Numerical Approximations of the Hodgkin–Huxley Model

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May 4th, 2021

Abstract

The Hodgkin-Huxley Model is a system of differential equations created in 1952 that models the progression of an action potential in a neuron. An action potential is when an explosion of depolarizing current moves across a cell and occurs in neurons in order to relay important information throughout the body. In this paper, six numerical methods are applied to a simplified version of the Hodgkin-Huxley Model to understand how accurate the methods are in approximating the exact solution of the model. The numerical methods explored are Forward Euler, Backward Euler, Modified Euler, 4th Order Runge-Kutta (RK4), Adams-Bashforth-Moulton 4th Order Predictor-Corrector (ABMPC4), and ODE45. The average error and average order are calculated for each method. All methods, except for ODE45, had decreasing error as the number of time steps increased and had average orders comparable to the theoretical orders. When comparing the average error of each method, the methods that are the worst to the best at approximating the solution are Forward Euler, Backward Euler, Modified Euler, ABMPC4, RK4, and ODE45.

Introduction and Background

History of the Hodgkin–Huxley Model

The Hodgkin-Huxley Model, or also known as the conductance-based model, describes the initiation and progression of an action potential occurring in a neuron. The model includes a system of four nonlinear differential equations that approximates the electrical attributes of excitable cells by equating each part of the cell as an electrical current. Alan Lloyd Hodgkin and Andrew Huxley discovered the model in 1952 with the publication of five papers that described the ordinary differential equations that modelled action potentials through the squid giant axon in the Journal of Physiology. A squid's axon is typically 0.5mm in diameter and aids in the process of jetting out water to propel the squid. In 1963, both founders were awarded a Nobel Prize in Physiology and Medicine for their research on the axon [1] [4] [6].

Defining Action Potentials

An action potential is the action of an explosion of depolarizing current moving across a cell and occurs in excitable cells. Excitable cells are cells that can be stimulated to create a tiny electric current. Some examples of excitable cells include neurons, muscle cells, and endocrine cells. In this paper, the action potential in neurons is explored. Neurons have action potentials in order to send impulses or signals from the dendrites to other neurons to relay important information. In Figure 1 is a diagram of two neurons with certain anatomical parts labelled. The signal travels from one neuron to another through the axon, then reaches the synapse, where the action potential truly starts. After the action potential, the signal travels through the dendrites of the connecting neuron and the cycle continues. For an action potential to occur, the depolarization or membrane potential must reach some minimum voltage, called the firing threshold. Since the firing threshold is the same for every membrane, action potentials are always the same size, making action potentials easier to model. The membrane also has increased conductance during an action potential. This is because the action potential causes the permeability of potassium and sodium ions inside and outside the cell to change. The sodium and potassium ion channels involved in an action potential are also modeled by the Hodgkin-Huxley Model [1].

In Figure 2 is the graph of the voltage or potential of an action potential over time. Starting from the part of the graph labelled as 1, voltage builds up from the resting voltage of around -65mV until the firing threshold is reached, at which point the action potential begins. The yellow lines showcase the voltages of failed action potentials. For these lines, since the voltage never reaches the firing threshold, the action potential does not occur. Part 2 is the Depolarization Phase where the sodium channels begin to open and sodium enters the cell. The cell becomes more positive due to the influx of sodium ions. At part 3, the sodium channels becomes refractory such that no more sodium can enter the cell. The action potential is at its peak, which is the maximum voltage of the action potential. The voltage drops at part 4, which is the Repolarization Phase. The rise in positive charge due to the sodium ions causes the potassium channels to open and potassium to leave the cell. The potassium channels begin to close at part 5, the Hyperpolarization Phase, and the potential drops below the resting membrane potential (-65mV), meaning that the membrane is hyperpolarized. At this phase, the cell is no longer excitable, preventing the action potential from traveling backwards, truly finalizing that the signal is going to reach the next neuron. Lastly, at part 6, the concentration of potassium ions outside the cell causes a slight increase in potential, which allows the voltage to return to the resting membrane potential.

