

Pharmacokinetic (PK) Modelling of Remdesivir

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Background & Aim

- **Remdesivir (RDV)** is used as a compassionate-use-drug for managing COVID-19 patients.
- Clinical performances of RDV were still controversial.
- PK model of RDV for intravenous dose has been developed for monkey.
- PK model extrapolation from monkey to human beings.
- Human RDV model with further modifications may be used to investigate population PK related studies of this drug.

Method

Adapted and modified ordinary differential equations (ODE) for monkey PK Model as the basis for this study (Fig.1)^[1].

Nonlinear Regression Analysis: estimation of PK parameters as well as their confidence of intervals by a non-linear regression analysis with least-square method.

Latin hypercube Sampling (LHS) Analysis : to detect the interplay among a set of simultaneously changing parameters.

Impact of each tested parameter on the system can be observed with LHS method.

$$\frac{dA_{NTP}}{dt} = K_{NTP} \times A_{Nuc} - CL_{NTP} \times A_{NTP}$$

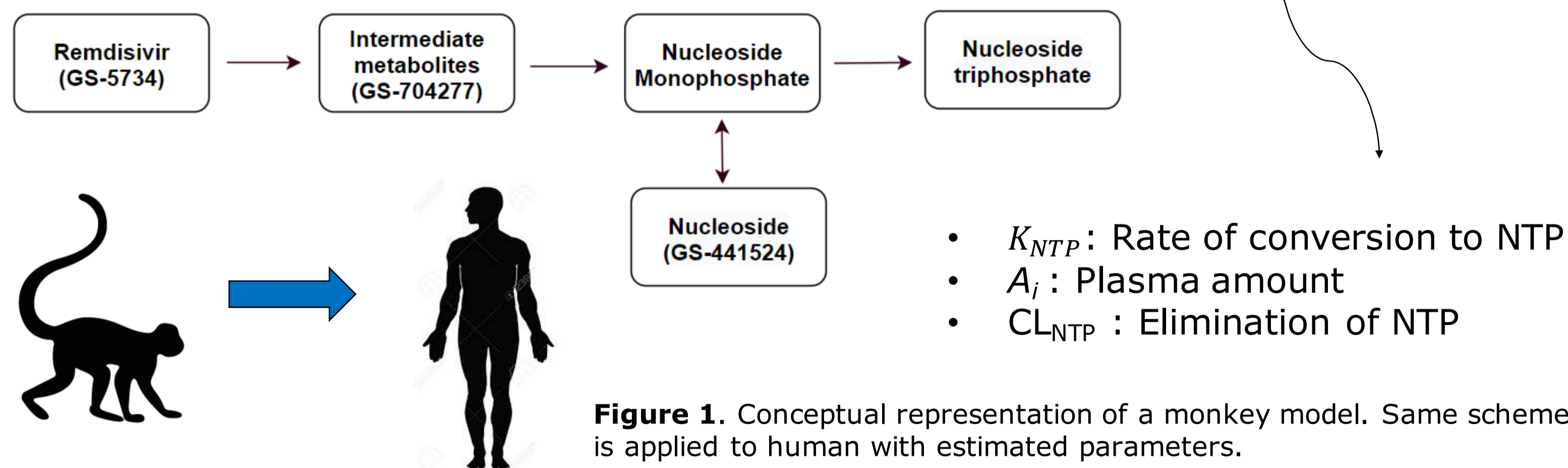


Figure 1. Conceptual representation of a monkey model. Same scheme is applied to human with estimated parameters.

