Bayesian ODE-penalized B-spline model with Gaussian mixture as error distribution

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Motivating example

Theophylline dataset

Data for the kinetics of the anti-asthmatic drug theophylline with 12 subjects, concentration were measured at 11 time point over 25 hours for each subject.

Differential equation

$$\begin{cases} \dfrac{dx_1}{dt}(t) &= -k_a x_1(t), \\ \dfrac{dx_2}{dt}(t) &= \dfrac{k_a}{V} x_1(t) - k_e x_2(t), \\ x_1(0) &= D \\ x_2(0) &= 0. \end{cases}$$

- $x_1(t)$ quantity of drug in stomach,
- $x_2(t)$ concentration of drug in blood.

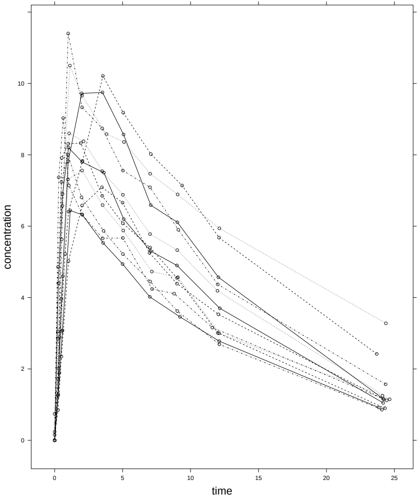

Figure : Plasma concentration of theophylline over time

Introduce the

Bayesian ODE-penalized B-spline approach

in the case of systems of affine differential equations

when the conditional error distribution is a

penalized mixture of Gaussian distributions

Theoretical part

Differential equation and observations

Differential equation

$$\begin{cases} \frac{d\mathbf{x}}{dt}(t) & = & \mathbf{f}(\mathbf{x}(t), \theta) \\ \mathbf{x}(0) & = & \mathbf{x_0} \end{cases}$$

with:
- $(\mathbf{x}(t))^T = (x_1(t), \ldots, x_d(t))$ the set of d state functions and $\mathbf{x_0}$ the set of initial conditions,
- $\theta \in \mathbb{R}^q$ the vector of unknown parameters,
- $\mathbf{f}$ a known affine function of $\mathbf{x}$.

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Measurement

A subset $\mathcal{J}$ of the d state functions are observed with additive measurement errors:

$$y_{jk} = x_j(t_{jk}) + \tau_j^{-1/2}\epsilon_{jk}$$

with $\mathbb{E}(\epsilon_j) = 0$ and $\mathbb{V}(\epsilon_j) = 1$.

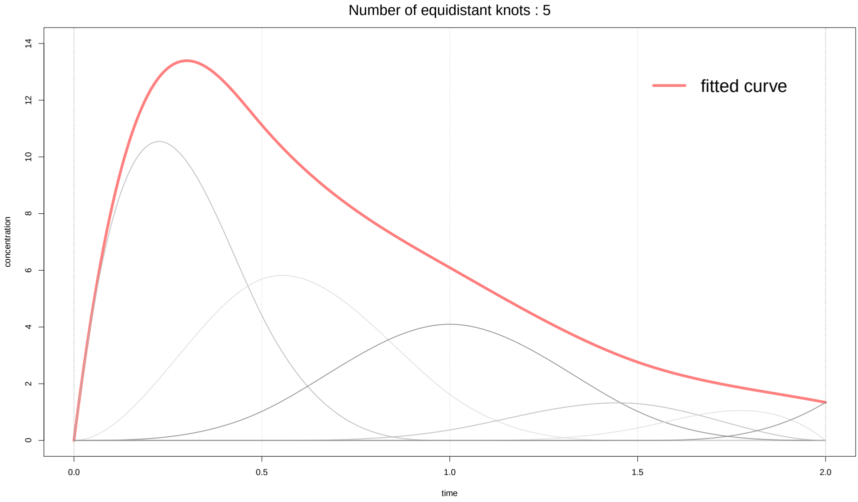
B-spline approximation

Each state function $x_j(t)$ is approximated using a B-spline basis function expansion:

$$
\begin{aligned}
\widetilde{x}_j(t) &= \sum_{k=1}^{K_j} B_{jk}(t)\, c_{jk} \\
&= \left(\mathbf{B_j}(t)\right)^T \mathbf{c_j}
\end{aligned}
$$

where:
- $\mathbf{B_j}(t)$ is the vector of B-spline basis function evaluated at time t,
- $\mathbf{c_j}$ is the vector of spline coefficients.