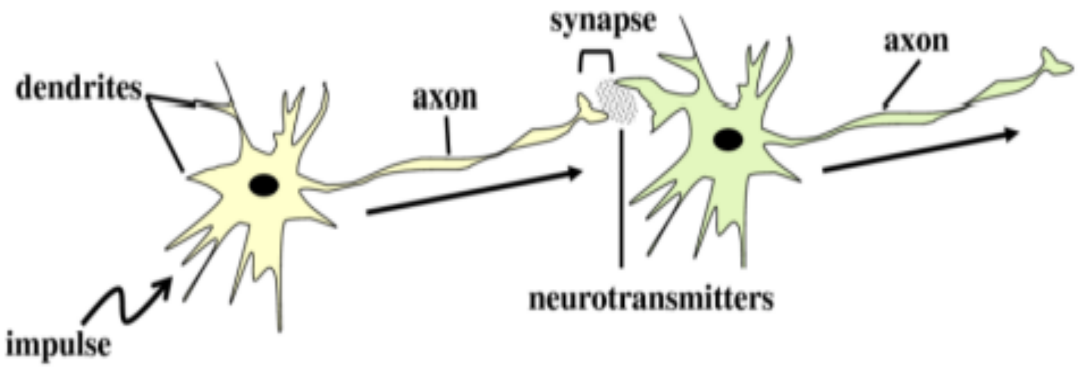

Figure 1. Pictorial representation of two neurons with certain anatomical parts labelled. The arrows represent the path of an action potential through the neurons. Figure taken from [1].

The Hodgkin–Huxley Model

The Hodgkin-Huxley Model is a mathematical model that describes how action potentials are fired in neurons. The model involves a system of four nonlinear differential equations where t is time and v is the voltage of the membrane. One equation, $\frac{dv}{dt}$, measures the voltage difference between the inside and outside of the cell. The other three equations, $\frac{dn}{dt}, \frac{dm}{dt}, and\ \frac{dh}{dt}$, model the activation level of the ion channels, which are responsible for moving potassium and sodium ions. The three channels modelled are the sodium, potassium, and leakage channels. The differential equations involved in the Hodgkin-Huxley Model are below:

$$\frac{dv}{dt} = \frac{1}{C_m}\left(I - \overline{g}_{Na}m^3h(v - E_{Na}) - \overline{g}_K n^4(v - E_K) - \overline{g}_L(v - E_L)\right),$$

$$\frac{dn}{dt} = \alpha_n(v)(1 - n) - \beta_n(v)n,$$

$$\frac{dm}{dt} = \alpha_m(v)(1 - m) - \beta_m(v)m,$$

$$\frac{dh}{dt} = \alpha_h(v)(1 - h) - \beta_h(v)h.$$

In the system of equations, there are 11 constants and 6 supporting functions. All supporting functions and constants are labelled and defined in Table A1 in Appendix A. C_m is the constant representing the capacitance of the membrane. Capacitance is the ratio of the amount of electric charge stored on a conductor to a difference in electrical potential. Capacitance is mathematically modelled in the system of equations by imaging the axon membrane as a long thin cylindrical capacitor. Each $\overline{g}$ represents the maximum conductance for the specified channel type. Conductance is the potential for a substance to conduct electricity. The maximum amount of conductance occurs when all the channels of the specified type are open. Each E is the equilibrium potential, also referred to as reversal potential, for the specified channel type. The equilibrium potentials are equal to the voltage value required to form the boundary between the currents flowing inward and outward. The dimensionless quantities n, m, and h are between 0 and 1 and are associated with potassium channel activation, sodium channel activation, and sodium channel inactivation, respectively. These quantities can also be used to define the types of gates a channel has. For example, the sodium channel has three m gates and one h gate [1][4][5].

