Accurate Approximation of Models of Epidemics (with interventions)

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Abstract

International experts in computational biology have developed models of epidemics and most of these involve systems of ordinary differential equations (ODEs) and some data fitting. In this talk, we will consider models based on an underlying classical SEIR epidemic model and show that dramatic improvements in the accuracy and reliability of simulations of these models can be obtained by employing carefully chosen numerical methods to approximate the ODEs and using inverse data fitting to match the observed data (of the simulation) to the model parameters.

In particular the ODE method must automatically detect and handle discontinuities that are often associated with the true solutions of these simulations. In addition the component-wise relative error of the approximate solution must be directly estimated and controlled.

We show, using an example of modelling a COVID-19 outbreak and employing an order 6 CRK ODE method (developed locally), that our approach is able to efficiently determine an accurate simulation of a real epidemic over different accuracy requests (without making strong assumptions regarding the problem or data).

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A Typical SEIR Model

$$\frac{dS}{dt} = \mu N - \mu S - \frac{\beta}{N} IS \quad (1)$$

$$\frac{dE}{dt} = \frac{\beta}{N} IS - aE - \mu E \quad (2)$$

$$\frac{dI}{dt} = \alpha E - \gamma I - \mu I \quad (3)$$

$$\frac{dR}{dt} = \gamma I - \mu R \quad (4)$$

- $S(t)$, $E(t)$, $I(t)$ and $R(t)$ denote the populations of Susceptible, Exposed, Infectious and Recovered individuals at time t.
- μ, β and γ are the replenishment, transmission and recovery rates.
- α^{-1} is the incubation period and N is the total population.
- The initial state $[S(0), E(0), I(0)\ R(0)]$ is assumed to be given and the model predicts future states for $t > 0$.

Approximating Mathematical Models

Reliable approximate solution of Models arising in scientific computation involves four key stages:

- Formulate the mathematical model of the system being investigated. (The model may involve parameters, some data-fitting and systems of ODEs.)
- Approximate the exact solution of this model relative to a specified accuracy parameter, *TOL*.
- Visualize the approximate solution.
- Consider the well-posedness and the stability of the approximate solution (may involve sensitivity analysis).

Implications for an ODE Method

- An approximate solution of an IVP must be delivered in a way that is easy to understand, display, and manipulate by a casual user.
- The accuracy (or *quality*) of an approximate solution must be easy to quantify and interpret.
- Method must be adaptive and easy to invoke –(only need specify the error tolerance, TOL, and those parameters necessary to define the mathematical model).
- A discrete approximate solution (available at only a finite number of time points) is not sufficient (as it is difficult to visualize and its overall accuracy is difficult to interpret).

Continuous Runge-Kutta Methods

- Consider an IVP defined by the system

$$y' = f(x, y), \ \ y(0) = y_0, \ \ \text{for } x \in [0, b].$$

- A numerical method will introduce a partitioning $0 = x_0 < x_1 < \cdots < x_N = b$ and corresponding discrete approximations $y_0, y_1 \cdots y_N$. The y_i's are usually determined sequentially.

- On step i let $z_i(x)$ be the solution of the local IVP:

$$z_i' = f(x, z_i(x)), \ \ z_i(x_{i-1}) = y_{i-1}, \ \ \text{for } x \in [x_{i-1}, x_i].$$

CRK methods (cont)

A classical p^{th}-order, s-stage, discrete RK formula determines

$$y_i = y_{i-1} + h_i \sum_{j=1}^{s} \omega_j k_j,$$

where $h_i = x_i - x_{i-1}$ and the j^{th} stage is defined by,

$$k_j = f(x_{i-1} + h_i c_j,\ y_{i-1} + h_i \sum_{r=1}^{s} a_{jr} k_r).$$

An accurate Continuous extension (CRK) is determined by introducing $(\tilde{s} - s)$ additional stages and obtaining an order p approximation for any $x \in (x_{i-1}, x_i)$

$$u_i(x) = y_{i-1} + h_i \sum_{j=1}^{\tilde{s}} b_j(\frac{x - x_{i-1}}{h_i}) k_j,$$

where $b_j(\tau)$ is a polynomial of degree at least p and $\tau = \frac{x - x_{i-1}}{h_i}$.

CRK methods (cont)

- We consider accurate CRK extensions, satisfying:

$$u_i(x) = y_{i-1} + h_i \sum_{j=1}^{\tilde{s}} b_j(\tau) k_j = z_i(x) + O(h_i^{p+1}).$$

- The $[u_i(x)]_{i=1}^N$ define a vector of piecewise polynomials, $U(x)$, for $x \in [0, b]$. This is the <u>approximate solution</u> generated by the CRK method.
- The columns of $U(x) \in C^0[0, b]$ and will interpolate the underlying discrete RK approximations, y_i (for each component of the ODE), if $b_j(1) = \omega_j$ for $j = 1, 2 \cdots s$ and $b_{s+1}(1) = b_{s+2}(1) = \cdots b_{\tilde{s}}(1) = 0$.
- Similarly a simple set of constraints on the $\frac{d}{d\,\tau}(b_j(\tau))$, and requiring that $k_{s+1} = f(x_i, y_i), k_1 = f(x_{i-1}, y_{i-1})$, will ensure $U'(x)$ interpolate $f(x_i, y_i), f(x_{i-1}, y_{i-1})$ and therefore $U(x) \in C^1[0, b]$.

