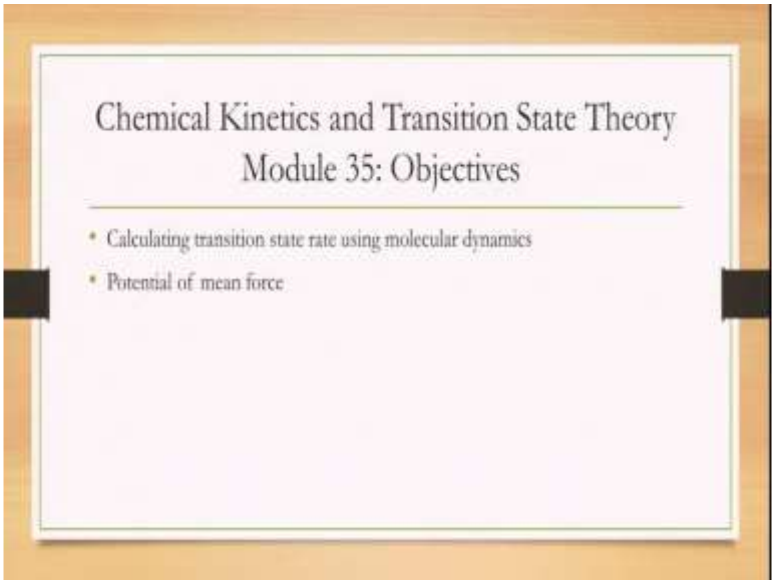
Chemical Kinetics and Transition State Theory
Professor Amber Jain
Department of Chemistry,
Indian Institute of Technology Bombay
Lecture 35
Free energy and potential of mean force

(Refer Slide Time: 00:16)



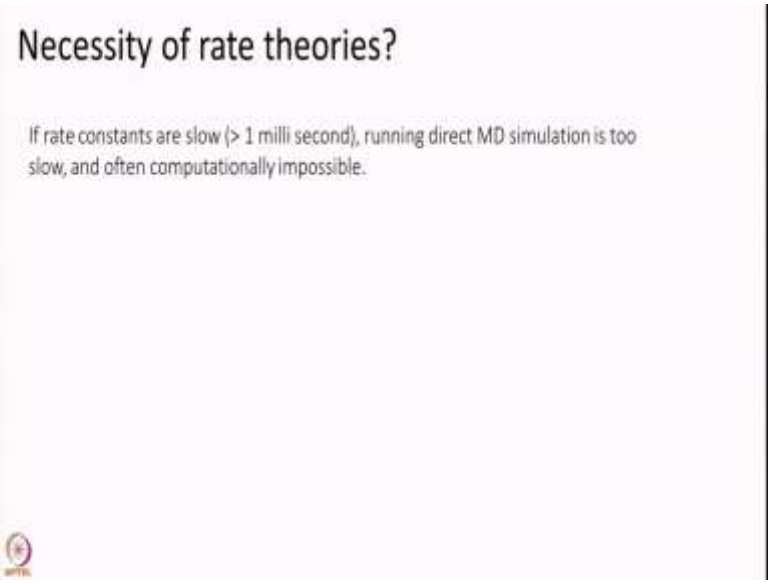
Chemical Kinetics and Transition State Theory
Module 35: Objectives

- Calculating transition state rate using molecular dynamics
- Potential of mean force

Hello, and welcome to module 35 of Chemical Kinetics and Transition State Theory. Today's contents are going to be somewhat different than what you will typically study in your courses. But I believe it is still very important to learn this point. Remember, we are learning, so that we can calculate rate constants for a general problem.

What we have learned so far is we started with these rate theories, we looked at transition state theory in great detail and in the last few modules we looked at molecular dynamics as an alternate way to calculate rate constants. We, in the last module we looked at how rolling spheres on potential energy surfaces can lead to more insights on chemical reactions. Today, we will ask a different question.

(Refer Slide Time: 01:14)



Necessity of rate theories?

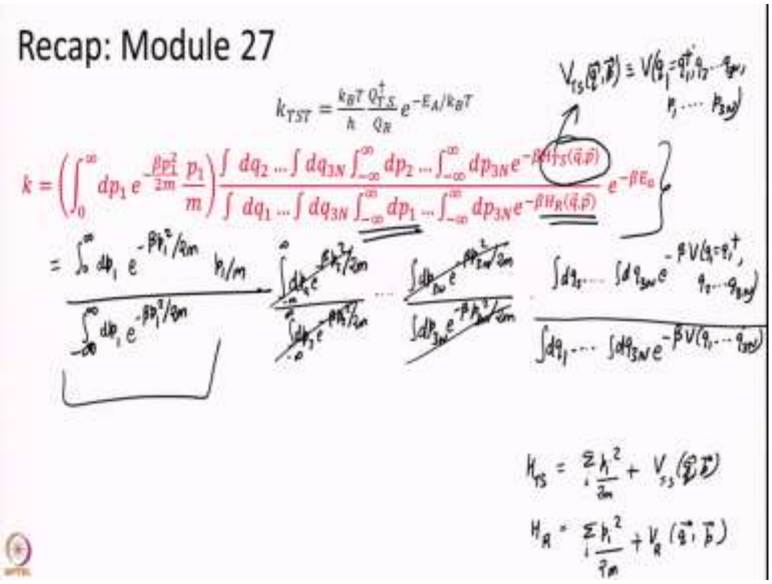
If rate constants are slow (> 1 milli second), running direct MD simulation is too slow, and often computationally impossible.