Influence of the number of knots and the spline coefficients



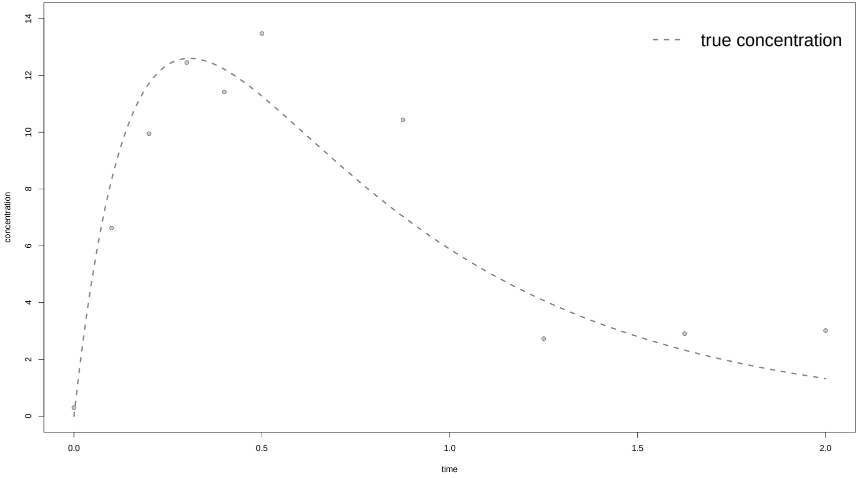
ODE-penalty (Ramsay et al., 2007)

The penalty for the jth equation quantifies the proximity of the approximation $\widetilde{x}_j(t)$ to the jth component of the solution $\mathbf{x}(t)$:

$$\begin{aligned} PEN_j &= \int \left(\frac{d\widetilde{x}_j}{dt}(t) - f_j(\widetilde{\mathbf{x}}(t), \theta) \right)^2 dt \\ PEN &= \sum_{j=1}^{d} \gamma_j PEN_j \\ &= \mathbf{c}^T \mathbf{R}(\theta, \gamma) \mathbf{c} + 2\mathbf{c}^T \mathbf{r}(\theta, \gamma) + l(\theta, \gamma) \end{aligned}$$

where:
- $\mathbf{c}^T = \left(\mathbf{c_1}^T, \ldots, \mathbf{c_d}^T\right)$ is the vector of spline coefficients,
- $\gamma^T = (\gamma_1, \ldots, \gamma_d)$ is the vector of ODE-adhesion parameters.

Influence of the ODE-adhesion parameter



Prior distribution for the spline coefficients & the ODE-adhesion parameters

Prior distribution for the spline coefficients (Jaeger and Lambert, 2011)

$$p(\mathbf{c}|\theta, \gamma) \quad \propto \quad \exp\left(-\frac{1}{2}\sum_{j=1}^{d} \gamma_j PEN_j\right)$$

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$$p\left(\mathbf{c}|\theta,\gamma\right) \quad \propto \quad \exp\left(-\frac{1}{2}\sum_{j=1}^{d}\gamma_j PEN_j - \frac{1}{2}\left(\mathbf{c}-\mu_{\mathbf{c}}\right)^T \mathbf{P_c}\left(\mathbf{c}-\mu_{\mathbf{c}}\right)\right)$$

with:

- $\mu_{\mathbf{c}}$ and $\mathbf{P_c}$ to express uncertainty w.r.t initial conditions of the states,

