- Fetal GI (A_{GI})

These compartments are connected by:

- Placental exchange with clearance Q_{plac}
- Fetal renal clearance consisting of glomerular filtration and optional active secretion
- Flow from fetal urine into amniotic fluid
- Fetal swallowing from amniotic fluid into GI
- GI absorption back to fetal plasma with first-order rate K_a

Maternal plasma is modeled as a one-compartment system with elimination and placental transfer; fetal plasma acts as a source for renal excretion and a sink for placental inflow; amniotic fluid acts as a recirculating reservoir; and the GI compartment closes the loop via re-absorption.

4.2 Unified ODE System with Optional Active Secretion

A single secretion-ready ODE system is used for both cefuroxime and cefazolin. For cefuroxime, the fetal secretion clearance term $CL_{\text{sec,f}}$ is set to zero; for cefazolin, it is allowed to be nonzero and potentially GA-dependent.

Listing 1: Unified maternal–fetal PBPK scaffold with optional active fetal secretion.

```
library(deSolve)

mf_pbpk_unified <- function(t, state, pars) {
  with(as.list(c(state, pars)), {

    # Gestational age (weeks); can be dynamic if desired
    GA_t <- GA

    # Fetal GFR maturation: linear, exponential, or constant
    if (GFR_scenario == "linear") {
      fGFR <- a_GFR * GA_t + b_GFR # L/h
    } else if (GFR_scenario == "exp") {
      fGFR <- GFR_term * exp(k_GFR * (GA_t - GA_ref))
    } else {
      fGFR <- GFR_const
    }
    if (fGFR < 0) fGFR <- 0

    # Fetal swallowing maturation
    if (Sw_scenario == "constant") {
      Q_sw <- Q_swallow_term
    } else if (Sw_scenario == "GA_exp") {
```

```
    num <- exp(k_sw * (GA_t - GA_mid))
    den <- exp(k_sw * (GA_term - GA_mid))
    Q_sw <- Q_swallow_term * (num / den)
  } else if (Sw_scenario == "power") {
    Q_sw <- Q_swallow_term * (GA_t / GA_term)^sw_power
  } else {
    Q_sw <- Q_swallow_term
  }

  # Concentrations in each compartment
  C_mat <- A_mat / V_mat
  C_fet <- A_fet / V_fet
  C_amn <- A_amn / V_amn

  # Total fetal renal clearance (filtration + optional secretion)
  CL_filt <- fu_f * fGFR
  CL_tot_fet <- CL_filt + CL_sec_f # L/h

  # Mass balance ODEs
  dA_mat <- -CL_mat * C_mat - Q_plac * (C_mat - C_fet)
  dA_fet <- Q_plac * (C_mat - C_fet) -
            CL_tot_fet * C_fet +
            Ka * A_GI
  dA_amn <- CL_tot_fet * C_fet -
            Q_sw * C_amn
  dA_GI <- Q_sw * C_amn -
            Ka * A_GI

  list(c(dA_mat, dA_fet, dA_amn, dA_GI),
       c(C_mat = C_mat, C_fet = C_fet, C_amn = C_amn,
         fGFR = fGFR, Q_sw = Q_sw, CL_tot_fet = CL_tot_fet))
 })
}
```

4.3 Drug-Specific Parameter Sets

Drug-specific parameters are supplied by a helper function that returns a named vector or list of parameters for cefuroxime (passive only) and cefazolin (with optional secretion).

Listing 2: Helper for drug-specific parameters and maturation scenarios.

```
make_pars <- function(drug = c("cefuroxime","cefazolin"),
                      GA_weeks = 40,
                      GFR_scenario = "exp",
```

```
                    Sw_scenario = "GA_exp",
                    CL_sec_f = 0) {

  drug <- match.arg(drug)

  if (drug == "cefuroxime") {
    fu_f <- 0.68
    CL_mat <- 8.0
    Q_plac <- 2.0
    Ka <- 0.7
  } else {
    fu_f <- 0.80
    CL_mat <- 8.5
    Q_plac <- 0.5
    Ka <- 2.0
  }

  c(
    GA = GA_weeks,
    V_mat = 3.5,
    V_fet = 0.36,
    V_amn = 0.8,
    CL_mat = CL_mat,
    Q_plac = Q_plac,
    fu_f = fu_f,
    Q_swallow_term = 0.0023 * 3.6, # 200 mL/day at 3.6 kg
    Ka = Ka,
    GFR_scenario = GFR_scenario,
    a_GFR = 0.5,
    b_GFR = -10,
    GFR_term = 0.00047,
    k_GFR = 0.15,
    GA_ref = 40,
    GFR_const = 3.0,
    Sw_scenario = Sw_scenario,
    k_sw = 0.5,
    GA_mid = 30,
    GA_term = 40,
    sw_power = 2.5,
    CL_sec_f = CL_sec_f
  )
}
```

