

Simulation Languages for PBPK Modeling

A Course on Physiologically Based Pharmacokinetic (PBPK)
Modeling in Drug Development and Evaluation

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Center for Human Health Assessment
Center for Drug Safety Sciences



Numerical integration algorithms

“Inching along in the dark”

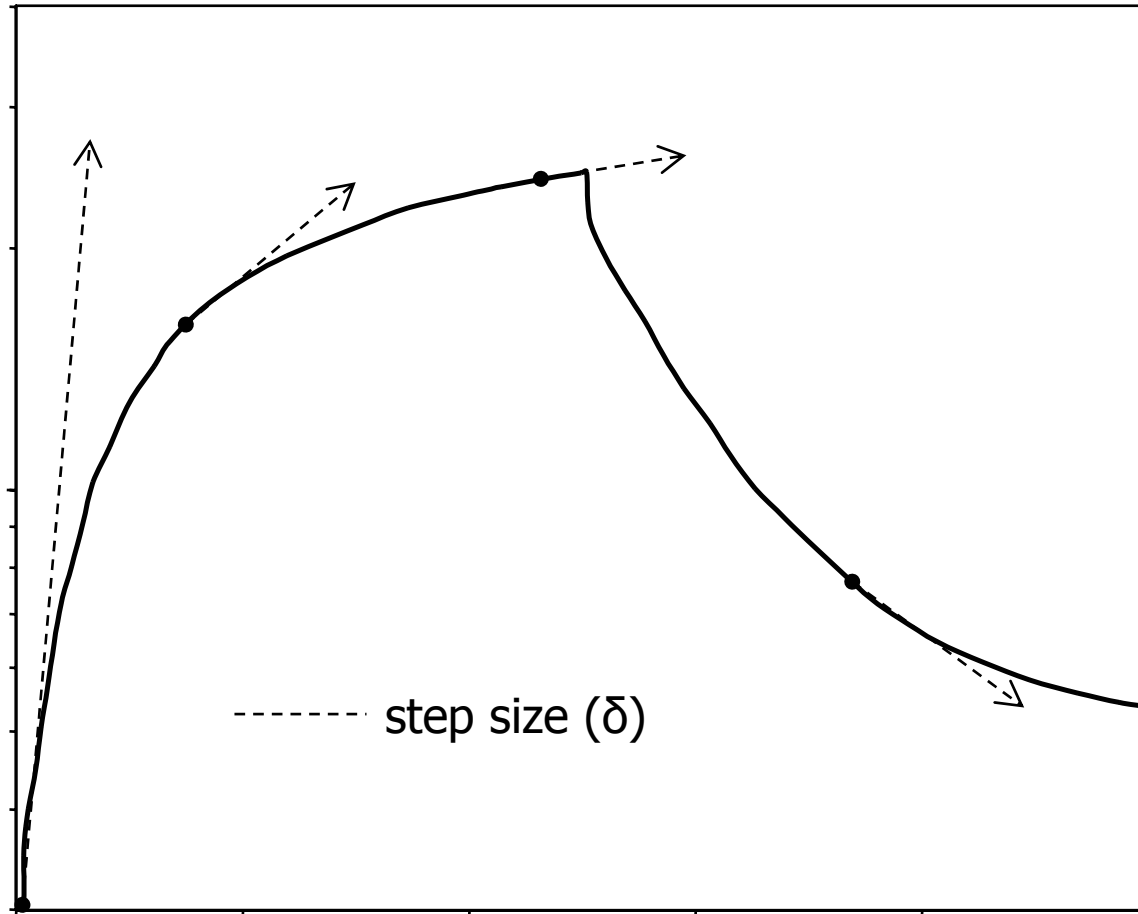
Mathematically, PBPK models represent a system of ordinary differential equations (ODEs) defining an initial value problem.

A number of simulation languages are available to solve this type of problem numerically.

The approach generally used to solve ODE initial value problems is referred to as “numerical integration”.

