Computer Aided Drug Design
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Lecture - 21
ODES and Numerical methods

Hello everyone, welcome to the course on computer aided drug design. We have been talking about numerical methods for finding out differentials. Now, we will look at numerical methods for solving differential equation, okay. Numerical methods are a course by itself, so I am just going take 1 or 2 lectures on this topic, okay just as a prelude to the entire concept of numerical methods because they are used when you talk about minimum energy confirmation and so on actually, okay.

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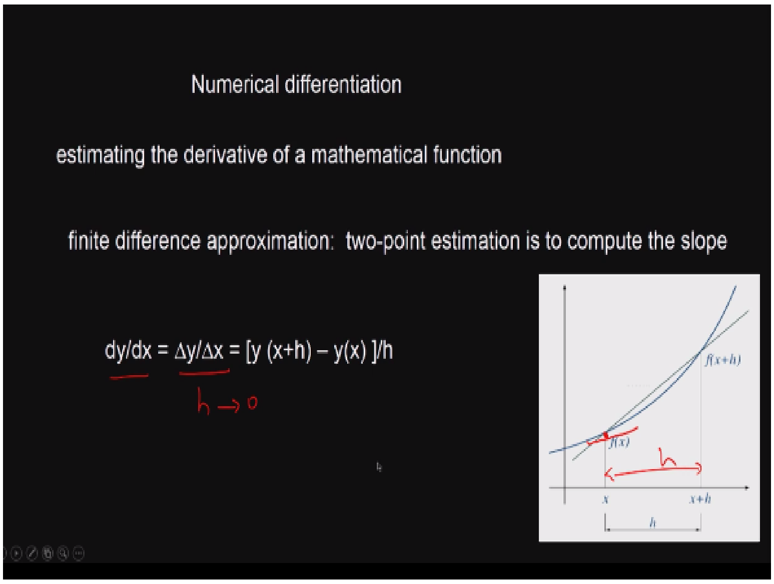

So, we were talking about numerical differentiation that means estimating the derivative of a mathematical function is called a finite difference approximation based on 2-point estimation. So, if you have dy/dx as you know it can be approximated as delta y/delta x which is delta y is y at x+h – y at x/h, okay. So, basically y at x+h will be here and y at x will be here, okay. So you take this difference and / h, okay.

That gives you the dy/dx as you know dy/dx is the slope. Actually you would like to do it here, okay whereas you take the much bigger region, so if the h is small then your approximating or to the exact slope at this point of place at x, okay that is how it is. So, smaller the h more accurate is your answer larger the h as you can see in this figure you are not reaching the correct answer, okay.

So, dy/dx as this becomes the dy/dx delta y/delta x becomes dy/dx only when h becomes smaller and smaller and smaller actually, okay sending to 0. So, there are as I said this normal simple method 2-point method which calculates the dy/dx as you go along the slope. The error in this particular case is in the order of h square, so which could be very high and yesterday I showed you an example of this how much the h change depending upon h.

If h is 0.001 you may get 0.1% error, if h is 0.01 you may get 1% error if h is 0.1 you may get 10% error depending upon on how the equation is because if you have parabolic type of relationship errors could be much larger.

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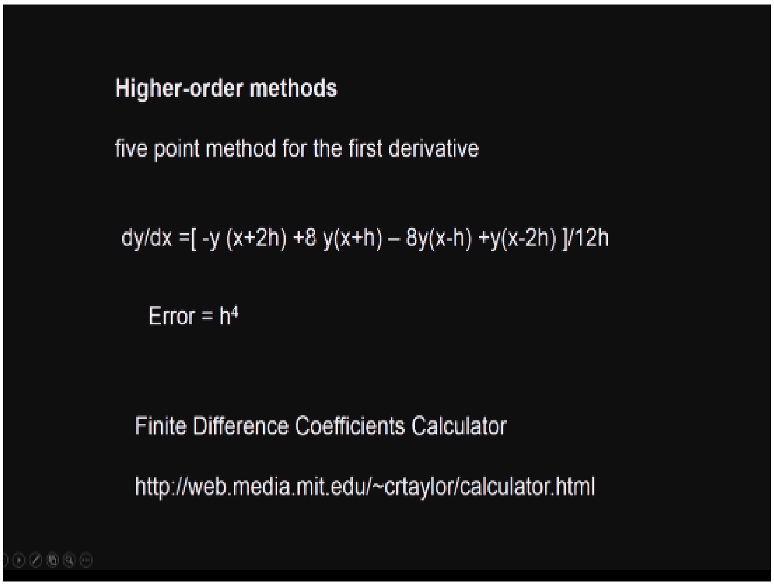

There are higher order methods also which can do a better job of estimating dy/dx here the error is of the order of h raised to the power 4, okay. So, that is quite small. The higher order methods is as I showed here you have estimate the y at x+2h estimate the y at x-2h then estimate the y at x+h, x-h and then use different coefficients I shown here, okay divided by 12h and you get the dy/dx, okay.

So, depending upon where you estimate these coefficients can change in fact this particular website gives you values of the coefficient.