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$$p\left(\mathbf{c}|\theta,\gamma\right) \quad \propto \quad \exp\left(-\frac{1}{2}\left\{\mathbf{c}^T\left(\mathbf{R}\left(\theta,\gamma\right)+\mathbf{P_c}\right)\mathbf{c}-2\mathbf{c}^T\left(-\mathbf{r}\left(\theta,\gamma\right)+\mathbf{P_c}\mu_\mathbf{c}\right)\right\}\right)$$

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with:

- $\mu_{\mathbf{c}}$ and $\mathbf{P_c}$ to express uncertainty w.r.t initial conditions of the states,
- $\mathbf{v_1}=-\mathbf{r}\left(\theta,\gamma\right)+\mathbf{P_c}\mu_{\mathbf{c}}$ and $\mathbf{V_1}=\mathbf{R}\left(\theta,\gamma\right)+\mathbf{P_c}$,

Prior distribution for the spline coefficients & the ODE-adhesion parameters

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$$p(\mathbf{c}|\theta,\gamma) \quad \propto \quad (\det(\mathbf{V_1}))^{1/2} \exp\left(-\frac{1}{2}\left\{\mathbf{c}^T\mathbf{V_1}\mathbf{c} - 2\mathbf{c}^T\mathbf{v_1} + \mathbf{v_1}^T\mathbf{V_1}^{-1}\mathbf{v_1}\right\}\right)$$

with:
- $\mu_{\mathbf{c}}$ and $\mathbf{P_c}$ to express uncertainty w.r.t initial conditions of the states,
- $\mathbf{v_1} = -\mathbf{r}(\theta,\gamma) + \mathbf{P_c}\mu_{\mathbf{c}}$ and $\mathbf{V_1} = \mathbf{R}(\theta,\gamma) + \mathbf{P_c}$,

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Prior distribution for the ODE-adhesion parameters

$$\gamma_j \sim \mathcal{E}xp\left(10^{-8}\right)$$

It indicates the prior confidence on the proposed ODE to model the dynamic of the state $\mathbf{x}(t)$.

Specification of the conditional distribution

Conditional error distribution (Komárek and Lesaffre, 2008)

$$\epsilon_{jk}|\mathbf{d_j} \sim \sum_{l=-L_j}^{L_j} \pi_{jl}\left(\mathbf{d_j}\right)\mathcal{N}\left(\mu_{jl};\sigma_j^2\right)$$

where $(\mu_{jl})_{l=-L_j}^{L_j}$ is a fixed large number of pre-selected equidistant means and σ_j^2 is a fixed variance, with constraints $\pi_{jl} > 0$ and $\sum_l \pi_{jl} = 1$.

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Generalized logit transformation of the mixture weights

$$\pi_{jl} = \frac{\exp\left(a_{j,l}\right)}{\sum_{k=-L_j}^{L_j} \exp\left(a_{j,k}\right)}$$

with identifiability constraints $a_{j,L_j} = 0$ for all $j \in \mathcal{J}$.
Only $\mathbf{d_j} = \mathrm{vec}\left(a_{j,l}; l = -L_j, \ldots, L_j - 1\right)$, $j \in \mathcal{J}$ have to be estimated to estimate the error distributions.

Fitted error densities

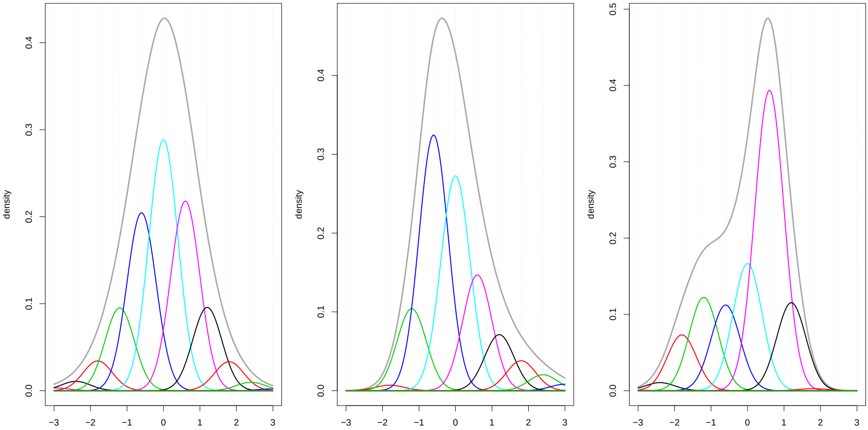

Figure : Fitted error densities (Student, extreme value and mixture of 2 Gaussians)

