Parameter Estimation for Ordinary Differential Equations

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CAIMS
Whistler, B.C
June 11, 2019

Outline

Parameter Estimation for ODEs

Two Stage Algorithm

Numerical Results

Discussion

Motivation

- Mathematical models describing natural phenomena often take the form of systems of ordinary differential equations (ODEs).
- These models usually contain unknown parameters, $\boldsymbol{p}$.
- The goal is to estimate the parameters, $\hat{\boldsymbol{p}}$, that best fit the observed data ($\hat{\boldsymbol{y}}(t_i)\ \boldsymbol{y}(t_i) + N(0, \sigma^2),\ i = 1, \ldots, n_o$).
- This is a non-linear least squares problem.

$$\hat{\boldsymbol{p}} = \arg\min_{\boldsymbol{p}} \sum_{i=1}^{n_o} \frac{\|\hat{\boldsymbol{y}}(t_i) - \boldsymbol{y}(t_i, \boldsymbol{p})\|^2}{2\sigma^2}$$

We will consider using the **simple (single) shooting approach** (Bard, 1974).

Definitions
ODEs

We consider the initial value problem (IVP),

$$\dot{\boldsymbol{y}}(t) = \boldsymbol{f}(t, \boldsymbol{y}(t), \boldsymbol{p})$$
$$\boldsymbol{y}(0) = \boldsymbol{y}_0$$
$$t \in [0, T]$$

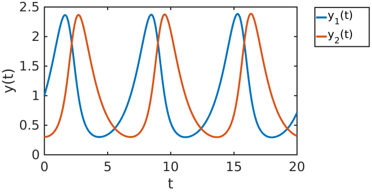
- Numerous numerical methods exist for approximating $\boldsymbol{y}(t, p)$ that satisfy this IVP, for a given value of $\boldsymbol{p}$
- Most methods simulate the **trajectory**, $\boldsymbol{y}(t, p)$, starting from $\boldsymbol{y}(0)$. (e.g. continuous Runge-Kutta with defect control Enright and Yan (2010))

Examples I

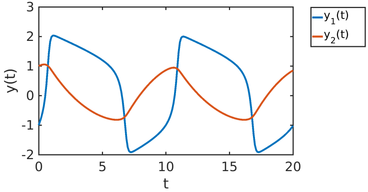
- Systems biology - enzyme kinetics, population dynamics, predator-prey models
- Epidemiology - spread of disease models such as SIR or SEIR
- Chemistry - rate equations, chemical kinetics
- Many more

Examples II

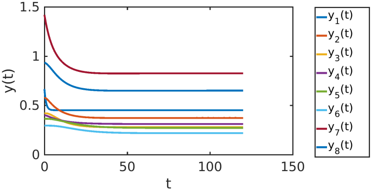
Predator-Prey model



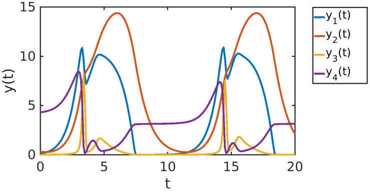
model of squid neuron spikes



a biochemical model



Calcium Ion model



Motivation

This non-linear least squares problem may be challenging if:

1. $\boldsymbol{y}(t, \boldsymbol{p})$ needs to be approximated (using a numerical method)
2. a good initial guess for $\hat{\boldsymbol{p}}$ is unavailable (only know broad ranges that parameters can take)
3. observations are only available for a subset of the components of $\boldsymbol{y}$ or the observations are **noisy** or **sparse** (potential identifiability issues)

Two Stage ODE Parameter Estimation

First Stage: find a suitable initial guess, $\boldsymbol{p}_o$

- use a heuristic global search
- solve an alternative optimization problem
- This first stage is similar to the ideas of proposal generation in computer vision or a warm start when training neural networks.