Results

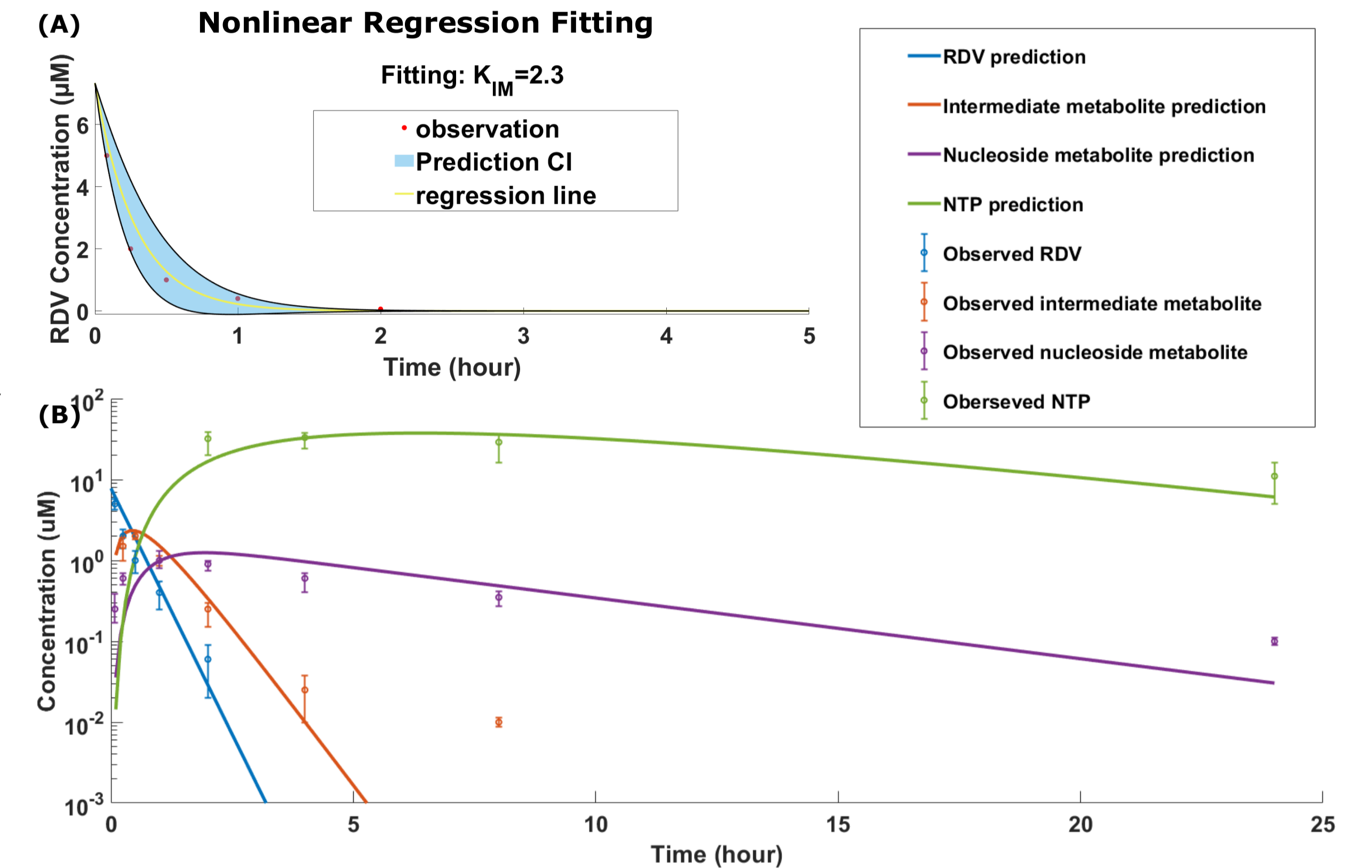


Figure 2. (A) Nonlinear regression fitting of RDV for the monkey model. **(B)** Plasma concentration prediction of RDV and metabolites after I.V. administration of 10mg/kg RDV dose in healthy male rhesus macaques.

