PARAMETER IDENTIFICATION PROBLEM IN THE HODGKIN-HUXLEY MODEL: **SUPPLEMENTARY MATERIAL**

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RESUMO. This paper is the supplementary material from article [3]. Here, We use a simple model to explain the calculation of the Gateaux derivative adjoint, and also compare the method proposed (Minimal Error Iteration), in the paper [3], with other methods. The goal of this work is to estimate an unknown parameter in the exponential decay model, which is an ordinary differential equation (ODE). The conclusions made in this paper are also fulfilled for article [3].

1. INTRODUCTION

The exponential model is given by

$$\dot{N} = -rN; \quad N(0) = N_0, \tag{1}$$

where $\dot{N} = dN/dt$ is the growth rate of the population in a given instant, N is population size, t is time, $r > 0$ is the intrinsic growth, and N_0 represents the initial condition.

The goal of this supplementary material is to estimate r, given N, from Eq. (1).

We consider that N is a function of the following form $N : [0,T] \to \mathbb{R}$, where T is the final time. Consider also the set of square integrable functions $L^2[0,T]$, we assume that $N \in L^2[0,T]$.

We define the nonlinear operator

$$F : \mathbb{R} \to L^2[0,L], \tag{2}$$

defined by $F(r) = N$, where N solves Eq. (1).

Remark 1. *In practical terms, the real data N are obtained by noisy measurements denoted by N^δ. The calculation of the adjoint of the Gateaux derivative, for the exact case N and the measure N^δ, are equal. In this sense, we consider only the exact case.*

We assume that there is a unique r such that $F(r) = N$. To obtain an approximation of r, we used the gradient type iteration

$$r^{k+1} = r^k + w^k F'(r^k)^*(N - F(r^k)) + \alpha^k(r^1 - r^k), \tag{3}$$

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where $F'(r^k)$ is the Gateaux-derivative of F computed at r^k, $F'(r^k)^*$ is its adjoint, and $N^k = F(r^k)$. In Theorem 1.1, we calculate $F'(r^k)^*(N - F(r^k))$. The coefficients w^k and α^k are chosen as:

(*i*) Classical Landweber Method

$w^k = 1$ and $\alpha^k = 0.$

(*ii*) Modified Landweber Method

$w^k = 1$ and $\alpha^k \in (0, 1/2).$

In this method, we choose a sequence $\{\alpha_k\}$ such that $\sum \alpha_k$ converge.

(*iii*) Steepest Descent Method

$$w^k = \frac{\|F'(r^k)^* \left(N - F(r^k)\right)\|^2_{\mathbb{R}}}{\|F'(r^k)F'(r^k)^* \left(N - F(r^k)\right)\|^2_{L^2[0,T]}} \quad \text{and} \quad \alpha^k = 0,$$

where $F'(r^k)F'(r^k)^* \left(N - F(r^k)\right)$ is the Gateaux derivative of F at r^k in the direction $F'(r^k)^* \left(N - F(r^k)\right)$, see definition in Eq. (8).

(*iv*) Minimal Error Method

$$w^k = \frac{\|N - N^k\|^2_{L^2[0,T]}}{\|F'(r^k)^*(N - F(r^k))\|^2_{\mathbb{R}}} \quad \text{and} \quad \alpha^k = 0.$$

It is possible to show that, under certain conditions, r^k converges to r as $k \to \infty$; see [1, 2]. Note that $N^k = F(r^k)$ solves

$$\dot{N}^k = -r^k N^k; \quad N^k(0) = N_0. \tag{4}$$

Theorem 1.1. *We consider nonlinear operator* (2)*. Then, Gateaux derivative adjoint*

$$F'(r^k)^*(N - F(r^k)) = \int_0^T N^k U^k \, dt, \tag{5}$$

where U^k solves

$$-\dot{U}^k + r^k U^k = N - N^k; \qquad U^k(T) = 0. \tag{6}$$

Demonstração. Let $\theta, \lambda \in \mathbb{R}$, then evaluating $r^k + \lambda\theta$ in the operator F, we have $F(r^k + \lambda\theta) = N^k_\lambda$, where N^k_λ solves

$$\dot{N}^k_\lambda = -\left(r^k + \lambda\theta\right) N^k_\lambda; \quad N^k_\lambda(0) = N_0, \tag{7}$$

