A hierarchical Bayesian model for an in vitro-in vivo correlation (IVIVC)

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INTRODUCTION

In vitro–in vivo correlation (IVIVC): Defined by the **FDA** as "predictive mathematical model describing the relationship between an *in vitro* property of a dosage form and an *in vivo* response" $\rightarrow$ can act as a **surrogate for bioequivalence or bioavailability testing** in human subjects $\rightarrow$ support biowaivers $\rightarrow$ **reduce costs and duration** of optimization process.

Problem: Current IVIVC models often entail complex potentially unstable mathematical deconvolution operations, are assessed applying purely frequentist methods on averaged data.

METHODS I

We propose a Bayesian convolution-based IVIVC approach including:

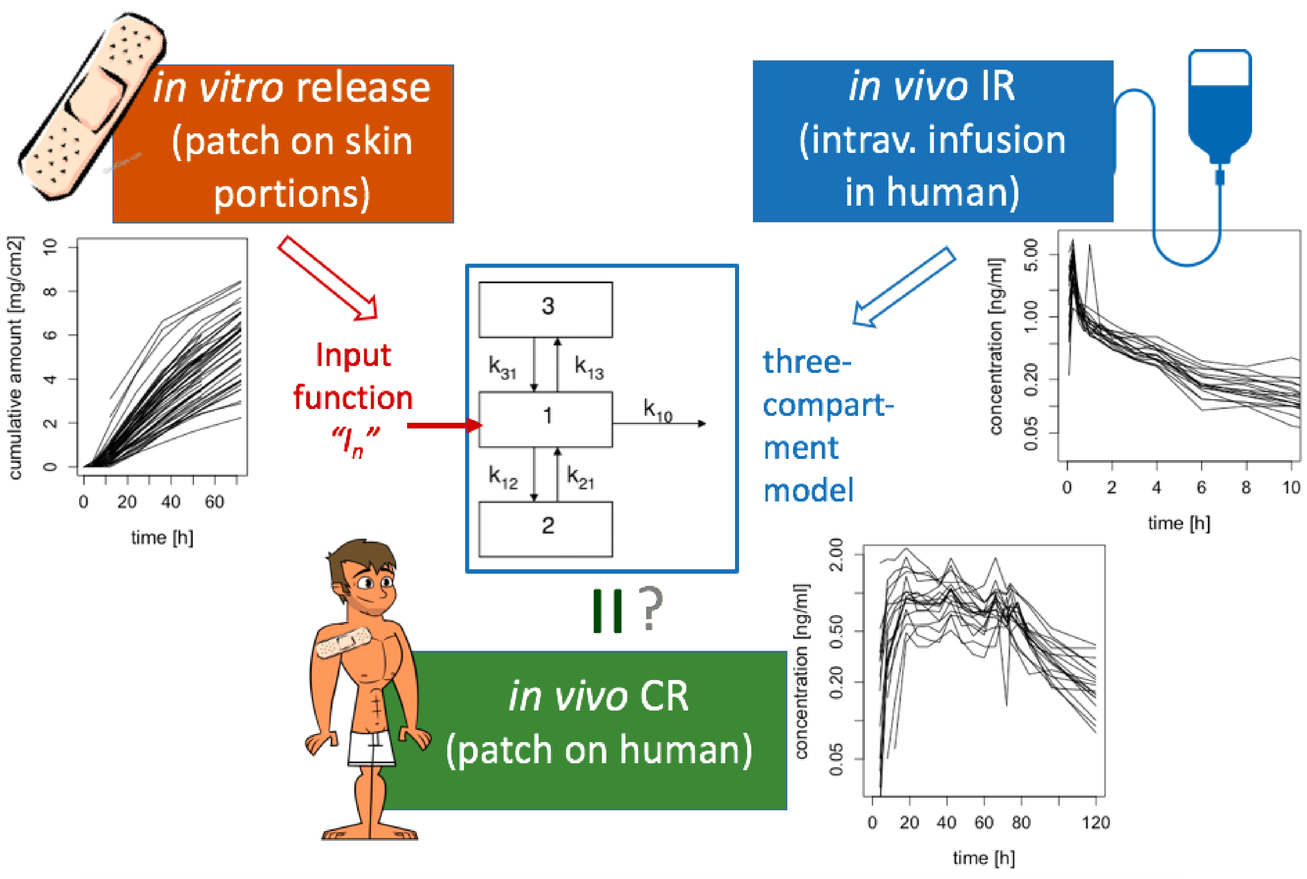
(1) a nonlinear mixed effects model for the *in vitro* **release/permeation** data;

(2) a population pharmacokinetic (PK) compartment model for the *in vivo* **immediate release (IR)** data;

(3) a system of ordinal differential equations (ODEs), containing the submodels (1) and (2), which approximates and predicts the *in vivo* **controlled release (CR)** data.

