Cellular Biophysics
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Random walk statistics, Stoke-Einstein
Part: 02

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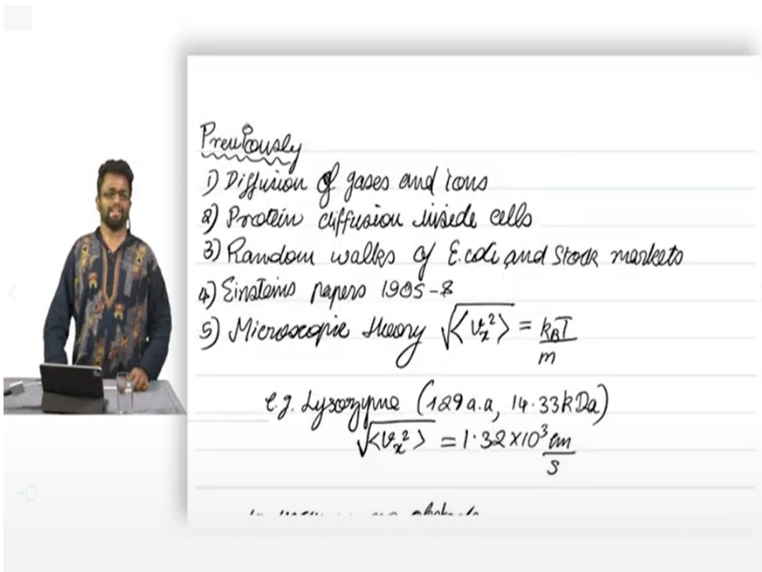

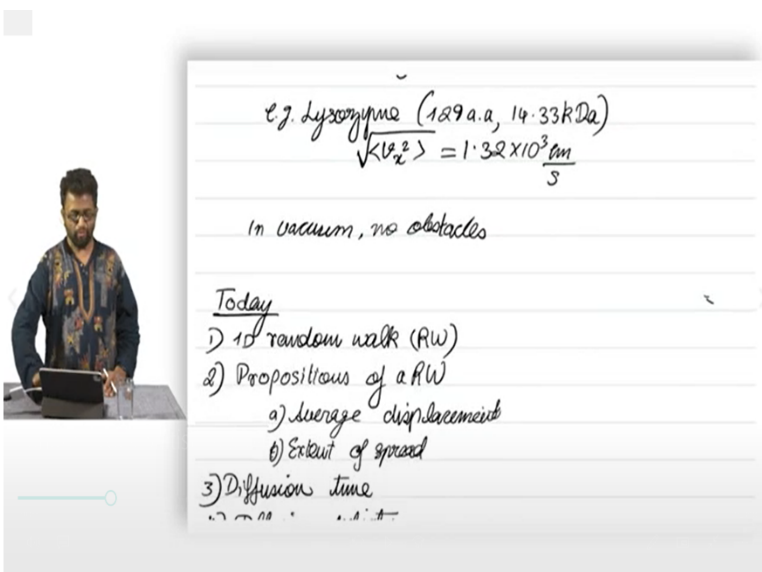

Hi, welcome back. Previously we had been talking about motivation for understanding diffusion from a biophysical perspective but applied to what is critical to all of human life and physiology namely diffusion of gases for respiration and ions for nerve transmission. We then went on to talk a little bit about how fast proteins diffuse inside cells and it is an under appreciated mechanism by which transport can occur. We then went on to speak very briefly about the fact that even cells themselves small cells like e coli can undergo random walks which is itself a hallmark of diffusion or kind of nature of diffusion.

And in fact you will find that the mathematics of diffusion statistics or what are called random walk statistics have wide applications. So in a way it is a standard model that if you understand once you might even be able to have some fun I do not know whether you will make a profit at the stock market. I talked very briefly about Einstein's papers 1905 to 1908 which formed the foundation of many of the physical theory or the mathematical reasoning that came out of that period of work of his and of a few other people including Smolokowski and I will elaborate on that a little later.

Finally, we ended with this idea that microscopic thermodynamic theory gives us a basis for diffusion in terms of the root mean square velocity which is under root V_x square those angled brackets simply indicate average is equal to $k_B T$ by m. Now I did not show you the solutions I am telling you the answer already that if you take lysozyme which has 1029 amino acids and 14.33 kilo Delton molecular weight molecular mass in Dalton units.

Then the v root mean square velocity in one dimension of such a lysozyme molecule is 1.32 into 10^3 centimeters per second. Now this is just a number and you can argue about it but just think about it like this it is moving roughly 1000 centimeters in 1 second that is about 10 meters per second. 10 meters per second is so fast that if you had wave of 10 meters per second coming at you would call it an explosion you understand that.

So since that is not happening I am standing here there is no explosion going on I know lysozyme molecules are not diffusing but all the other air molecules are diffusing. Even if they are smaller in fact it turns out that $k_B T$ by m indicates that smaller mass means higher velocity I mean so even faster motion is possible but we do not see that we do not see explosions around us in the air so what is going on. So this is the reason why the physicists who pioneered the study of diffusion came up with random walk theory.

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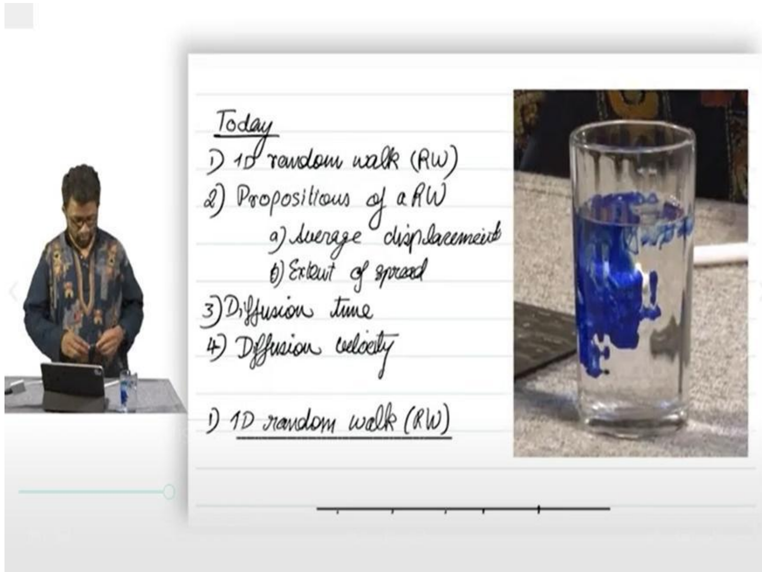

And this is what we are going to talk about today, because nothing happens in vacuum. All these assumptions of RMS velocity are based on vacuum assumptions and in the absence of any collisions we know that in a solution and in fact in any fluid like air yes air is a fluid one can show prove experimentally that molecules are undergoing collisions constant collisions and changing direction all the time. So even though the instantaneous very tiny tiny minuscule velocity is very high of tens of meters per second the net velocity the net movement is very minuscule and we will see from random walk statistics how to make sense of this.