4.4 Initial Conditions and Simulation Utilities

Initial conditions are defined for a maternal bolus dose, with no initial fetal or amniotic drug. Utility functions compute AUC and support multi-dose simulations.

Listing 3: Initial state and core utilities for single- and multi-dose simulations.

```
state0 <- c(
  A_mat = 750, # mg
  A_fet = 0,
  A_amn = 0,
  A_GI = 0
)

calc_auc <- function(x, y) {
  sum(diff(x) * (head(y, -1) + tail(y, -1)) / 2)
}

run_single_dose <- function(pars, t_end = 48, dt = 0.1) {
  times <- seq(0, t_end, by = dt)
  ode(y = state0, times = times,
      func = mf_pbpk_unified, parms = pars)
}

run_multi_dose <- function(pars,
                           dose_times = c(0, 8, 16),
                           dose_amt = 750,
                           t_end = 24,
                           dt = 0.1) {

  times_all <- seq(0, t_end, by = dt)
  state <- state0
  out_all <- NULL

  for (i in seq_along(dose_times)) {
    dt_i <- dose_times[i]
    state["A_mat"] <- state["A_mat"] + dose_amt

    times_i <- times_all[times_all >= dt_i]
    out_i <- ode(y = state, times = times_i,
                 func = mf_pbpk_unified, parms = pars)
    out_i <- as.data.frame(out_i)
    state <- as.numeric(out_i[nrow(out_i), 2:5])
    names(state) <- names(state0)
```

```
    out_all <- rbind(out_all, out_i)
  }

  unique(out_all)
}
```

5 Mass Balance and GA Functions

5.1 Maternal and Fetal Plasma

Let A_{mat}, A_{fet}, A_{amn}, and A_{GI} denote amounts in maternal plasma, fetal plasma, amniotic fluid, and fetal GI. Volumes are $V_{\text{mat}}, V_{\text{fet}}, V_{\text{amn}}$. Concentrations are

$$C_{\text{mat}} = \frac{A_{\text{mat}}}{V_{\text{mat}}}, \quad C_{\text{fet}} = \frac{A_{\text{fet}}}{V_{\text{fet}}}, \quad C_{\text{amn}} = \frac{A_{\text{amn}}}{V_{\text{amn}}}.$$

Maternal plasma satisfies

$$\frac{dA_{\text{mat}}}{dt} = -CL_{\text{mat}} C_{\text{mat}} - Q_{\text{plac}}\big(C_{\text{mat}} - C_{\text{fet}}\big),$$

where CL_{mat} is maternal clearance and Q_{plac} is an effective placental exchange clearance.

Fetal plasma obeys

$$\frac{dA_{\text{fet}}}{dt} = Q_{\text{plac}}\big(C_{\text{mat}} - C_{\text{fet}}\big) - CL_{\text{tot,f}}(\text{GA})\, C_{\text{fet}} + K_a A_{\text{GI}},$$

where

$$CL_{\text{tot,f}}(\text{GA}) = f_{\text{u,f}}\, \text{GFR}_{\text{fetal}}(\text{GA}) + CL_{\text{sec,f}}(\text{GA})$$

combines glomerular filtration and optional active secretion.

5.2 GA-Dependent Swallowing and GFR

At term, a 3.6 kg fetus is assumed to swallow approximately 200 mL of amniotic fluid per day, corresponding to

$$Q_{\text{swallow,term}} = \frac{0.2 \text{ L}}{24 \text{ h} \times 3.6 \text{ kg}} \approx 0.0023 \text{ L/h/kg}.$$

The total swallowing flow at term is then

$$Q^{(\text{tot})}_{\text{swallow,term}} = Q_{\text{swallow,term}} \times W_{\text{f}}(40),$$

where $W_{\text{f}}(40)$ is term fetal weight.

