Cellular Biophysics
Professor – Dr. Chaitanya Athale
Department of Biology
Indian Institute of Science Education and Research, Pune
Brownian Ratchets and Molecular Motors

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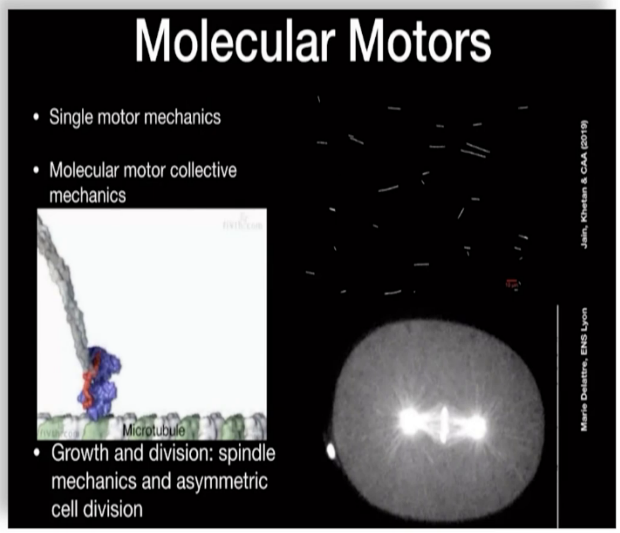
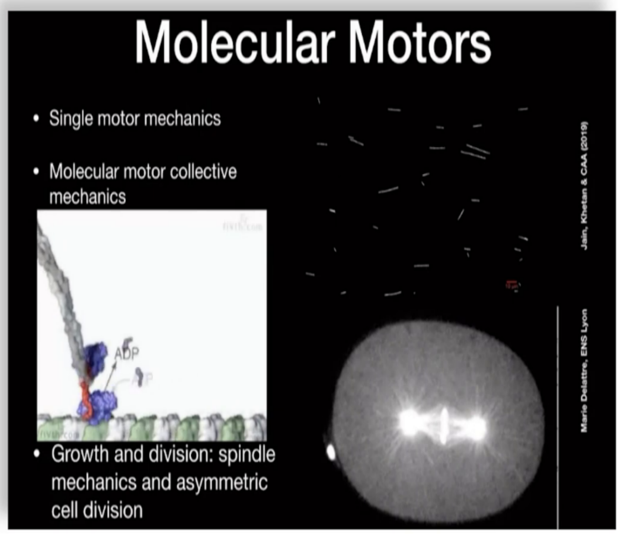
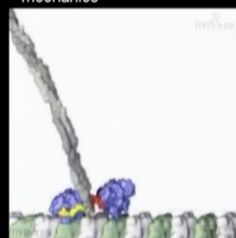


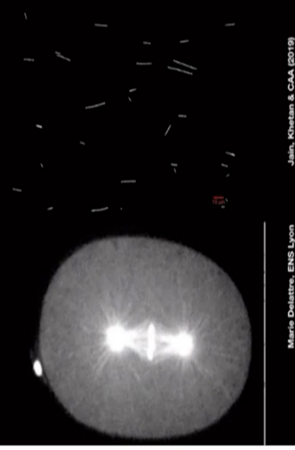


Molecular Motors

- Single motor mechanics
- Molecular motor collective mechanics



- Growth and division: spindle mechanics and asymmetric cell division



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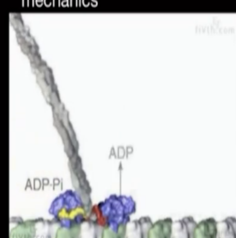

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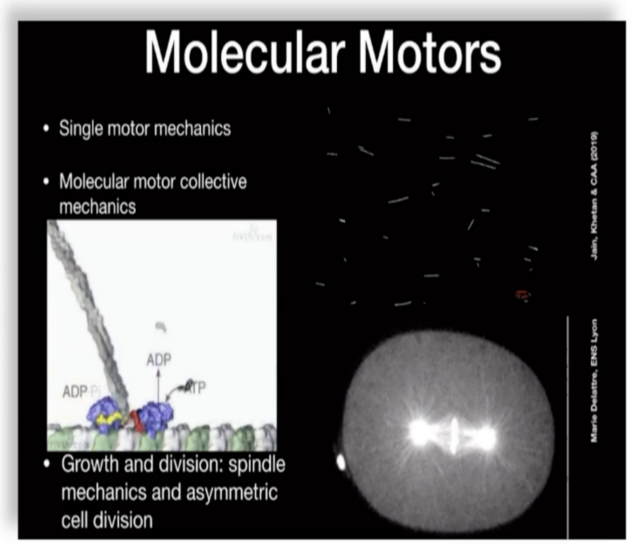

So, what you are looking at here is a cartoon from Whale and Milligan's paper and science which is a new paper of exactly this kind of ATP, ADP cycling which is a summary, in some senses, of decades of work that they have done. This demonstrates those sort of hand-over-hand movement based on a hybrid of structures, some imagination, some stochasticity and a lot of artistry. This is not exactly how a motor moves, but this is definitely a conceptual picture that helps us think about it.

This is of course a single motor and this is supposed to be Kinesin. So, the initial stages, it is sort of just landing. There it lands, one head lands, binds to an ATP exchanging out the ADP. The other one lands, exchanging out the ADP once more, but at the same time the previous one has digested or hydrolyzed its ATP to ADP leading to a conformational change in a forward movement. So, all this is nice, but when you do this in experiment, this is how we would actually evaluate it.

Much less exciting perhaps, in the sense that what you are looking at in the upper panel is a movie from one of our older papers where we looked at single microtubule filaments that were gliding on a surface that was coated with molecular motors that were pointing upwards. This is otherwise called a gliding assay. And in fact, the context of these is in fact clear in the most obvious cases in spindle assembly where you are looking in a single one celled stage of the primary division of C elegans. when it divides from one to two cells, forming in fact, a smaller cell in one end.

Now, the reason why I bring this up is of course, these are the so called cellular and multimolecular applications of these concepts, but in order to make sense of it, in a biophysics course, we really wanted to go back and look at the models. And one of the most clear models for this has been the so-called thermal ratchet model, and that is the discussion for today.