So today I am going to talk to you about random walk in terms of 1d propositions of a random walk in terms of its average displacement and extent of speed and I will stop there and we will continue with diffusion and in terms of diffusion time or time it takes to diffuse and velocity of diffusion. So what is a one dimensional random walk now I am going to do a little poor man's experiment. This is an ink pen and you can see that I have a glass of water it is drinkable so this is drinking water and I am going to spoil my drinking water by putting a drop of ink in it.

Now all of you potentially know the answer to this question but I want to demonstrate it because it is something that is as I keep reminding you there are some experiments that are quite cheap to do and you can do them and test them. Because science is all about testing our curiosity we have I do not mean kill an ant and find out if it is dead that is obvious these are slightly more sophisticated thoughts. Simple experiments means experiments that are simple in implementation but sophisticated in concept.

So here I drop let us see if this ink comes out there it is so what you should see is a cloud of ink in the center of my glass and what you should see is I am not touching it I am not moving it but its moving by itself. What is this motion due to and that is the foundational question that diffusion theory attempts to answer. Because one of the things you also see along with the fact that it has gone to the bottom probably because ink is more viscous material than the water itself its water based ink though.

Eventually after we finish this module of the lecture we will look at it and ask the question what happened to the position of the ink is it all still in one place is it moved has it gone up a gradient down a gradient what happened. So in that spirit we will continue back with our theory and will return to this glass of spoiled water which I will not drink after this and see what happens.

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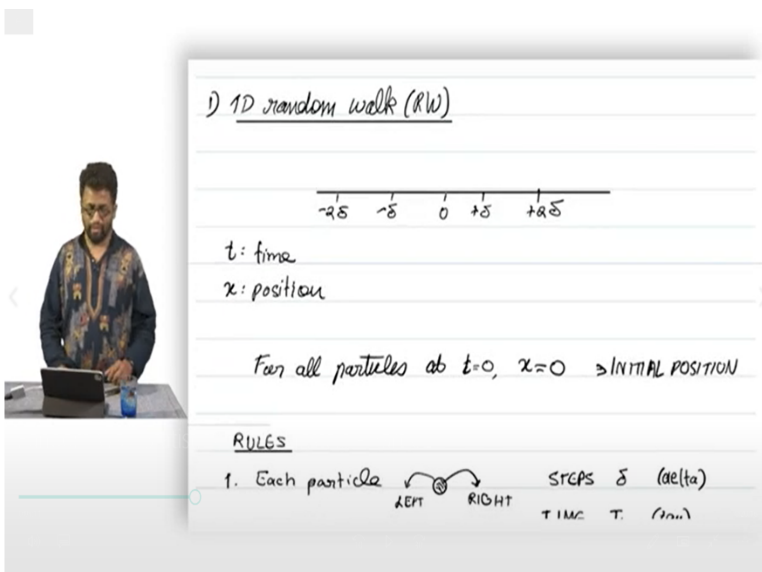

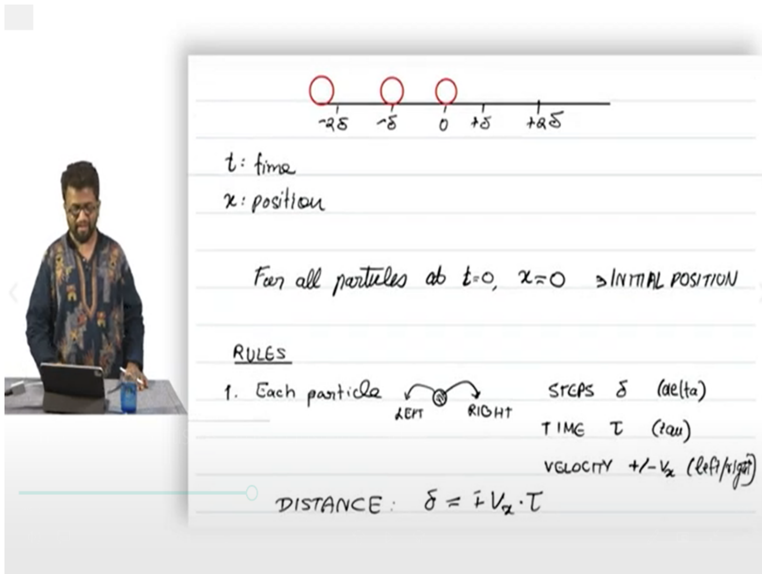

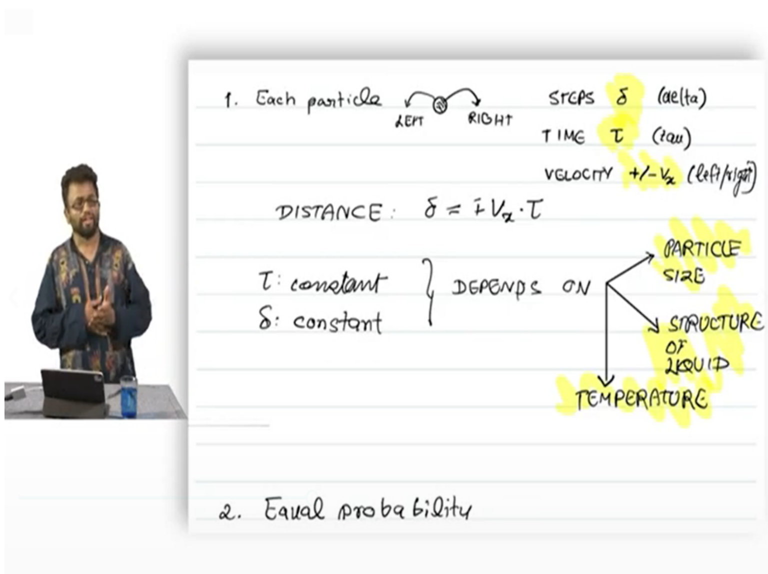

So what is a 1 dimensional random walk. So imagine we have a particle of a certain size positioned at 0 or an x axis. Now this particle can undergo motion by either going here or here we call this plus δ and minus δ. And in fact at the next step this particle may choose to go can I move this may choose to go right or left. So I do not want to change the size so it may go right or it may go left so return to its original position.