The innovation consists of splitting the parameter space between submodels (1) and (2) versus (3) and, subsequently, accounting for the uncertainty around the parameters via prior distributions in a Bayesian framework.

Case study example: transdermal patch, in (1) and (3), intravenous infusion, in (2).

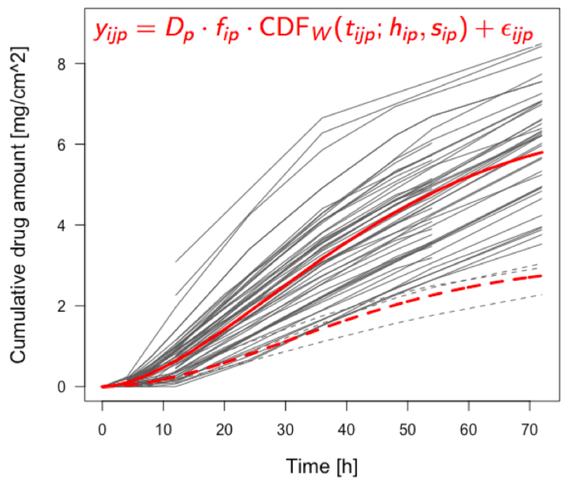


Cumulative amount of drug permeated through skin portions

Dose D_p $(p = 1, 2)$; Weibull distribution CDF_W.

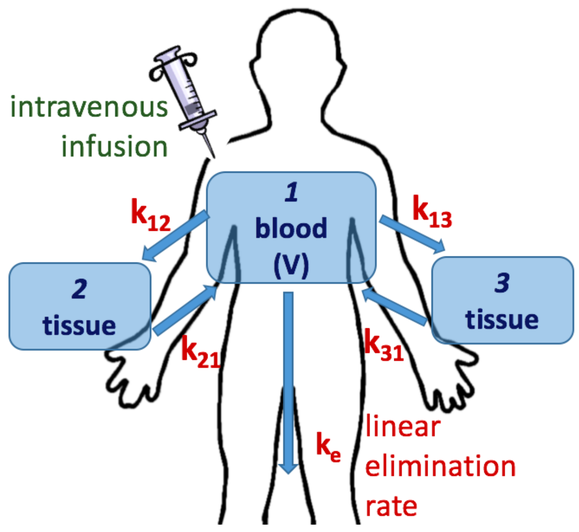
To estimate: shape h_{ip}, scale s_{ip},

fraction of dose delivered f_{ip}.



3-compartment-model for intravenous infusion

To estimate: $V_{1,i}$, k_e, k_{12}, k_{21}, k_{13}, k_{31}.



Combined ODE system to model the *in vivo* CR

$$I_n(t_{ijp}) = D_p \cdot F_{ip} \cdot B_{ip} \cdot \frac{h_{ip}}{s_{ip}} \cdot \left(\frac{t_{ijp}}{s_{ip}}\right)^{h_{ip}-1} \cdot \exp\left\{\left(-\frac{t_{ijp}}{s_{ip}}\right)^{h_{ip}}\right\},$$

$$\frac{da_1(t_{ijp})}{dt} = I_n(t_{ijp}) + k_{21}a_2(t_{ijp}) + k_{31}a_3(t_{ijp}) - [k_{12}a_1(t_{ijp}) + k_{13}a_1(t_{ijp}) + k_e a_1(t_{ijp})]$$

$$\frac{da_2(t_{ijp})}{dt} = k_{12}a_1(t_{ijp})) - [k_{21}a_2(t_{ijp}))]$$

$$\frac{da_3(t_{ijp})}{dt} = k_{13}a_1(t_{ijp})) - [k_{31}a_3(t_{ijp}))],$$

$$C_1(t_{ijp}) = \frac{a_1(t_{ijp})}{V_{1,i}}.$$

METHODS II

$I_n(t_{ijp})$: input function, a_c: amount of drug in compartment c, $(c = 1, 2, 3)$. At time $t = 0$: $a_1(0) = a_2(0) = a_3(0) = 0$.

F: fraction of dose delivered; B: fraction of dose delivered which is actually absorbed into the systemic circulation.