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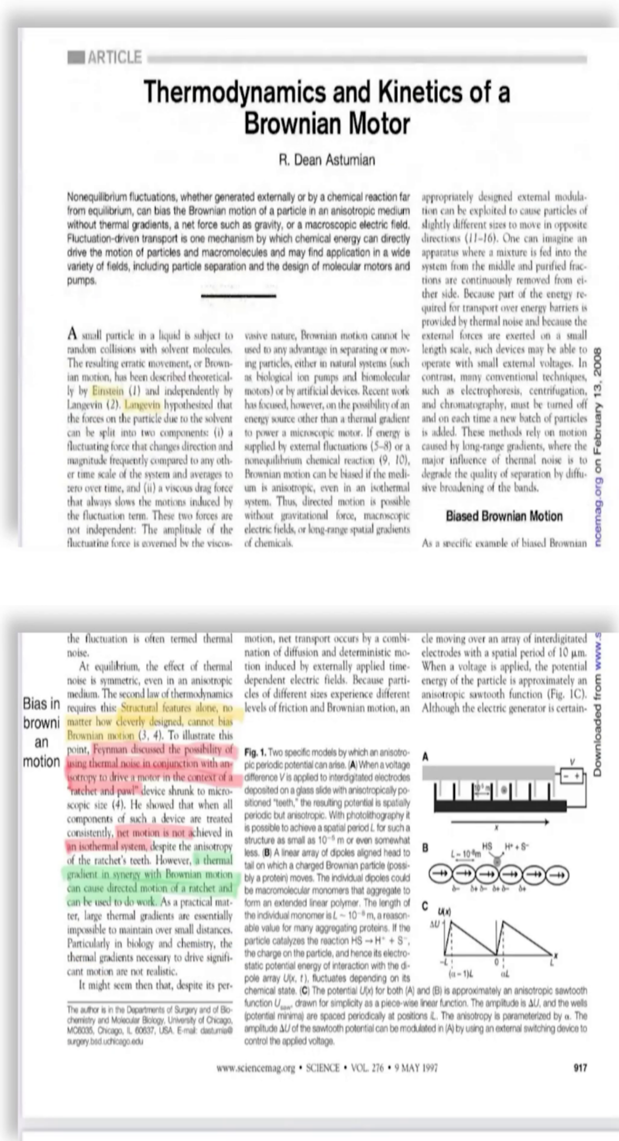

ARTICLE

Thermodynamics and Kinetics of a Brownian Motor

R. Dean Astumian

Nonequilibrium fluctuations, whether generated externally or by a chemical reaction far from equilibrium, can bias the Brownian motion of a particle in an anisotropic medium without thermal gradients, a net force such as gravity, or a macroscopic electric field. Fluctuation-driven transport is one mechanism by which chemical energy can directly drive the motion of particles and macromolecules and may find application in a wide variety of fields, including particle separation and the design of molecular motors and pumps.

A small particle in a liquid is subject to random collisions with solvent molecules. The resulting erratic movement, or Brownian motion, has been described theoretically by Einstein (1) and independently by Langevin (2). Langevin hypothesized that the forces on the particle due to the solvent can be split into two components: (i) a fluctuating force that changes direction and magnitude frequently compared to any other time scale of the system and averages to zero over time, and (ii) a viscous drag force that always slows the motions induced by the fluctuation term. These two forces are not independent: The amplitude of the fluctuating force is governed by the viscos-

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appropriately designed external modulation can be exploited to cause particles of slightly different sizes to move in opposite directions (11–16). One can imagine an apparatus where a mixture is fed into the system from the middle and purified fractions are continuously removed from either side. Because part of the energy required for transport over energy barriers is provided by thermal noise and because the external forces are exerted on a small length scale, such devices may be able to operate with small external voltages. In contrast, many conventional techniques, such as electrophoresis, centrifugation, and chromatography, must be turned off and on each time a new batch of particles is added. These methods rely on motion caused by long-range gradients, where the major influence of thermal noise is to degrade the quality of separation by diffusive broadening of the bands.

Biased Brownian Motion

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Bias in browni an motion

At equilibrium, the effect of thermal noise is symmetric, even in an anisotropic medium. The second law of thermodynamics requires this: Structural features alone, no matter how cleverly designed, cannot bias Brownian motion (3, 4). To illustrate this point, Feynman discussed the possibility of using thermal noise in conjunction with anisotropy to drive a motor in the context of a "ratchet and pawl" device shrunk to microscopic size (4). He showed that when all components of such a device are treated consistently, net motion is not achieved in an isothermal system, despite the anisotropy of the ratchet's teeth. However, a thermal gradient in synergy with Brownian motion can cause directed motion of a ratchet and can be used to do work. As a practical matter, large thermal gradients are essentially impossible to maintain over small distances. Particularly in biology and chemistry, the thermal gradients necessary to drive significant motion are not realistic.

It might seem then that, despite its per-

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motion, net transport occurs by a combination of diffusion and deterministic motion induced by externally applied time-dependent electric fields. Because particles of different sizes experience different levels of friction and Brownian motion, an