First thing is if I can run these molecular dynamics, are rate theories really necessary? Well, they are. The reason is these molecular dynamics are very computationally expensive. If, specifically if rate constants are slow, if you, let us say, have a reaction that is happening on a millisecond timescale, running a molecular dynamic simulation for that longer time is extremely hard. Very few computers in the world can do that kind of simulation. And it is not needed necessarily.

We have transition state theory or alternate rate theories if you wish that can calculate these rate constants anyway. So, if all that you want is to calculate a rate constant, then MD is not necessary. It is one of the tools. So, transition state theory is computationally cheap. It is effective. However, and we looked at how to use transition state theory to actually calculate rate constants as well. We can divide partition functions into a translational, rotational and vibrational and then calculate a rate constant.

However, there are situations when this separation of partition functions is not always possible. It is not always accurate. So, is there a way for me to use the power of molecular dynamics simulations to calculate transition state rate? Actually, answer is of course, yes. And it is commonly being used. So I wanted to give you a little glimpse of it in this module and the next module on how we can use the power of simulations to calculate a transition state rate.

(Refer Slide Time: 03:13)



Recap: Module 27

$$k_{TST} = \frac{k_B T}{h}\frac{Q^{\dagger}_{TS}}{Q_R} e^{-E_A/k_B T}$$

$$k = \left(\int_0^{\infty} dp_1\, e^{-\frac{\beta p_1^2}{2m}} \frac{p_1}{m}\right) \frac{\int dq_2 \dots \int dq_{3N} \int_{-\infty}^{\infty} dp_2 \dots \int_{-\infty}^{\infty} dp_{3N}\, e^{-\beta H_{TS}(\vec{q},\vec{p})}}{\int dq_1 \dots \int dq_{3N} \int_{-\infty}^{\infty} dp_1 \dots \int_{-\infty}^{\infty} dp_{3N}\, e^{-\beta H_R(\vec{q},\vec{p})}} e^{-\beta E_0}$$

$$H_{TS} = \sum_i \frac{p_i^2}{2m} + V_{TS}(\vec{q},\vec{p})$$

$$H_R = \sum_i \frac{p_i^2}{2m} + V_R(\vec{q},\vec{p})$$

So, we will have to go back to a rather old expression I derived some time ago, almost six, seven modules ago. We derived transition state theory in two ways. And in the second approach that we looked at, this integral we had derived. If you do not remember, you can go back to your module 27. This is nothing but this integral is your forward flux.

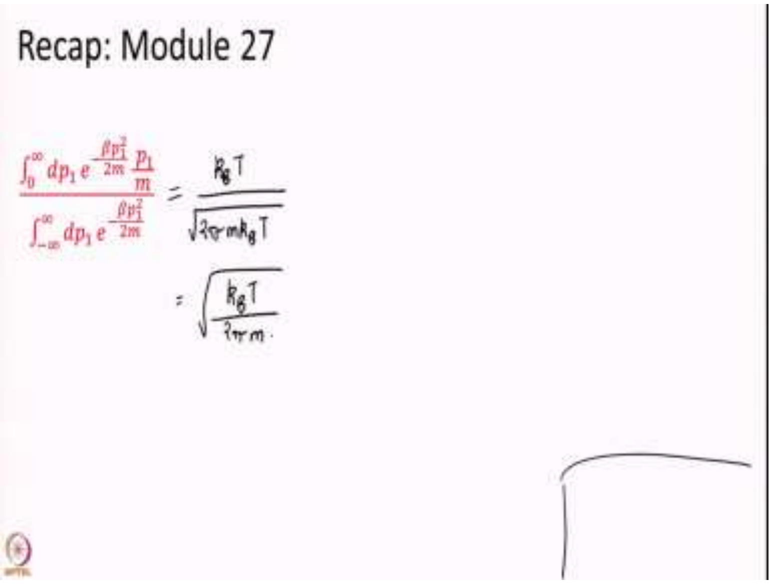
This is an integral over the dividing surface of e to the power of minus beta H and this is nothing but your partition function of the reactant. So this is going to be my starting point. I will manipulate this thing a little bit more. So let me start with this. So I will do the following. First thing, I will separate out all momentum integrals completely. In the denominator, I will take out the momentum term.