The Gateaux derivative of F at r^k in the direction θ is given by

$$W^k = F'(r^k)(\theta) = \lim_{\lambda \to 0} \frac{F(r^k + \lambda\theta) - F(r^k)}{\lambda}. \tag{8}$$

Considering the difference between ODEs (7) and (4), diving by λ and taking the limit $\lambda \to 0$, we have the following ODE

$$\dot{W}^k = -r^k W^k - \theta N^k; \quad W^k(0) = 0. \tag{9}$$

From gradient type iteration (3) and $\theta \in \mathbb{R}$ arbitrary, we have

$$\begin{aligned}\langle r^{k+1} - r^k - \alpha^k(r^1 - r^k), \theta\,\rangle_{\mathbb{R}} &= w^{k,\delta}\langle F'(r^k)^*(N - F(r^k)), \theta\,\rangle_{\mathbb{R}} \\ &= w^{k,\delta}\langle F'(r^k)^*(N - N^k), \theta\,\rangle_{\mathbb{R}}\end{aligned}$$

By definition of adjoint operator

$$\langle r^{k+1} - r^k - \alpha^k(r^1 - r^k), \theta\,\rangle_{\mathbb{R}} = w^k\langle N - N^k, F'(r^k)(\theta)\,\rangle_{L^2[0,2]}$$

From Eq. (8) and the previous equation, we obtain

$$\begin{aligned}\langle r^{k+1} - r^k - \alpha^k(r^1 - r^k), \theta\,\rangle_{\mathbb{R}} &= w^k\langle N - N^k, W^k\,\rangle_{L^2[0,2]}, \\ &= w^k\int_0^T (N - N^k)W^k\,dt. \qquad (10)\end{aligned}$$

Multiplying ODE (9) by U^k, and integrating in the interval $[0,T]$ it follows that

$$\int_0^T \dot{W}^k U^k = -\int_0^T r^k W^k U^k dt - \int_0^T \theta N^k U^k dt$$

Integrating the first term from previous equation by parts, and from the initial ($W^k(0) = 0$) and final ($U^k(T) = 0$) conditions, we obtain

$$\int_0^T \left(-\dot{U}^k + r^k U^k\right) W^k dt = -\int_0^T \theta N^k U^k dt$$

Substituting Eq. (6) in the previous equation, we gather that

$$\int_0^T \left(N - N^k\right) W^k dt = -\int_0^T \theta N^k U^k dt.$$

From the previous equation and from Eq. (10), we obtain

$$\begin{aligned}\langle r^{k+1} - r^k - \alpha^k(r^1 - r^k), \theta\,\rangle_{\mathbb{R}} &= -w^k\int_0^T \theta N^k U^k dt, \\ &= -w^k\theta\int_0^T N^k U^k dt, \\ &= \Big\langle -w^k\int_0^T N^k U^k dt, \theta\Big\rangle_{\mathbb{R}}.\end{aligned}$$

Since $\theta \in \mathbb{R}$ is arbitrary, we gather

$$r^{k+1} = r^k - w^k\int_0^T N^k U^k\,dt + \alpha^k(r^1 - r^k). \qquad (11)$$

From the previous equation and from iteration (3), we together Eq. (5).

$\square$

We next describe the computational scheme.

Algorithm 1: Gradient type iteration to obtain intrinsic growth. The ODEs (4) and (11) are solved with a finite difference method, and we obtain numerical solutions $\boldsymbol{N} \approx N$, $\boldsymbol{N}^k \approx N^k$, $\boldsymbol{U}^k \approx U^k$ and $\boldsymbol{W}^k \approx W^k$. The norm $\|\cdot\|_{\mathbb{R}^J} \approx \|\cdot\|_{L^2[0,T]}$ is defined in Eq. (12). For iteration (11), we use the trapezoidal rule to estimate the integral.

