Delay Differential Equation Solver in ADAPT 5

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Objectives: Delay differential equations (DDEs) are an important tool to model delays in biological systems, and become increasingly relevant in pharmacokinetics / pharmacodynamics (PK/PD) modeling \cite{1}. In contrast to ordinary differential equations, in DDEs the derivative of the states depends on both the current and past times. To efficiently solve DDEs, we extended the PK/PD software ADAPT 5 \cite{2} with a DDE solver.

Methods: RADAR5 is the state-of-the-art DDE solver that can detect and solve stiff problems with state dependent delays \cite{3}. RADAR5 subroutines were included in ADAPT 5 and its modeling language was expanded to account for additional DDE features such as delayed states and user defined history of the states. The DDE implementation was validated against published PK/PD models involving delays.

Results: PK/PD models in DDE formulation for cell maturation, infectious diseases, rheumatoid arthritis, and oncology were implemented in the extended ADAPT 5 software and applied to fit data. Model solutions were compared to the simulated results obtained by the DDE solver dde23 from MATLAB \cite{4}. The PK/PD model library of ADAPT 5 was extended with examples of DDE based models from the above areas to demonstrate new DDE features.

Conclusions: RADAR5 allows applications of DDE based PK/PD models using ADAPT 5 algorithms that yield identical results with well-established DDE solvers.

References:
\cite{4} MATLAB Release (2014b) The MathWorks, Inc. MathWorks, Natick