Defect Error Control for CRKs

$U(x)$, the approximate solution, has an associated defect or residual,

$$\delta(x) \equiv f(x, U(x)) - U'(x) \equiv f(x, u_i(x)) - u_i'(x), \quad \text{for} \quad x \in [x_{i-1}, x_i].$$

It can be shown that, for sufficiently differentiable f,

$$\delta(x) = G(\tau) h_i^p + O(h_i^{p+1}),$$

where $G(\tau)$ depends only on the problem and on the CRK formula and not on the value of h_i.

Methods have been derived to adaptively determine h_i in an attempt to ensure that the maximum magnitude of $\delta(x)$ is bounded by TOL (Strict Defect Control, SDC). The quality of an approximate solution can then be described in terms of the max of $||\delta(x)||/TOL$.

Cost of Strict Defect Control

$$p^{th} - \text{order, discrete RK} : y_i = y_{i-1} + h_i \sum_{j=1}^{s} \omega_j k_j,$$

$$SDC : \quad u_i(x) = y_{i-1} + h_i \sum_{j=1}^{\tilde{s}} b_j(\tau) k_j = z_i(x) + O(h_i^{p+1}).$$

Formula	p	s	$\tilde{s}$
CRK4	4	4	8
CRK5	5	6	12
CRK6	6	7	15
CRK7	7	9	20
CRK8	8	13	27

Table: SDC-CRK methods we have introduced and investigated

(Note that $\tilde{s} \approx 2\, s$.)

SDC-CRK on Discontinuous IVPs

- If a successful step of a SDC-CRK from x_{i-1} to x_i was preceded by a failed attempt from x_{i-1} to $x_{i-1} + H$ (with a large defect estimate) then a possible discontinuity at $t^* \in [x_i, x_i + 2 * h_i]$ is suspected.
- To verify that one exists the defect of $z_{i-1}(x)$ (of the failed step) is sampled using bisection to find the first $t^* \in [x_i, x_i + h_i]$ where this defect is much larger than TOL. If this search succeeds the step to x_i is "extended" to $x_i = t^* + \Delta$ and the integration is continued for the next step $(i+1)$ with the approximation for the solution defined by $z_{i-1}(t^* + \Delta)$ and the approximation for the derivative at this point defined by $f(t^* + \Delta, z_{i-1}(t^* + \Delta))$.
- If the discontinuous IVPs that arise in the model can be written as: $y' = f_1(t, y)$ if $g_1(t, y) \leq 0$ and $= f_2(t, y)$ otherwise; then replacing the bisection search with a newton iteration to find the first t^* such that $g_1(t^*, z_i(t^*)) = 0$ can result in superlinear convergence to locate t^*.

Simulation of a real Epidemic

Christara introduced a simulation of COVID-19 in Canada as an interesting use of numerical analysis. It is a general SEIR model:

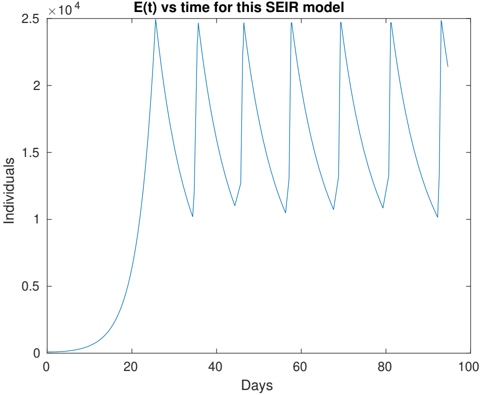
- The independent variable $t \in [0, 95]$ with the vector of dependent variables $[S(t), E(t), I(t), R(t)]$.
- The initial conditions represent the populations of susceptible, exposed, infectious and recovered individuals on a day in early 2020, when $E(0) = 37740896.0$.
- The model parameters (assumed to be fixed) are $\alpha = .125, \gamma = 0.06, \beta = 0.9, \mu = 0.01/365.0$.
- β is piecewise constant initially equal to 0.9 and reset to 0.2 when $E(t) \geq 25000$ (reflecting an attempt to control the spread of the epidemic by limiting interactions between infectious and susceptible individuals). When $\beta = 0.2$, its value is reset to 0.9 when $E(t)$ drops below 10000. Each change in the value of β introduces a discontinuity in this SEIR model.

