

An approximation to the solution of systems of nonlinear ordinary differential equations in pharmacokinetics-pharmacodynamics



Stephen Duffull¹, Gareth Hegarty²

School of Pharmacy¹, Departments of Mathematics and Statistics²,
University of Otago, Dunedin, New Zealand



Background

- PKPD models are commonly defined as a set of ordinary differential equations (ODEs) of the general form

$$\frac{dy}{dt} = f(t, y) + A(t, y)y; \quad y(t_0) = y_0. \quad (1)$$

- Solutions to these ODEs are available in closed form for systems that are linear in the parameters.
- Typically nonlinear ODEs are solved by time stepping algorithms (e.g. the Runge Kutta techniques).

Aims

To propose and evaluate a rapid iterative solution that is exact to any level of accuracy and is continuously differentiable over time.

Theory

- The ODE represented in (1) can be approximated with a linear time-varying form by defining a sequence of observations $y^{\{n\}}$ that conditionally depend on the previous iteration.

$$\frac{dy^{\{n\}}}{dt} = A(t, y^{\{n-1\}})y^{\{n\}} + f(t, y^{\{n-1\}}); \quad y^{\{n\}}(t_0) = y_0 \quad (2)$$

- Since (2) no longer depends on $y^{\{n\}}$ it is therefore a first-order linear system and can be solved by writing as an integrating factor solution and solving the integrals using Gaussian quadrature.

$$y^{\{n\}}(t) = e^{\left(\int_{t_0}^t A(\tau, y^{\{n-1\}}(\tau) d\tau\right)} y_0 + \int_{t_0}^t e^{\left(\int_{\tau}^t A(s, y^{\{n-1\}}(s) ds\right)} f(\tau, y^{\{n-1\}}(\tau)) d\tau \quad (3)$$

- In this sequence the value of $y^{\{n\}}$ is updated at each iteration and will converge to the exact solution with increasing accuracy as n increases.

Application - Methods

- We choose a simple one-compartment first-order input model with Michaelis-Menten elimination (see [1]).
- Some exact solutions exist for special cases of this model (see for example [2]).
- The form is given here:

$$V \frac{dC}{dt} = k_a D e^{-k_a t} - \frac{V_{max}}{k_m + C} C; \quad C(t_0) = 0. \quad (4)$$

- For the purposes of this example $D = 1$, $k_a = 1$, $V = 1$, $V_{max} = 0.0734$, $k_m = 0.367$.
- The iterative solution for (4) is given by,

$$V \frac{dC^{\{n\}}}{dt} = k_a D e^{-k_a t} - \frac{V_{max}}{k_m + C^{\{n-1\}}(t)} C^{\{n\}}; \quad C(t_0) = 0. \quad (5)$$

- The form given in (5) is now linear and using the solution from (3) can be solved using quadrature.
- If we use N –point abscissas and weights for the quadrature and choose n –iterations of the linearisation then the problem simplifies to $2 \times N \times n$ quadrature steps (there are two integrals to solve)

Application - Results

- In this example we found $N_1 = N_2 = 5$ was sufficient.
- We see (Figure 1), that as n increases the solution approaches that of the 4th order Runge Kutta method (ode45 – MATLAB)
- When $n = 7$ the solution from the linearized example were within 10^{-5} of the time stepping solution
- The initial values $C^{\{1\}}(t) = 0$ for all t worked well in this example, a more informative starting values could be given by the linear solution setting $CL = V_{max}/k_m$ as an initial guide.
- Plotting the relative error of successive iterations shows an exponential decay indicating the series will be convergent (Figure 2).