And this hopping from left to right and right to left is random this is partly why the nature of that term originates that it is a random walk. Because there is no guiding principle there is no other influence in such a conceptual pure random walk. And you should go back and look at physical chemistry textbooks Atkins is a standard reference in the field to ask the question why is there no direction why should there be why is up down left right forward backward they are all equal why why.

And you may find stumble across a principle which you may have come across earlier also in chemistry and physics which is the equi partition theorem and I will not dwell on that because that's not the focus of today's lecture but please go back and look.

So for our purposes we define time as t and position as x because remember this is one dimensional we are simplifying. Remember this is another fundamental principle in physics that we are applying to biology which is we may have a very complex cow we simplify it to a sphere we want to know the typical size of a cow. So we take its radius because these are simplifications does it mean that a cow is a sphere obviously not. But this is important because simplification allows us to think allows us to intuit. So simplification of our system in one dimension for all particles at t is equal to 0, x is equal to 0 is the initial position.

And we have rules of motion this rules are what constitute the random walk model this is a conceptual theoretical model and we will see in the later segments of this module where the rules actually show up in real life in terms of biology also. So each particle can go left or right in steps of δ that is the symbol here that you see δ. And the time that it does each of these steps is called is referred to as tau τ as you remember δ δ and τ symbols used to represent very small infinite extremely small steps in space and time.

So then the distance is even in fact is equal to δ is equal to plus or minus V_x times τ because we have now in added another term which is Vx which is the x velocity one dimensional velocity which then allows us to say that the distance is nothing but the product of time and velocity.

And so since we have defined that τ and δ are both constant we need to answer the question what decides these constants I mean is it universal for every particle, no. The idea is that τ and δ are both capable of depending on particle size, structure of the liquid meaning viscosity any obstacles whatever there is and temperature of the system. So in that sense our τ and δ are going to vary if we have a big particle or a small particle whether we have motion in water or in ethanol or in air and so on and so forth.

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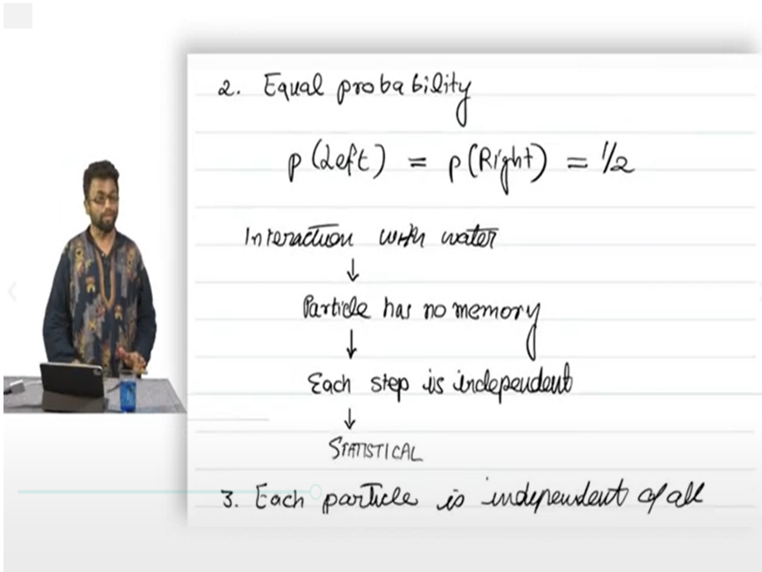

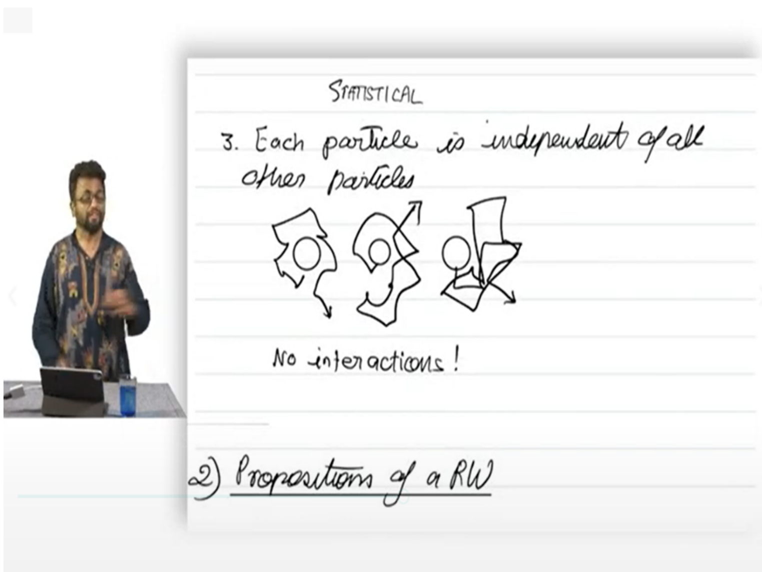

So the second part of the rules of the random walk are that the probability is equal that is to say p left is equal to p right is equal to 1 by 2 or 0.5. This is nothing but the familiar problem that you have all had to deal with in statistics class that is the problem of heads and tails. Every cricketer knows this every football coach knows this heads and tails this is tail the number 5 for the 5 rupee dollar coin and this is the head Ashoka lion and when I toss it if the coin is fair I will get either tail or I will get tail or I will get tail or this is a bias coin and then I get heads.

Now this is important because in the later segments we return to this question of heads versus tails and the nature of a so called fair coin and fair coin tossing even if it is fair you just saw this

I may be I will repeat this if I now start tossing just three tosses one I get a head I am not a magician do not worry head head my god I got three heads. How is that possible I am not a magician I am not playing tricks this coin is fair I bought I got it from the bank.