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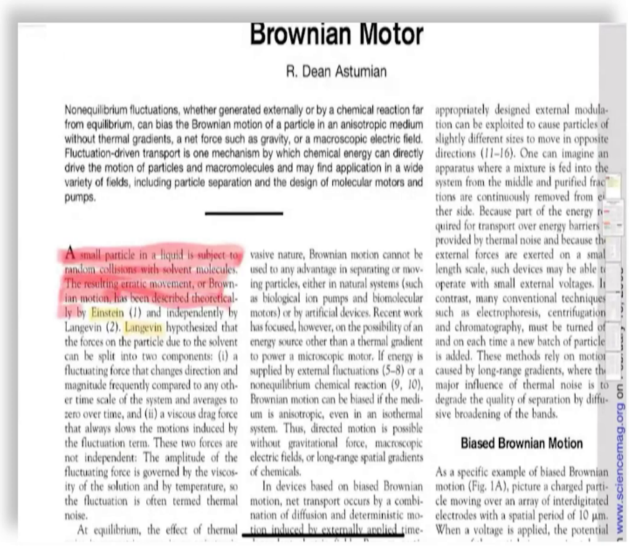
Fig. 1. Two specific models by which an anisotropic periodic potential can arise. (**A**) When a voltage difference V is applied to interdigitated electrodes deposited on a glass slide with anisotropically positioned "teeth," the resulting potential is spatially periodic but anisotropic. With photolithography it is possible to achieve a spatial period L for such a structure as small as 10^{-5} m or even somewhat less. (**B**) A linear array of dipoles aligned head to tail on which a charged Brownian particle (possibly a protein) moves. The individual dipoles could be macromolecular monomers that aggregate to form an extended linear polymer. The length of the individual monomer is $L \sim 10^{-8}$ m, a reasonable value for many aggregating proteins. If the particle catalyzes the reaction $HS \rightarrow H^+ + S^-$, the charge on the particle, and hence its electrostatic potential energy of interaction with the dipole array $U(x, t)$, fluctuates depending on its chemical state. (**C**) The potential $U(x)$ for both (A) and (B) is approximately an anisotropic sawtooth function U_{saw}, drawn for simplicity as a piece-wise linear function. The amplitude is ΔU, and the wells (potential minima) are spaced periodically at positions iL. The anisotropy is parameterized by α. The amplitude ΔU of the sawtooth potential can be modulated in (A) by using an external switching device to control the applied voltage.



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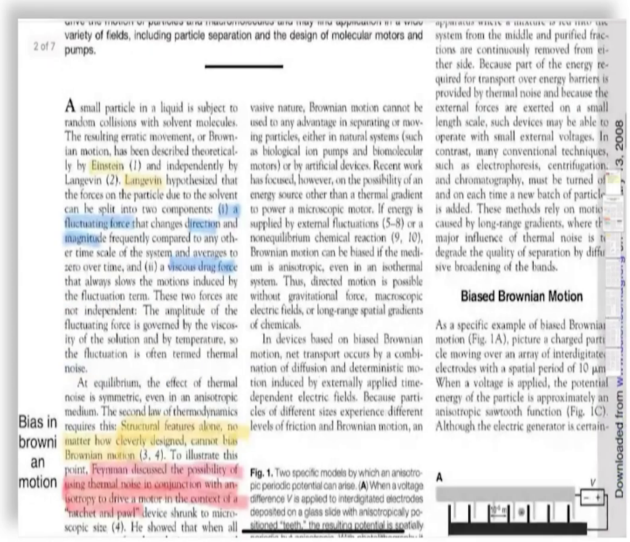

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Professor: I am only going to probably discuss the first two figures because of how much time we have left. I hope at least some of you have had a chance to go through the paper. Those of you have not, after this please, do go through it because posting some questions for you tomorrow, after the lecture tomorrow.

So, paper itself is a funny paper, it is an article but as you might have realized, this article is a review of a lot of different things. Now, according to the basic background, it is obvious that Brownian motion, so this is titled Thermodynamics and Kinetics of Brownian Motor, and it is from 1997.

As the title might suggest, it is effectively putting two things together, Brownian and Motor. We talked about motors, we know they are energy dependent. Since 1997, actually things have progressed quite a lot. Having said that, the theory is in fact still a little murky, and that is partly why we want to go back to the most basic theory and one of the older papers that discussed something called a Brownian motor and its kinetics.

So, in fact as you probably should remember, the idea of a Brownian motor is in a way contrary to the idea of Brownian motion itself, and this is what is illustrated here with the idea that highlighted that a small particle in a liquid is subjected to random collisions with solving molecules resulting in attic motion of Brownian motion has been described periodically.

And we have spent the whole first quarter of this course discussing Brownian motion. So I really do not want to elaborate on it. Suffice to say that Langevin, who also came up with the same theory at about the same time, divided the forces acting on a molecule into a fluctuating force, both in terms of its direction and magnitude and a viscous drag force being the two primary motor forces acting on molecules.

So, if that be the case, then it is reasonable to ask how can we convert this into directed motion which is what a motor seems to involve. And to answer that, we discuss some things about biases in Brownian motion. Now, kind of like a biased coin, your biased dice, something else to change. Otherwise, you are equal, probabilities are clear. You will get non-directional transport.

Has any one of you read Feynman's electricity, or maybe you have to refer to it in your introductory course, world of physics, sorry. Did any of you do that?

Student: Parts of it, but it is very huge, sir.

Professor: Yeah, I know. Did any of you come across the so-called Brownian ratchet of flashing put in, something, something about ratchets? No?

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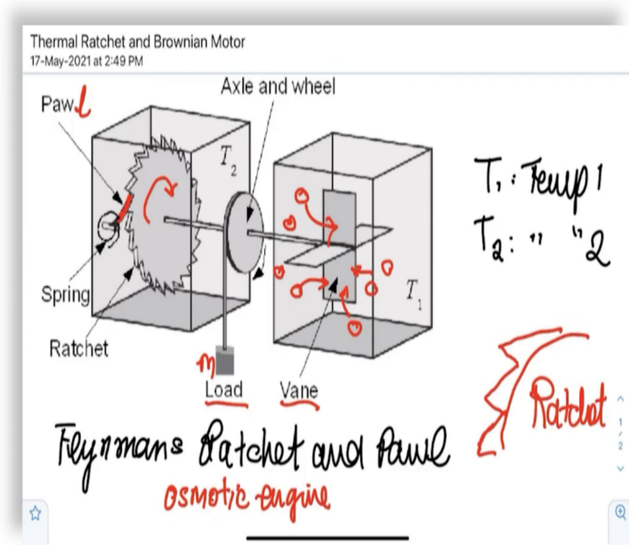

Student: Yeah, I have…

Professor: You remember this picture?

Student: Yes, yes. The ratchet and the pawl.

Professor: You remember this picture? Okay! Very good. Those of you who do not remember, just let me remind you, actually, this should read not paw but pawl. This is a Pawl, P-A-U-L, no, P-A-W-L, not Paul the boy but Pawl the device, and a toothed wheel. which I hope you recognize by looking at this toothed wheel, that its teeth, if you look in profile, if I were to draw this, my drawing is really bad that is why I take other people's drawings instead, is not uniform like you would expect a normal toothed wheel to be, a gear wheel for instance.