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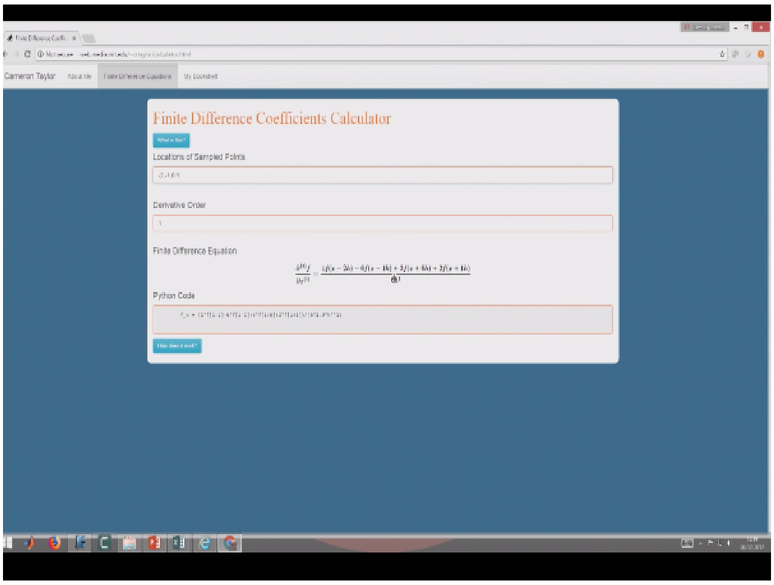

Okay, for example, let us have a look at it actually. Yes, so if those 5 points are at -2, -1 then at +2, +1, okay. This is of the equation we look like, like I showed you here, okay if x-h, okay like I showed here. So, we have an 8-1+1. So, we can change this sample points and you will end up with the different coefficients. For example, if I change it 2, 1, 0, 1, 2, okay, so you see this is how it will look like.

So, it is estimated at 0 it is estimated at +h, +2h and the coefficients are -3, +4 and -1, okay. So, depending upon which are the 4 points you planned to do -1, 0, +1, 2, okay. So, it gives you different sets of coefficients here as you can see here, okay. So, depending upon which points we want to use it gives you different sets of equations when coefficient values.

As you can see for x+3h, x+2h, x+h because this is what we have written 3, 2, 1 and this is x+0 that is at x itself and then -1. So, we have a different sets of coefficients here, okay. So, depending upon how you want to estimate your dy/dx which 5-points you planned to use then it changes accordingly, okay as you can see here, okay. So, here I have taken only 4 points -2, -1, 0, 1, okay.

So, it is not really symmetric on both sides of 0, so you have different sets of coefficients here and the denominator also is very different as against this. Here we are considering symmetric +2h, -2h, +h, -h, okay whereas here we are taking -2, -1, 0 and 1 here. So, you have different sets of coefficients here, okay. So, this is a very useful, okay website where we can get the coefficients depending upon how we are going to use the sampling points, okay.

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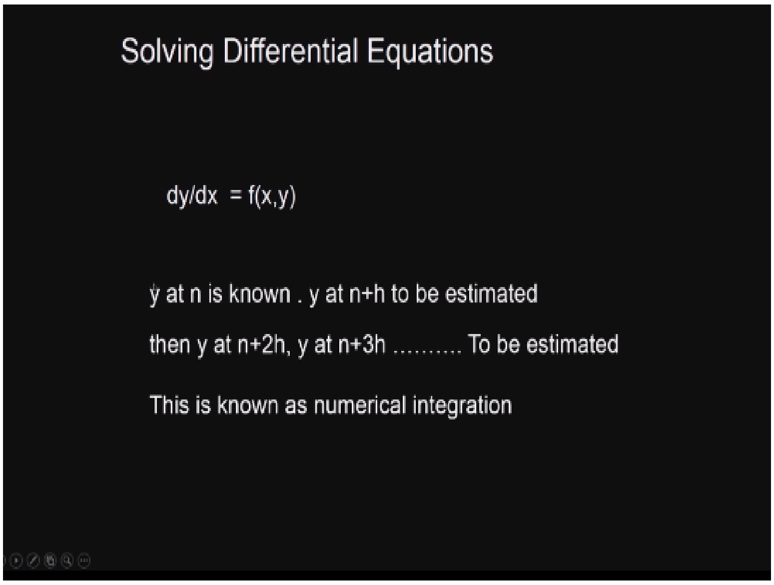

So, now how do you solve differential equations? Suppose I have dy/dx = fxy, okay. So, y at n is known I want to find out y at n+h, y at n+3h, 2h, 3h, 4h like that, okay is called the numerical integration or solving differential equations, okay. This is also very useful because we want to differentiate and then calculate y at different values of x.

The x could be time especially if you are doing a molecular dynamic study and as time changes you want to know how the coordinates change in the molecule, okay. So, you may have differential equations you may calculate as a function of time at t=t0, t=t0+h, t0+2h like that you want to find out the coordinates, okay. So, in such situations you will be solving differential equation, okay.