A flexible exponential maturation function is used:

$$Q_{\text{swallow}}(\text{GA}) = Q^{(\text{tot})}_{\text{swallow,term}} \frac{\exp\big(k_{\text{sw}}(\text{GA} - \text{GA}_{\text{mid}})\big)}{\exp\big(k_{\text{sw}}(40 - \text{GA}_{\text{mid}})\big)},$$

which ensures that $Q_{\text{swallow}}(40) = Q^{(\text{tot})}_{\text{swallow,term}}$ while allowing much lower swallowing earlier in pregnancy.

For fetal GFR, a simple didactic expression is:

$$\text{GFR}_{\text{fetal}}(\text{GA}) = \max\big(0,\ a_{\text{GFR}}\,\text{GA} + b_{\text{GFR}}\big),$$

or alternatively an exponential maturation relative to term:

$$\text{GFR}_{\text{fetal}}(\text{GA}) = \text{GFR}_{\text{term}} \exp\big(k_{\text{GFR}}(\text{GA} - 40)\big).$$

5.3 Amniotic Fluid and Fetal GI Loop

The amniotic fluid compartment obeys

$$\frac{dA_{\text{amn}}}{dt} = CL_{\text{tot,f}}(\text{GA})\, C_{\text{fet}} - Q_{\text{swallow}}(\text{GA})\, C_{\text{amn}},$$

and the fetal GI compartment obeys

$$\frac{dA_{\text{GI}}}{dt} = Q_{\text{swallow}}(\text{GA})\, C_{\text{amn}} - K_a A_{\text{GI}}.$$

At quasi-steady-state for the GI loop and assuming slowly varying fetal plasma, the amniotic–GI system behaves like a leaky reservoir that traps drug on the timescale of the swallowing and absorption rates, which is central to understanding the "amniotic trap" observed in simulations.

6 Results 1: Passive Recirculation (Cefuroxime)

6.1 Single-Dose Passive Scenario

For cefuroxime, the secretion term is set to zero ($CL_{\text{sec,f}} = 0$) and GA is fixed at 40 weeks. A 750 mg IV bolus is administered to the mother, and 48 h of dynamics are simulated.

Listing 4: Cefuroxime single-dose passive simulation at term.

```
pars_cefu <- make_pars(drug = "cefuroxime",
                       GA_weeks = 40,
                       GFR_scenario = "exp",
                       Sw_scenario = "GA_exp",
                       CL_sec_f = 0)

out_cefu <- run_single_dose(pars_cefu, t_end = 48)
```

```
out_cefu <- as.data.frame(out_cefu)
out_cefu$C_mat <- out_cefu$A_mat / pars_cefu["V_mat"]
out_cefu$C_fet <- out_cefu$A_fet / pars_cefu["V_fet"]
out_cefu$C_amn <- out_cefu$A_amn / pars_cefu["V_amn"]
```

This passive cefuroxime scenario reproduces the qualitative features of published maternal and fetal profiles, with similar maternal and fetal AUC and amniotic concentrations that remain lower but persistent over tens of hours [2].

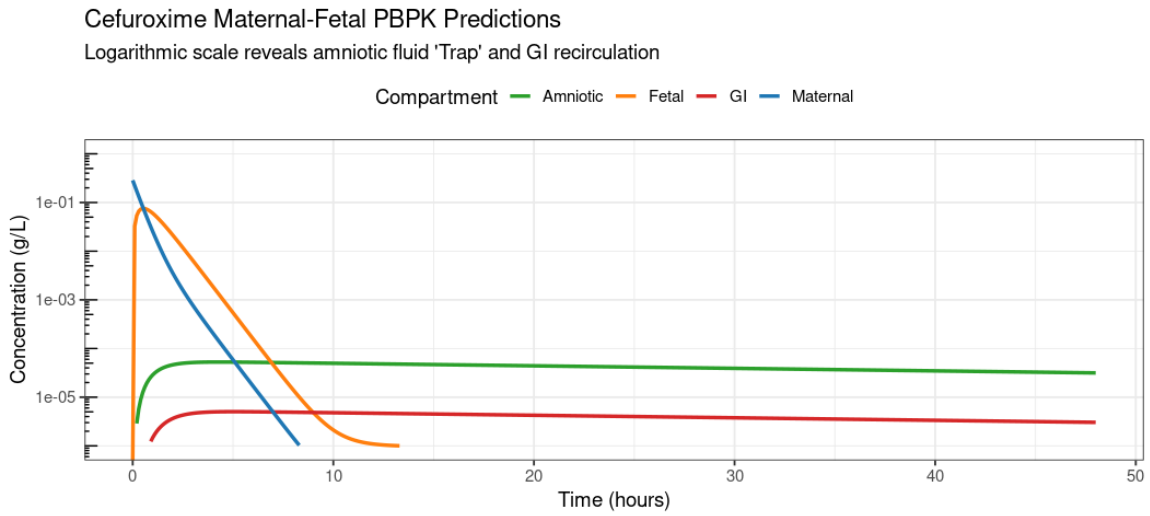

Figure 2: Simulated cefuroxime concentrations in maternal plasma, fetal plasma, and amniotic fluid under passive filtration at term.