So what is going on and this is something interesting because statistically speaking in terms of actual theory of numbers these are called low number limits and we will talk about distributions fair coins probabilities and the nature of low number events or rare events in other words. And I think the word that you all remember probably is binomial, binomial distribution and we will talk a little bit about it later segments. But for now we will say that since the probability of left and right is equal each individual particle must follow that rule even though it is random.

Interaction with water results in the fact that particle has no memory and each step is independent and this is a statistical process this is what I have been trying to say. And if you remember in your high school and college and university statistics the definition of statistical means large numbers correct large numbers. Statistics I mean I cannot say I go to a classroom and I do a statistics of heights of boys and girls with three boys and two girls and say the boys are taller than girls I mean it makes no mean it has no meaning stat the word statistics has no meaning it is just anecdotes otherwise.

Now there is a detailed statistics of such experiments where numbers are themselves limiting and this is a typical problem in cell biology and biology in general and we will discuss it because of that reason. Because in a way these are real world problems or you may say applied statistics problems but the word statistics implies large numbers. So each particle is independent of all other particles the third law so the first two laws are each particle has an a the ability to step left or right by a step δ and time t with a velocity Vx leading to δ is equal to plus minus Vx into τ.

The second rule is that there is an equal probability of left and right and the third rule is that each particle is independent of all other particles. Meaning to say when a particle is moving here it does not influence the motion of a particle nearby or even further away. There is no action at a distance there is no memory there is no interaction between the particles. And these are important so please bear this in mind we will return to these and use them for our derivation.

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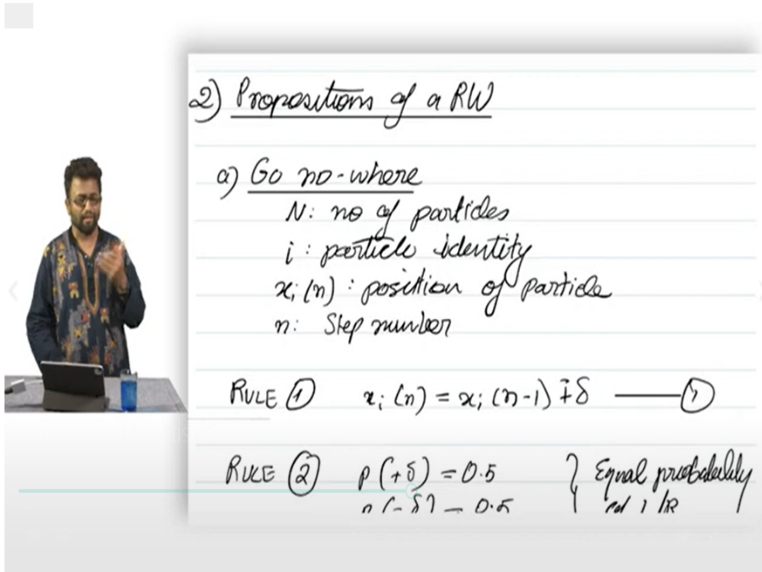