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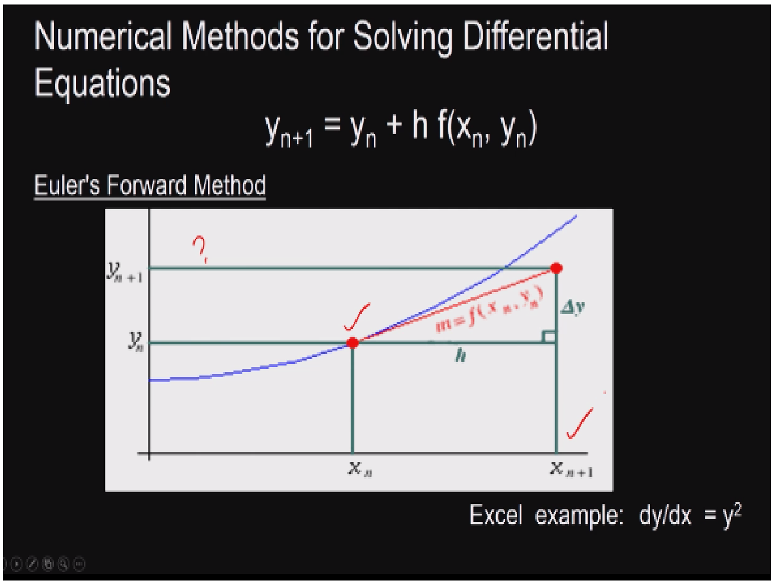

So, the simplest method is the Euler's Forward method, okay. So, what it does is just like the original we looked at it in this, okay this one use the similar one. So, yx+h, so we can put this on this back, so you get yx+h. So, here also yn+1=yn+h f xn yn, okay. So, if I know the value of y at certain time point, okay if I want to find out at the next time point +h time point then I do yn+h*f xn yn, okay.

So, for example you are here xn yn this is xn, yn and you want to find out what will be the yn+1, okay what will be the yn+1 at this particular time point. So, what do you? You do like this yn+h f xn, yn, okay. So, this is the function which you have to substitute here actually. Then the next time point you go. So, depending upon how large is your step length, okay how large is your step length the error also goes down, okay.

Just like the other which I showed you the numerical, okay differentiation. And so, smaller the step length more accurate will be the answer as you can see when you have very quadratic or very sharp change in graphs you are going to have problem in estimating the yn+1 starting from yn, okay again there are many different methods here. But Euler's method is the easiest one and so, if there is a sharp change unless the h is very small, okay.

For example, if your xn+1 is here that means h is very small you will get a very accurate answer here as you can see here. But if your h is large as you can see here there is a lot of error in estimating yn+1 this is the actual whereas this is what the numerical method will tell you. So, smaller the h more accurate you can go along this graph. So, we can have small h then that way you will go along this graph.

Larger the h you may end up with this type of graph here, okay. So, the step length makes lot of difference and the error in estimation of yn+1, okay smaller the step, okay. For example, let us look at this dy/dx= y square, okay. I want to calculate at some other next time point and so on.

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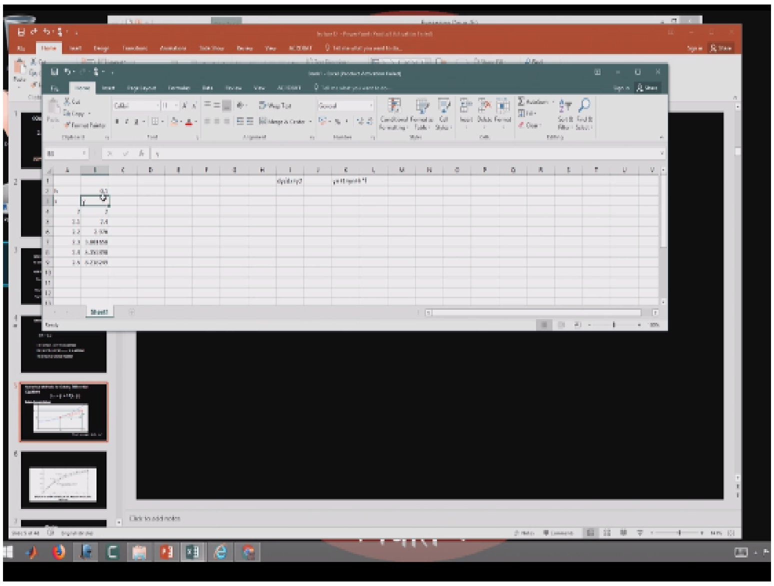

So, this can be done, so if you want to solve for example equation like this dy/dx = say y square, okay imagine this is x and this is y, okay may put it at say 2 then we can say put it as the step length can be 0.01. So this can be, so you want to calculate, so like I mentioned yn+1 = yn+h multiplied by the function, okay. So, how do you that? So, we will take this is = this + the h step length, okay multiplied by the y square that means we take this raised to power 2, okay.

So, h 2.04 at this at 2.01, okay and so on actually. So, we can calculate each step and if 4 * $ b2 + b4 square, so then we can calculate, okay. So, as you can see it keeps y keeps increasing, okay suppose if the step length is, okay, so as you can see it is rising very drastically the y value if the step length is very large whereas the step length is very small it will not rise so drastically write 01, okay as you can see here.