Each dataset consists of j repeated measurements originating from different subjects/skins $i \Rightarrow$ **Nonlinear mixed effects** modelling

$$y_{ijp} = f(t_{ijp}; \theta_{ijp}) + \epsilon_{ijp}, \quad \epsilon_{ijp} \sim \mathcal{N}(0, \sigma^2), \quad i = 1, \dots N, \quad j = 1, \dots T_i.$$

Parameters are varying between subjects/skins i, thus, are the sums of population (fixed) effects μ and individual (random) effects η_i:

$$\theta_i = \mu + \eta_i \qquad \text{with} \qquad \eta_i \sim \mathcal{N}(0, \Omega^2).$$

Bayesian hierarchical 2-stage model

Likelihood: Observed conc. $y(t_{ijp}) \sim \mathcal{G}((C_1(t_{ijp})/\sigma)^2, C_1(t_{ijp})/\sigma^2)$

Joint prior: Normally distributed population parameters

$$\theta_i = (B, \ell h_{ip}, \ell s_{ip}, \ell V_i, \ell k_{12}, \ell k_{21}, k_{13}, \ell k_{31}, \sigma^2) \sim \mathcal{N}(\cdot, \cdot)$$

PK and Weibull parameters are assumed to be log-normally distributed $\rightarrow$ priors of $\ell k_e := \log(k_e)$ etc. are normal distributions, each with specific mean and variance - obtained via frequentist estimation in (1) and (2).

RESULTS

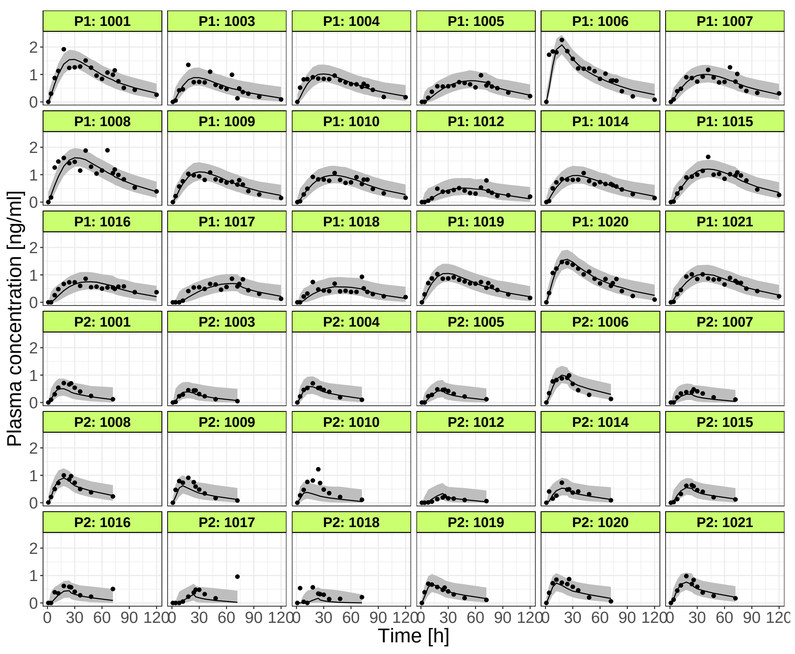


Figure 1: Serum concentrations (dots) with posterior median (black lines) and 90% credible bands of predicted individual observations in study subjects.

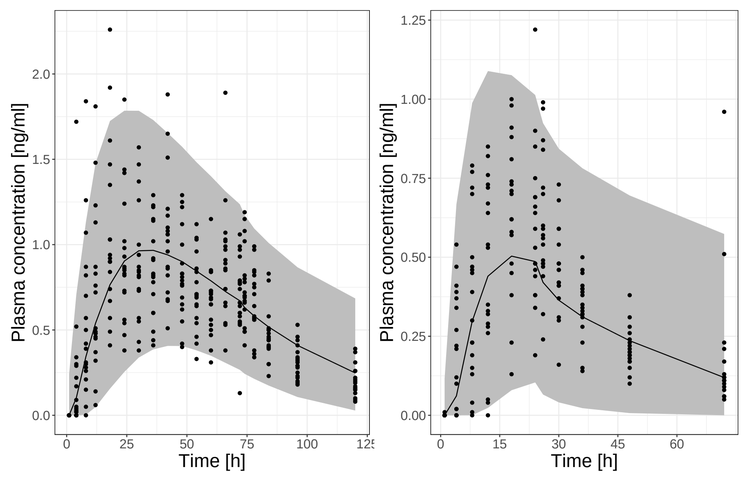


Figure 2: Serum concentrations (dots) with posterior median (black lines) and 90% credible bands of predicted population observations in new subjects. Left: 72 h formulation; right 24 h formulation of patch.

DISCUSSION

The developed IVIVC model provides a **satisfactory estimation** of the PK population data of a transdermal patch. The Bayesian framework allows a natural **integration** of knowledge from one source of information into another (*in vitro* to *in vivo*), while accounting for the parameters uncertainties. This work is an **extension** of the current IVIVC methodology where biased deconvolution techniques and averaged data are common.

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