So I have taken of this term and HR I am saying is equal to Pi square over 2m plus V of R multiplied by all kind of other integrals, dP2 I am also assuming this HTS is equal to sum over i Pi square over 2m plus V of transition state q comma p. So, I will have to delete thing because I will run out of space. I will just write it below for your convenience. And in the denominator, I will have the actually the exact same term, both of them having the same limits.

You will notice I will have these for all 3N integrals. And then I will have the position integrals that I cannot do anything about not yet. I will simplify this a little bit. What does this mean really? This term is really the potential of transition state at q comma p really means V of the reaction coordinate equal to q1 dagger, the transition state geometry comma all other coordinates.

This is basically the definition of VTS that my V is set of, q1 is set at q1 dagger, which is my transition state geometry. So this is q1 equal to q1 dagger comma q2 to qn, q3N sorry divided by an integral over q1 to q3N e to the power of minus beta V q1 to q3N. So I have just written everything very, very clearly, every term explicitly. So, all the momentum comes here cancel. Let me just simplify this term.

(Refer Slide Time: 07:17)



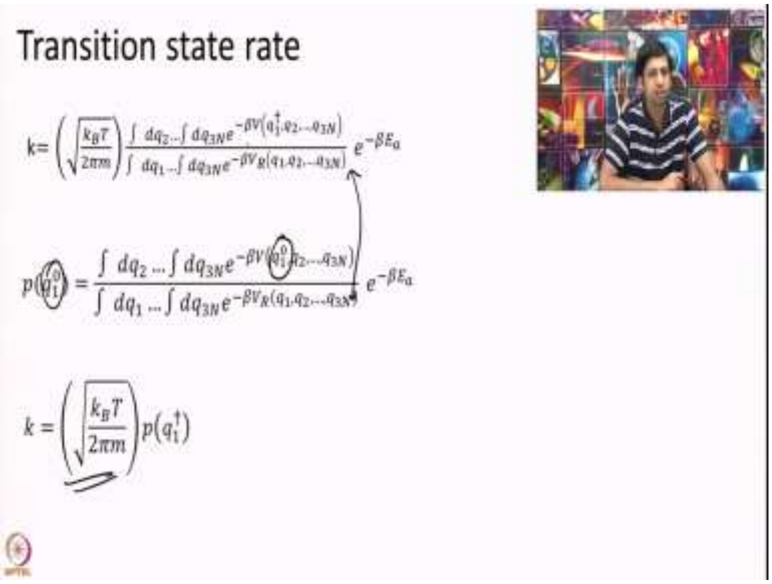
Recap: Module 27

$$\frac{\int_0^\infty dp_1\, e^{-\frac{\beta p_1^2}{2m}} \frac{p_1}{m}}{\int_{-\infty}^{\infty} dp_1\, e^{-\frac{\beta p_1^2}{2m}}} = \frac{k_B T}{\sqrt{2\pi m k_B T}}$$

$$= \sqrt{\frac{k_B T}{2\pi m}}$$

So this term that I have, well, we have been doing these kind of integrals very frequently. Today, I have forgotten to provide you the integral equations here. But that is not a big deal. These, you can look up for your integration tables. The numerator is kBT and the denominator is going to be root 2 pi m kBT. So these integrals are just looking up integral tables. Do not worry too much about them. So this is nothing but root of kT over 2 pi m. So that is nothing but your average velocity, average momentum.

(Refer Slide Time: 08:01)



Transition state rate

$$k=\left(\sqrt{\frac{k_BT}{2\pi m}}\right)\frac{\int dq_2\ldots\int dq_{3N}e^{-\beta V(q_1^{\dagger},q_2\ldots q_{3N})}}{\int dq_1\ldots\int dq_{3N}e^{-\beta V_R(q_1,q_2\ldots q_{3N})}}e^{-\beta E_a}$$