You can also check out what is the actual value, so if the step length is very small, so the rise is small. So, it is much more accurate whereas, if I put larger step length as you can see here, okay I tries as very fast and the system can become very unstable, okay. So, these type of methods we need to have every small step length. So, the number of calculations keep increasing if you have smaller step length.

So there are other methods are all there which can give a better accuracy that is the it is very simple as you can see. It just takes the h multiplies by the y value, I mean the function value that is dy/dx value adds it up to the y starting y. So, it calculates yn+1. And as I said if the step length is smaller, okay you are going to have following slowly with this the step length is very large then you will take large steps.

So, you can see the error in this case actually quite large error actually. But as I said there are many other methods which are more accurate we will look at them little bit which gives values, so that it follows the curve.

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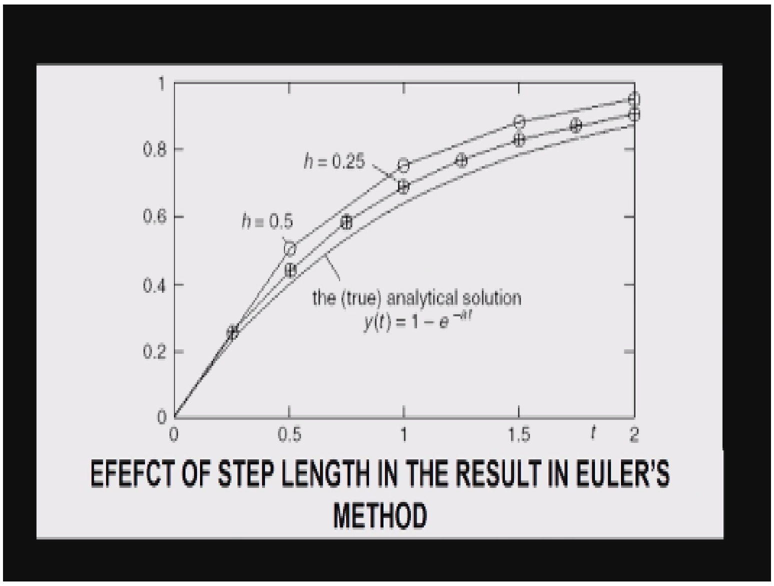

So, if I have a larger step length like I showed you in the excel suppose this is the true value, okay if I have larger step lengths, okay especially for an equation like this 1-e power - at 0.25 step length as you can see it is deviated. If I taken 0.5 as my step length you can see it is deviate in much more.

These problems will all arrives when you have quadratic terms, quadric terms, exponential terms and as you know in our force wheels we come across quadratic, quadric and exponential terms for most field. So, you will find large variations if you have large step length. So, this is the effect of step length. Okay, so as I showed you, if the step length is very large that is the x axis the actual value if this is the actual value you may be going like this actually like I showed you in this example, right.

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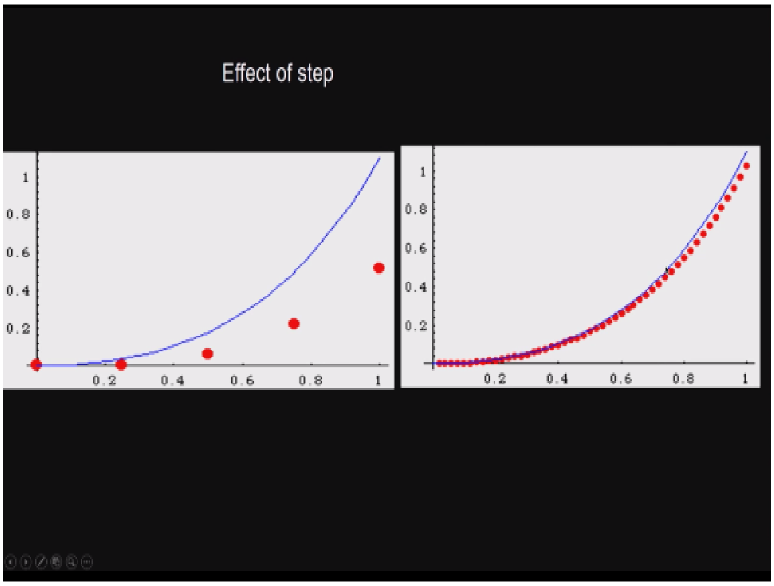

You may be going like this whereas the actual graph is like this, okay. So, when we have a very small step length we should be going along this graph, okay.