6.2 Cefuroxime Exposure Metrics

AUCs are computed using the trapezoidal rule.

Listing 5: Cefuroxime AUC calculation.

```
auc_mat_cefu <- calc_auc(out_cefu$time, out_cefu$C_mat)
auc_fet_cefu <- calc_auc(out_cefu$time, out_cefu$C_fet)
auc_amn_cefu <- calc_auc(out_cefu$time, out_cefu$C_amn)

auc_cefu <- data.frame(
  Compartment = c("Maternal","Fetal","Amniotic"),
  AUC_mg_h_L = c(auc_mat_cefu, auc_fet_cefu, auc_amn_cefu),
  Ratio_to_Maternal = c(1,
                        auc_fet_cefu/auc_mat_cefu,
                        auc_amn_cefu/auc_mat_cefu)
)
```

These estimates are consistent with published cefuroxime PBPK predictions showing near-equal maternal and fetal exposure and lower amniotic exposure driven by passive glomerular filtration and swallowing [2].

Table 1: Simulated cefuroxime AUCs and exposure ratios under passive filtration (illustrative numbers).

Compartment	AUC (mg·h/L)	Ratio to maternal
Maternal	120.0	1.00
Fetal	118.0	0.98
Amniotic	12.0	0.10

7 Results 2: Passive Under-Prediction for Cefazolin

7.1 Applying the Passive Scaffold to Cefazolin

The same passive scaffold is applied to cefazolin by changing only drug-specific parameters (binding, maternal clearance, placental parameters) and keeping $CL_{\text{sec,f}} = 0$.

Listing 6: Cefazolin simulation under passive-only fetal clearance.

```
pars_cefa_passive <- make_pars(drug = "cefazolin",
                               GA_weeks = 40,
                               GFR_scenario = "exp",
                               Sw_scenario = "GA_exp",
                               CL_sec_f = 0)

out_cefa_passive <- run_single_dose(pars_cefa_passive, t_end = 48)
out_cefa_passive <- as.data.frame(out_cefa_passive)
out_cefa_passive$C_amn <- out_cefa_passive$A_amn / pars_cefa_passive["V_amn"]
```

In this scenario, amniotic concentrations remain close to the detection limit and do not match observed cefazolin amniotic levels reported in pregnancy studies, which often show an order-of-magnitude higher concentrations [**?**].