Instead, the profile of the wheel is such that the teeth are longer in one direction and shorter in the other, tempering off sooner. This is what is then called a Ratchet. Those of you who play badminton, sometimes called a Puna game, you may have recognized this when in the old-fashioned badminton courts when you want to tighten your net. Either way, what it does is it allows direction, movement in one direction and this is what the pawl does, the job of the pawl is exactly that, but not in the other.

That is to say you can turn it in this way but in the opposing direction there is an enormous penalty due to the presence of this latch or pawl, which itself is spring loaded. So, you can keep turning it ahead but you cannot turn it backwards, got it? One directional movement, that is one thing. And the second part is that if you want to measure any kind of work being done in an energetic or thermodynamic sense, if you remember last year, we talked quite a bit about this thought experiment of the osmotic engine.

And we said that the osmotic engine can only do work if it actually lifts, a load or mass over some height, h or whatever it is, against gravity, then only can we consider that to be doing work. So, in that sense the thought experiment of Feynman was the following, if you just have a ratchet and pawl, will it spontaneously, using the thermal bumping around of molecules in the air that hit a vane, this is a vane or you can say a windmill or a propeller or whatever you want to call it, vane is the technical term for this at least in the Feynman diagram, diagram by Feynman, I am sorry.

In such a case, you could of course get a work done for free. I mean in other words you have done nothing, there is random movement and that random movement is converted into the external motion, this is your, back to our perpetual motion machines. So, does anyone want to hazard a guess whether this would work?

Student: Considering the two chambers, then the effect the random motion has on the pedals has the same effect on the pawl also. So, if it is able to turn the pawl, then it can also cancel the effect of the power also, right?

Professor: Very good, have you read the Feynman Ratchet-Pawl mechanism explanation or did you think of this right now?

Student: No, like there was another left…

Professor: Maxwell…

Student Like the Silicon Motors.

Professor: Silicon Motors?

Student: Like, they extendedly created this…

Professor: What are you, can you just, okay, so you read somewhere. Very good, very good, I am glad to hear that.

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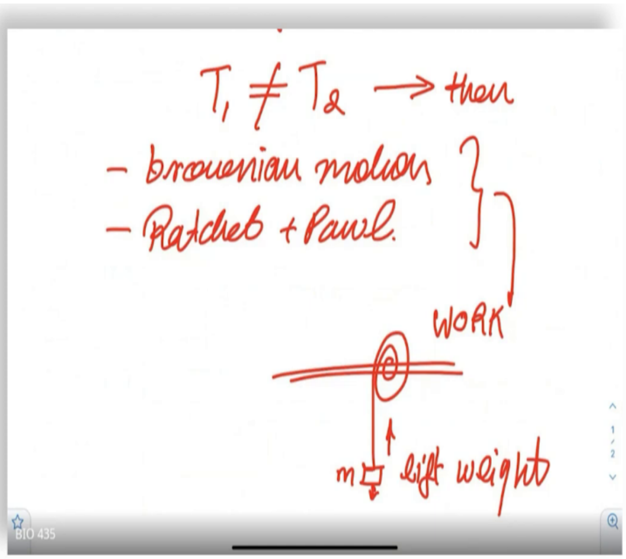

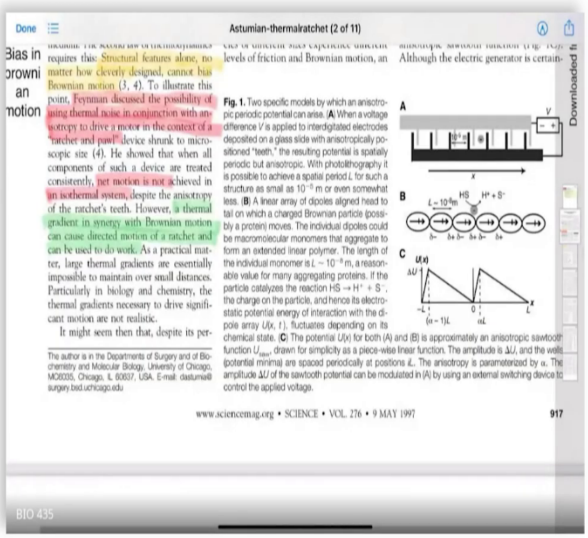

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So, suffice to say, indeed, thank you Swaraj. So, I am just going to continue maybe where I was. Suffice to say that only when T 1 is not equal to T 2, in other words when there is a temperature gradient, then such a coupling of the Brownian motion with the Ratchet ball mechanism can do work and this was proved, provided by Feynman, in theoretical work and you can go back and refer to it.

But given that this basic concept can be made to work in the presence of a thermal gradient, and this is very important right, that the two things are not isothermal, in other words, then and only then will this work. And this is the reason that Astumian and Company in the past have been motivated to look at Brownian motion and its conversion to biased from emotion or what are called Brownian Motors.

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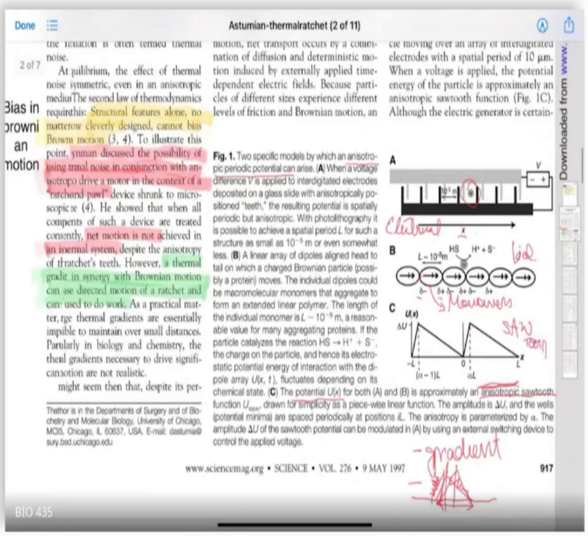

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Professor: So, we will go to the first figure and look at what they represent here. What you are looking in A at is the presence of two inter-digitating electrodes with a spacing of 10 micrometres between them and a small charged particle, this minus sign here, the electron like object. That is your electron. And that this is along some one-dimensional axis X and the question is will this geometry give us directional motion?