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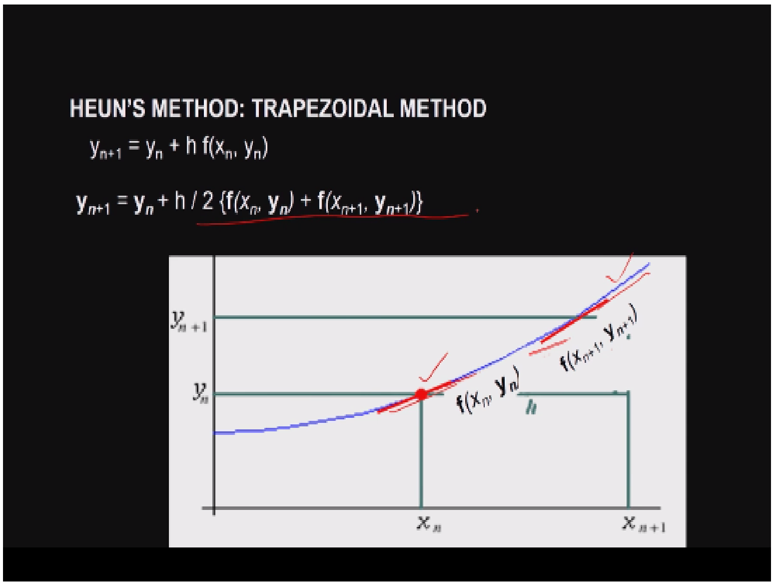

Then there is another method that is called Trapezoidal method, okay. This method is slightly more accurate. So, what you do is yn+1= yn h f xn yn, okay then you also calculate f xn+1 yn+1 and you calculate fxn yn and then take half of then that means you take average of these 2 slopes, okay one slope which comes here and one slope which comes here and then you take the average. That is what this particular term is all about actually.

So, by doing that you get better accuracy. So, you look at this Euler's method, okay. You take the slope only at this place, okay only at this place whereas in this method in Heun's method or Trapezoidal Rule method you take at these 2 places and then you take an average. That is all you calculate yn+1. So, how do you get? This is the first approximation for yn+1 and then you substitute in your equation and then you take the average, okay.

So, that method gives you better answer, okay. So, as you can see this is like predicted for yn+1. This is like your original Euler's method but you do not stop there. You put that into the function, okay, so get the function and then you take the average of the functions the xn, yn, xn+1, yn. So, this is corrector, this is predictor. We call this as predictor, okay. This is the predictor equation which is like your Euler's method.

But you are improving on the yn+1 by having another equation we call is corrector, okay. This is the Trapezoidal method as such. Okay, then we also have the backward Euler's method just backward differentiation method, okay.

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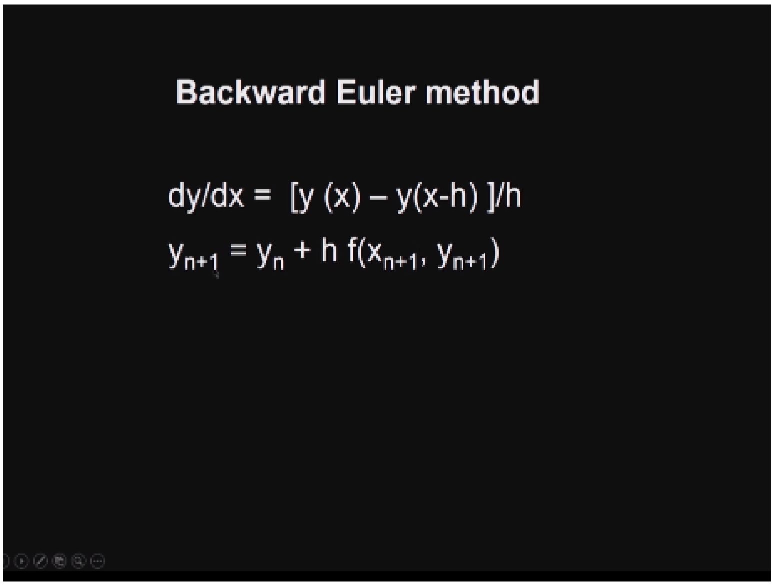

So, as you can see dy/dx=yx – yx-h, okay. So, instead of you taking x+h you are taking yx-h and then you calculate yn+1 = so, you take the differential from the previous and then use that for your yn+1, okay. As I said this is the method, Euler's method then we have the Trapezoidal method which takes an average of slope at xn, yn and xn+1 yn and then so, if you look at Euler's method simple least accurate this is the first order method.

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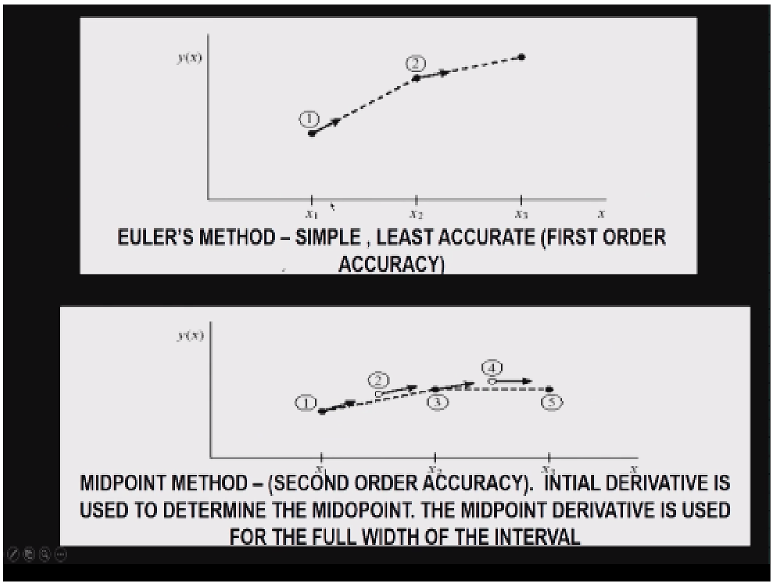

Then we also have the mid-point method where you take, okay at the middle point derivatives for the full width calculation which is slightly more accurate, okay. Then we looked at backward Euler's method.