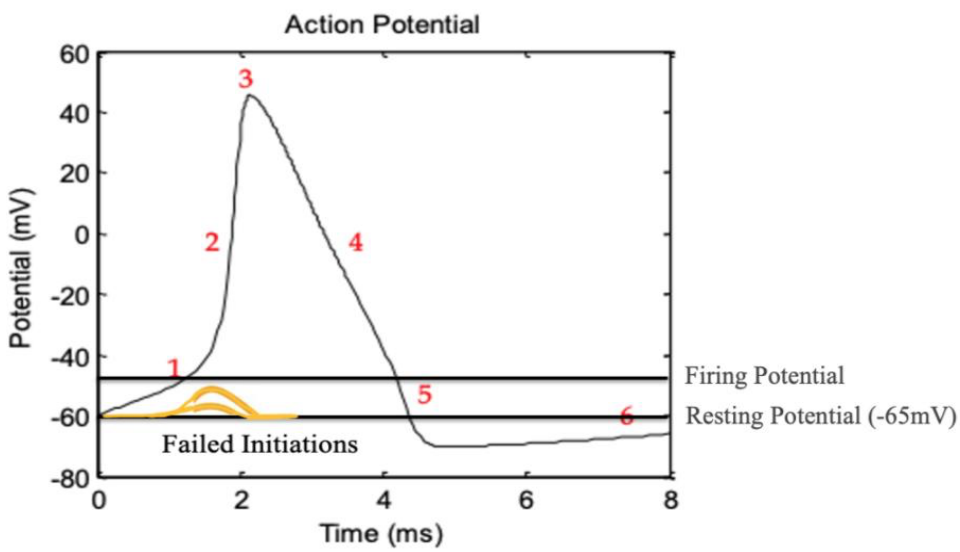

Figure 2. Graph of the voltage measured throughout an action potential. The numbers represent time points. Each time point is detailed in *Defining Action Potentials.* The firing and resting potentials are labeled. The yellow lines represent failed initiations. Figure taken from [1].

Numerical Methods Utilized for Numerical Analysis

Each method used in this paper's analysis is commonly used to solve ordinary differential equations for the form $y'(t) = f(t, y(t))$ with the initial condition $y(t_0) = y_0$. The endpoints for the schemes are t_0, the initial time, and $t_n = t_0 + Nh$, the final time, where h is the time step size and N is the total number of time steps. Although each numerical integration method approximates the solution to the same differential equation, each yields that solution using a different formula. Therefore, these methods have different orders and errors.

The specific methods analyzed through the Hodgkin-Huxley Model are the Forward Euler, Backward Euler, Modified Euler, 4th Order Runge-Kutta (RK4), Adams-Bashforth-Moulton 4th Order Predictor-Corrector (ABMPC4), and ODE45 methods. The equations used to compute the approximate solution of each method are in Table A2 in Appendix A.

Generally, the Euler methods are some of the simplest numerical methods, as they can be easily programmed and involve little computational time. However, the Euler methods are also some of the most unstable and inaccurate methods, resulting in more iterations being needed compared to other methods to achieve the same error. The theoretical order for the Forward and Backward Euler methods are 1st order, while the Modified Euler method is theoretically 2nd order. Another method examined is RK4 and is the most commonly used Runge-Kutta method. It involves using the previous solution value and the weighted averages of four increments, $k_1, k_2, k_3,$ and k_4, to find the approximate solution at the next time step [1].

ABMPC4 is an Adam-Type scheme used with the predictor-corrector method. An Adam-Type scheme is of the form $\frac{y_{i+1}-y_i}{\Delta t} = \beta_0 f_{i+1} + \beta_1 f_i + \cdots + \beta_m f_{i-m+1}$. A predictor-corrector method is an algorithm which involves two separate steps. The first step is an initial, commonly explicit predictor equation y_p that is fitted to the function and derivative values to extrapolate the function value at the next time step. The next step is an implicit correction equation, y_c, that refines the approximate function value calculated by y_p by utilizing another numerical method, which is the 4th Order Adams-Bashforth-Moulton method in this case. ABMPC4 requires four previous function values or terms to get the first calculated n+1 term, y_{n+1}. Therefore, any of the above methods can be used to find all the necessary initial function values before using ABMPC4. In this paper, RK4 is used to find the initial four terms, then ABMPC4 is used afterwards to calculate all the other terms involved in the approximate solution [1] [2].

ODE45 is a MATLAB build-in function that solves the specified differential equation or system of differential equations (odefun) by integrating the system from t_0 to t_n (tspan) with initial condition y_0 (y0). The function utilizes a variant of Runge-Kutta and a variable time step to efficiently find the solution. The outputs of the function are t and y. The output t is a column vector with the time steps. The output y is an array with the corresponding solution values. Although the exact theoretical order for this method is unknown, it is known that ODE45 is a higher-order method [1] [3].