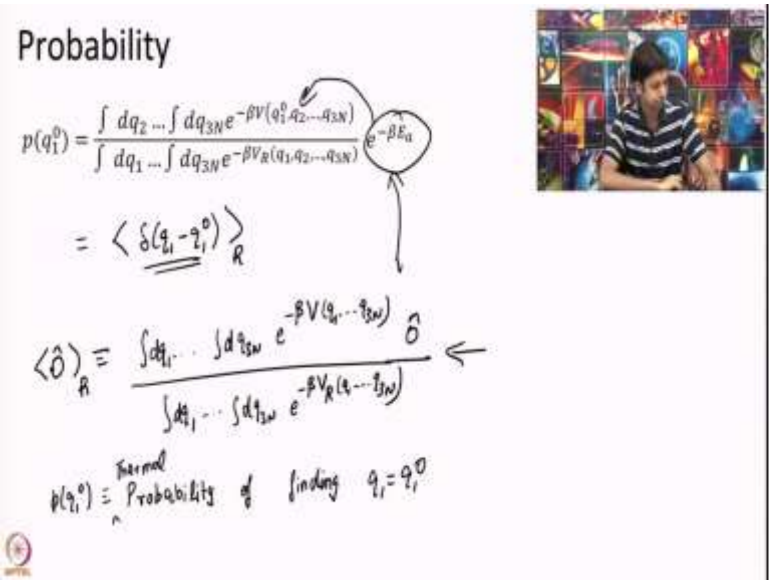
$$p(q_1^0)=\frac{\int dq_2\ldots\int dq_{3N}e^{-\beta V(q_1^0,q_2\ldots q_{3N})}}{\int dq_1\ldots\int dq_{3N}e^{-\beta V_R(q_1,q_2\ldots q_{3N})}}e^{-\beta E_a}$$

$$k=\left(\sqrt{\frac{k_BT}{2\pi m}}\right)p(q_1^{\dagger})$$

So I end up with this equation now. The, all the momentum integrals had got cancelled, except for p1 and the p1 integral gave me this term kT over 2 pi m square root. And I am left with still the integrals over all other coordinates dq2 to dq3N, dq1 to dq3N, this, this. Now the fun will begin. I am going to define a function p of q1 naught to be this, where instead of q1 dagger I have written q1 naught here. So just be careful here. I have, this is not a mistake. I have consciously written this.

So q1 naught is some variable. It can take any value, not necessarily only the transition state value. Some q1 naught, call it X if you want, call it Y if you want. I will call it q1 naught because that is what I want. And the denominator is exactly the same here. So k is nothing but this square root of kT over 2 pi m term into p of q1 dagger specifically. So if I put q1 dagger here, I will get q1 dagger here and I will get exactly this term. Sound something trivial to do, something stupid to do, but let us do it nonetheless.

(Refer Slide Time: 09:32)



Probability

$$p(q_1^0) = \frac{\int dq_2 \ldots \int dq_{3N} e^{-\beta V(q_1^0, q_2, \ldots q_{3N})}}{\int dq_1 \ldots \int dq_{3N} e^{-\beta V_R(q_1, q_2, \ldots q_{3N})}} \boxed{e^{-\beta E_a}}$$

$$= \langle \underline{\underline{\delta(q_1 - q_1^0)}} \rangle_R$$

$$\langle \hat{O} \rangle_R \equiv \frac{\int dq_1 \ldots \int dq_{3N} e^{-\beta V(q_1 \ldots q_{3N})} \hat{O}}{\int dq_1 \ldots \int dq_{3N} e^{-\beta V_R(q_1 \ldots q_{3N})}} \leftarrow$$

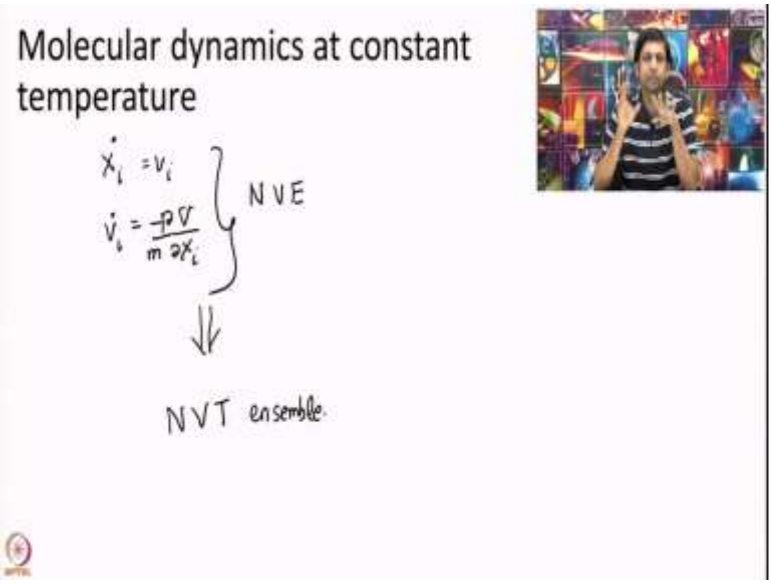
$p(q_1^0) \equiv$ Thermal Probability of finding $q_1 = q_1^0$

Let us now think of what I have defined here, this p of q1 naught. Actually this p of q1 naught is nothing but average of q1 minus q1 naught delta. So let me just be clear, average of any quantity O over reactant, this I am defining to be 3N divided by, sorry, operator O here, e to the power of minus beta VR. So that is how averages are defined, that is how thermal averages are taken. And here I am specifically taking thermal average with a denominator specified to only reactants. That is how transition state theory does to you.