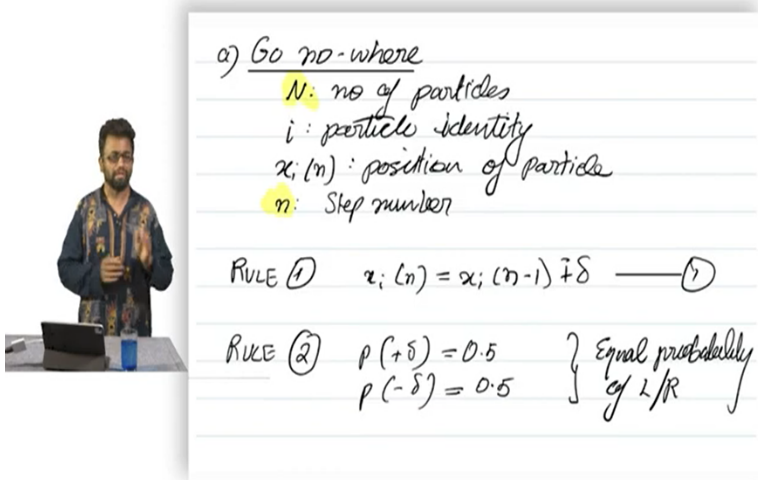

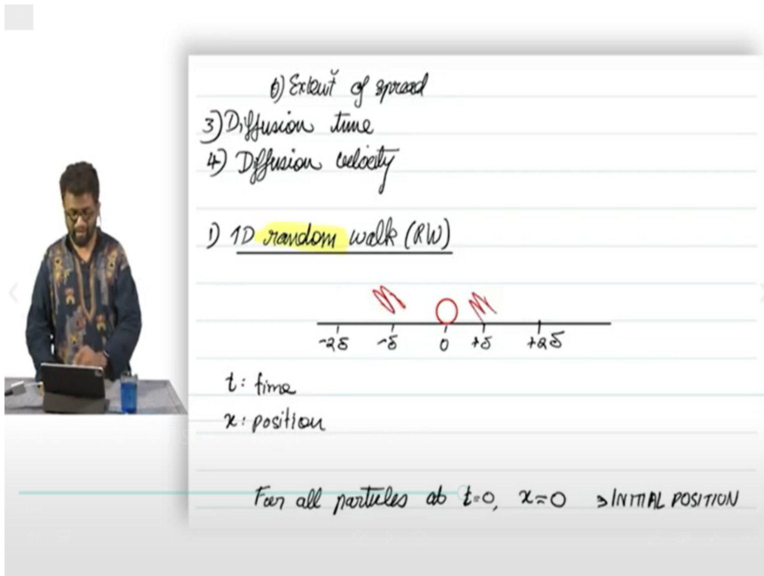

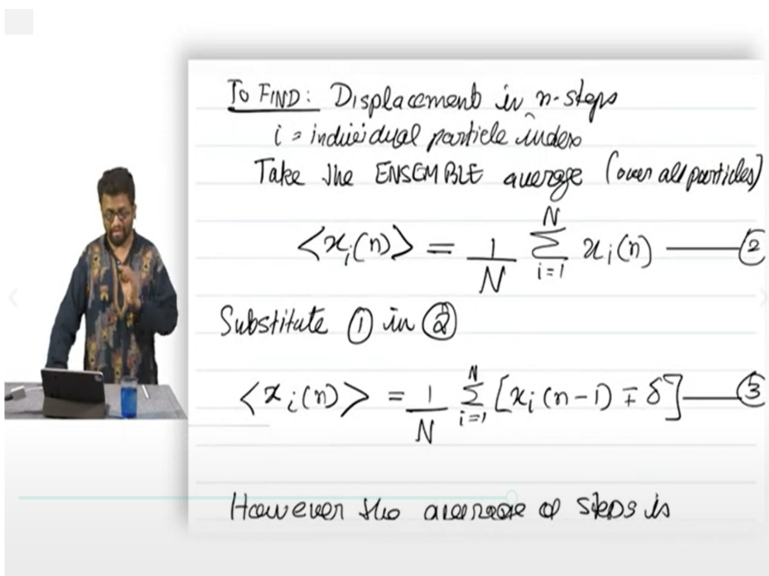

So the next thing that we want to do is make propositions meaning to say what does the random walk imply. Where what things do we learn from the mathematics of random walk statistics or the model of random walk.

So remember in physics model has a very precise meaning you have to write down an equation you have to write down mathematical laws that define it. And this is what makes biophysics so powerful because we employ the laws that we have learnt in physics over 200 years 300 years and apply them to biology in a way that we had not thought of before and test them with experiment. This is why we become quantitative biology and not just by physics or structural biology or something like that.

So the first proposition is a very funny proposition it says go nowhere what does this mean this is almost like some philosophy I mean I do not go anywhere who am I where am I what is going on. But no let us define it precisely n is the number of particles, i is the particle identity x_i of n is the position of the particle and n is the small n is the step number this you can see here capital N is the number of particles this is the difference please note this.

Rule one so now we come to rules rule one of the random walk says that x_i of n that is to say the ith particle let us say there are five particles in the first particle in the nth step number meaning its first step second step third step fourth step etcetera, will move in a way that is the sum of $x_i(n-1)$ meaning its previous position in x plus or minus δ.

This is nothing but what we said earlier that the particle jumps from one position to the next and it is moving either left or right depending on the exact random choice made at that instant and that is what that plus and minus sign indicates and δ indicates the fact that it is of a finite step size.

A rule 2 says that the probability of plus δ is equal to 0.5 and the probability of minus δ is equal to 0.5 in other words there are equal probabilities of left and right and we will use terms in a few minutes. So the first task in this proposition we said go nowhere go nowhere random walk goes nowhere those of you who are fond of reading look up a classic textbook by on Mr Tompkins I will keep the list of reading extra reading at the end you are welcome to read it and go back.

This is about a story told by George Gamou who is the author of the book about a drunkard who comes out of a bar. The question he asks is that when the drunkard walks out of a bar he or she yes we are modern India so everything is possible can step out and then he or she wants to find the way home I mean. And because they are in a state of inebriation in a state of unable to decide where is home and where is the bar they try to walk they try walk left walk right they do not remember what happened they stumble. And this I mean jokes apart this is exactly what a random walker does because at the end of the day there is a very good chance that the drunkard and the particle do not go anywhere.

And so in order to know mathematically to come back to the science what is the displacement in n steps we need to consider I individual particles and take the ensemble average over all particles. Because of course we say one drunkard okay maybe this drunkard was really stupid so he or she did not get home but the third drunkard maybe gets home. So we want to find out how many drunkards can how many drunkards does it take to reach home.

So average of x_i (n) the averaging sign is that these angular brackets here this is telling us that it is average overall particles whose indices go from 1 to capital N i from i is equal to 1 to capital N and the small n indicates the number of steps they take the nth step.

So that can be written as an equality of 1 by n which is the average so 1 by N capital N is equal to the summation this Σ sign is just summation over all particles of the ith particle in the nth position and summed and averaged over all particles we said that. So the sum of positions in time averaged overall particles should tell you how far the particles get. If we substitute one which was this equation that is x_i (n) is equal to x_i (n-1) plus or minus δ meaning to say what is the x_i value it is the previous type position plus or minus δ we decided that was rule 1 in fact.

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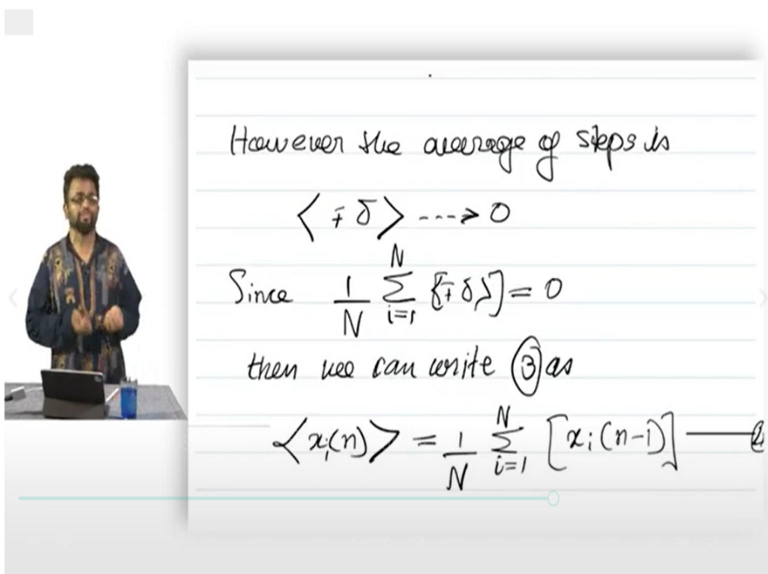

N

then we can write (3) as

$$\langle x_i(n)\rangle = \frac{1}{N}\sum_{i=1}^{N}\left[x_i(n-1)\right] \text{ —— }$$

$$= \langle x_i(n-1)\rangle$$

$\therefore$ Avg position at n^{th} step = Position at $(n-1)^{th}$ step

Position unchanged on AVERAGE!