Prior distribution for the (transformed) weights and the roughness penalty parameters

Finite difference penalty on the transformed weights

$$
\begin{aligned}
Q\left(\mathbf{a_j} \mid \lambda_j\right) &= -\frac{\lambda_j}{2} \sum_{l} \left(a_{j,l} - 3a_{j,l-1} + 3a_{j,l-2} - a_{j,l-3}\right)^2 \\
&= -\frac{\lambda_j}{2} \left(\mathbf{D a_j}\right)^T \mathbf{D a_j}
\end{aligned}
$$

Prior distribution for the (transformed) weights and the roughness penalty parameters

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where:
- λ_j, $j \in \mathcal{J}$ is the roughness penalty parameter,
- $\mathbf{P}$ is the submatrix of $\mathbf{D}^T\mathbf{D}$ without the last line and last column.

Prior distribution for the (transformed) weights and the roughness penalty parameters

Prior distribution for the transformed weights $\mathbf{d_j}$

$$p\left(\mathbf{d_j}|\lambda_j\right) \propto \exp\left(-\frac{\lambda_j}{2}\mathbf{d_j}^T\mathbf{P}\mathbf{d_j}\right)$$

Prior distribution for the (transformed) weights and the roughness penalty parameters

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$$p\left(\mathbf{d_j}|\lambda_j\right) \propto \lambda_j^{L_j-1} \exp\left(-\frac{\lambda_j}{2}\mathbf{d_j}^T\mathbf{P}\mathbf{d_j}\right)$$

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Prior distribution for the roughness penalty parameters

$$\lambda_j \sim \mathcal{E}xp\left(10^{-8}\right)$$

It indicates the prior confidence on the Gaussian distribution for the error distribution.

Bayesian model (Jaeger and Lambert, 2012a)

$$
\left\{
\begin{array}{rcl}
y_{jk} & = & \widetilde{x}_j\left(t_{jk}\right) + \tau_j^{-1/2}\epsilon_{jk} \\
\epsilon_{jk}|\mathbf{d_j} & \sim & \displaystyle\sum_{l=-L_j}^{L_j} \pi_{jl}\left(\mathbf{d_j}\right)\mathcal{N}\left(\mu_{jl} + \alpha_j; \left(\frac{\sigma_j}{\beta_j}\right)^2\right) \\
p\left(\mathbf{c}|\theta,\gamma\right) & \propto & \left(\det\left(\mathbf{V_1}\right)\right)^{1/2}\exp\left(-\frac{1}{2}\left\{\mathbf{c}^T\mathbf{V_1}\mathbf{c} - 2\mathbf{c}^T\mathbf{v_1} + \mathbf{v_1}^T\mathbf{V_1}^{-1}\mathbf{v_1}\right\}\right) \\
\gamma_j & \sim & \mathcal{E}xp\left(10^{-8}\right) \\
p\left(\mathbf{d_j}|\lambda_j\right) & \propto & \lambda_j^{L_j-1}\exp\left(-\frac{\lambda_j}{2}\mathbf{d_j}^T\mathbf{P_{d,j}}\mathbf{d_j}\right) \\
\lambda_j & \sim & \mathcal{E}xp\left(10^{-8}\right) \\
\tau_j & \sim & \mathcal{G}\left(a_{\tau_j}; b_{\tau_j}\right) \\
\theta & \sim & p\left(\theta\right).
\end{array}
\right.
$$

ODE-model validation (Jaeger and Lambert, 2012b)

If the ODE model is adequate, then one can show that:

$$\lim_{\gamma \to \infty} \left(\log p\left(\gamma | \boldsymbol{\theta}, \boldsymbol{\tau}, \mathbf{y}\right) - \log p\left(\gamma\right)\right) \doteq 0$$

when no prior information is used for the state functions and one common ODE-adhesion parameter γ for the complete ODE, where:

- $\log\left(p\left(\gamma | \boldsymbol{\theta}, \boldsymbol{\tau}, \mathbf{y}\right)\right)$ is the log conditional posterior distribution for γ (marginalized w.r.t the spline coefficients),
- $\log\left(p\left(\gamma\right)\right)$ is the log prior distribution for γ.