Numerical Analysis of the Hodgkin-Huxley Model

To perform effective numerical analysis and compare the various iterative numerical methods used to get an approximate solution to the Hodgkin-Huxley Model, an exact solution needs to be obtained. Unfortunately, obtaining the exact solution for the model is not straightforward unless some restrictions are placed to simplify the model. To simplify the model, the sodium and potassium maximum conductance, $\overline{g}_{Na}$ *and* $\overline{g}_K$ respectively, are set equal to zero. Due to the constraints, the terms in $\frac{dv}{dt}$ containing n, m, and h are now equal to 0, thereby making it unnecessary to calculate the differential equations $\frac{dn}{dt}, \frac{dm}{dt}, and\ \frac{dh}{dt}$. The simplified model now has no supporting functions, four constants, and one differential equation, which is below:

$$\frac{dv}{dt} = \frac{1}{C_m}\left(I - \overline{g}_L(v - E_L)\right).$$

The constants used in the differential equation are listed and defined in Table A1. Using the separation of variables technique, $\frac{dv}{dt}$ can be solved and the exact solution *v* can be found. With the initial voltage set as -60mV, *v* is defined as the equation below [1]:

$$v = \frac{1}{\overline{g}_L}\left(-e^{\left(-\frac{\overline{g}_L}{C_m}t\right)}\left(I + 60\overline{g}_L + \overline{g}_L E_L\right) + I + \overline{g}_L E_L\right).$$

The methods utilized in the numerical analysis of the simplified Hodgkin-Huxley Model were the Forward Euler, Backward Euler, Modified Euler, RK4, ABMPC4, and ODE45 methods. For each of the six methods, the approximate solution was found for when N = 10, 20, 40, 80, 160, and 320 where N equals the number of time steps. The size of each time step is equal to h. The timespan is from t_0 = 0 ms to t_n= 25 ms. The approximate solutions were compared to the exact solution to calculate the infinity norm. The infinity norms of all the approximate solutions are then used to calculate the average error and average order for each numerical method. These quantities are gathered to compare the methods to one another and to understand how accurate each method is in calculating the approximate solution of the simplified Hodgkin-Huxley Model. Most of the code used in calculating the average order was provided from [7].

Results

Tables with the infinity norm and approximate order of the approximate solution for each N value for each numerical method are in Appendix B. The h value is also displayed in each table. The infinity norm is labelled as the error. Except for the ODE45 method, all the methods observed a decrease in error as the value of N increased. The approximate order of each method, except for the ABMPC4 and ODE45 methods, converged to the method's theoretical order as the value of N increased. For ABMPC4, the results showed that the method is closer to being 5^{th} order rather than 4^{th} order. The errors decreasing and the order converging to the theoretical result as N increases signals that the methods are working as expected when applied to the modified Hodgkin-Huxley Model. The reasons why ODE45 does not experience the same decrease in error or convergence in order is explained in the Discussion section.

Despite Forward and Backward Euler both having similar theoretical and observed orders, the errors observed are substantially different. The error for when N = 10 for the Forward Euler method is about the same as when N = 80 for the Backward Euler method. This one error comparison illustrates that the Backward Euler method is more accurate, despite being of the same order as the Forward Euler method, and that small changes to a method can result in a new method that behaves differently. All the Euler methods have a decreasing error and increasing order as N increases. The same is observed for the ABMPC4 method. However, RK4 is the only method where the observed order decreases as N increases, even though it still does converge to the theoretical order.

The table with the average error and average order calculated for each method, along with the average errors calculated in [1] is in Table A3 in the Appendix. In terms of average error, the methods ranked from worst to best are: Forward Euler, Backward Euler, Modified Euler, ABMPC4, RK4, and ODE45. In terms of average order, the methods ranked from worst to best are: Backward Euler, Forward Euler, Modified Euler, RK4, and ABMPC4. The reasoning why ODE45 is not included in the average order ranking, as well as a comparison of the average errors calculated in this paper and in [1], will be in the Discussion section.

Discussion

In Table A3 are the values of the average errors for each method calculated in this paper and in [1]. For the Forward Euler, RK4, ABMPC4, and ODE45 methods, all the errors from [1] are significantly smaller than those calculated in this paper. Unfortunately, [1] did not perform numerical analysis on the Hodgkin-Huxley Model using the Backward Euler and Modified Euler methods. The main reason as to why the average errors vary drastically could be because [1] did not provide its methodology on how the numerical analysis was performed. The values of h chosen, the number of approximate solutions calculated for each method, and how the average error and average order was ultimately calculated were not specified. Therefore, the results in [1] could not be exactly replicated. It is speculated that the values of h chosen were considerably smaller than the h values in this paper, resulting in obtaining a smaller average error.