Now the assumption is that this charged particle is capable of moving randomly, diffusing, in other words, thermally. A similar analogy is also made with a, so this was of course electrical. So, what about biological? So, Astumian proposes that a 10 nanometre structure, that is 10^{-8} meter structure, meaning to say, these are something like monomers, often nanometres, and this is reasonable for you to assume that it is some kind of protein structure.

I mean 8 nanometres is your dimeric size of a, of tubulin and 4 nanometres is approximately the size of actin, G actin. So, this is a reasonable number. That they have a charge, a polarity of delta plus and delta minus, which means that they are little, little dipoles pointing in one direction. And this forming a linear chain allows you, given one additional criterion, that the potential energy that is U of x here forms what is now called a saw to thread potential. Does anyone want to try to explain what they understand of this saw toothed? What is saw toothed potential? Perhaps I can leave this like. Yes, anybody, anybody? What is saw toothed potential?

Student: Sir, it could be a potential having a curve like the sawtooth. Like, if we are looking at the peaks, it will be the position where the positive electrodes are. And at one part, the negative electrode is close to the positive electrode, then the gradient will be higher. Like, the slope will be higher and negative. And in the other part, the electrodes are somewhat more separated and the gradient will be lower. So, essentially having a higher gradient on one side and a lower grade on another side.

Professor: Very good, thank you, Swaraj. Exactly. The idea is that, and I may have also left out one word that I should have probably mentioned, this is indeed the illustration of an isotropic saw toothed potential or a function. You could have an isotropic one. So without saying that, it is not really obvious. An isotropic one, just to contrast the two, an isotropic saw tooth would look something like this where the central point is right at half the width of the tooth.

Whereas here, it is shifted to one side. As Swaraj correctly points out, that means that the gradient in one direction is sharper than the gradient in the other direction, which also means that since particles follow the minimum potential energy direction and transitions down a shallower gradient are less like, or transition, climbing up a shallower gradient is more likely than climbing up a steeper gradient, you can kind of imagine this might be useful.

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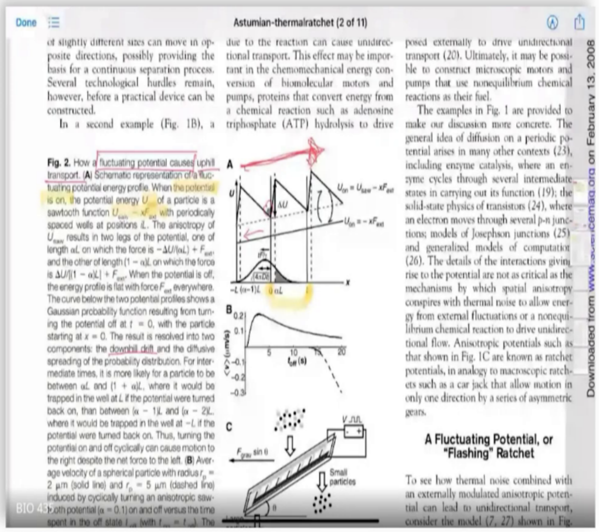
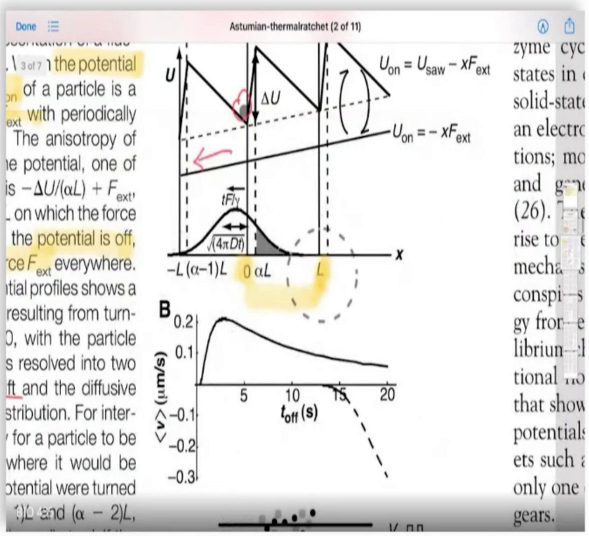
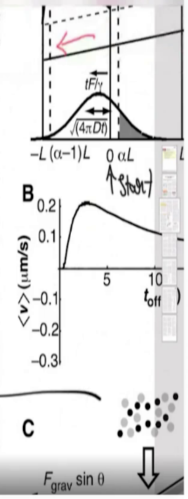




spaced wells at positions iL. The anisotropy of U_{saw} results in two legs of the potential, one of length αL on which the force is $-\Delta U/(\alpha L) + F_{ext}$, and the other of length $(1 - \alpha)L$ on which the force is $\Delta U/[(1 - \alpha)L] + F_{ext}$. When the potential is off, the energy profile is flat with force F_{ext} everywhere. The curve below the two potential profiles shows a Gaussian probability function resulting from turning the potential off at $t = 0$, with the particle starting at $x = 0$. The result is resolved into two components: the downhill drift and the diffusive spreading of the probability distribution. For intermediate times, it is more likely for a particle to be between αL and $(1 + \alpha)L$, where it would be trapped in the well at L if the potential were turned back on, than between $(\alpha - 1)L$ and $(\alpha - 2)L$, where it would be trapped in the well at $-L$ if the potential were turned back on. Thus, turning the potential on and off cyclically can cause motion to



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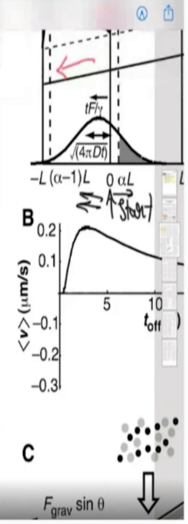

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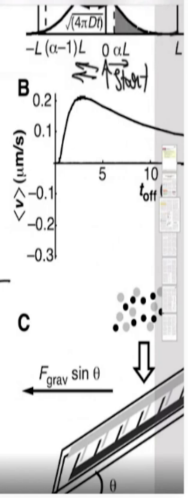