Application

Theophylinne dataset

Differential equation

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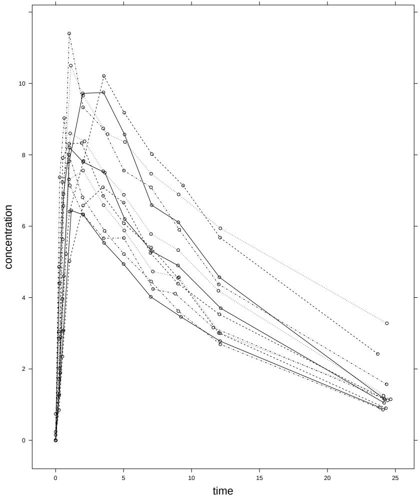

Figure : Plasma concentration of theophylline over time

Theophylinne dataset

Prior information

- The drug cannot be eliminated more quickly that it is absorbed: $k_a > k_e$,
- Total confidence on the initial condition of the state function

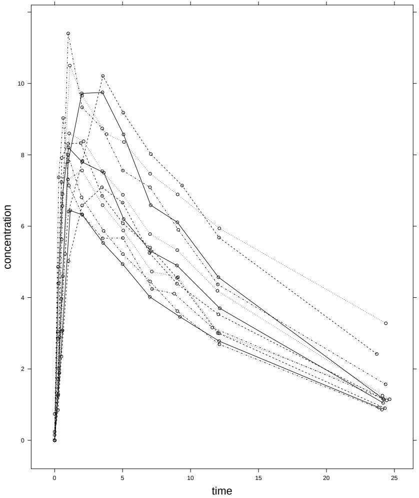

Figure : Plasma concentration of theophylline over time

Fitted error density

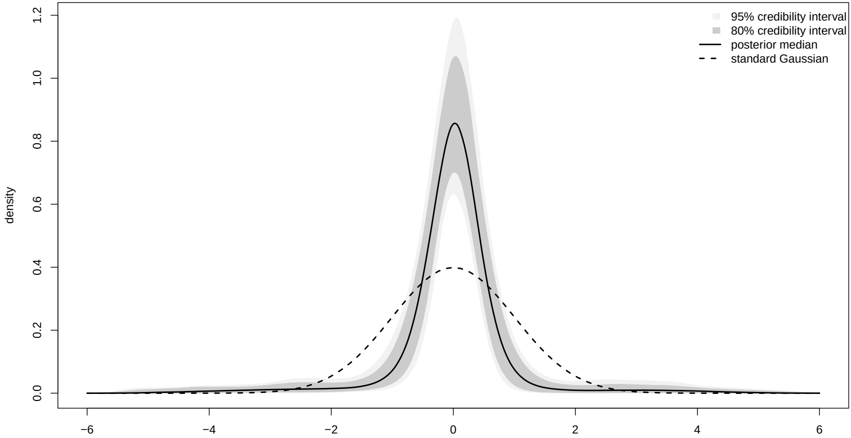

Figure : Fitted error densities with pointwise 80% and 95% credibility interval

Suitability of the ODE-model

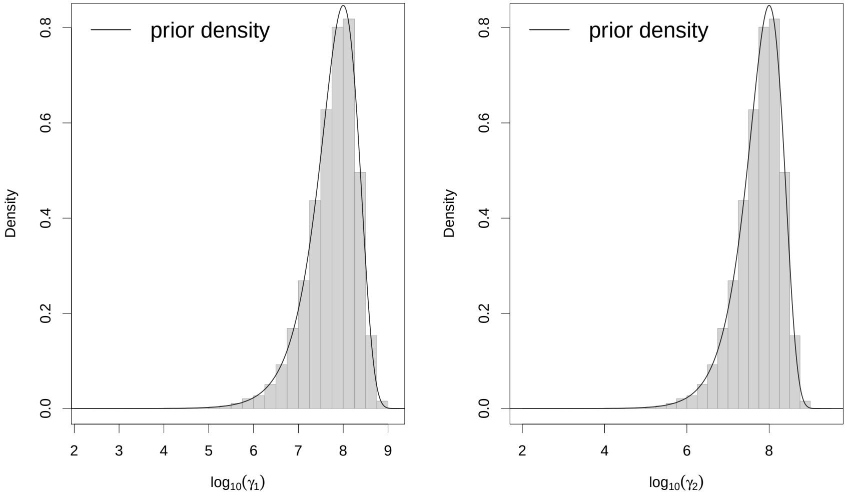

Figure : Histograms of the posterior distribution for γ_1 and γ_2 with prior density (log10 scale)

Posterior credibility intervals for the quantity of drug in stomach

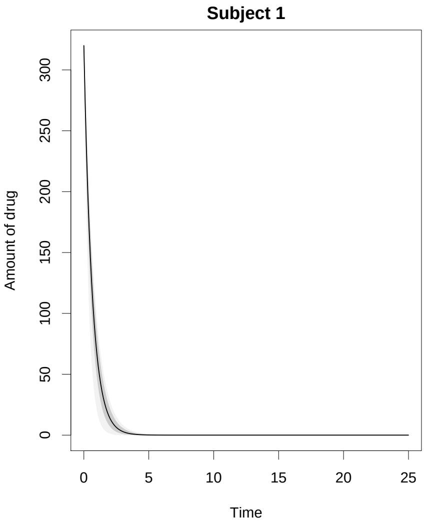

Figure : Pointwise 80% (dark grey) and 95% (light grey) posterior credibility intervals for the quantity of drug in stomach with posterior median