So I am saying that this pq1 naught is nothing but average of this function. And I do not want to get into the technical nuances here. This is called derived delta function, but if you do not know then no problem. Physically this is p of q1 naught is the probability, thermal probability of finding q1 equal to q1 naught. So if I take this integral here and I think that q1 is fixed, there is no integral over q1, q1 is a specified, q1 is specified to q1 naught in the numerator, then I will get exactly this. This thing I do not worry about. This I have included in my potential.

So do not worry about this part that much. So pq1 naught effectively tells me, if I am at thermal equilibrium, what is the probability that q1 is equal to q1 naught? Particularly, it is a probability density to be more accurate.

(Refer Slide Time: 12:01)



Molecular dynamics at constant temperature

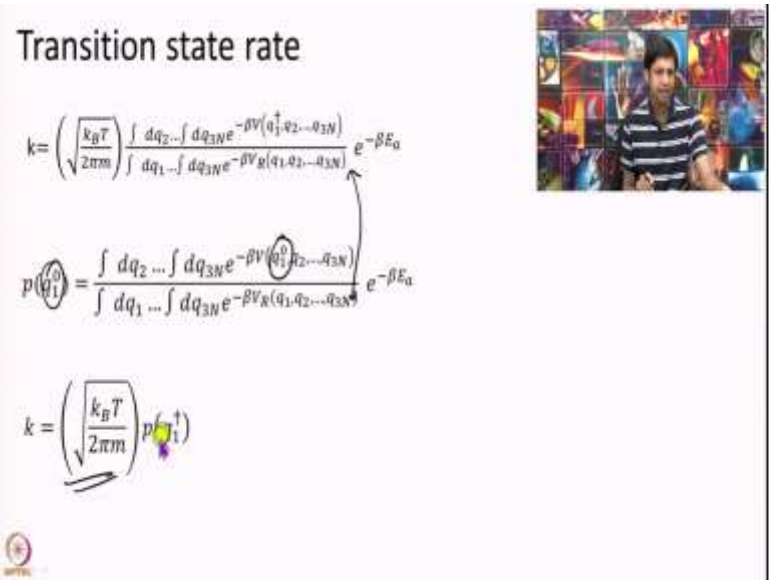
$$\dot{x}_i = v_i$$

$$\dot{v}_i = \frac{-\partial V}{m\,\partial x_i}$$

N V E

⇓

N V T ensemble.



Transition state rate

$$k = \left(\sqrt{\frac{k_B T}{2\pi m}}\right) \frac{\int dq_2 \ldots \int dq_{3N} e^{-\beta V(q_1^\dagger, q_2 \ldots q_{3N})}}{\int dq_1 \ldots \int dq_{3N} e^{-\beta V_R(q_1, q_2 \ldots q_{3N})}} e^{-\beta E_a}$$

$$p(q_1^0) = \frac{\int dq_2 \ldots \int dq_{3N} e^{-\beta V(q_1^0, q_2 \ldots q_{3N})}}{\int dq_1 \ldots \int dq_{3N} e^{-\beta V_R(q_1, q_2 \ldots q_{3N})}} e^{-\beta E_a}$$

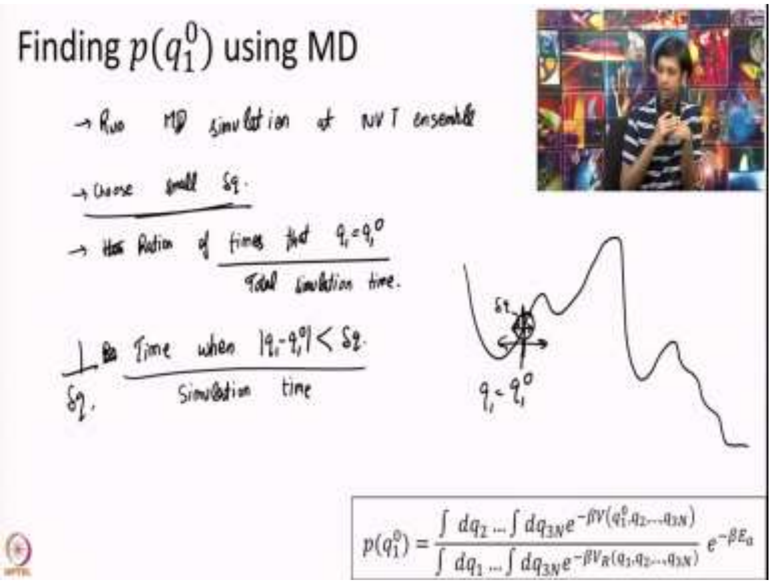
$$k = \left(\sqrt{\frac{k_B T}{2\pi m}}\right) p(q_1^\dagger)$$

This pq1 naught, is there any way we can calculate it? So that is the question. Remember, our rate constant, my transition state theory rate constant is nothing but some constant that I anyone know, I know temperature, I know masses and all this, into p. So if I can tell you how to calculate p, I can tell you how to calculate rate constant. So, actually, molecular dynamics can calculate p. That is the point.