Second Stage: apply a local, fast converging optimization to obtain $\hat{\boldsymbol{p}}$

- Levenberg-Marquardt (Quasi-Newton)
- Full Newton (accelerated least squares (ACCEL) method (Dattner and Gugushvili, 2015))

The combination of a global heuristic search and a local optimizer is sometimes referred to as a **hybrid optimizer** (Rodriguez-Fernandez et al., 2006b)

Methods for obtaining a suitable p_0

- Smooth and match estimator (SME) (Gugushvili et al., 2012)
  - Numerical Discretization based estimation (DBE) is similar (Wu et al., 2012)
  - Gradient Matching (Macdonald and Husmeier, 2015) in the ML literature
  - Varah (1982); Bellman and Roth (1971) and others recognized that if one uses the observed values of $\boldsymbol{y}(t)$ to approximate $\boldsymbol{y}'(t)$, then one can formulate a related least squares problem,

$$\boldsymbol{p}_{\text{sme}} = \arg\min_{\boldsymbol{p}} \int_0^T \left\|(\tilde{\boldsymbol{y}}'(t) - \boldsymbol{f}(t, \tilde{\boldsymbol{y}}(t), \boldsymbol{p}))\right\|^2 dt.$$

Integral smooth and match (INT-SME)

- A benefit of SME is that the numerical derivative approximations can be significantly faster than a simulation of an ODE IVP trajectory.
- Furthermore, an ODE IVP trajectory simulation may fail for certain parameter values - not a problem for SME
- SME can't estimate intial conditions (could use nearby data points)
- Gugushvili et al. (2012) proposed using the integral form of the ODE IVP instead:

$$\min_{\boldsymbol{y}_0,\boldsymbol{p}} \int_0^T \left\| \tilde{y}(t) - \left(\boldsymbol{y}_0 + \int_0^t f(s, \tilde{y}(s), \boldsymbol{p})\, ds\right) \right\|^2 dt, \qquad (1)$$

where $\boldsymbol{y}_0$ are the initial conditions to be estimated. Note, this formulation is linear in $\boldsymbol{y}_0$. Unlike SME, this does not require us to approximate $\boldsymbol{y}'(t)$.

Exploiting ODE Structure - Linear Parameters

- Some parameters may appear linearly in $f(t, \boldsymbol{y}(t), \boldsymbol{p})$.
- $\boldsymbol{p} = [\boldsymbol{q}\,,\, \boldsymbol{r}]$

$$f(t, \boldsymbol{y}(t), \boldsymbol{p}) = G(t, \boldsymbol{y}(t), \boldsymbol{q})\boldsymbol{r} + g(t, \boldsymbol{y}(t), \boldsymbol{q})$$

- SME becomes:
$$\min_{\boldsymbol{q}} \int_0^T \left\| (\tilde{\boldsymbol{y}}'(t) - G(t, \tilde{\boldsymbol{y}}(t), \boldsymbol{q})\boldsymbol{r}(\boldsymbol{q}) - g(t, \tilde{\boldsymbol{y}}(t), \boldsymbol{q}) \right\|^2 \, dt.$$
- Since $\boldsymbol{r}$ appears linearly in SME, we can view this as a minimization over only the nonlinear parameters, $\boldsymbol{q}$.

Exploiting ODE Structure - Decoupling

- the system of ODEs can sometimes be decoupled
- subsets of the parameters may appear in f, such that each subset can be independently determined (Kotte and Heinemann, 2009)

Example: Goodwin Model

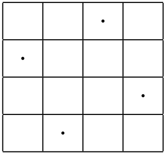
$$f(t, y(t), p) = \begin{pmatrix} \boxed{\frac{1}{q_1 + y_3(t)^{q_2}} \quad -y_1(t)} & 0 & 0 & 0 & 0 \\ 0 \quad 0 & \boxed{y_1(t) \quad -y_2(t)} & 0 & 0 \\ 0 \quad 0 & 0 \quad 0 & \boxed{y_2(t) \quad -y_3(t)} \end{pmatrix} \begin{pmatrix} r_1 \\ \vdots \\ r_6 \end{pmatrix}$$

Subproblem #	$\lvert\boldsymbol{q}\rvert$	$\lvert\boldsymbol{r}\rvert$
1	2	2
2	0	2
3	0	2
total	2	6

- 3 independent subproblems
- reduces the size of the search space

Latin Hypercube Sampling (LHS)

- For our application, in Stage 1 it is often recommended to sample from the log of the parameter space ((Raue et al., 2013; Maiwald and Timmer, 2008))
- $q \in [10^a, 10^b]^{n_q}$
- $\log q \in [a, b]^{n_q}$
- the scale is usually more important than the exact value
- we used lhsdesign in MATLAB - attempts to distribute points more appropriately when generating the LHS samples
- 2-D example:



