

Modelling of Glucose and Insulin profiles in Patients with Type 2 Diabetes Mellitus treated with a GLP-1 analogue

Background

- Diabetes is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The primary aim of treatment is to control the blood glucose and obtain normal or near-normal blood glucose levels.
- The hormone Glucagon-like peptide-1 (GLP-1) stimulates insulin secretion in a glucose dependent manner, slows gastric emptying, inhibits glucose-dependent glucagon secretion and improves β -cell function [1].
- As the insulinotropic effect of GLP-1 is preserved in type 2 diabetes mellitus (T2DM), GLP-1 analogues with a prolonged duration of action have been developed for the treatment of T2DM.

Aim

- To incorporate the effect of an exogenously administered GLP-1 analogue on glucose homeostasis in the integrated glucose-insulin (IGI) model [2].

Methods

- Data for model development were from a randomized, placebo-controlled, double-blind, two-period, crossover trial, comparing the effect of steady-state liraglutide at three dose levels (0.6, 1.2, and 1.8 mg/day) versus placebo on the responses of fasting plasma glucose and post-prandial glucose, insulin, and gastric emptying in T2DM patients [3].
- After one week of treatment at each dose level, an energy fixed meal tolerance test (MTT) was performed during which serum insulin and glucose profiles were obtained.

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- A semi-mechanistic, integrated glucose-insulin (IGI) model has previously been developed to describe MTTs for T2DM patients. The IGI model consists of glucose and insulin compartments and control mechanisms in the form of effect compartments [2]. The IGI model was extended to allow incorporation of a GLP-1 analogue and its effects on blood glucose.

Results

- The IGI model was extended to describe the post-prandial glucose profiles in T2DM patients treated with a GLP-1 analogue. The effect of the GLP-1 analogue on glucose homeostasis was incorporated in the model by including:
 - 1) a stimulatory effect on insulin secretion
 - 2) an inhibitory effect on glucose absorption, which was included to account for a delay in gastric emptying during the early phase after the MTT.
- In Figure 1, time courses for plasma glucose and insulin concentrations are shown together with the model fit.
- The predictive performance of the model was graphically evaluated by a VPC based on 1000 simulations. The VPC, shown in Figure 2, shows that the main trend and the variability of glucose and insulin is well captured by the model at all dose levels.

