SENSITIVITY ANALYSIS – THEORY AND PBPK APPLICATIONS

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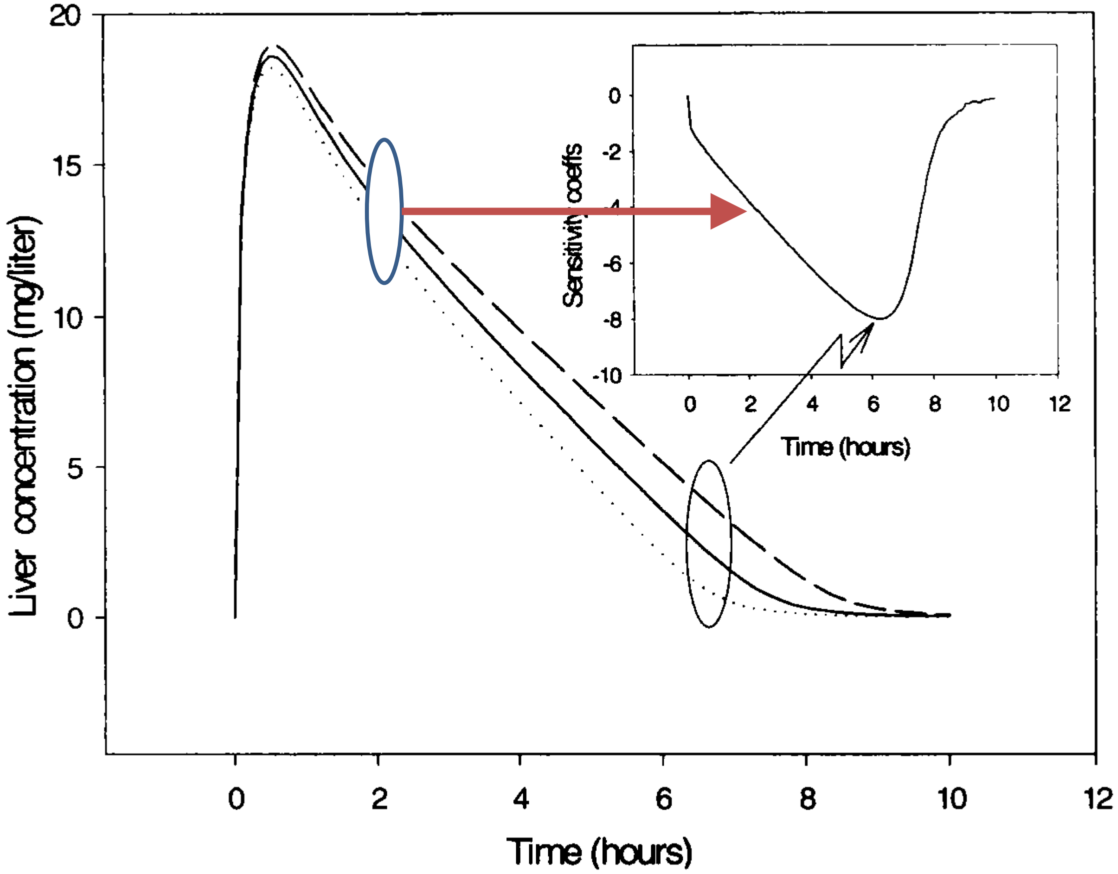
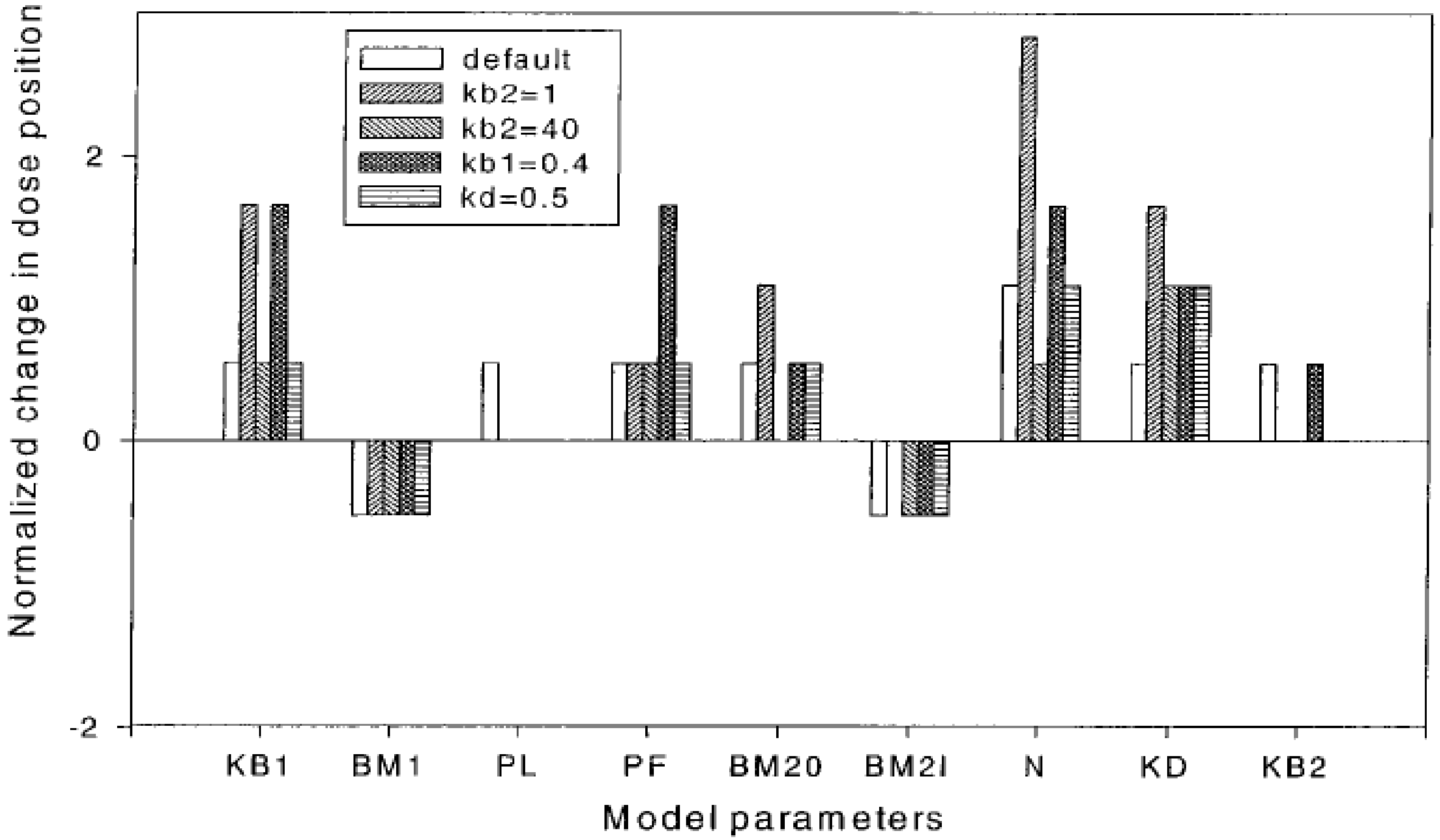
Sensitivity Analysis