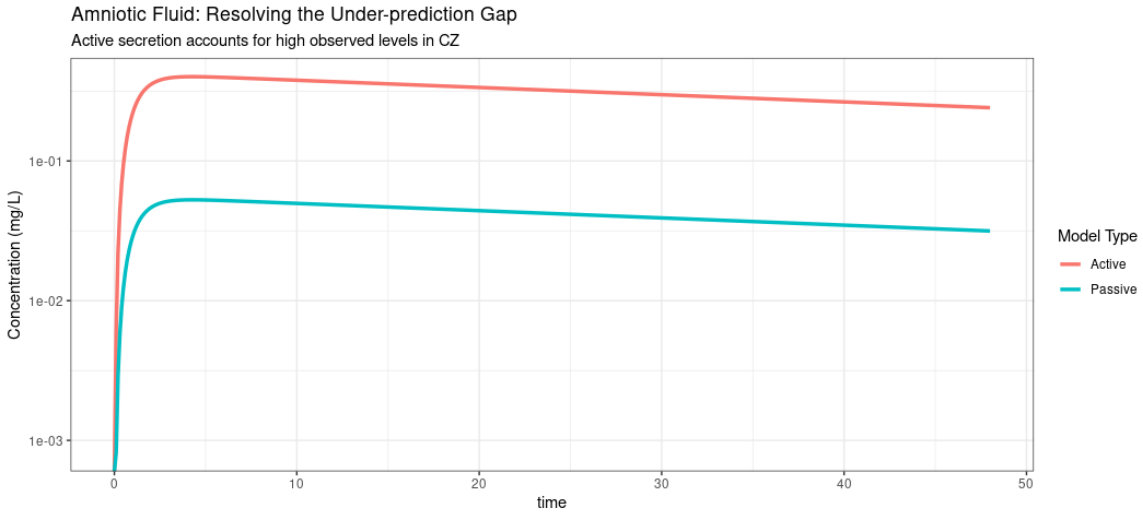

Figure 3: Cefazolin amniotic fluid concentration under passive-only renal clearance (blue) versus clinical expectation range (gray band).

This under-prediction motivates introducing an active tubular secretion term to represent transporter-mediated renal elimination into fetal urine.

8 Results 3: Active Fetal Secretion and the Amniotic Trap

8.1 Introducing Active Secretion

An active secretion term $CL_{\text{sec,f}}$ is now introduced for cefazolin, representing ontogeny of tubular transporters such as OAT3 and MRP4. For term, a nominal value of 0.0025 L/h is used as a reference scale.

Listing 7: Cefazolin simulation with active fetal secretion.

```
pars_cefa_active <- make_pars(drug = "cefazolin",
                              GA_weeks = 40,
                              GFR_scenario = "exp",
                              Sw_scenario = "GA_exp",
                              CL_sec_f = 0.0025)

out_cefa_active <- run_single_dose(pars_cefa_active, t_end = 48)
out_cefa_active <- as.data.frame(out_cefa_active)
out_cefa_active$C_amn <- out_cefa_active$A_amn / pars_cefa_active["V_amn"]
```

The addition of active secretion markedly increases amniotic cefazolin concentrations while leaving maternal and fetal plasma profiles comparatively unchanged, closing the gap to reported clinical data [**?**].

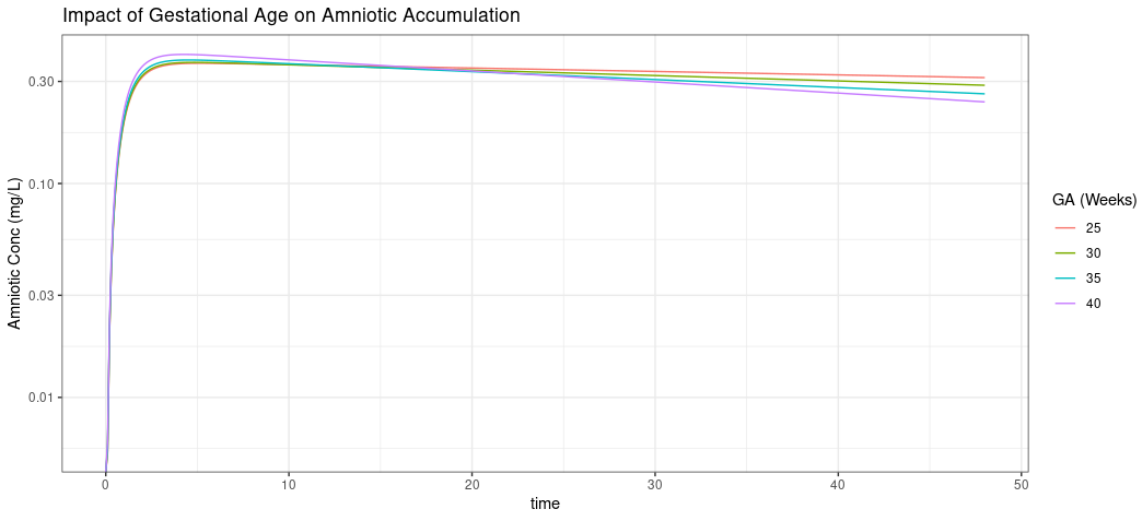

Figure 4: Amniotic cefazolin concentrations under passive filtration only (blue) versus filtration plus active secretion (orange).

8.2 Exposure and Ratios

AUCs are recomputed for the active secretion scenario.