Numerical integration algorithms

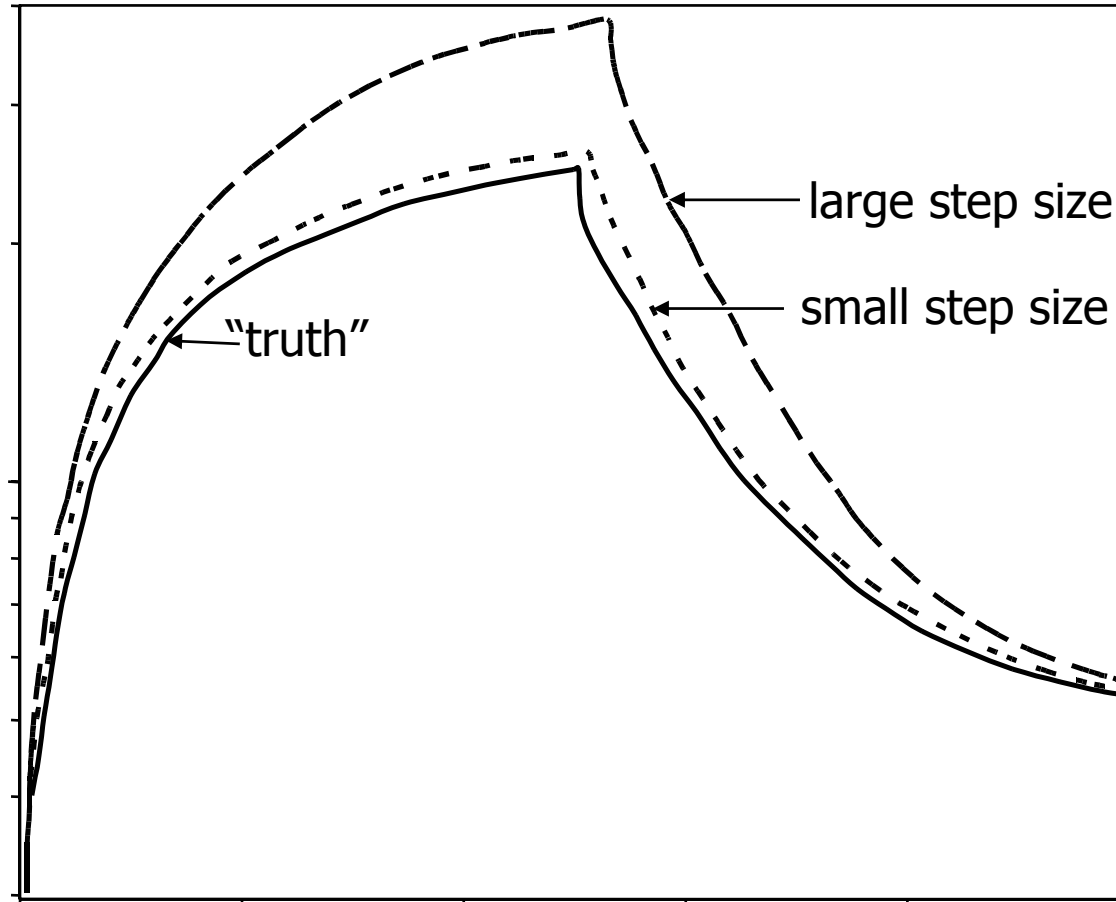
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$$Y(t + \delta) = Y(t) + Y' \bullet \delta$$

Numerical integration algorithms

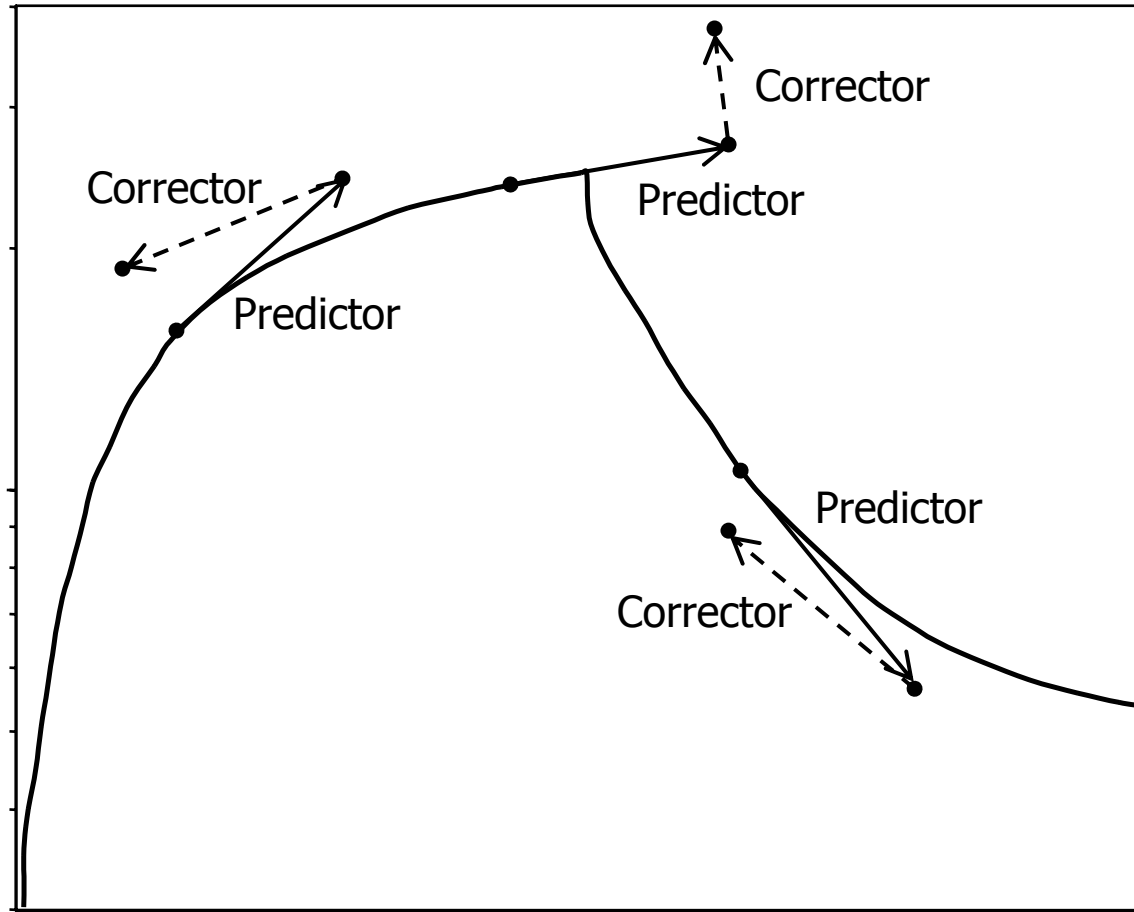
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The larger the step size, the larger the potential for systematic error.