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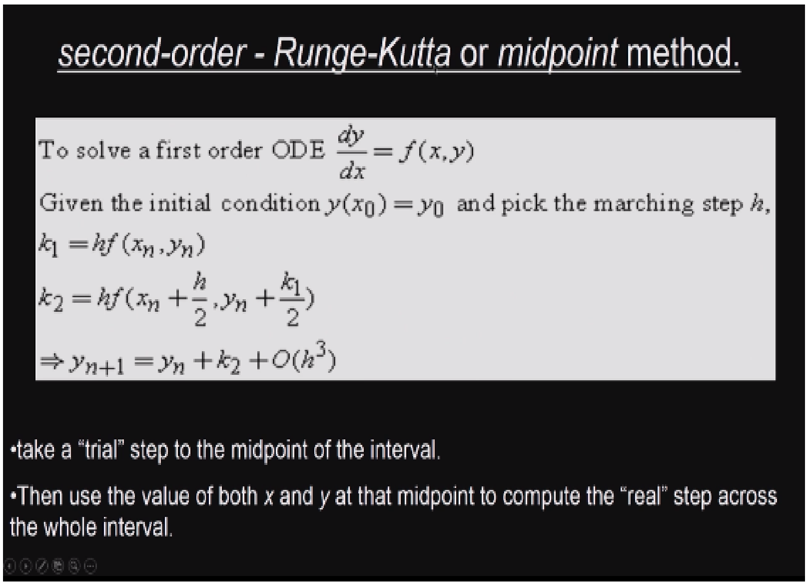

Then we have second order Runge-Kutta method. This is the mid-point method, okay that is mid-point here which you make use of to calculate at the yn+1. So, if you want to solve dy/dx = fxy the initial condition is yx0 = y0, okay. So, we have this step length. So, first calculate k1 which is h * f xn yn that is at the starting point. Then you calculate k2 at the mid-point h/2, okay so, xn at h/2 yn at k1/2 and then make use of to calculate yn+1.

So, yn+1= yn+k2. So, here the error is of the order of h raised to the power 3, okay. So, this is called the mid-point method as you can see you calculate the slope at xn+h/2 yn+k1/2 here as you can see here k1/2 and then make use of to calculate yn+1 value, okay. That is called take a trial step, okay here and then determine for here. That is called the mid-point method. Say this is called second order Runge-Kutta method and error is of the order of h cube, okay which is good.

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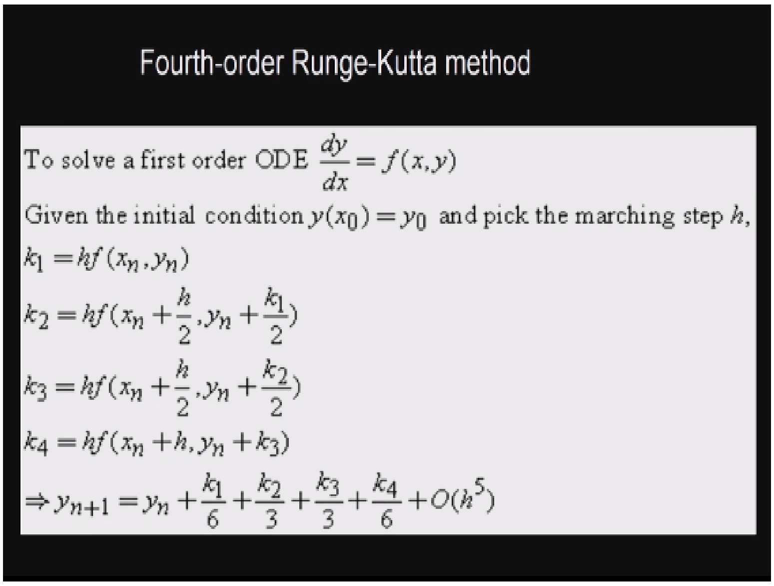

Then we have 4th order Runge-Kutta method. The error is of the order of h raised to the power 5, okay. So, here we do lot of mid-point corrections as you can see you have k1 hf xn yn, k2 xn+h/2 yn+k1/2, okay again you calculate k3 making use of the k2 here yn+k2/3 and then you calculate k4, okay and then yn+1 is calculated like this, kn/6, k2/3, k3/3, k4/6.

So, you calculate the slope at many places, okay 1, 2, 3, 4 that is why it is called 4th order Runge-Kutta method. But the errors have dramatically decreased h raised to the power 5, okay whereas if we look at starting from your Euler's method then going to your Trapezoidal rule then going to second order Runge-Kutta method then going to 4th order Runge-Kutta method error keeps coming down from h, h square, h cube, h raised to the power 5.