Full Algorithm

Stage I: **foreach** *subproblem* S_k, $k = 1, \ldots, K$ **do**

- obtain samples of q^k from the log of the parameter space using LHS
- calculate the subproblem objective function for each sample and sort them
- run local optimizer from the N_{best} samples of q^k
- let P_k be the set of unique minimizers found for subproblem S_k

end

let $P_0 = P_1 \times P_2 \times ... \times P_K$ (Cartesian product)

compute the objective function for each $p_0 \in \{P_0\}$ and sort them

Stage II:

run local optimizer on p_0's from $\{P_0\}$ until satisfied that $\hat{\boldsymbol{p}}$ has been found

Algorithm 1: Two Stage Parameter Estimation Procedure

Choice of Smoother

We have considered:

- cubic splines (Varah, 1982)
- smoothed splines (e.g. splinefit in MATLAB)
- local polynomial estimation (lpe) (Dattner, 2015)

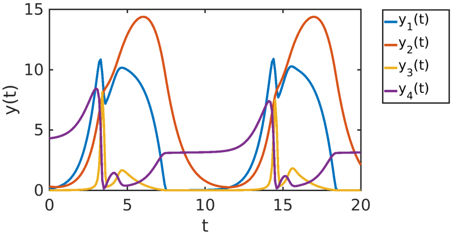
Other approaches:

- neural net or any other function approximator
- for SME, can use the Koopman operator to approximate $\boldsymbol{y}'(t)$ (Mauroy and Goncalves, 2017)

Calcium Ion Test Problem [Kummer et al. (2000) ?]

$$
\begin{aligned}
{G^*_\alpha}' &= k_1 + k_2 G^*_\alpha - k_3 PLC^* \frac{G^*_\alpha}{G^*_\alpha + Km_1} - k_4 Ca_{cyt} \frac{G^*_\alpha}{G^*_\alpha + Km_2}, \\
PLC^{*\prime} &= k_5 G^*_\alpha - k_6 \frac{PLC^*}{PLC^* + Km_3}, \\
{Ca_{cyt}}' &= k_7 PLC^* Ca_{cyt} \frac{Ca_{er}}{Ca_{er} + Km_4} + k_8 PLC^* + k_9 G^*_\alpha - k_{10} \frac{Ca_{cyt}}{Ca_{cyt} + Km_5} - k_{11} \frac{Ca_{cyt}}{Ca_{cyt} + Km_6}, \\
{Ca_{er}}' &= -k_7 PLC^* Ca_{cyt} \frac{Ca_{er}}{Ca_{er} + Km_4} + k_{11} \frac{Ca_{cyt}}{Ca_{cyt} + Km_6},
\end{aligned}
$$

- 11 linear parameters (k)
- 6 non-linear parameters (Km)
- Km_2 kept fixed for identifiability.
- 6.5% relative noise added to true trajectory sampled at 200 uniformly spaced times



Mendes Problem

- test problem that was originally posed in Moles et al. (2003)
- subsequently studied in Rodriguez-Fernandez et al. (2006b,a); Balsa-Canto et al. (2008); Gábor and Banga (2015).

$$f(t, y(t), p) = \begin{bmatrix} G_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & G_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & G_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & G_4 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & G_5 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & G_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & G_{78} \end{bmatrix} \begin{bmatrix} r_1 \\ \\ \\ \vdots \\ \\ \\ r_{15} \end{bmatrix}$$

$$G_1 = \left[\frac{1}{1+\left(\frac{P}{q_1}\right)^{q_2}+\left(\frac{q_3}{S}\right)^{q_4}} \quad -y_1 \right]$$

$$G_2 = \left[\frac{1}{1+\left(\frac{P}{q_5}\right)^{q_6}+\left(\frac{q_7}{y_7}\right)^{q_8}} \quad -y_2 \right]$$

$$G_3 = \left[\frac{1}{1+\left(\frac{P}{q_9}\right)^{q_{10}}+\left(\frac{q_{11}}{y_8}\right)^{q_{12}}} \quad -y_3 \right]$$