- Mathematical application – estimates the impact a parameter change has on a model output over time.
    - How much change in output occurs due to change in a parameter.
    - Each parameter will have a related sensitivity coefficient.
    - Application: slopes from gas uptake chambers are related to ability to estimate Vmax and Km.
    - Different concentrations have different slopes and groups of data are needed for a single estimate.
    - Because of different slopes we can get unique estimates.

Liver concentration prediction after inhalation in rats– slopes are time dependent.

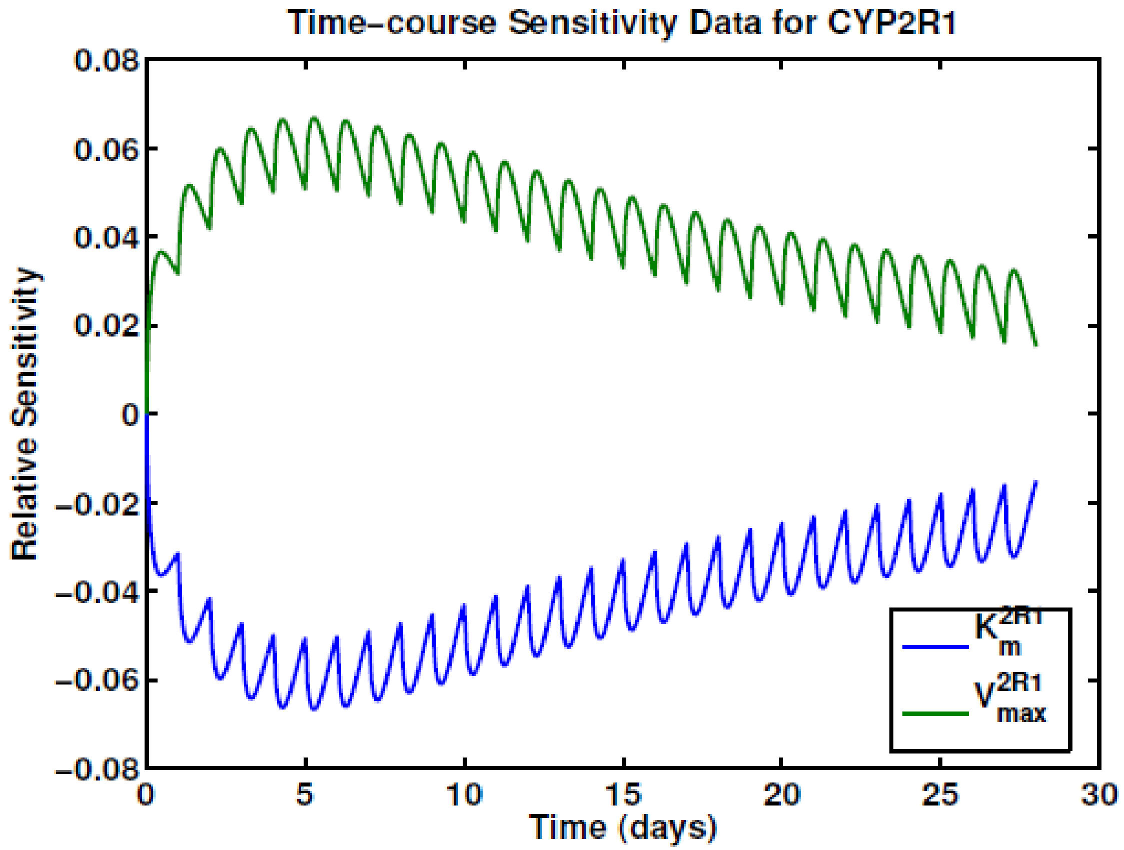


Normalized change in dose (measurement) for each model parameter at a fixed point in time.



KB1= Ah binding constant
BM1 =Ah availability
PL = liver PC
PF = fat PC
BM20 = CYP1A2 basal
BM2I = CYP1A2 induction
N = Hill coefficient
KD =complex binding constant
KB2 = CYP1A2 binding constant

Sensitivity coefficients add to zero-not uniquely identifiable for a human model.