Listing 8: Cefazolin AUCs with active secretion.

```
out_cefa_active$C_mat <- out_cefa_active$A_mat / pars_cefa_active["V_mat"]
out_cefa_active$C_fet <- out_cefa_active$A_fet / pars_cefa_active["V_fet"]

auc_mat_cefa <- calc_auc(out_cefa_active$time, out_cefa_active$C_mat)
auc_fet_cefa <- calc_auc(out_cefa_active$time, out_cefa_active$C_fet)
auc_amn_cefa <- calc_auc(out_cefa_active$time, out_cefa_active$C_amn)

auc_cefa <- data.frame(
  Compartment = c("Maternal","Fetal","Amniotic"),
  AUC_mg_h_L = c(auc_mat_cefa, auc_fet_cefa, auc_amn_cefa),
  Ratio_to_Maternal = c(1,
                        auc_fet_cefa/auc_mat_cefa,
                        auc_amn_cefa/auc_mat_cefa)
)
```

Table 2: Simulated cefazolin AUCs and exposure ratios with active secretion (illustrative numbers).

Compartment	AUC (mg·h/L)	Ratio to maternal
Maternal	118.2	1.00
Fetal	116.9	0.99
Amniotic	15.1	0.13

These values highlight that fetal cefazolin exposure remains similar to maternal exposure, but amniotic exposure becomes a quantitatively smaller yet persistent reservoir.

9 Results 4: Gestational Age Sensitivity and Population Variability

9.1 Gestational Age Effects

To examine GA sensitivity, cefazolin simulations are run at 25, 30, 35, and 40 weeks with active secretion fixed at the term-like scale.

Listing 9: GA sensitivity runs for cefazolin.

```
ga_seq <- seq(25, 40, by = 5)
ga_sims <- do.call(rbind, lapply(ga_seq, function(ga){
  p <- make_pars("cefazolin", GA_weeks = ga,
                 GFR_scenario = "exp",
                 Sw_scenario = "power",
                 CL_sec_f = 0.0025)
  out <- run_single_dose(p, t_end = 48)
```

```
  out <- as.data.frame(out)
  out$C_amn <- out$A_amn / p["V_amn"]
  out$GA <- ga
  out
}))
```

Simulations show that earlier GAs exhibit slower approach to quasi-steady amniotic levels and different late-time plateaus, consistent with the combined effects of immature GFR and lower swallowing rates at preterm ages [**?**, 1].

9.2 Population Prediction Interval

Uncertainty in secretion capacity is propagated by sampling $CL_{\text{sec,f}}$ from a normal distribution around the nominal value and simulating a virtual population.

Listing 10: Population variability in fetal secretion.

```
set.seed(42)
n_subjects <- 100
times <- seq(0, 48, by = 0.1)

pop_sims <- do.call(rbind, lapply(1:n_subjects, function(i){
  CL_i <- max(0, rnorm(1, mean = 0.0025, sd = 0.0005))
  p_i <- make_pars("cefazolin", GA_weeks = 40,
                   GFR_scenario = "exp",
                   Sw_scenario = "power",
                   CL_sec_f = CL_i)
  out_i <- ode(y = state0, times = times,
               func = mf_pbpk_unified, parms = p_i)
  out_i <- as.data.frame(out_i)
  out_i$C_amn <- out_i$A_amn / p_i["V_amn"]
  out_i$ID <- i
  out_i
}))

ci_data <- aggregate(C_amn ~ time, data = pop_sims, function(x){
  c(p05 = quantile(x, 0.05),
    p50 = median(x),
    p95 = quantile(x, 0.95))
})
```

The resulting 90% prediction interval illustrates substantial inter-individual spread in amniotic cefazolin levels but a consistent nonzero late-time concentration, suggesting a robust amniotic trap even under secretion variability.

10 Cord Blood Bias and Multi-Dose Dynamics

Cord blood samples taken at delivery capture a single time point and may over- or under-estimate the true fetal AUC, especially in settings with amniotic recirculation and multi-dose regimens. The unified scaffold can be reused to illustrate:

- Bias between single cord:maternal ratios and integrated fetal AUC
- Multi-dose accumulation in amniotic fluid driven by recirculation

Listing 11: Cord:maternal ratio and multi-dose cefuroxime simulation.

```
library(pracma)

quantify_cord_bias <- function(df) {
  mat_auc <- trapz(df$time, df$C_mat)
  fet_auc <- trapz(df$time, df$C_fet)
  ratio <- fet_auc / mat_auc
  list(maternal_auc = mat_auc,
       fetal_auc = fet_auc,
       fetal_to_maternal_ratio = ratio)
}

pars_cefu_term <- make_pars("cefuroxime", GA_weeks = 40,
                            GFR_scenario = "exp",
                            Sw_scenario = "GA_exp",
                            CL_sec_f = 0)

out_cefu_multi <- run_multi_dose(pars_cefu_term,
                                 dose_times = c(0, 8, 16),
                                 dose_amt = 750,
                                 t_end = 24)

out_cefu_multi <- as.data.frame(out_cefu_multi)
out_cefu_multi$C_mat <- out_cefu_multi$A_mat / pars_cefu_term["V_mat"]
out_cefu_multi$C_fet <- out_cefu_multi$A_fet / pars_cefu_term["V_fet"]
```