$$G_4 = \left[\frac{y_1}{y_1+q_{13}} \quad -y_4 \right]$$

$$G_5 = \left[\frac{y_2}{y_2+q_{14}} \quad -y_5 \right]$$

$$G_6 = \left[\frac{y_3}{y_3+q_{15}} \quad -y_6 \right]$$

$$G_{78} = \begin{bmatrix} \frac{y_4(\frac{1}{q_{16}})(S-y_7)}{1+(\frac{S}{q_{16}})+(\frac{y_7}{q_{17}})} & -\frac{y_5(\frac{1}{q_{18}})(y_7-y_8)}{1+(\frac{y_7}{q_{18}})+(\frac{y_8}{q_{19}})} & 0 \\ 0 & \frac{y_5(\frac{1}{q_{18}})(y_7-y_8)}{1+(\frac{y_7}{q_{18}})+(\frac{y_8}{q_{19}})} & -\frac{y_6(\frac{1}{q_{20}})(y_8-P)}{1+(\frac{y_8}{q_{20}})+(\frac{P}{q_{21}})} \end{bmatrix}$$

- 36 parameters to be estimated (15 linear, 21 non-linear)
- Hill coefficients $(q_2, q_4, q_6, q_8, q_{10}, q_{12})$ are assumed to be in $[0.1, 10]$.
- Other parameters are assumed to be in $[10^{-12}, 10^6]$.
- true values are all close to 1
- The initial conditions, as well as S and P, are assumed to be known.
- The data for this test problem consists of 21 uniformly spaced observations of the 8 state variables (over the interval $[0, 120]$), for each of 16 pairs of values for P and S.
- Either 3% or 5% relative noise added to simulated data.

Calcium Ion Results

initial	smoother	Average Time			success
		initial	opt	total	
SME	spline	0.62	7.57	8.19	98 / 100
SME	lpe	0.50	6.82	7.32	81 / 100
INT-SME	spline	0.93	5.52	6.45	77 / 100
INT-SME	lpe	0.79	5.49	6.28	70 / 100

SME more likely to succeed than INT-SME, but slightly slower

- SME produces more initial guesses to try than INT-SME

spline seems to be better than lpe

- smoothing can dampen the peaks in the noisy data (worse p_o)

Mendes Results

initial	smoother	noise (%)	Average Time			success
			initial	opt	total	
SME	cubic spline	3	5.0	2.6	7.5	77 / 100
SME	cubic spline	5	5.0	3.0	8.1	80 / 100
SME	lpe	3	5.1	3.4	8.6	73 / 100
SME	lpe	5	5.1	3.2	8.4	84 / 100
SME	splinefit	3	5.1	2.7	7.8	84 / 100
SME	splinefit	5	5.0	2.4	7.4	83 / 100
INT-SME	cubic spline	3	3.0	0.6	3.6	100 / 100
INT-SME	cubic spline	5	3.0	0.7	3.7	100 / 100
INT-SME	lpe	3	3.3	0.6	3.8	100 / 100
INT-SME	lpe	5	3.3	0.6	3.9	100 / 100
INT-SME	splinefit	3	3.0	0.6	3.5	100 / 100
INT-SME	splinefit	5	3.0	0.7	3.7	100 / 100

Mendes Results

- 10^4 seconds, global-local hybrid optimizer (Rodriguez-Fernandez et al., 2006b).
- $\approx$ 300 seconds, global scatter search heuristic (Rodriguez-Fernandez et al., 2006a).
- $\approx$ 30 seconds, scatter search with additional heuristics (Gábor and Banga, 2015)
- Our approach is competitive with this. ($\approx$ 4 seconds with INT-SME)

Difficulties

- numerical gradients are not likely to be accurate if default tolerances used in MATLAB
  - choose appropriate tolerances for finite differences to provide accurate gradients
  - simulate the variational equations to approximate the required gradients
  - use a different (more reliable or faster) ODE solver (e.g. DDEM Zivari-Piran and Enright (2012) / CRK56 Enright and Yan (2010))

Numerical Uncertainty

What about the fact that $\boldsymbol{y}(t, p)$ is a numerical approximation to the solution of the ODE IVP?