Data:
Parameters: N
ODE initial condition: N_0
Initial approximation: r^1
Result: Compute an approximation for r using gradient type iteration scheme
k=1;
Compute N^1 from Eq. (4), replacing r^k by r^1;
while $10^{-14} < \|N - N^k\|_{L^2[0,T]}$ **do**
  Compute U^k from Eq. (6);
  Compute r^{k+1} using Eq (11), where we choose one of the methods $(a)-(d)$;
  Compute N^{k+1} from Eq. (4), replacing r^k by r^{k+1};
  $k \leftarrow k+1$;
end

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2. Numerical Simulations

Each *while-loop* of the Algorithm 1 involves solving of ODEs. Of course, there is no analytical solution for those equations, and the use of numerical methods is necessary. We use explicit Euler method with a fixed time step Δt to find approximate values of the ODEs. Accordingly, the norms involved in the estimation are discrete approximations of the $L^2[0,T]$ norm. We discretize the time variable $t_j = (j-1)\Delta t$ for $j = 1, 2, \ldots, J$, with time steps $\Delta t = T/(J-1)$. The points $N_j = N(t_j)$, for all $j = 1, 2, \ldots, J$. We denote $\boldsymbol{N} = (N_1, N_2, \ldots, N_J)$, and consider

$$\|N\|^2_{L^2[0,T]} \approx \|\boldsymbol{N}\|^2_{l^2} := \Delta t \|\boldsymbol{N}\|^2_{\mathbb{R}^J} = \Delta t \sum_{j=1}^{J} |N(t_j)|^2. \tag{12}$$

For our examples computed: $\Delta t = 0.01$ and $T = 10$.

We define the percentage error and the residual norm, respectively,

$$\text{Error}_{r^k} = \frac{|r - r^k|}{|r|} \times 100\%, \qquad \text{Res}_k = \|N - N^k\|_{L^2[0,T]}. \tag{13}$$

To design our numerical experiments, we first choose r and compute N, from Eq. (1), with finite difference method. Then, we consider r unknown and N known. To estimate r we use iteration (11), the parameters w^k and α^k, for this problem, are:

(a) Classical Landweber Method (CLM)

From (i), we have $w^k = 1$ and $\alpha^k = 0$.

(b) Modified Landweber Method (MLM)

From (ii), we get $w^k = 1$ and we choose $\alpha^k = 1/2k$.

(c) Steepset Descent Method (SDM)

From (iii) and Theorem 1.1, we together

$$w^k = \frac{\left\| \int_0^T N^k U^k dt \right\|_{\mathbb{R}}^2}{\left\| F'(r^k)\left(\int_0^T N^k U^k dt\right) \right\|_{L^2[0,T]}^2} \quad \text{and} \quad \alpha^k = 0,$$

where

$$W^k = F'(r^k)\left(\int_0^T N^k U^k dt\right)$$

solves

$$\dot{W}^k = -r^k W^k - \int_0^T N^k U^k dt \; N^k; \;\; W^k(0) = 0.$$

In this method, for each iteration k we solve three ODEs (4), (6) and the previous ODE.

(d) Minimal Error Method (MEM)

From (iv) and Theorem 1.1, we obtain

$$w^k = \frac{\left\| N - N^k \right\|_{L^2[0,T]}^2}{\left\| \int_0^T N^k U^k dt \right\|_{\mathbb{R}}^2} \quad \text{and} \quad \alpha^k = 0,$$

In this method, for each iteration k we solve two ODEs (4) and (6).

In this section, we will present three numerical simulations. In Example 2.1, we obtained $r = 2$, and in Examples 2.2 and 2.3, we estimated $r = 10$. For numerical schemes 2.1 and 2.2, we consider the initial guess $r^1 = 0$. For numerical test 2.3, we assume the guess initial $r^1 = 1$.

Example 2.1. *This example is a particular case from Eq.* (1). *The initial guess in this test is* $r^1 = 0$.

The CLM and MLM methods diverge. The SDM and MEM methods needed $k^* = 10$ *iterations to obtain convergence, that is, each method performed 10 iterations so that residual* *norm* $Res_{k^*} < 10^{-14}$. *In iteration 10, whit the SDM method, we got a percentage error of* $Error_{r^{k^*}} = 1.9\times10^{-12}\%$, *and with the MEM method we got a error of* $Error_{r^{k^*}} = 1.3\times10^{-12}\%$.