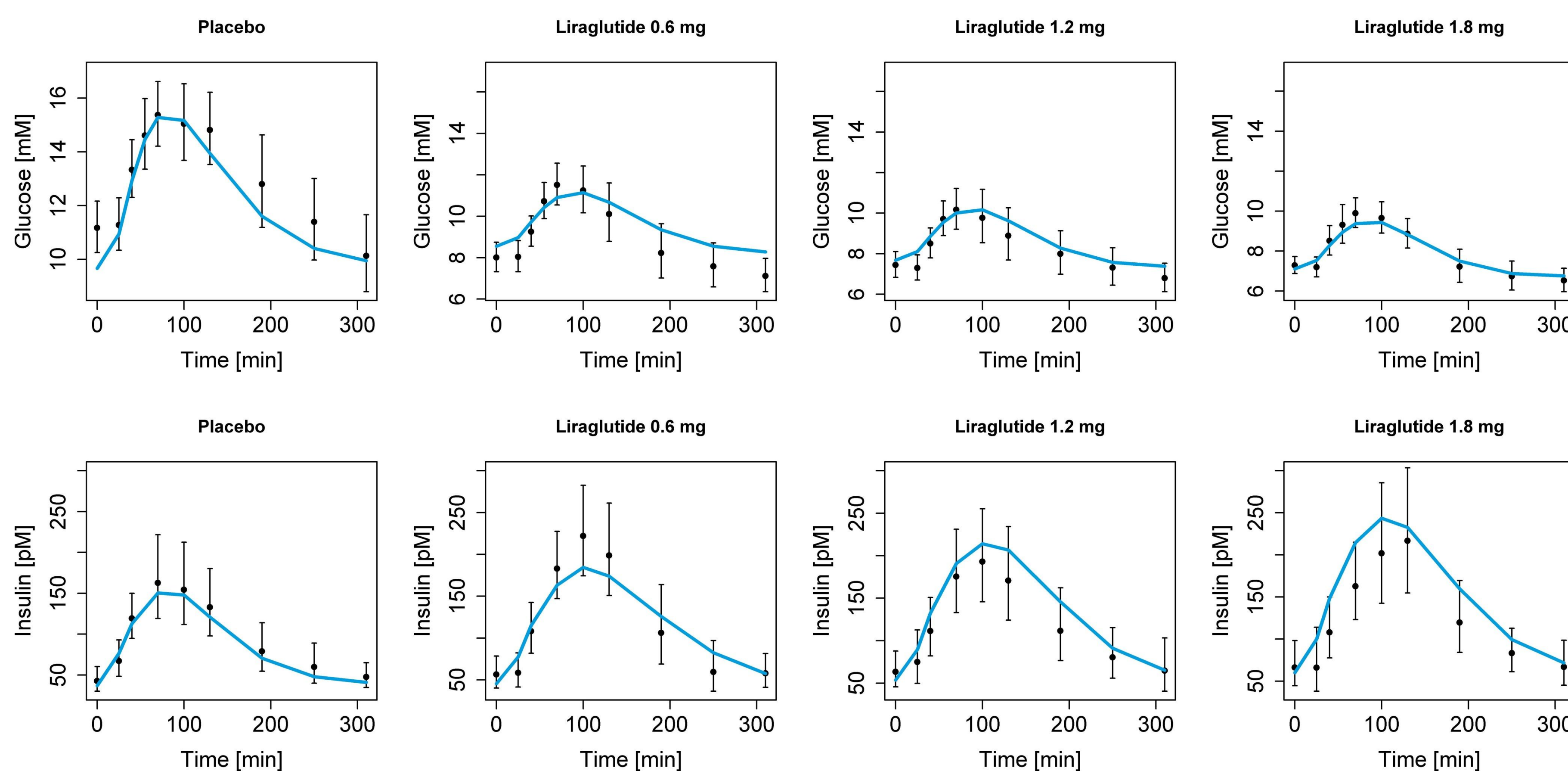


Figure 1: Time courses for plasma glucose and insulin concentrations. The dots show the geometric mean and the corresponding 95% confidence interval of the data. The solid lines show the geometric mean of the individual predictions.

Conclusion

- The IGI model was successfully extended to describe glucose homeostasis in T2DM patients treated with the GLP-1 analogue liraglutide.
- As other GLP-1 analogues have similar mode of action it is believed that the model can also be used to describe the effect of other GLP-1 analogues on glucose homeostasis.

References

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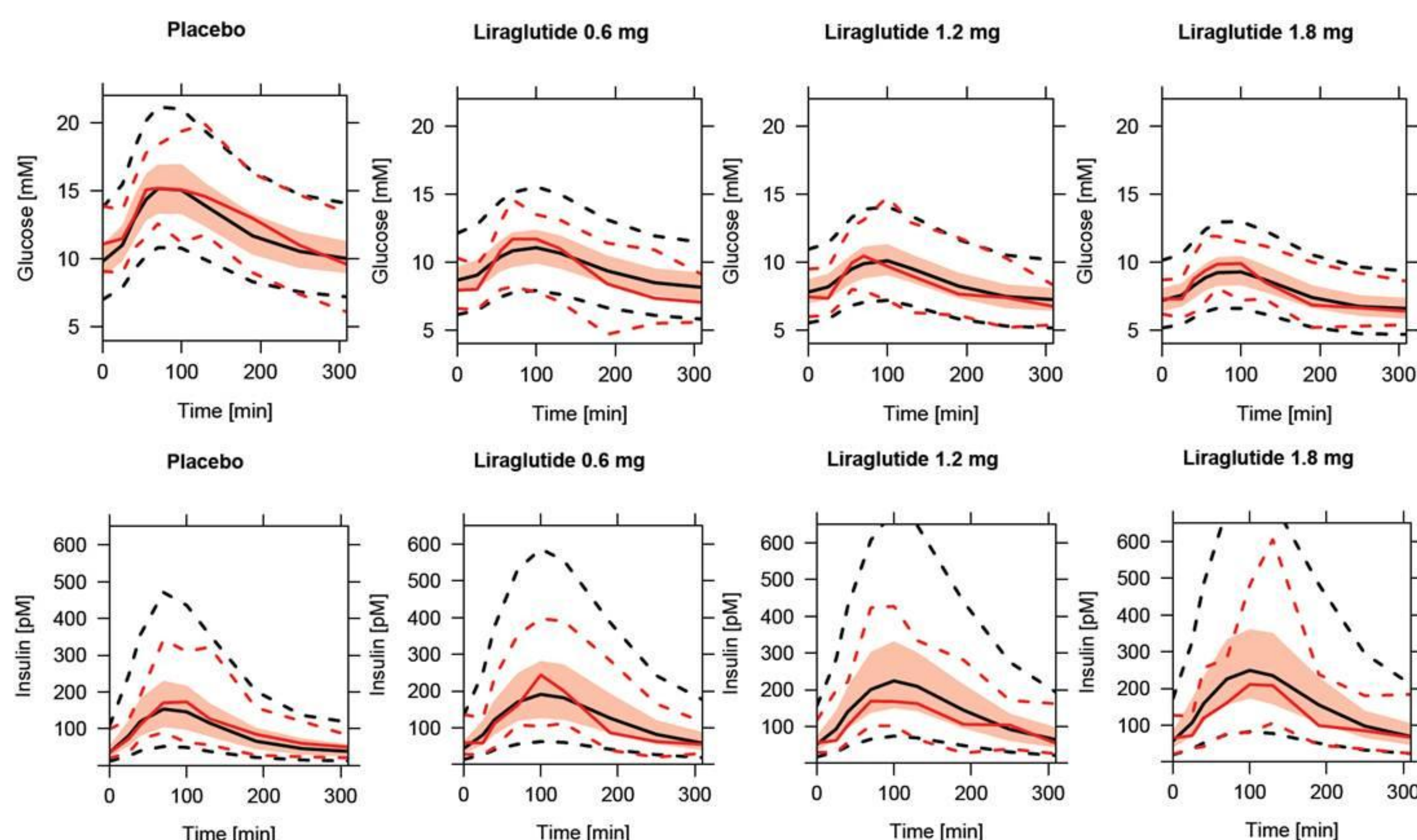


Figure 2: Visual predictive check. Solid lines represent median concentrations and dashed lines represent 5th and 95th percentiles. The red lines represent the data and the black lines represent simulations from the model. The shaded areas represent 95% confidence intervals for the simulated median

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