So first thing is, what was molecular dynamics again, molecular dynamics was Xi dot equal to Vi. Vi dot equal to Y acceleration, which is nothing but minus 1 over mass. Well, this thing, solving these equations gives you NVE ensemble. But actually there are ways of solving equations that gives me NVT ensemble as well. I am not going into these details. But effectively you can add a thermal bath to your simulation.

It is as the same way as Brownian dynamics work. You think of this system, which is open, which has been constantly being colliding from other particles at some temperature t and that can be simulated. There are many, many different ways of doing that. So, for now, just assume that we, I can simulate an NVT ensemble as well.

(Refer Slide Time: 13:37)



Finding $p(q_1^0)$ using MD

→ Run MD simulation at NVT ensemble

→ Choose small δq.

→ Ratio of $\frac{\text{times that } q_1 = q_1^0}{\text{Total simulation time.}}$

$\frac{1}{\delta q} \cdot \frac{\text{Time when } |q_1 - q_1^0| < \delta q}{\text{Simulation time}}$

$$p(q_1^0) = \frac{\int dq_2 \dots \int dq_{3N} e^{-\beta V(q_1^0, q_2, \dots, q_{3N})}}{\int dq_1 \dots \int dq_{3N} e^{-\beta V_R(q_1, q_2, \dots, q_{3N})}} e^{-\beta E_a}$$

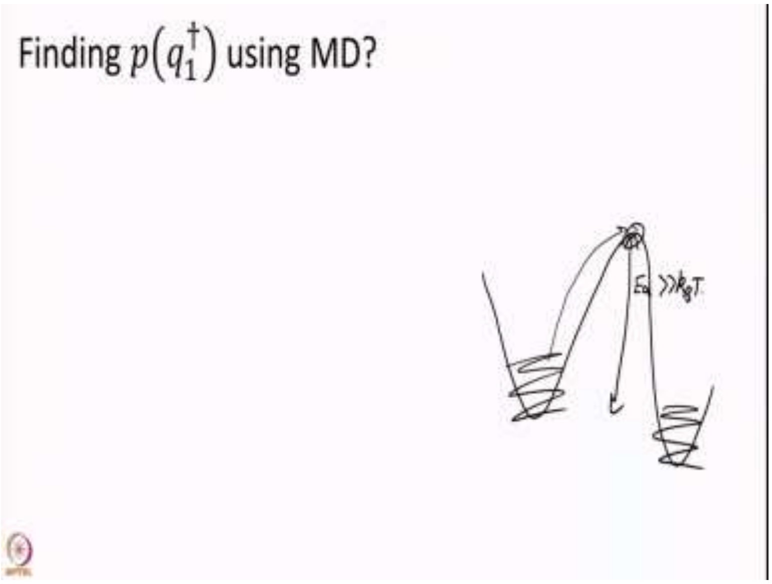
Well, pq1 naught then it is not that hard to find really. Pq1 naught I can find using MD using the following way. Run MD simulation at this NVT ensemble. So you have some energy surface with you. I do not even care about this energy surface is. I am trying to ask you, what is the probability density of finding the particle at some q1 naught? Well, the idea is I define a very small distance here and I asked to choose a small delta q. So in my MD simulation the point is how many times ratio of times that q1 was equal to q1 naught divided by total simulation time.

So what I am saying is, if I run, let us say a 1 nanosecond simulation, and out of that 1 nanosecond, q1 was equal to, my system was exploring this region for 1 picosecond, then the probability that I am at that region is 1 picosecond divided by 1 nanosecond. I explored this whole region in 1 nanosecond. And in that 1 nanosecond, I was here only for this much time only, for 1 picosecond only. So if I take the ratio, I will get the probability density at that point.

Well, there is one little trick here. In an MD simulation, you have discrete times. So q1 equal to q naught mathematically might not happen. You might come very close to q1 naught, but not exactly on top. And that is a little just nuance. And the way to solve that nuance is that we choose this small dt, delta q. And so we find this ratio for time when q1 is really close to q1 naught instead of equal to q1 naught. So when q1 minus q1 naught is less than delta q.