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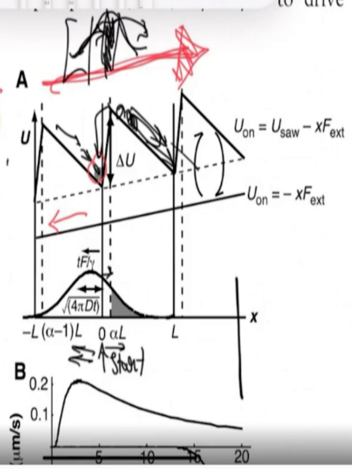

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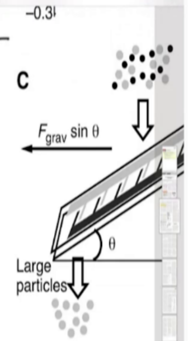

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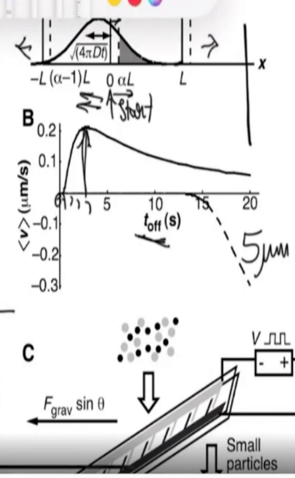

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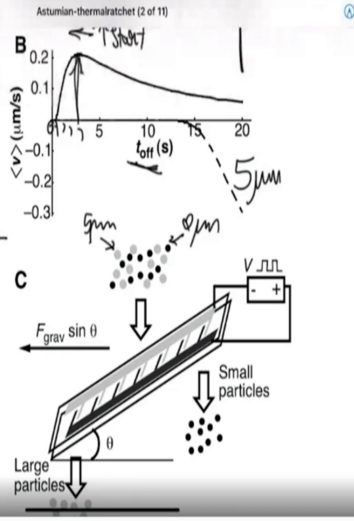

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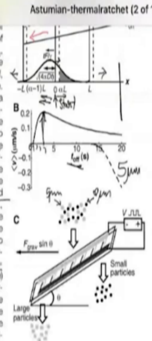

tions; models of Josephson junctions (25); and generalized models of computation (26). The details of the interactions giving rise to the potential are not as critical as the mechanisms by which spatial anisotropy conspires with thermal noise to allow energy from external fluctuations or a nonequilibrium chemical reaction to drive unidirectional flow. Anisotropic potentials such as that shown in Fig. 1C are known as ratchet potentials, in analogy to macroscopic ratchets such as a car jack that allow motion in only one direction by a series of asymmetric gears.

A Fluctuating Potential, or "Flashing" Ratchet

To see how thermal noise combined with an externally modulated anisotropic potential can lead to unidirectional transport, consider the model (7, 27) shown in Fig. 2A. A particle subject to viscous damping moves along a track where an anisotropic potential with periodically spaced wells at positions iL cyclically turns, or "flashes," on and off. To show that work can be done against an external force, the potential profiles are illustrated with a net force F_{ext} acting from right to left.

If the external force is not too large, the particle is pinned near the bottom of one of

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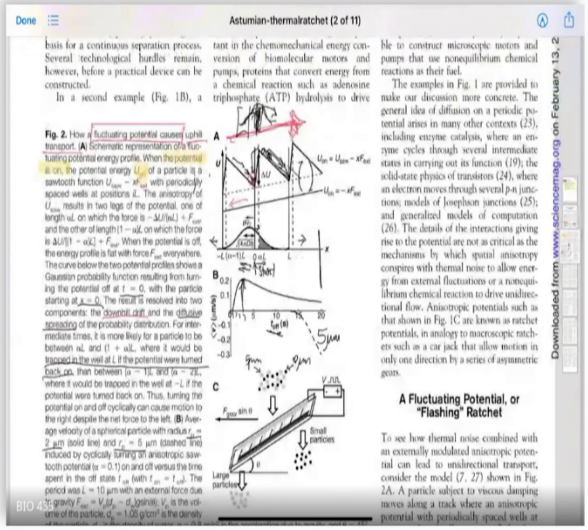

Professor: So, going to the next figure we will see what they try to do in terms of implementation because what you are looking at here is now a further complication of the matter. Earlier our saw toothed potential was only in terms of the baseline being flat. Here, in addition, you have a gradient which represents something like a downhill drift.

So, particles like this one here can, of course, at any given time land in the lowest potential well. They can diffusively spread or they can go downhill, down this way, which is where the gradient due to gravity is going to drive them. Gravity, or whatever other radiant that they have set up as a base.

And so the energy potential with a so-called fluctuating potential is claimed in this particular figure to be able to result in uphill transport, meaning net transport in this direction. Now this is a little unusual. So part of the trick, if you want to call it, in this flashing potential of fluctuating potential ratchet is that when the potential is on, there are two states in it, on and off.

When the potential is on, the potential energy U on, is the saw toothed function minus x of f external. That x times f external is representing the gradient. The periodically spaced wells are at some position iL. That is, these guys here, i being some index 1, 2, 3, 4. The anisotropy results in two legs of the potential, one at length alpha L on which the forces delta U upon alpha L plus f external.

$$\frac{\Delta U}{\alpha L} + F_{ext}$$

And so, this is now the force, not the energy, that is why you dropped the x. And the other is at length 1 minus alpha L on which the force is delta U upon 1 minus alpha times L plus f external.

$$\frac{\Delta U}{(1-\alpha L)} + F_{ext}$$

So, when the potential is off, the energy profile is flat and there is only force of f external everywhere.

So, if you remember, we went back and forth and we basically concluded in our own course that we would rather stay with the analogy of, with the reference to energies, not to forces. but suffice to say that this is not the approach used here. So, the Gaussian probability function that results from turning the potential off at t is equal to 0 with particles starting at x is equal to 0.

So the particles start here and this is resolved into two components, obviously. One is diffuser, which means they will go in equally in all directions, this way as well as this way, but it is also likely that they will go this way, leftwards, because of the whole intrinsic downhill drift or the gradient. For intermediate times, we argue, that it is more likely for a particle to be between alpha L and 1 plus alpha L.

Now, this is an interesting argument. Alpha L is the little bit over here ahead. Now if you go back and look at the figure, alpha L is the peak of the potential gradient. The right hand side of the drift, I am sorry, the, yeah, the right hand side of the initial position. The idea is that this is effectively the distance that in an off state, it could travel, and 1 plus alpha L is effectively the next point, the next trough.