- add the numerical error, $\sigma_{num}(t)$, to the error model (usually try to choose TOL such that $\sigma_{num} << \sigma$)
- can use an estimate of the global error to approximate $\sigma_{num}(t)$ (Rive and Pasciutti, 1975; Constantinescu, 2015).

$$\hat{\boldsymbol{p}} = \arg\min_{\boldsymbol{p}} \sum_{i=1}^{n_o} \frac{\|\hat{y}(t_i) - y(t_i, \boldsymbol{p})\|^2}{2(\sigma_{num}^2(t_i) + \sigma^2)}$$

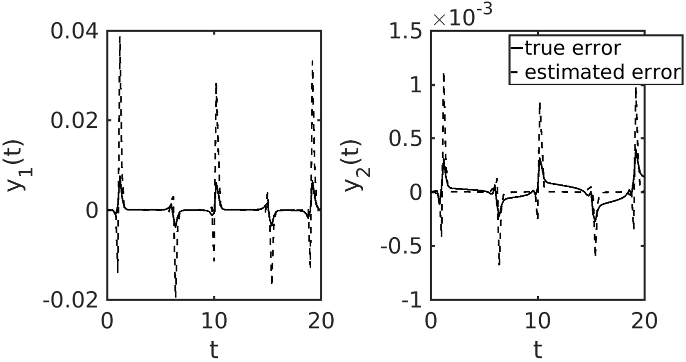
- uncertainty quantification for ODEs / probabilistic numerical methods (PNMs) (Teymur et al., 2018; Tronarp et al., 2018; Schober et al., 2014)

Example - FitzHugh-Nagumo Model

A model of squid neuron electrical potentials (FitzHugh, 1961).

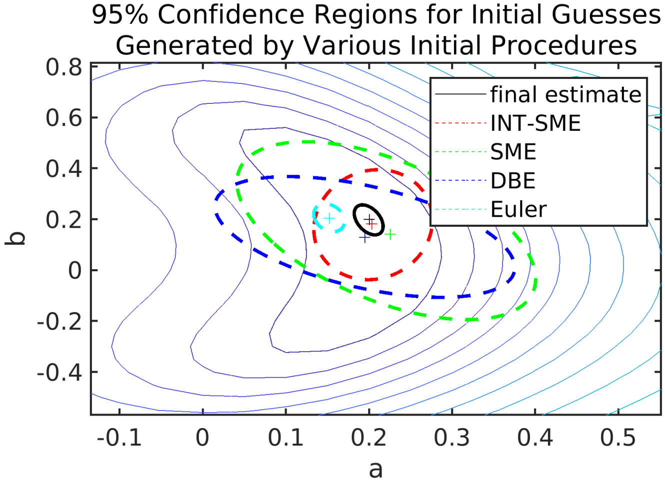
$$V'(t) = {y_1}'(t) = c\left(y_1(t) - \frac{y_1(t)^3}{3} + y_2(t)\right),$$

$$R'(t) = {y_2}'(t) = \frac{-\left(y_1(t) - a + by_2(t)\right)}{c},$$



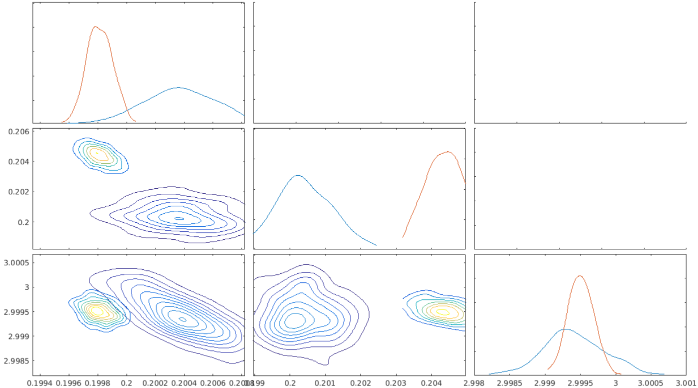
Numerical error varies with t.

Example - FitzHugh-Nagumo Model



The error introduced by using a fixed step size Euler ODE solver results in **biased** estimates.

Example - FitzHugh-Nagumo Model
Distribution of MAP estimates



Inclusion of the numerical error increases the uncertainty and may change the estimates.

Summary

- Presented a two stage procedure for the ODE IVP parameter estimation problem
  1. obtain a set of candidate $\boldsymbol{p}_o$'s
  2. use Levenberg-Marquardt to find $\hat{\boldsymbol{p}}$
- Demonstrated the performance of the procedure on two test problems from the literature
- Discussed how numerical error can impact $\hat{\boldsymbol{p}}$.

Joint work with Wayne Enright and Jienan Yao

Thanks for Listening

Questions?

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