Posterior credibility intervals for the drug concentration in the plasma

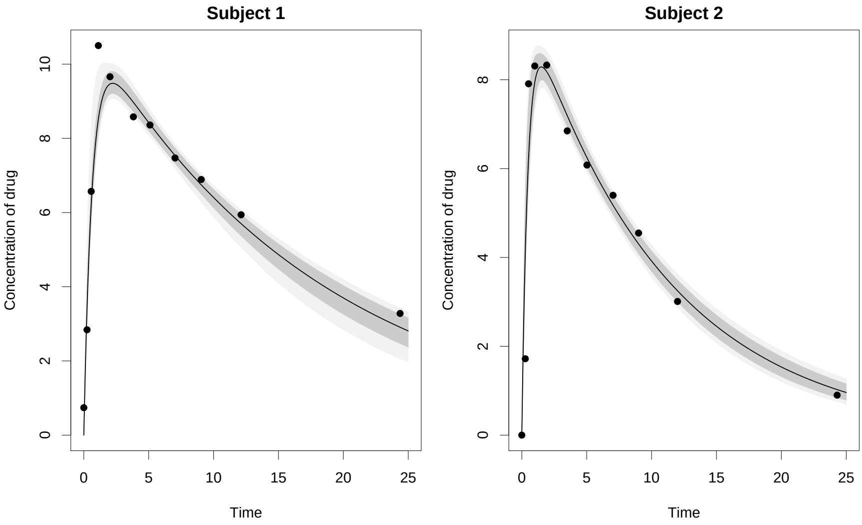

Figure : Pointwise 80% (dark grey) and 95% (light grey) posterior credibility intervals for the drug concentration with posterior median

Conclusion

Conclusion and further work

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- Powerful tool that overcomes solving the DE using a numerical method,
- Convenient implementation of the Bayesian ODE-penalized B-spline approach,
- Simple method to include prior information about ODE parameters,
- Possibility to express uncertainty with respect to initial conditions,
- Automatic selection of the ODE-adhesion parameters and of the roughness penalty parameters,
- ODE-model validation,
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Current/further work

- How to deal with non-homogeneous (non) Gaussian data distribution?
- How to deal with input functions?
- Generalize this approach for nonlinear differential equations.

References

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