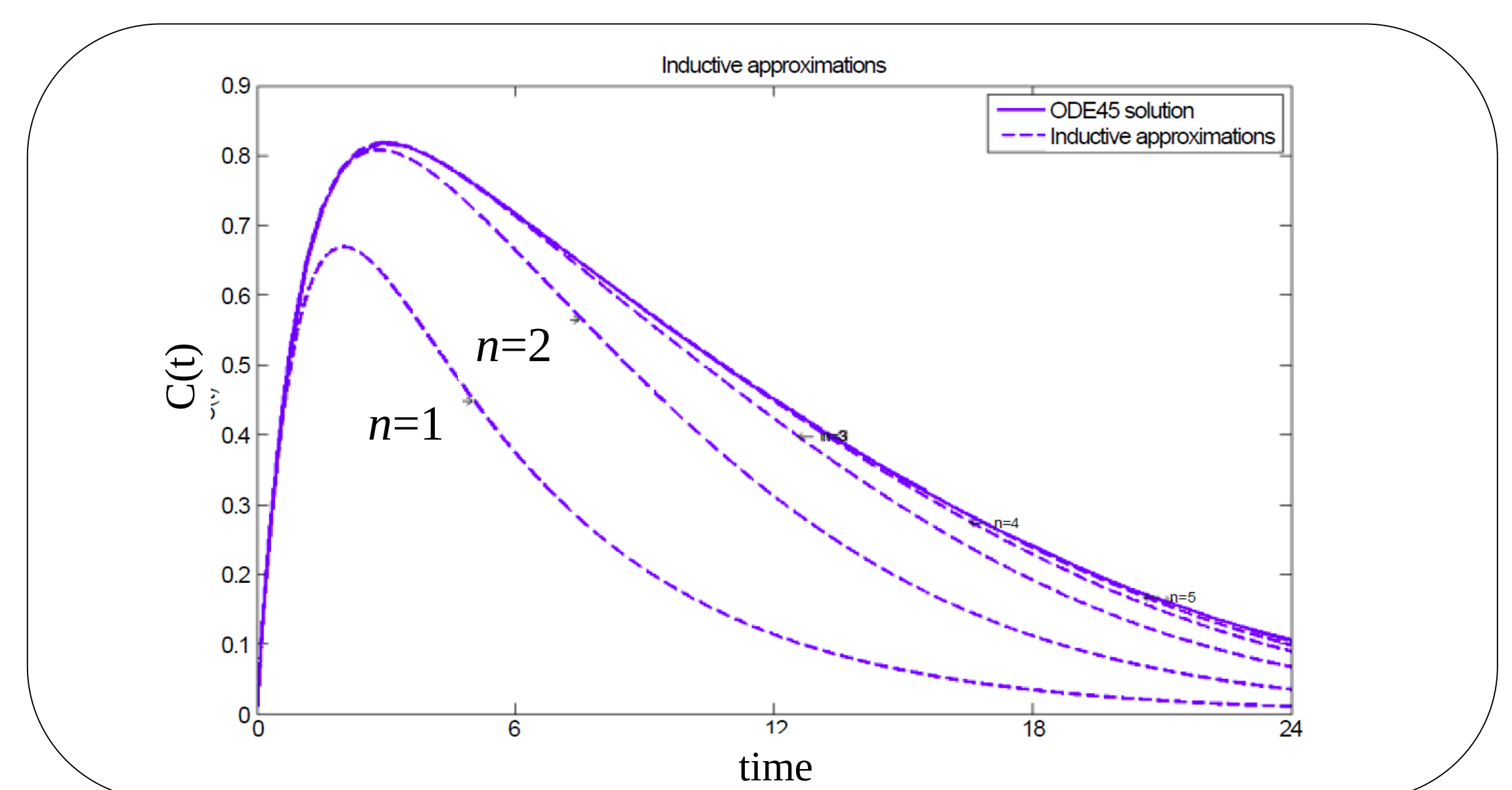


Figure 1. Convergence of inductive estimates $C^{\{n\}}(t)$ to solutions of (equation 5), $n = 1, \dots, 5$.