Although ODE45 is a higher-order accurate method, the average order calculated does not follow this observation. If the average order calculated were to be the true order of the method, then ODE45 would be less than 1st order accurate, making it less accurate than the Forward Euler method. The reason why the average order does not reflect the true order of ODE45 is because how ODE45 is designed. The method is automatically optimized depending on the parameters given and utilizes inconsistent time step sizes to be more efficient. The only parameter that changed each time ODE45 was used to get an approximate solution was the value of N. However, N is hardly influential in the algorithm. In the table showing the errors and observed orders for the ODE45 method in Appendix B, the error barely changes as N increases, illustrating the lack of influence N has on the ODE45 method. Since the error does not change much as N increases, the observed order is not as high as expected. The observed order is also sometimes negative because the error increased as N doubled. Although the true order of ODE45 could not be observed, the method still has errors comparable to the RK4 and ABMPC4 methods when N is below 40. Therefore, ODE45 is still considered a highly accurate method.

Although the average order of ODE45 does not accurately portray it as a higher-order method, ODE45 still produced the approximate solutions that were the closest to the exact solution for $N \leq 20$. Due to the error not decreasing as N increased, however, the method is not the most accurate for higher values of N. Therefore, ODE45 is the most ideal method if implementing a higher-order method is not possible or if the value of $N < 40$. Otherwise, the ABMPC4 method is the most accurate method, as it has the smallest error for when $N \geq 40$ and is the highest order method.

Conclusion

In conclusion, the Hodgkin-Huxley Model is important to understanding the progression of an action potential, which is a vital process in most, if not all, living creatures. By simplifying the model to only include the DE equation modelling the difference in voltage and a handful of constants, numerical analysis can easily be used to approximate the solution to the model. With the exception of ODE45, each of the methods had decreasing error and converged to the theoretical order as N increased. Based on the average errors in Table A3, the methods that are the worst to the best at approximating the simplified Hodgkin-Huxley Model are: Forward Euler, Backward Euler, Modified Euler, ABMPC4, RK4, and ODE45. However, ODE45 was the most accurate numerical method only when $N < 40$. For $N \geq 40$, RK4 and ABMPC4 resulted in significantly less error. Therefore, the methods that are the worst to the best at approximating the solution to the simplified Hodgkin-Huxley Model for when $N \geq 40$ are: Forward Euler, Backward Euler, Modified Euler, ODE45, RK4, and ABMPC4.

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Appendix A

Table A1. Constants and Supporting Functions in the Hodgkin-Huxley Model

Function or Constant	**Definition**
$I = 0.1\ \frac{\mu F}{cm^2}$	Input current per unit area
$\alpha_n(v) = \frac{0.01(v+50)}{1-e^{\left(\frac{-(v+50)}{10}\right)}}$	Function of voltage that represents one of the rate constants of the *n* ion channel
$\beta_n(v) = 0.125e^{\left(\frac{-(v+60)}{80}\right)}$	One of the rate constants for the *n* ion channel
$\alpha_m(v) = \frac{0.1(v+35)}{1-e^{\left(\frac{-(v+35)}{10}\right)}}$	One of the rate constants for the *m* ion channel
$\beta_m(v) = 4e^{(-0.0556(v+60))}$	One of the rate constants for the *m* ion channel
$\alpha_h(v) = 0.07e^{(-0.05(v+60))}$	One of the rate constants for the *h* ion channel
$\beta_h(v) = \frac{1}{1+e^{(-0.1(v+30))}}$	One of the rate constants for the *h* ion channel
$C_m = 0.01\frac{\mu F}{cm^2}$	Capacitance of the membrane
$E_{Na} = 55.17mV$	Equilibrium potential for the sodium (Na) channels
$E_K = -72.14mV$	Equilibrium potential for the potassium (K) channels
$E_L = -49.42mV$	Equilibrium potential for the leakage (L) channels
$\overline{g}_{Na} = 1.2\frac{mS}{cm^2}$	Maximum conductance measured when all the sodium (Na) channels are open
$\overline{g}_K = 0.36\frac{mS}{cm^2}$	Maximum conductance measured when all the potassium (K) channels are open
$\overline{g}_L = 0.003\frac{mS}{cm^2}$	Maximum conductance measured when all the leakage (L) channels are open