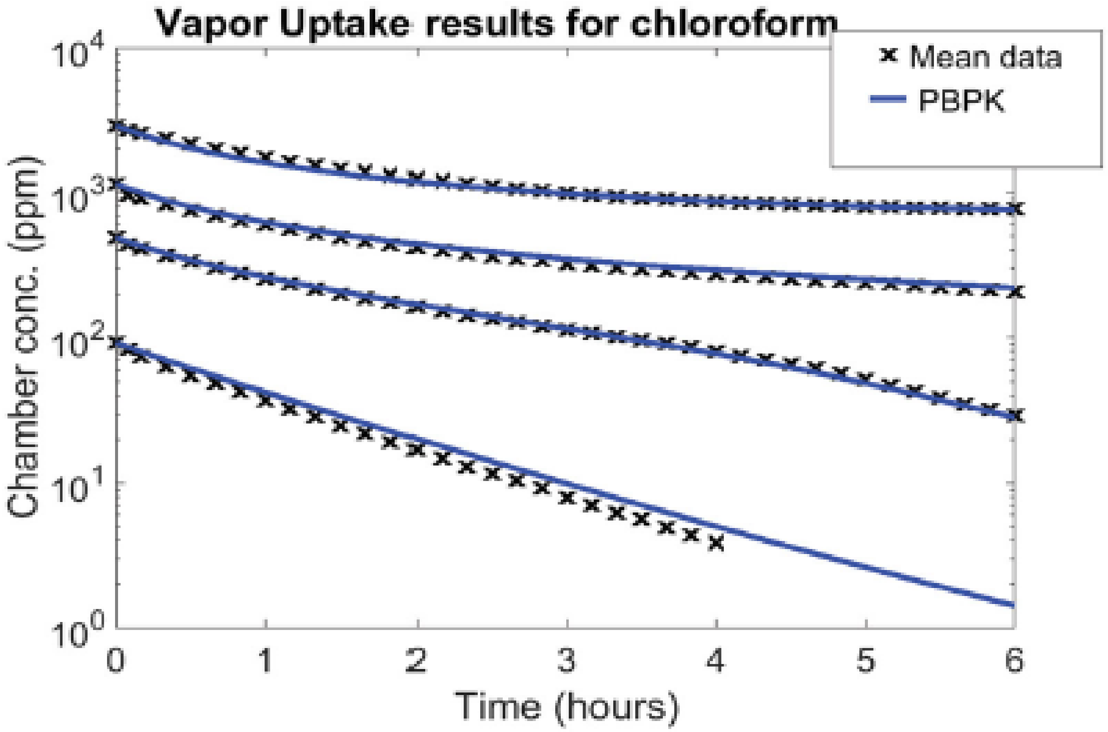
(a) K_m^{2R1} and V_{max}^{2R1}

Mathematical tools used to rank Sensitivity Coefficients

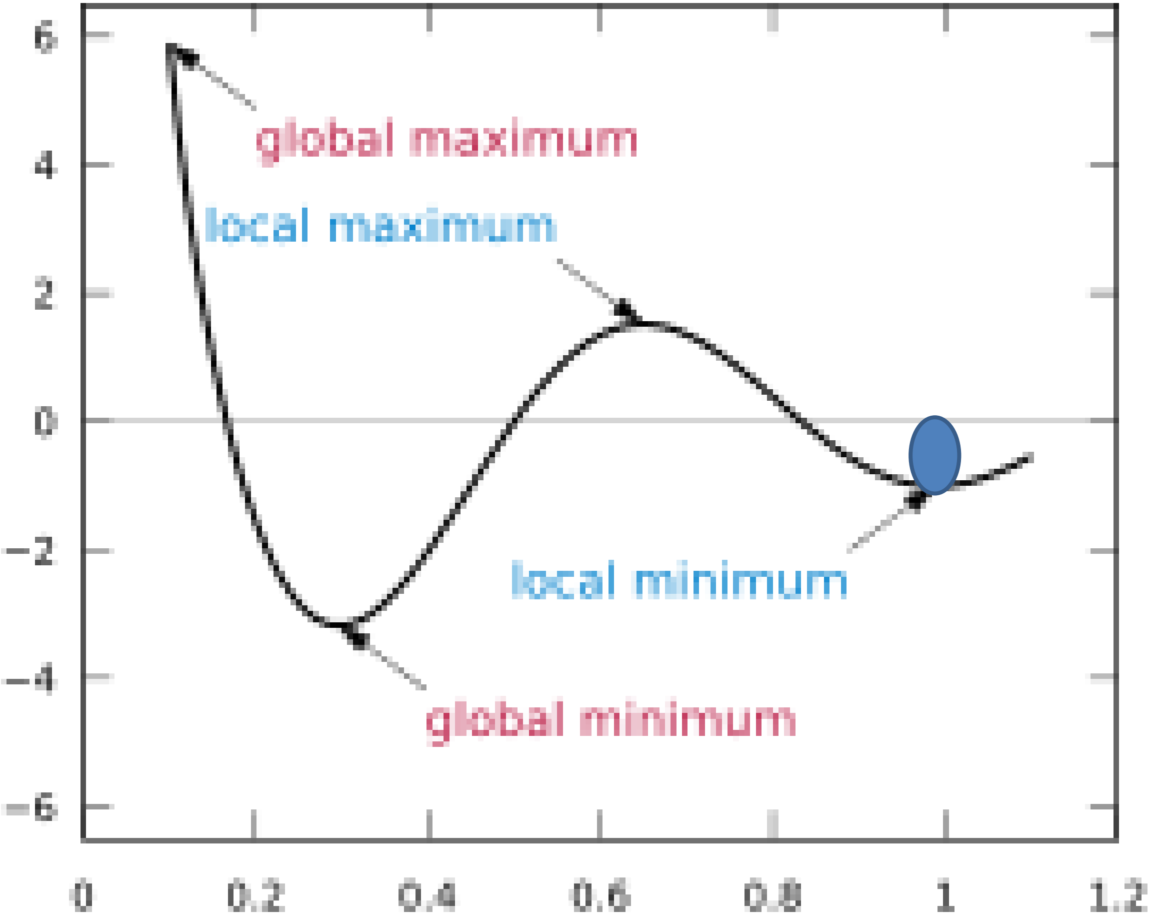
	Model Structure	Application
Mathematical Techniques	Linearization Taylor Series Expansion	Fisher Information Matrix Graphical or Visual Inspection Correlation matrix
Model Complexity	Difficult for more than 10 parameters and states	Can assess in models with more than 50 parameters and states

How do we estimate unknowns?