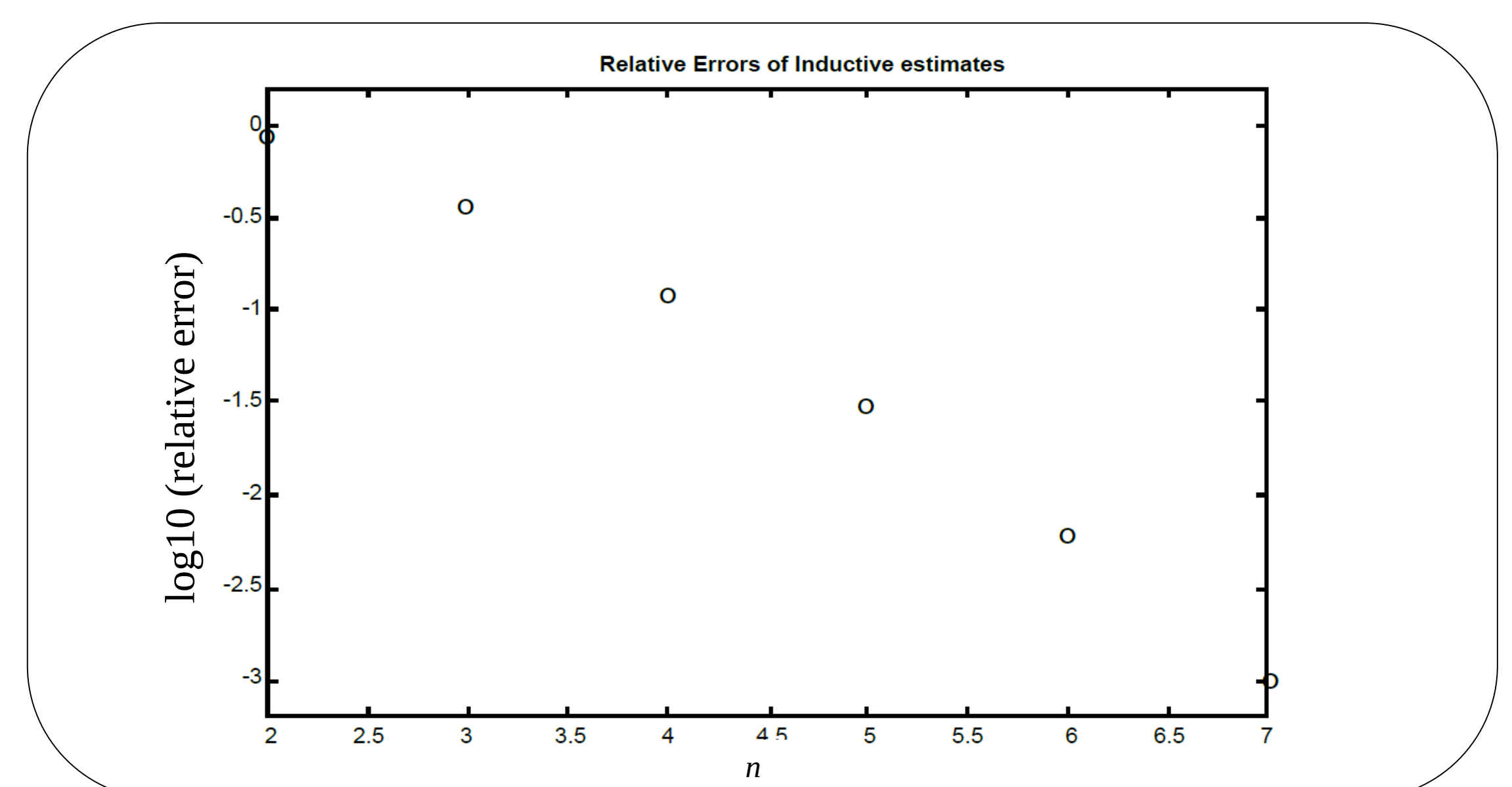


Figure 2. Relative errors of successive inductive approximations (plotted in log10 scale and calculated as $\left(\int_0^T |C^{\{n\}}(t) - C^{\{n-1\}}(t)|^2 dt\right)^{\frac{1}{2}}$ for $n = 2, \dots, 7$

- Run times for the quadrature were fast in MATLAB with speed increases in the order of 20 fold when comparing ode45 vs quadrature for a time-varying linear example.
- Speed increments will be less with the linearization approach with n –iterations (note here that $n \ll 20$).

Discussion

- A method is described that provides an arbitrarily exact solution to non-linear ODEs.
- Advantages of this approximation include: (1) the function depends continuously on time (interpolation is not required), (2) the solution depends on the algebraic function (hence understanding the stiffness of the system is not required), (3) solutions to the derivatives are available analytically, (4) the solution is not dependent on the parameter values.

References

1. Duffull et al. *J Theor Comput Sci* 2014 doi <http://dx.doi.org/10.4172/jtco.1000119>

2. Beal. *J Pharmacokinet Biopharm* 1982 10:109-119