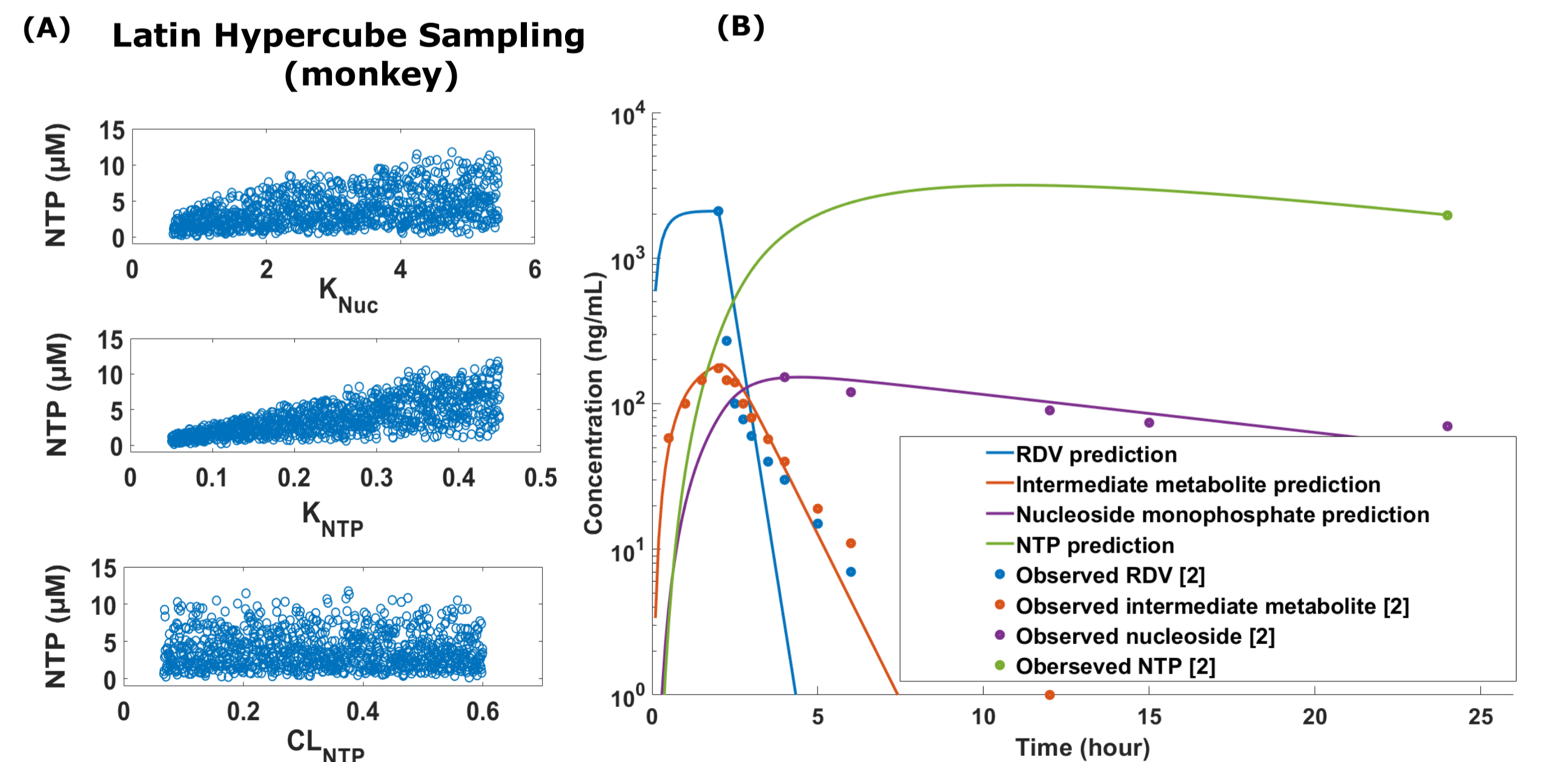


Figure 3. (A) Latin hypercube sampling results of the monkey model. **(B)** Plasma concentration prediction of RDV and metabolites after I.V. administration of 150mg RDV dose in human.

References

- [1] Goyal A, Cardozo-Ojeda EF, Schiffer JT. Potency and timing of antiviral therapy as determinants of duration of SARS CoV-2 shedding and intensity of inflammatory response. MedRxiv 2020:2020.04.10.20061325. <https://doi.org/10.1101/2020.04.10.20061325>.
- [2] Humeniuk R, Mathias A, Cao H, Osinusi A, Shen G, Chng E, et al. Safety, Tolerability, and Pharmacokinetics of Remdesivir, An Antiviral for Treatment of COVID-19, in Healthy Subjects. Clinical and Translational Science 2020;13:896-906. <https://doi.org/10.1111/cts.12840>.