$$= \langle x_i(n-1)\rangle$$

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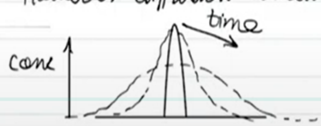
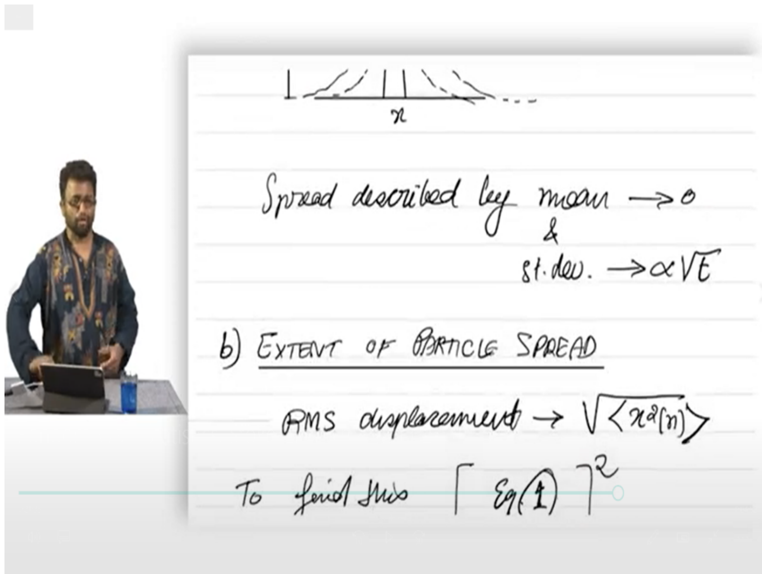
Position unchanged on AVERAGE!

However diffusion results in spread!





So we substitute that and put it in here but the average of n steps that is to say plus or minus δ. If I toss my coin and I ask if I say heads is 1 and tails is minus 1 and I do this 100 times the average is expected to be 0. Because plus 1 minus 1 plus 1 minus 1 minus 1 plus 1 0. Since 1 by n is equal to into 1 by n or the average over all particles of the summation of δ averaged is equal to 1. So we can rewrite this equation just simply as x_i (n) is equal to one by n this what you notice is that I dropped out this term correct.

Now this leaves me with the idea that x_i (n) is equal to x_i (n-1). what does this mean mathematically you can see it but what does this mean, this means nothing but where it was it stayed there. The average position of nth step is the position at n minus 1 step that is what we mean.

The position is unchanged on an average but as you see with this glass here now. Remember we started with a drop of large drop of ink in the center what do you see now. The thing is completely blue that is amazing who did it what drove it what is the cause of this motion I mean something has to move there has to be some driving force to it. This is nothing but the magical effect or the physical effect of diffusion. I say magical not because it is magic but because there is some simple physics in it and this simple physics if you understand it you will also understand a lot of biology from it and biological transport.

So the reason why it is spread here was and you will all have learned this that if you have an initial position where all the particles were concentrated and you let it you wait for a while then it will spread it. And that is what happened it spread it distributed itself uniformly in the glass of water the colorless what to our eyes all wavelengths of light are transmitted by this so it was colorless.

Now suddenly it is reflecting blue we can see blue in it and that is because the ink molecules have nicely uniformly distributed it has spread in other words. But I just said to you in my derivation that the particle on an average does not go anywhere so what is going on. We need to make reconcile these two things the physical reality that we can observe and the mathematical rules that we have just written down.

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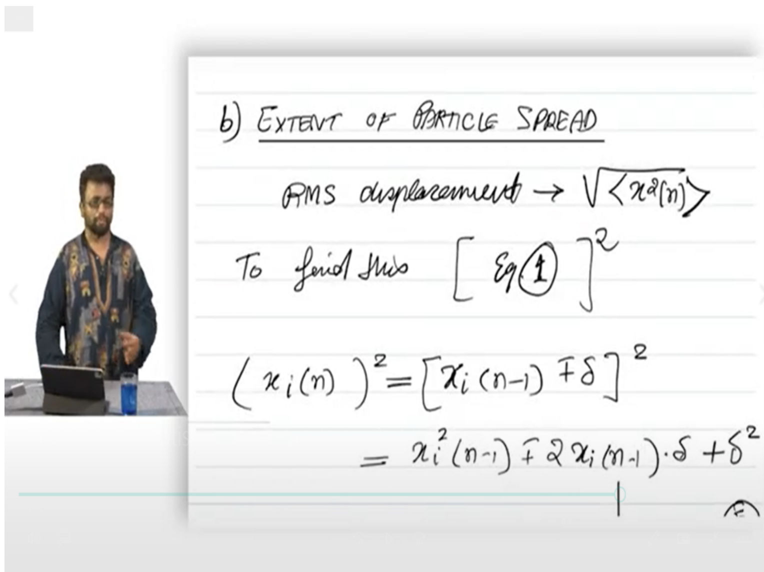

$$= x_i^2(n-1) \mp 2\,x_i(n-1)\cdot\delta + \delta^2 \qquad (5)$$

RMS displacement requires mean average ensemble,
which we take from equation (2)

$$\langle x_i^2(n)\rangle = \frac{1}{N}\sum_{i=1}^{N} x_i^2(n) \qquad (6)$$

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Subs. (5) in (6)

$$\langle x_i^2(n)\rangle = \frac{1}{N}\sum_{i=1}^{N}\left[x_i^2(n-1) \mp 2\delta\cdot x_i(n-1) + \delta^2\right]$$

$$\langle 2\cdot\delta\cdot x_i(n-1)\rangle \ldots \longrightarrow 0$$

$$\langle x_i^2(n)\rangle = \frac{1}{N}\sum_{i=1}^{N}\left[x_i^2(n-1) \mp 2\delta\cdot x_i(n-1) + \delta^2\right]$$

$\langle \mp\delta\rangle = 0$

$$\langle 2\cdot\delta\cdot x_i(n-1)\rangle \ldots \longrightarrow 0$$

$\because$ +/- sign

e.g.

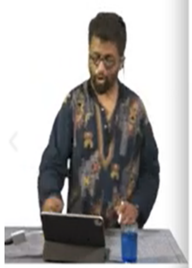
$-1 \times +1 = -1$

$+1 \times -1 = -1$

$-1 \times -1 = +1$

$+1 \times +1 = +1$

SUM 0



$$\langle 2\cdot\delta\cdot x_i(n-1)\rangle \ldots \longrightarrow 0$$

$\because$ +/- sign

e.g.