So q1 minus q naught, q1 naught is very small divided by simulation time. And since I have included this delta 1, I have to divide it by delta q, because if delta q is large, then, well, you will spend more time there. So if I choose, instead of choosing this box, if I choose this box, well, of course, you are going to spend relatively more time. So we divided by delta q. So this is the prescription using MD you can actually find p of q1 naught now. And once you have p of q1 naught, you can also calculate p of q1 dagger.

(Refer Slide Time: 16:55)

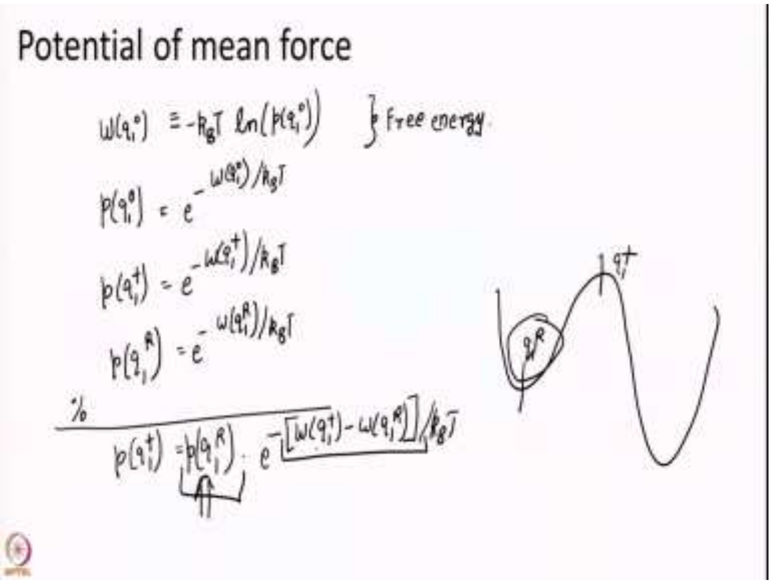


Finding $p(q_1^\dagger)$ using MD?

And remember the transition state rate is proportional to this term multiplied by some root of kT over 2 pi m. But we actually have another snag here, another problem here. The problem is, if the barrier height is quite large, if this is much larger than kT, then if you run an MD simulation, the time that you will spend here is extremely small. Most of the times you will be exploring this region or you are going to explore this region.

And once in a blue moon you will actually explore this region. So if I run a 1 nanosecond simulation, you might spend 1 femtosecond here. So it is not very efficient. We have not achieved much here so far. We have to just hit this, remove this little trouble that we have. And there is a very clever way of doing it.

(Refer Slide Time: 17:55)



Potential of mean force

$$w(q_1^0) \equiv -k_BT \ln(p(q_1^0)) \quad \} \text{ Free energy}$$

$$p(q_1^0) = e^{-w(q_1^0)/k_BT}$$

$$p(q_1^\dagger) = e^{-w(q_1^\dagger)/k_BT}$$

$$p(q_1^R) = e^{-w(q_1^R)/k_BT}$$

%

$$p(q_1^\dagger) = \underbrace{p(q_1^R)}_{\Uparrow} \cdot e^{-\underbrace{[w(q_1^\dagger) - w(q_1^R)]}/k_BT}$$

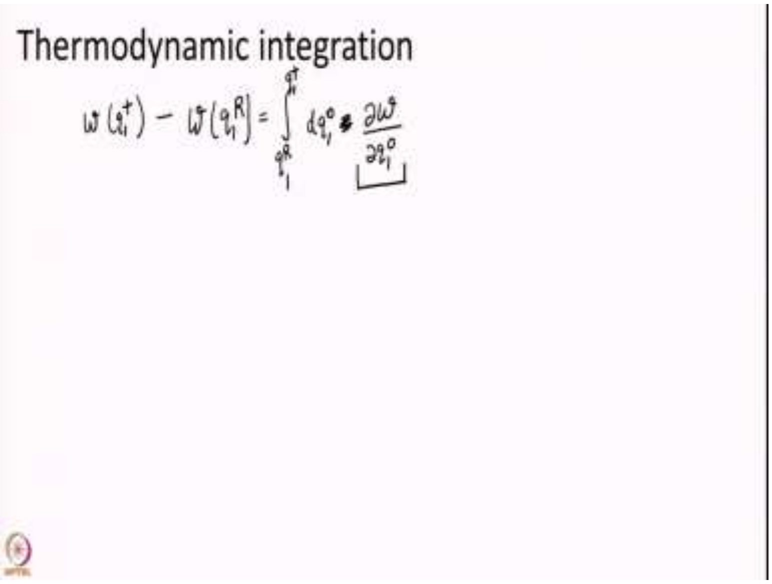
So I just wanted to show that and this is a very common trick. We define a function now, just bear with me. See this is going to be very beautiful. Minus kT ln of p of q1 naught, just bear with me. Let me define this function. For those who are familiar with a little bit more thermodynamics and statistical mechanics, this is a definition of free energy. This is how free energies are defined in stat mech. But do not worry if you have not seen this. You can take this as a definition.