So, why are they even claiming this? Because they claim that it would be trapped in the well at L if the potential were turned back on. The idea is that because of this on and off state, you can freeze the diffusion state temporarily and force things to fall into the nearest potential minimum. So, everything that was at this point, is all going to fall here. So, all of these particles will go here, whereas all these will go back to this minimum point.

So, not much will move from 0. In fact, this will also go here and this will go here. So, in, from your initial distribution, let us say we started not with x is 0 but a diffusive distribution, then this part of the distribution that is the 0 to 1, 0 to alpha will all shift right ward. The one that was left over here will also shift to the right, and this is what will give you your net rightward current.

But in their calculations, when they do a, an explicit simulation, there is something tricky also about it. And this is the fact that if they take two particle sizes, one which is bigger which therefore has a smaller diffusion coefficient, and one which is smaller, therefore at a higher diffusion coefficient, and remember from our analogy about, our entire exercise is about diffusion coefficients and the spread of the, diffusive spread, that you should get a higher velocity according to this flashing potential on off, as the time for which the potential is off is increased from some 0 to some non-zero value reaching a maximum at some approximately 2.5 seconds.

On the other hand, the 5 micron particle will indeed undergo negative velocity. And positive and negative is in with respect to the X axis over here. Negative is this direction, positive is this direction. So this should be sort of straightforward. This also means that now if you take a mixture of particles, which is what is represented in C, bigger ones which are 5 micron, assumed to be, and smaller ones which assumed to be 2 micron, set up a potential which has the same electrode like nature which we talked about in figure 1, have an overarching gradient.

Now, you can actually combine flushing potential, that is to say on off, on off, on off potentials with a gradient to separate large and small particles, with the small particles going up the gradient and large particles going down the gradient. And that is pretty cool. So, in a way, with this clever use of a combination of Brownian motion with an external gradient, which they call gravity here, and a flashing potential which is the bias, you can actually separate particles. And this is kind of a cool application that they claim is possibly implementable. Some of these have been implemented in the past.

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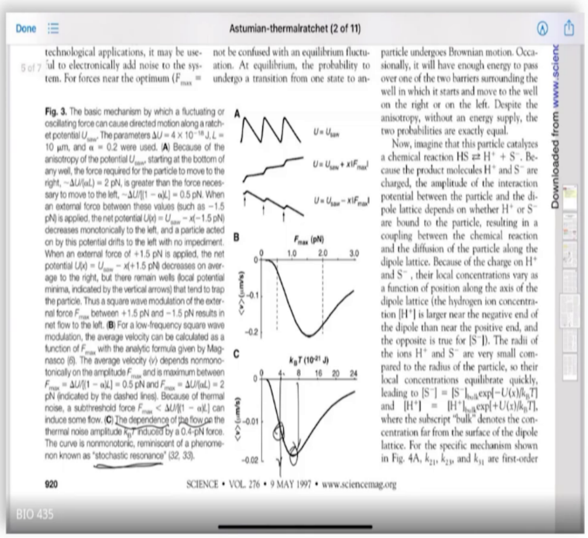

Professor: And there are some references in the literature, and there is some interesting arithmetic for understanding this. So, for the last two figures in the remaining 15 minutes, the basic mechanism of the flashing potential is illustrated with the shape and the addition of the gradient being described, giving rise to velocities as a function of F max.

To conclude, in some senses, they look at the velocity as a function of k_BT which is what our thermal noise is, and they show that 4.1 which is somewhere here, which is our thermal pico Newton nanometre, 4.1 pico Newton nanometer which is our ideal thermal regime, is fairly close to a high velocity in terms of the absolute possible maximal velocity which is seen at 8.

In a way, they refer to this optimum that may emerge with increased noise as something that in the literature has been cited as stochastic resonance. And some of you may have come across it in some other unrelated literature in physics or, physics in general. These are some slightly esoteric phenomena. Suffice to say, the idea is that with increasing noise, in other words, increasing randomness, you can actually get optimal directional motion as they show in this particular case.

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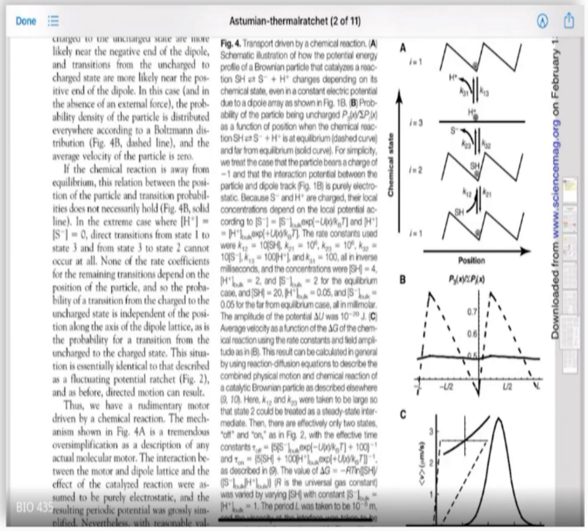

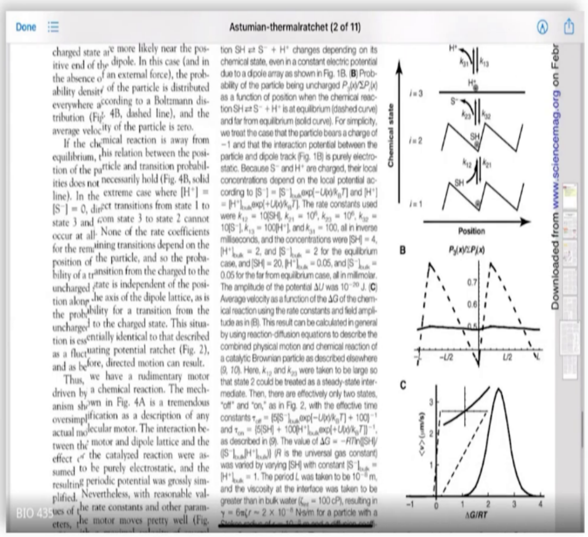

Professor: In the final figure, they talk about possible implementation, biochemical reaction and in the first 2 figures also, they have talked about this chemical product of sulphur and hydrogen breaking up with the addition of an electron, which then they cite as being a possible method by which such a flashing potential might be created, and the fluctuations of charge might be generated due to reversibility. And there is a little bit of more chemistry than I want to talk about today.