$-1 \times +1 = -1$

$+1 \times -1 = -1$

$1 \times 0 = 0$

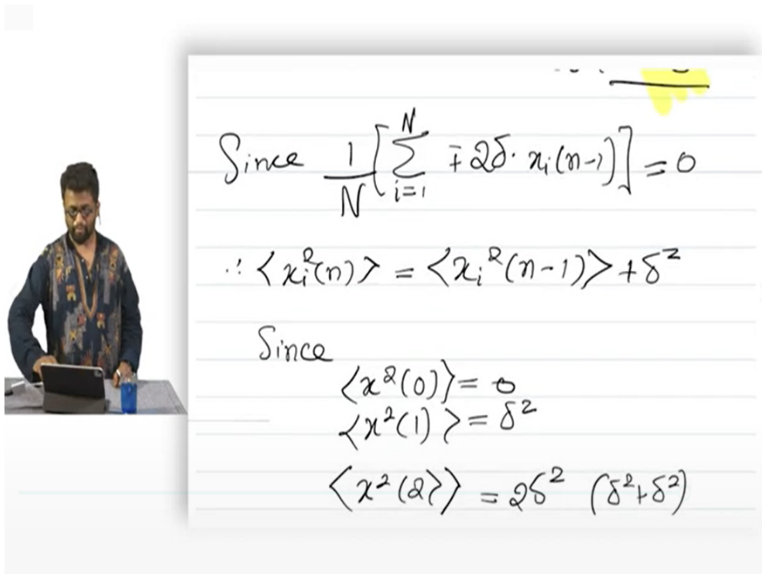
$0 \times 1 = 0$

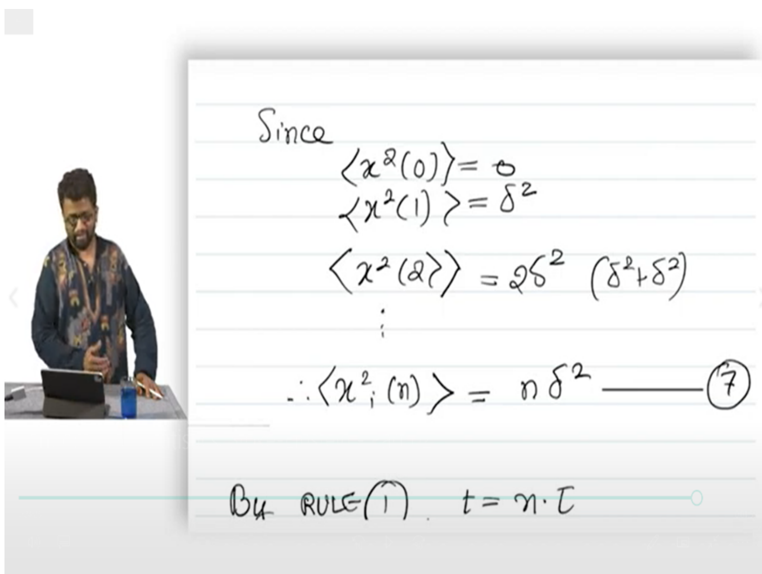
$-1 \times -1 = +1$

$+1 \times +1 = +1$

SUM 0

$$\text{Since } \frac{1}{N}\left[\sum_{i=1}^{N} \mp 2\delta\cdot x_i(n-1)\right] = 0$$





So for that we will talk about the second proposition which is the extent of particle spread we return to the slides again. So in that sense the we have to calculate something called the root mean square displacement or RMSD of the particle. And for that we write down root mean squared you see the signs. So the under root sign is for root mean is the pointy brackets and squared term of the displacement. So we want to find effectively equation one squared we want to take this equation and square both sides so we will do that.

Let us do that so when we square it we get this slightly larger term x_i (n-1) plus minus δ whole squared which we say is x_i (n-1) you open it out just in your high school method plus minus 2 x_i (n-1) δ n plus δ^2. RMS displacement requires mean average of ensemble which we take from equation 2 which was this if you remember $<x_i^2 (n)>$ is equal to 1 upon N summation over i where i is equal to 1 to n x_i^2 (n). Substituting 5 in 6 that is to say this opened out equation into 6 which is here.

So basically we are taking the right hand side and putting it inside the summation sign we get this term here and but we can show that so we had already shown that δ average is equal to 0. Now we say 2 δ x_i (n-1) tends to 0 why do I say this again the same thing we are multiplying x and n minus 1 could be 0 and or plus 1 and δ could be minus 1. It could be the other way around it could be so I have not added the zeros here which I assume to be obvious so you can lets add them here 0 into 1 1 into 0 also 0 also 0.

All of these therefore sum to 0 you want to take an average you have to sum and divide by the total number the answer still remains 0. So as a result we can ignore that and we say that this sum 1 by n into summation i 2 sigma of 2 plus minus δ into x_i (n-1) is equal to 0. Therefore x i n minus x i square n is equal to x i square n minus 1 plus δ square x i x x square of the 0th position 0th step is 0 because there is no motion yet. The first step is δ square the second step is 2 δ square third step is 3 δ square in other words it is x i square n is equal to n δ square.