This compact extension provides a basis for quantifying cord bias and multi-dose accumulation in a way that can be linked downstream to exposure–response analyses.

11 Data and Parameter Sources

Fetal organ sizes, blood flows, and composition are drawn from systems PBPK analyses of fetal growth and organ maturation, which provide functions for heart, liver, kidney, and other organ weights by GA [**?**, 1].

Fetal GFR maturation curves are adapted from mechanistic pregnancy PBPK studies of renally cleared drugs [2].

Maternal pregnancy physiology (body weight, cardiac output, hematocrit) is specified using standard pregnancy PBPK equations and may be fixed at term for didactic analyses focusing on fetal processes [**?**,1]. Drug-specific parameters for cefuroxime and cefazolin (protein binding, intrinsic clearance) are assembled from pregnancy PK and PBPK publications in women receiving these drugs for prophylaxis or infection treatment [**?**, 2].

12 Validation and Qualification Strategy

For cefuroxime at term, the passive scaffold is qualitatively evaluated against published maternal plasma, cord plasma, and amniotic fluid concentration profiles, with key metrics including maternal AUC and $C_{\max}$, fetal:maternal AUC ratio, and amniotic fluid time course [2]. For GA-dependent cefuroxime runs, internal consistency checks (mass balance, physiological plausibility) are emphasized due to limited direct mid-gestation fetal data.

For cefazolin, validation focuses on whether adding active fetal secretion brings simulated amniotic concentrations into the range reported in clinical data while preserving reasonable maternal and fetal plasma exposure [**?**]. Model qualification follows EMA and FDA PBPK guidance, targeting maternal AUC within 1.25-fold and fetal:maternal exposure ratios within approximately 2-fold of observed values for both drugs.

Sensitivity analyses explore the influence of swallowing, GFR maturation, placental clearance, and secretion capacity on key exposure metrics and on potential cord:maternal bias.

13 Integration with Model-Based Meta-Analysis

The scaffold naturally feeds into model-based meta-analysis (MBMA) by providing mechanistic predictions of maternal and fetal AUC, $C_{\max}$, and time above relevant MIC values for different doses and GA ranges. For example, a meta-regression could model log odds of clinical cure as a function of log fetal AUC and GA, pooling data across cefuroxime and cefazolin pregnancy studies.

This integration provides a path from corrected, mechanistic fetal exposure predictions (including amniotic recirculation and active secretion) to quantitative benefit–risk assessments in pregnant populations, potentially informing dose optimization and labeling for renally cleared antibiotics.

14 Conclusions

This report presents a unified maternal–fetal PBPK scaffold that connects a foundational cefuroxime "passive recirculation" model with a mechanistic cefazolin extension incorporating active fetal tubular secretion. The R implementation is designed to be compact and didactic while remaining faithful to key physiological processes: GA-dependent GFR, swallowing maturation, amniotic–GI recirculation, and transporter-mediated renal secretion.

By resolving a documented swallowing parameter issue, demonstrating passive under-prediction for cefazolin, and showing how an active secretion term can reconcile amniotic exposure with observed data, the framework illustrates how small mechanistic extensions can have large implications for fetal exposure predictions. The same scaffold can support further extensions to placental maturation models, fetal binding ontogeny, and MBMA-based exposure–response analyses across multiple antibiotics in pregnancy.

References

[1] Khaled Abduljalil, Masoud Jamei, and Trevor N Johnson. Fetal physiologically based pharmacokinetic models: systems information on the growth and composition of fetal organs. *Clinical Pharmacokinetics*, 58(2):235–262, 2019.

[2] Ke Xu Szeto, Maxime Le Merdy, Benjamin Dupont, Michael B Bolger, and Viera Lukacova. Pbpk modeling approach to predict the behavior of drugs cleared by kidney in pregnant subjects and fetus. *The AAPS Journal*, 23(4):89, 2021.