- Optimization –
  - Take the difference between data and model simulation.
  - Make sure difference is as small as possible- Least Squares Sum (LSS).

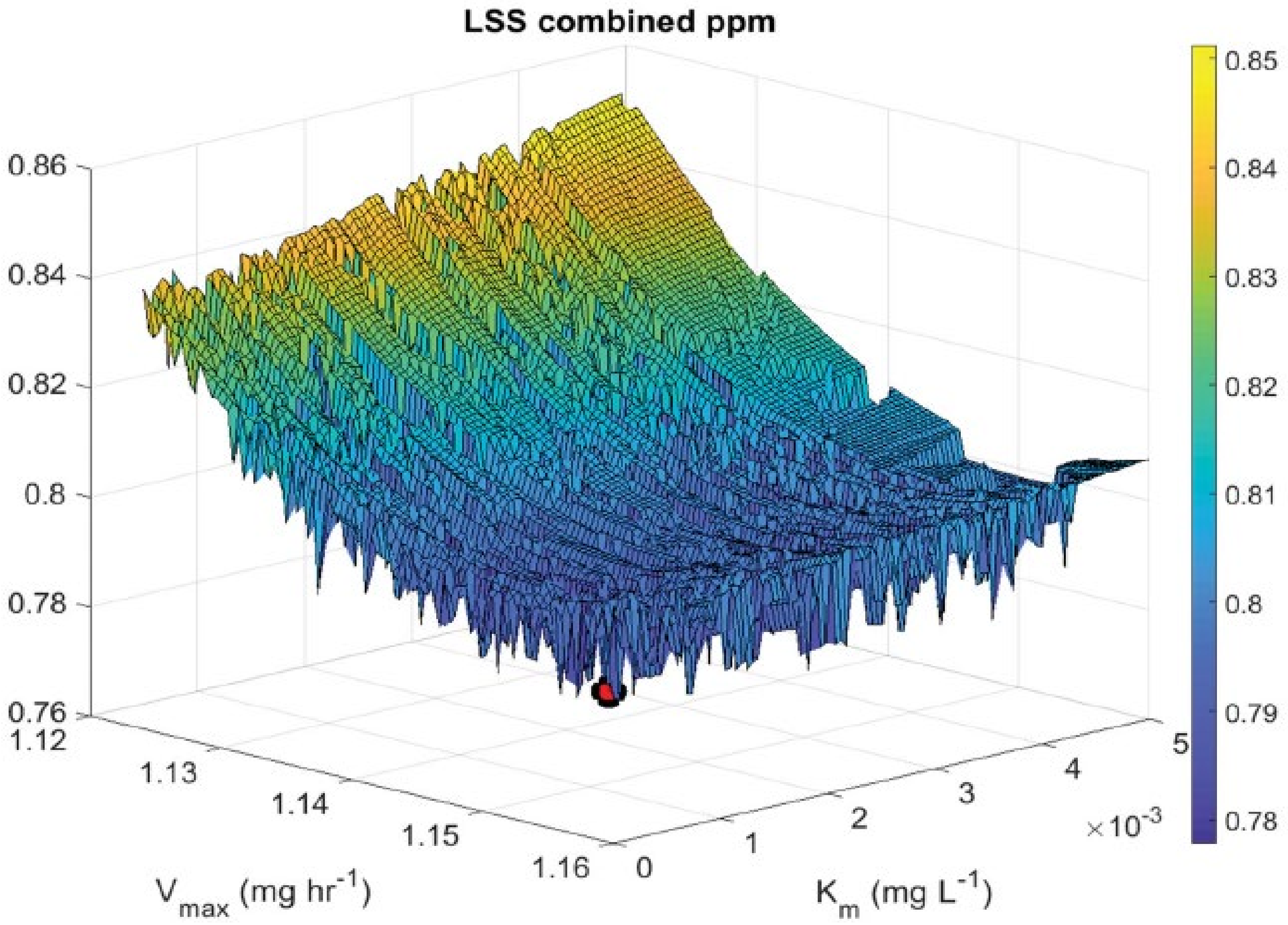


SA and global optimization

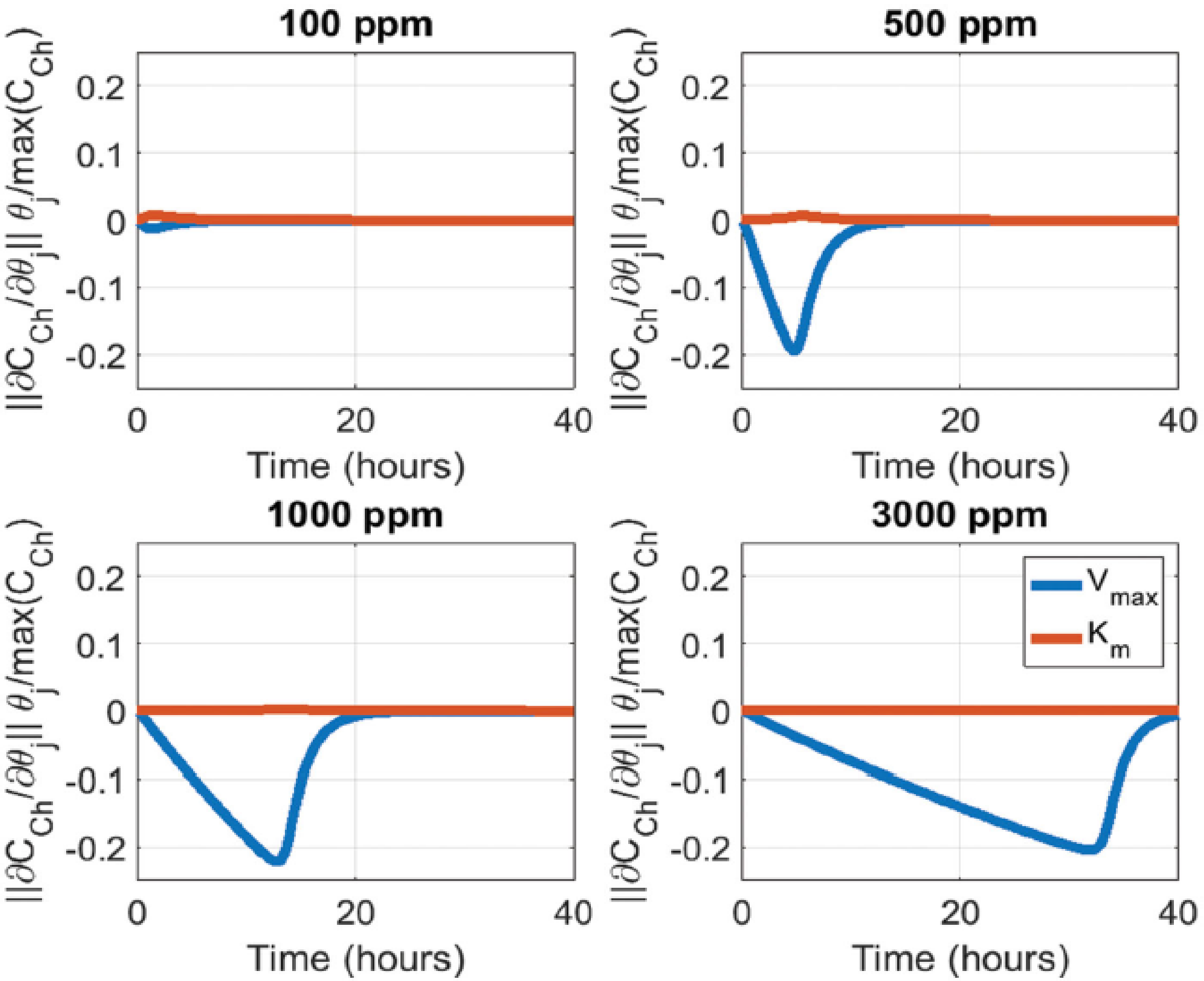


Use a global optimization algorithm to find true global minimum

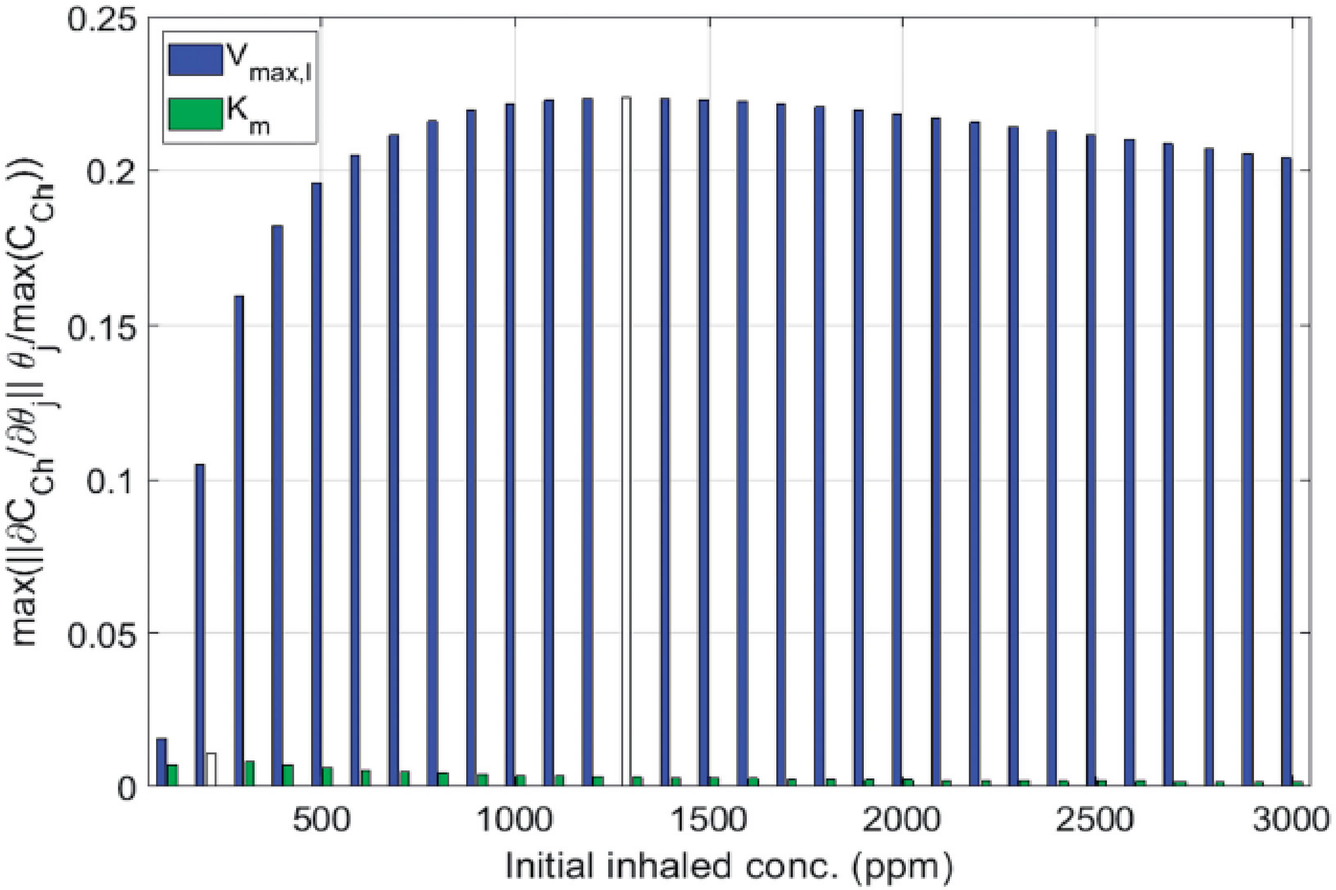
PBPK rat optimization surface with multiple peaks and valleys. Red dot is Vmax and Km values.



Normalized SC for different inhalation concentrations in rat experiments for previous surface.



Normalized SC for given exposure can predict experimental concentrations- e.g.1300 ppm for Vmax and 200 ppm for Km.



How is SA performed?

- Calculate Sensitivity Coefficients with Chain Rule and gradients (slopes) for each parameter of interest.
- Perform the calculations for each time point.
- Largest normalized sensitivity coefficients suggest time for estimable parameters.
- Ranking of most important parameters in model.
- Unique values will be obtained if SC do not cancel each other.

Thank You!