Table A2. Equations for Each Numerical Method Utilized for Numerical Analysis

Numerical Method	Equations
Forward Euler	$y_{n+1} = y_n + \Delta t f(t_n, y_n)$
Backward Euler	$y_{n+1} = y_n + \Delta t f(t_{n+1}, y_{n+1})$
Modified Euler	$y_{n+1} = y_n + \frac{\Delta t}{2}\left(f(t_{n+1}, y_{n+1}) + f(t_n, y_n)\right)$
4th Order Runge-Kutta (RK4)	$y_{n+1} = y_n + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4)$ where $k_1 = \Delta t f(t_n, y_n)$, $k_2 = \Delta t f\left(t_n + \frac{1}{2}\Delta t, y_n + \frac{1}{2}k_1\right)$, $k_3 = \Delta t f\left(t_n + \frac{1}{2}\Delta t, y_n + \frac{1}{2}k_2\right)$, $k_4 = \Delta t f(t_n + \Delta t, y_n + k_3)$
Adams-Bashforth-Moulton 4th Order Predictor-Corrector (ABMPC4)	$y_{n+1} = y_c + \frac{19}{270}(y_p - y_c)$ where $y_p = y_n + \frac{\Delta t}{24}(55f_n + 59f_{n-1} - 37f_{n-2} + 9f_{n-3})$, $y_c = y_n + \frac{\Delta t}{24}(9f_{n+1} + 19f_n - 5f_{n-1} + f_{n-2})$, $f_{n+1} = f(t + \Delta t, y_p)$.
ODE45	[t, y] = ode45(odefun, tspan, y0)

Table A3. Average Error and Average Order for Each Numerical Method

Numerical Method	Average Error from [1]	Average Error	Average Order
Forward Euler	0.034984	10.80680	1
Backward Euler	-	1.64465	0.91960
Modified Euler	-	0.54039	2.15031
RK4	1.0155e-7	0.01348	4.16538
ABMPC4	1.2004e-8	0.01599	4.63486
ODE45	3.0036e-4	0.00589	0.05527

Appendix B: Observed Errors and Orders for Each Numerical Method

Forward Euler

N	h	error	observed order
10.00000	2.50000	32.93500	NaN
20.00000	1.25000	16.46750	1.00000
40.00000	0.62500	8.23375	1.00000
80.00000	0.31250	4.11688	1.00000
160.00000	0.15625	2.05844	1.00000
320.00000	0.07812	1.02922	1.00000

Backward Euler

N	h	error	observed order
10.00000	2.50000	4.54066	NaN
20.00000	1.25000	2.63571	0.78471
40.00000	0.62500	1.40353	0.90913
80.00000	0.31250	0.72915	0.94477
160.00000	0.15625	0.37136	0.97341
320.00000	0.07812	0.18749	0.98600

Modified Euler

N	h	error	observed order
10.00000	2.50000	2.59512	NaN
20.00000	1.25000	0.50513	2.36107
40.00000	0.62500	0.10907	2.21135
80.00000	0.31250	0.02540	2.10248
160.00000	0.15625	0.00613	2.05119
320.00000	0.07812	0.00151	2.02546

RK4

N	h	error	observed order
10.00000	2.50000	0.07705	NaN
20.00000	1.25000	0.00362	4.41252
40.00000	0.62500	0.00019	4.21954
80.00000	0.31250	0.00001	4.11084
160.00000	0.15625	0.00000	4.05594
320.00000	0.07812	0.00000	4.02807

ABMPC4

N	h	error	observed order
10.00000	2.50000	0.09098	NaN
20.00000	1.25000	0.00477	4.25339
40.00000	0.62500	0.00020	4.54895
80.00000	0.31250	0.00001	4.69306
160.00000	0.15625	0.00000	4.78594
320.00000	0.07812	0.00000	4.89295

ODE45

N	h	error	observed order
10.00000	2.50000	0.00521	NaN
20.00000	1.25000	0.00521	0.00000
40.00000	0.62500	0.00792	-0.60583
80.00000	0.31250	0.00534	0.56944
160.00000	0.15625	0.00738	-0.46633
320.00000	0.07812	0.00430	0.77907