But the number of calculations increased but the h step can be dramatically decreased, okay. So, that we can do the calculations, I mean we can do the solving numerical solving much faster, okay. So, there are many more methods which let us not spend too much time on these methods because as I said this is not a course on numerical method.

But this meant to give you a flavor of the numerical differentiation and numerical solving of differential equation and so on actually.

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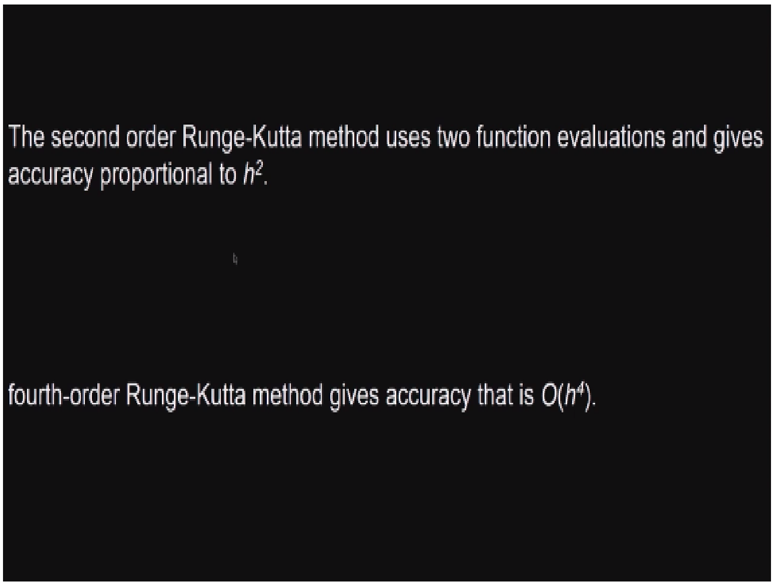

So, the second order Runge-Kutta method accuracy proportional h square 4th order Runge-Kutta method the accuracy that is proportional h power 5, 4, okay.

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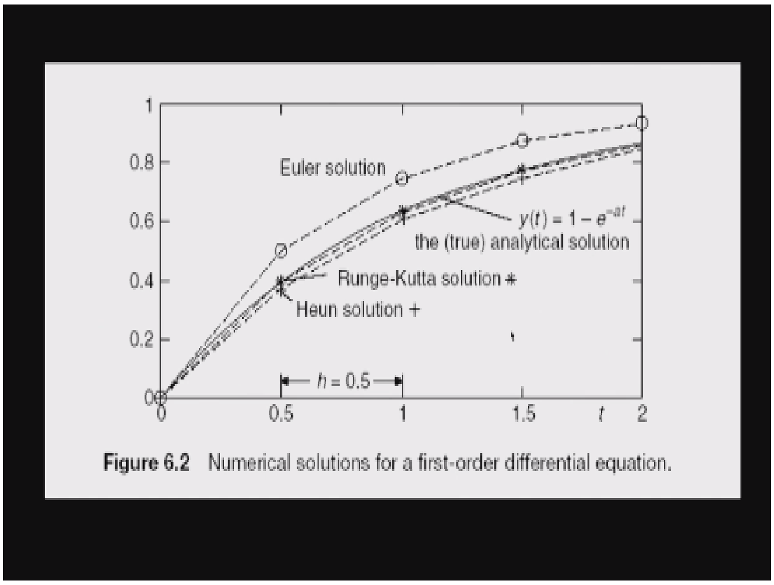

Figure 6.2 Numerical solutions for a first-order differential equation.

So, this is a nice comparative picture, okay this is nice. So, this is the true solution dark continuous line. Euler's method you can see here big one. This is Heun's method, the Runge-Kutta method which is following very closely this is the Heun's method and this is the Euler's method. We are using h=0.5, so for this particular equation 1-e power – at equation, okay.

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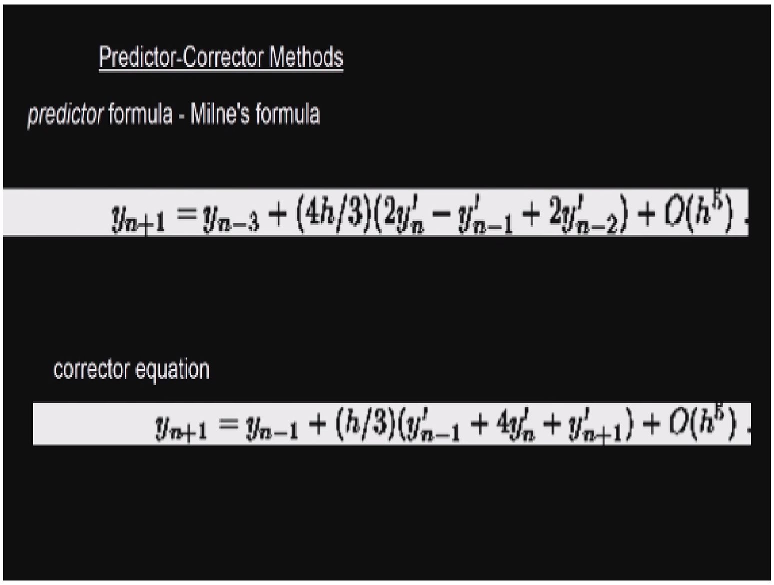

Then we have Predictor Corrector methods Milne's methods this is called Milne's method, so initially you predict for yn+1 and then you correct for yn+1, okay. So, we calculate at 3 different places n, n-1, n-2, okay and then we calculate yn+1 that is called the predictor n+1 and then again make use of that yn+1 and then again make use of that yn+1 to get corrected yn+1. This is called the Milne's method.