	Convergence	k^*	*Number of EDOs*	Res_{k^*}	*Time* (s)
CLM	*Diverges*	-	-	-	-
MLM	*Diverges*	-	-	-	-
SDM	*Converges*	*10*	*30*	*0*	*0.220*
MEM	*Converges*	*10*	*20*	*0*	*0.110*

TABELA 1. Computational result for Example 2.1. The first column describes the iterative methods. The second column shows the convergence or divergence of gradient-type methods. The third column represents the iteration number to obtain the method's convergence. The fourth column is the number of ODEs that were resolved to obtain the convergence of the methods. The fifth column lists the errors between exact value N and the approximation N^{k^*}, in iteration k^*, see Eq. (13). Finally, The last column is the running time of the algorithm, in seconds.

Example 2.2. *This example is also another particular case from Eq.* (1). *We consider that the initial guess is* $r^1 = 0$.

In this example, the CLM and MLM methods also diverge. The SDM and MEM methods converge at the iteration $k^* = 13$ *and* $k^* = 11$, *respectively. Errors for these methods are* $Error_{r^{k^*}} = 5 \times 10^{-13}\%$.

	Convergence	k^*	*Number of EDOs*	Res_{k^*}	*Time* (s)
CLM	*Diverges*	-	-	-	-
MLM	*Diverges*	-	-	-	-
SDM	*Converges*	*13*	*39*	*0*	*0.303*
MEM	*Converges*	*11*	*22*	*0*	*0.131*

TABELA 2. Computational result for Example 2.2. See Table 1 for a description of the columns.

Example 2.3. *In this numerical test, we assume that the initial guess is* $r^1 = 1$. *The purpose of this numerical test is the same as Example 2.2* (*to estimate* $r = 10$).

Methods CLM, MLM, SDM and MEM converge in this numerical test, whit percentage errors of $Error_{r^{k^*}} = 1$, $Error_{r^{k^*}} = 2$, , $Error_{r^{k^*}} = 2$ *and* $Error_{r^{k^*}} = 2$, *respectively.*

	Convergence	k^*	*Number of EDOs*	Res_{k^*}	*Time (s)*
CLM	*Converges*	*1453*	*2906*	9×10^{-15}	*16.268*
MLM	*Converges*	-	-	-	-
SDM	*Converges*	*9*	*27*	*0*	*0.184*
MEM	*Converges*	*9*	*18*	*0*	*0.099*

Tabela 3. Computational result for Example 2.2. See Table 1 for a description of the columns.

3. Conclusions

In this supplementary material, we have considered a simple model so that readers can better understand how to calculate the Gateaux derivative adjoint, see Theorem 1.1. Here, we also compare the MEM method, which was proposed in the main article [3], *with other numerical methods.*

In Example 2.1, CLM and MLM numeric methods diverge to any initial condition r^1*. SDM and MEM methods converge to the initial guess* $r^1 = 0$*, in Table 1 we show numerical results for this initial condition*

The goal of Examples 2.2 and 2.3 is to estimate $r = 1$*. In numerical Test 2.2, CLM and MLM iterations diverge for the initial condition* $r^1 = 0$*, but in Example 2.3 the methods converge to the initial condition* $r^1 = 1$*. Therefore, for that the CLM and MLM methods to converge, the initial estimate must be close to the exact solution. Regarding the efficiency of the methods, the CLM iteration is more efficient than the MLM method, given that the latter method depends on the initial condition in all iterative steps. On the other hand, SDM and MEM methods converge in the two numeric examples.*

In general, the SDM and MEM methods converge to any initial condition not so far from the exact solution, this is because the w_k *parameter changes with each iterative step* k*. This parameter better controls the instability of the problem, and makes the algorithm converge faster than the CLM and MLM methods, which consider* $w_k = 1$ *for the entire iteration. Also, the MEM method is more efficient than the SDM iteration since in each iteration* k*, the MEM method solves two ODEs and the SDM iteration solves three ODEs.*

Referências

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