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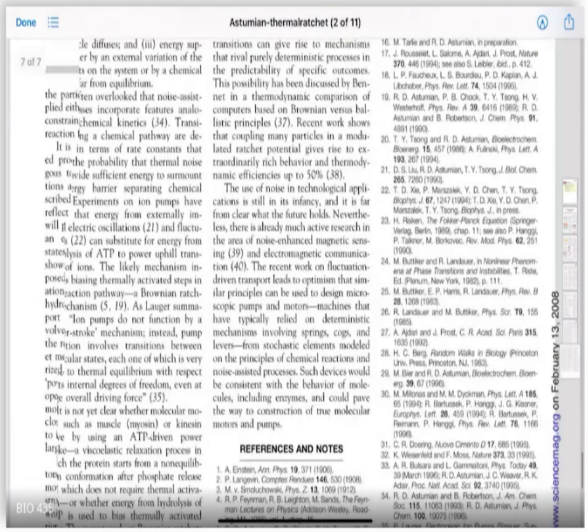

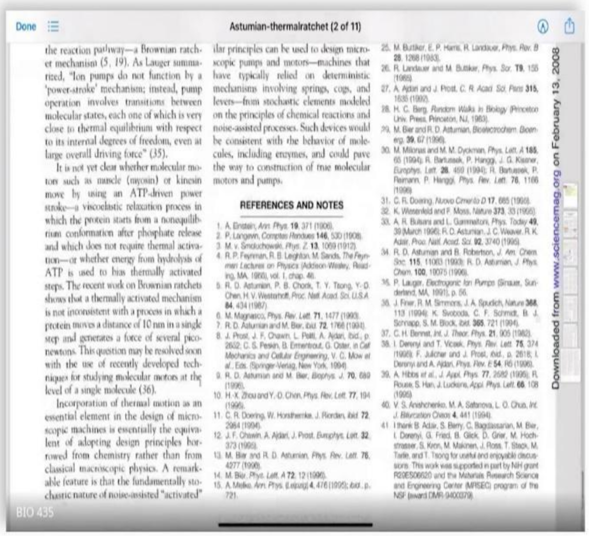

I am going to end here, and simply say that there are umpteen number of experimental data, particularly that they cite in terms of electrical circuits that are implemented but the exciting part is that the biochemistry of such thermal and directional motion is something that is probably more the domain for a chemical biology biochemistry and structural biology course. But there are interesting models that come out of it, and we, unfortunately, because of a shortage of time in this course, are not going to deal with them.

So, for the moment, I actually, I am going to put a halt to this, and ask you if there are any obvious questions at this stage, yes.

Student: Sir, could you explain the point of an isotropic function? Like how they, major, I mean I do not know, what is, how do they get the value of alpha out there in the paper?

Professor: That is what they put in, right? In fact, as I was trying to, I know I rushed things through but that was what also Swaraj very nicely explained. It is the very concept of the saw toothed potential, in other words, anisotropic saw toothed potential. In other words, if movement in one direction is more gradual, or it has a less steep energy gradient, delta U, as compared to the other, then for generating such a, so if you want, so let us take the counter example. If you did not have an anisotropic sawtooth, you would have an isotropic sawtooth.

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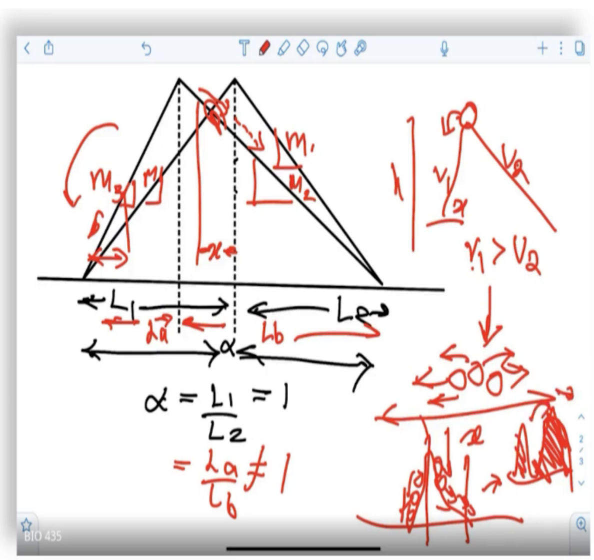

Professor: And that would look something like this. So, the idea is to have an approximately equal length here, and here. Saket, are you following?

Student: Yes, sir

Professor: So, you can say something like alpha is equal to, well, ratios of the halves, actually, maybe I, how do I put this? So, alpha is equal to L, I have to call this something.

So L1, L1 by L2. If I now move my saw tooth, I am sorry, if I create an anisotropy then I am going to have to do something like this. I am going to move my potential in one direction, while keeping the rest of the extent the same. So, in my symmetric case, L1 and L2 were identical, whereas in my asymmetric case La and Lb are not identical anymore.

That is all we were talking about. But what this also means is that the gradient here and the gradient here are not the same. In other words, going down this way is much steeper than going down this way. Or, per unit, the distance travelled in y is more here than here. And this means, and anyone who has been on top of a hill knows this, if you are a rock and you are standing on top of this hill, and if the rock can fall either way, if it falls this way, its velocity will be greater, one would assume, simply because it is moving through a larger distance in this direction for the same x displacement. Did you get what I am saying, Saket?

Student: Yes, sir.

Professor: And this, of course, with the consideration of the flashing potential, means that when there is no gradient here, then they can equally, particles, Brownian particles can move equally in all directions, both directions if it is along X. And now you turn back on the potential, so, those that moved here, in the next few seconds, are going to try and move here, and the rest are going to move here. But because this is a longer region, you are more likely over time to get a frequency distribution something like this. In other words, this is fatter than this. Means you will get net rightward movement.

And this is how this whole biasing is achieved, okay?

Student: Yes.

Professor: In other words, the bias in the gradient gives you the bias in the transport.