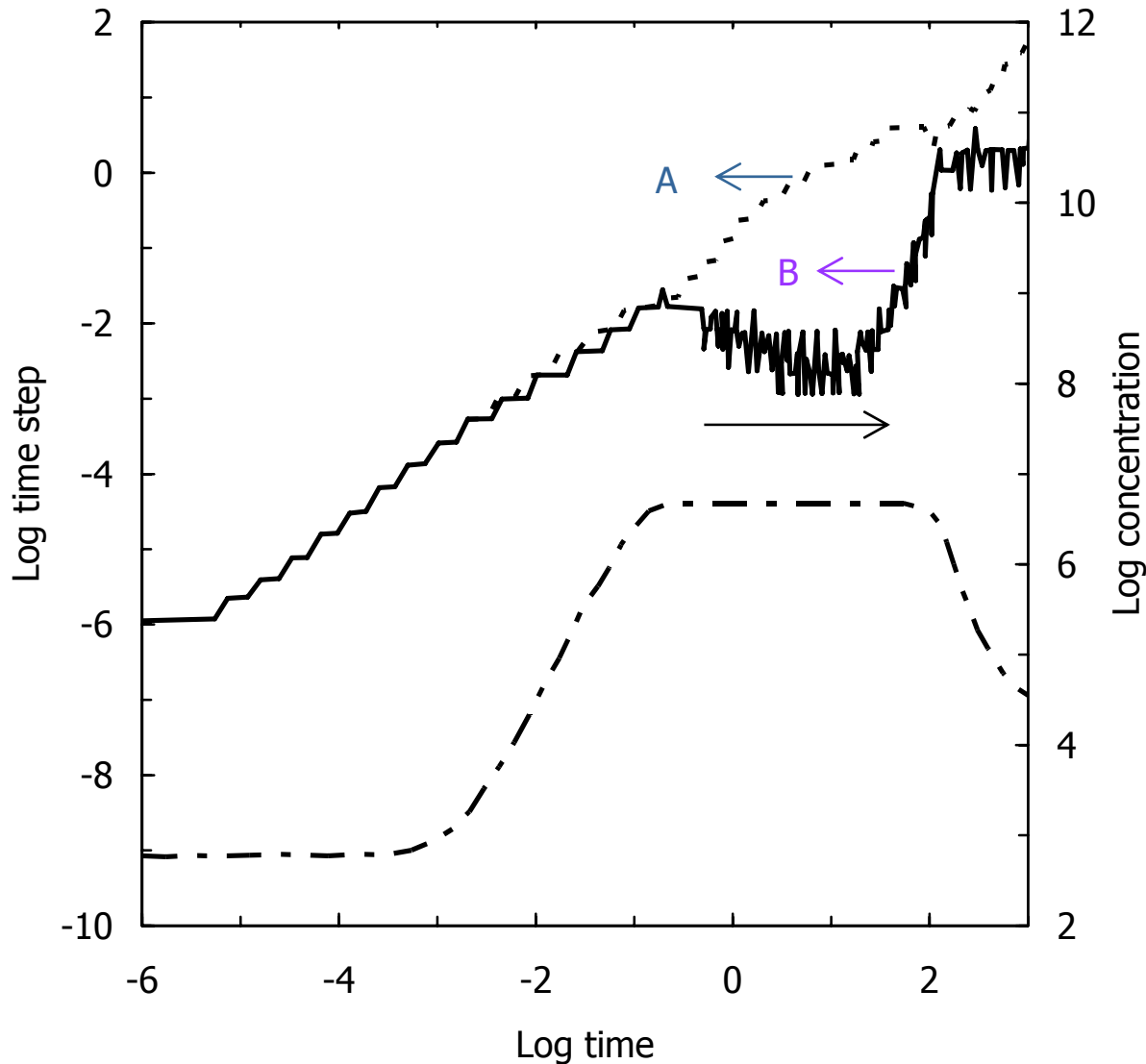
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Automatic step size adjustment based on error tolerance.

PBPK models with widely varying compartment time constants behave as stiff systems, fooling automatic step-size algorithms



Comparison of the performance of a stiff (A) and nonstiff (B) ODE solver for a problem exhibiting steady-state behavior (broken line). The time step of the nonstiff program is severely constrained during the steady-state period. The nonstiff program had about 75 times as many steps and took about 50 times as long to solve the problem.

Stiff ODE solvers:
Gear (LSODES)
Rosenbrock