Approximating this Model

- With an SDC-CRK , if a discontinuity is suspected, a search is used to locate the discontinuity (t^*, y^*). The search can be a newton iteration if the IVPs can be expressed in the form described earlier. With this model two types of discontinuities arise (corresponding to regions where $E(t)$ is increasing and regions where $E(t)$ is decreasing). In each case the IVPs can be expressed in the form that allows a newton iteration with $(g_1(t, y) = 25000 - E(t)$, or $g_1(t, y) = E(t) - 10000$, resp.).
- The SDC-CRK is also able to detect when a "converged" t^* value is not the first such t^*. It then resumes the search to find an earlier t^*.
- Approximating y_i on each step involves an iteration to determine y_i, as the discrete RK formula defining y_i is 'implicit' $(z_i(x) \in C^0(x_{i-1}, x_i))$. The SDC-CRK uses a single predictor-corrector iterate to approximate this y_i and the associated iteration error will be sufficiently small as the local adaptive error control of the underlying discrete RK formula is reliable.
- The SDC-CRK is also be able to detect and signal when rounding error or iteration error dominate the local error in a step.

An Example of the use of this Approach

We have determined the approximate solution U(t) using SDC-CRK on this model problem and display below only the plot of E(t) for TOL $= 10^{-6}$. The implementation we used (of our approach) and its performance follows.



A Description of use of our approach on this Example

A summary of the version of SDC-CRK we have used and its performance on the model problem is reported on the next two pages.

Algorithm 1 uses a bisection search to find the first t in [TL,TH] such that |defect(t,z_i(t)))| > expected. On each bisection iteration, |defect(TM,z_i(TM)))| is sampled and TH or TL is updated to TM accordingly. The iteration converges when |TH-TL| < TOL (relaxed termination criteria) or when |TH-TL| < TOL/10 (strict termination criteria). Below is a summary of the cost of Algorithm 1 to find a converged value for |TH-TL| for relaxed and strict termination.

Steps is a count of the number of integration steps to approximate this simulation over the complete interval [0, 95] (including all 13 discontinuities) and NFCN is a count the number of evaluations of the ODE required for the simulation.

Algorithm 2 uses a newton iteration with a strict termination criteria.

In all the reported approximations the location of each of the 13 discontinuity points, the approximations to the 4 components of the approximate endpoint solution, and the 4 components of the approximate solution at each discontinuity point were almost identical (agreement within a small multiple of DP unit roundoff) for both Algorithm 1 (with strict termination) and Algorithm 2.

Note:

1. We only report agreement of the results for the first two components of the approximate solution of the simulation at each sample point. Similar agreement for all other components was also observed.

2. The approach we have implemented is the only known approach that directly attempts to control accuracy of each component of the simulation at any t in the interval of interest.

3. If the model contains terms involving nonlinear delayed solution values, the approach can be extended.

Algorithm 1 with relaxed termination
Approximation at TEND = 95 determined using i=78 steps, NFCN=1999.

37567578.024061866	20609.350971249769	33097.027531986940
119715.32709324638		

Disc location and approx to the first 2 solution components at each of the 13 discontinuities:

25.604303798329667	37703219.414143994	25000.002000302837
34.582448968541456	37700261.938607164	9999.9995598852784
35.551732005969804	37683132.765110299	25000.009476318955
45.568398108379171	37678227.599334434	9999.9997879025468
46.291094363107320	37661639.858057864	25000.010980059160
56.970057475938439	37655498.602719232	9999.9999523579609
57.609563772080847	37639094.171753421	25000.001284598868
68.658273569940036	37632266.540197968	9999.9997610207647
69.263726065929063	37615937.376543753	25000.003715306331
80.500037906940108	37608765.075623289	9999.9998067691922
81.090662675675190	37592468.890384912	25000.005899158772
92.416386344852526	37585136.095015958	9999.9994753114843
93.000477491294248	37568854.640202619	25000.013092728885

Algorithm 1 with strict termination and Algorithm 2 with relaxed termination
Approximation at TEND = 95 determined using 98 steps, NFCN = 1904.

37567578.085742563	20609.380218518629	33096.983537964807
119715.28016857835		

Disc location and approx to the first 2 solution components at each of the 13 discontinuities:

25.604293963615767	37703219.417246170	25000.000011535216
34.582437602000780	37700261.942562103	9999.9999919650018
35.551720073204621	37683132.780744344	25000.000028762268
45.568382447383641	37678227.617781691	9999.9999991965778
46.291078352531734	37661639.888852812	25000.000104116963
56.970044294174386	37655498.632810272	9999.9999995363178
57.609550996420531	37639094.202259324	25000.000072339782
68.658279612761277	37632266.560039967	9999.9999937143875
69.263732836907081	37615937.398729302	25000.000134836882
80.500070086813921	37608765.085545048	9999.9999971555080
81.090696003433322	37592468.904025145	25000.000061617466
92.416407359874782	37585136.127829269	9999.9999997849354
93.000498624150111	37568854.686790824	25000.000049547176