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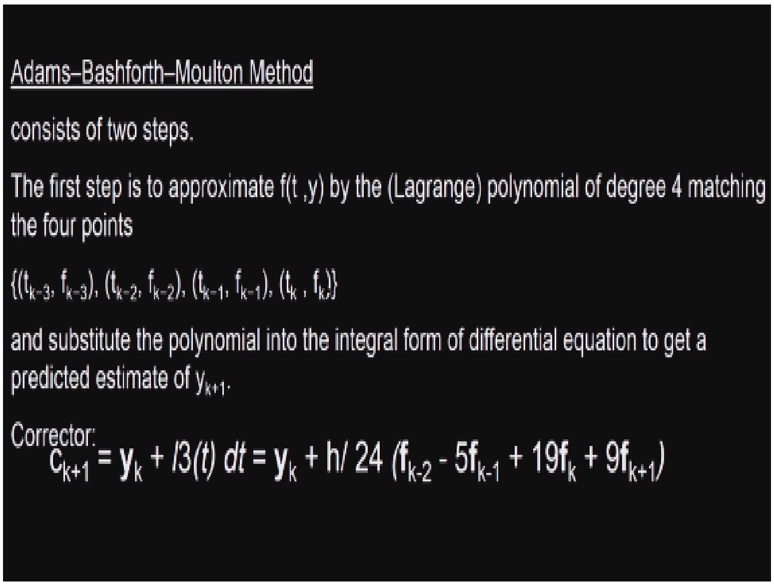

Then we have the Adams-Bashforth-Moulton method. So, there are so many different methods. We will not go as I said into this Adams-Bashforth-method. So, as you can see Runge-Kutta method, Adams-Bashforth, Heun's method these are methods used in math lab different types of method, okay.

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Table 6.2 Results of Applying Several Routines to solve a Simple Differential Equation

	ode_RK4()	ode_ABM()	ode_Ham()	ode23()	ode45()	ode113()
Relative error	0.0925×10^{-4}	0.0203×10^{-4}	0.0179×10^{-4}	0.4770×10^{-4}	0.0422×10^{-4}	0.1249×10^{-4}
Computing time	0.05 sec	0.03 sec	0.03 sec	0.07 sec	0.05 sec	0.05 sec

The computational time you can see 0.05 seconds, 0.03 seconds and so on relative error. You can see 0.09 Adams-Bashforth gives 0.02 raised 10 power -4, okay Heun's method 0.0179 okay. Then ode 23 at 45, 113 they all give these types of errors. So, you see depending upon the method you use we can get different levels of errors and we can get a different levels of computational time, okay changes dramatically.

As you can see 0.09 to 0.01, so almost 8 times less error when you use different types of methods, okay.

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Integration time step should be one order of magnitude smaller than the shortest motion

System	Types of motion present	Suggested time step (s)
Atoms	Translation	10^{-14}
Rigid molecules	Translation and rotation	5×10^{-15}
Flexible molecules, rigid bonds	Translation, rotation, torsion	2×10^{-15}
Flexible molecules, flexible bonds	Translation, rotation, torsion, vibration	10^{-15} or 5×10^{-16}

different types of motion present in various systems together with suggested time steps.

So, if you are looking at molecular dynamics you want to see how the atoms change as a function of time when you have certain forces acting on it. So, if you are looking at atoms when you want to see at the motion generally we are talking time step in the order of 10 per

-14 seconds. If you have rigid molecules you are looking at translation and rotation, then I should go 5*10 power-15 still smaller steps.

For looking at flexible molecules, rigid bonds, translation, rotation, torsion, so you need to have time steps 2*10 power-15. If you have flexible molecules, flexible bonds, so you want translation, rotation, torsion, vibration, so you go 10 power-15 you go almost to 10 power-16 times step very small time steps. So, the number of calculations, so if you are integrating for one second you need to do 10 power raised to power 16 calculations that is a huge set of calculations.

So, that is why there is lot of research that is being done to improve the integration that means so that we can increase the time step but at the same time keep our errors very small, okay. So, if you are looking at translation, rotation if this is your time step you are talking about, so the number of calculations are going to be a very large. Normally when we do a molecular dynamic study we do not go to seconds or milliseconds we stop much lower picoseconds.

Because total number of steps are going to be very large and especially if you are talking flexible molecules you are looking at translation, rotation, torsion, so number of calculations are going to be very large. So, with that we will stop up and we will continue more on these force wheel or molecular mechanics in the next class as well. Thank you very much for your time.