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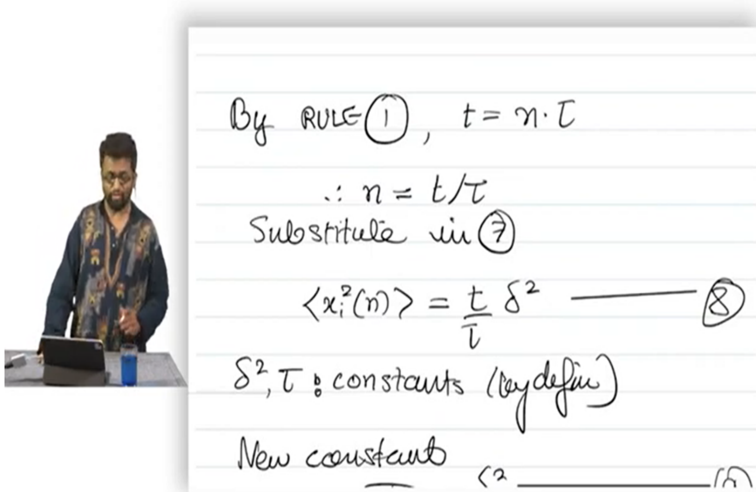
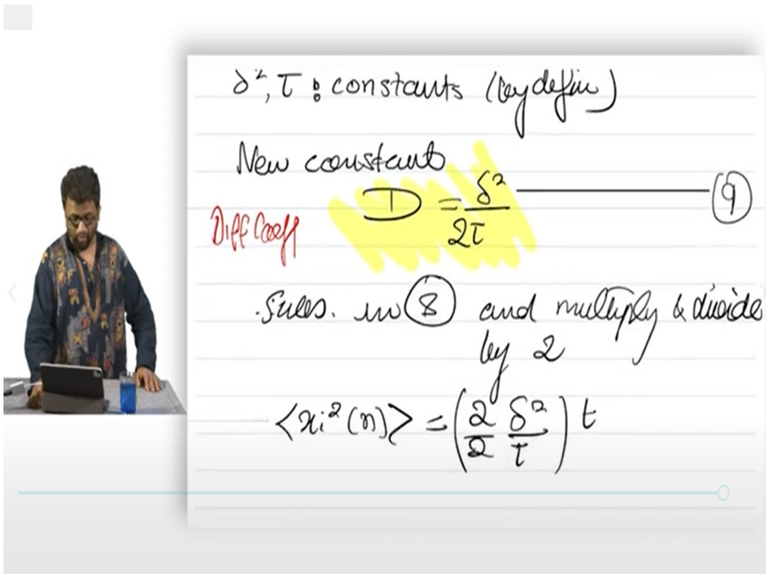
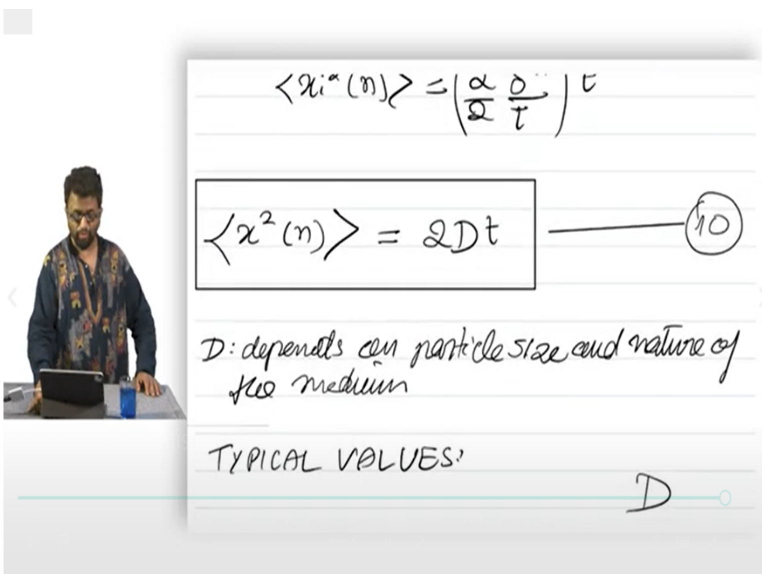
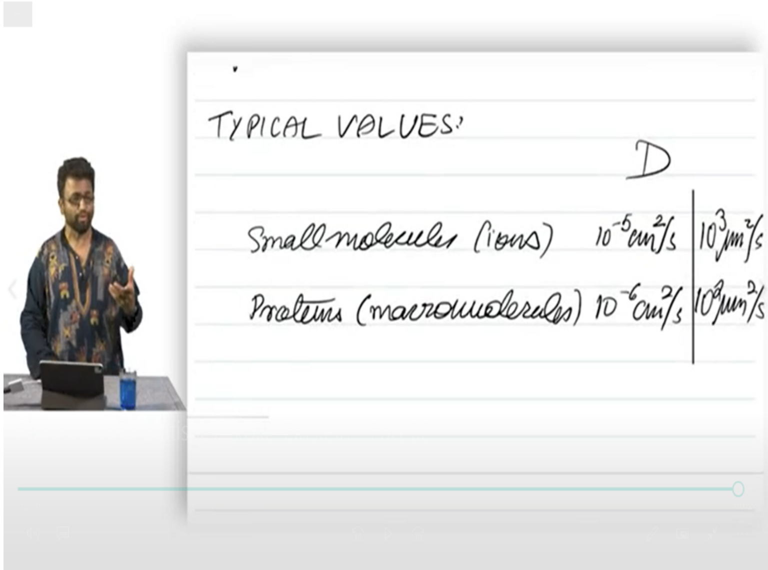



δ^2, τ : constants (by defin)
New constant
Diff Coeff
$D = \frac{\delta^2}{2\tau}$ (9)
Subs. in (8) and multiply & divide by 2
$\langle x_i^2(n) \rangle = \left(\frac{2}{2} \frac{\delta^2}{\tau} \right) t$


$\langle x_i^2(n) \rangle = \left(\frac{2}{2} \frac{\delta^2}{\tau} \right) t$
$\boxed{\langle x^2(n) \rangle = 2Dt}$ (10)
D: depends on particle size and nature of the medium
TYPICAL VALUES:
D



By the rule that we have n t of t is equal to n times tau meaning to say total time is equal to the number of steps into the time interval between each step τ. Then therefore we can say that t is equal to n is equal to t times tau. But since x_i^2 (n) averaged is equal to t by τ into δ square with δ^2 and τ as constants by definition the new constant becomes D is equal to capital D is equal to δ square by 2 tau.

Substituting in 8 so by the way this I have defined as a new term this is a new term this is nothing but something that we have heard of earlier which is called the diffusion coefficient. And substituting this into 8 will give us δ^2 by τ but where is the 2. So we multiply and divide by 2 and we then substitute and we get x square is equal to x square n averaged is equal to 2 Dt. D depends on particle size and the nature of the medium.

Now this is an important equation because this tells us that while on an average nothing happens motion does not go anywhere. The root the mean squared displacement indeed has a nature of spread which depends on time so depends on how long you observe for like we saw with the glass it took some time to move.

And the diffusion coefficient which itself depends on particle size and the nature of the medium typical values of diffusion coefficient for biologically interesting molecules. For small molecules 10^{-5} centimeters per second and protein macromolecules 10^{-6} centimeter square per second I have also converted these into micron square per second for you 10 to the 100 micron square per second respectively for small molecules and proteins. So I will stop here and we will continue with the next segment.