This will give me p of q1 naught to be e to the power of minus w of q1 naught divided by kT. That will give me p of q1 dagger to be e to the power of minus w q1 dagger over kT. Let me also define p of q1 reactant. So I am thinking of this energy surface. This is q1 dagger and let us say this is q1R, something that is close to a minima. It seems like I am doing some very stupid things. I am trying to confuse you or fool you. But I promise you I am not. I will take a, divide these two.

So, p of q1 dagger equal to p of q1R into e to the power of minus w of q1 dagger minus w of q1R over kT. I just taken a ratio of these two terms. Still seem silly. I have not achieved anything looks like. My point is, I will now figure out how to calculate this and this separately. P of q1R is easy. Q1R is close to a minima. So I can actually use MD effectively to calculate p of q1R. Why, because your simulation is going to spend a lot of time close to the minima.

So if I run a 1 nanosecond simulation or more than half a nanosecond we will be close to a minima. So you can get good statistics. You can quickly calculate p of q1R, because trajectories spend more time close to q1R. But what about that, I still have to calculate this w and w is some weird minus kT ln of the whatever.

(Refer Slide Time: 20:28)



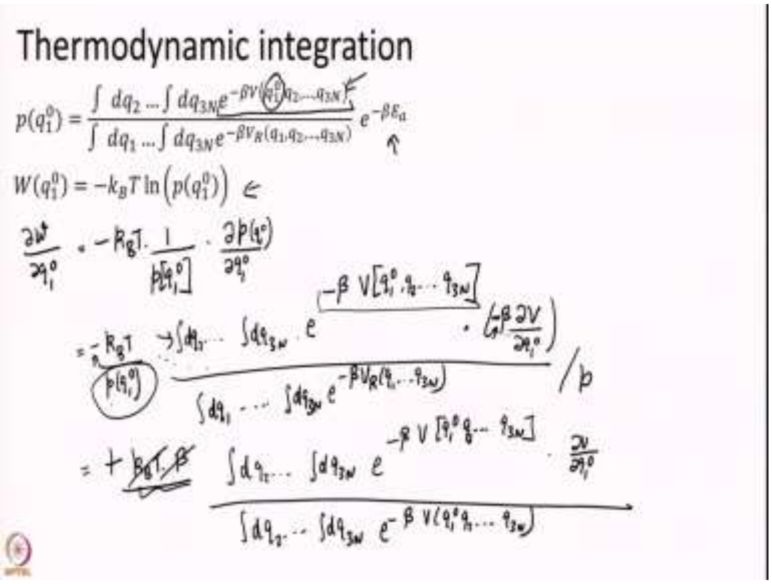
Thermodynamic integration

$$w(q_1^{\dagger}) - w(q_1^{R}) = \int_{q_1^{R}}^{q_1^{\dagger}} dq_1^{0} \, \underbrace{\frac{\partial w}{\partial q_1^{0}}}$$

So, now, let us see what we can do. This is real brilliance. It was originally given by Eyring and Keck Polanyi. These people developed this. I have to calculate this quantity. And Bennett and Chandler eventually made it very concrete in terms of a simulation. I am going to write this difference as an integral. You are rarely going to see this.

I take a simple subtraction of two terms and convert it into a complex integration, but it helps. So you can quickly verify that this equation is true. If I take the derivative and take the integral, I simply get w, w at q1 dagger minus w of q1R. Now, the point is this del w over del q1 naught, let us try to calculate that.

(Refer Slide Time: 21:40)



Thermodynamic integration

$$p(q_1^0) = \frac{\int dq_2 \dots \int dq_{3N} e^{-\beta V(q_1^0, q_2 \dots q_{3N})}}{\int dq_1 \dots \int dq_{3N} e^{-\beta V_R(q_1, q_2 \dots q_{3N})}} e^{-\beta E_a}$$

$$W(q_1^0) = -k_B T \ln\left(p(q_1^0)\right)$$

$$\frac{\partial W}{\partial q_1^0} = -k_B T \cdot \frac{1}{p[q_1^0]} \cdot \frac{\partial p(q_1^0)}{\partial q_1^0}$$

$$= \frac{-k_B T}{p(q_1^0)} \frac{\int dq_2 \dots \int dq_{3N} \, e^{-\beta V[q_1^0, q_2 \dots q_{3N}]} \cdot \left(-\beta \frac{\partial V}{\partial q_1^0}\right)}{\int dq_1 \dots \int dq_{3N} \, e^{-\beta V_R(q_1 \dots q_{3N})}} / p$$

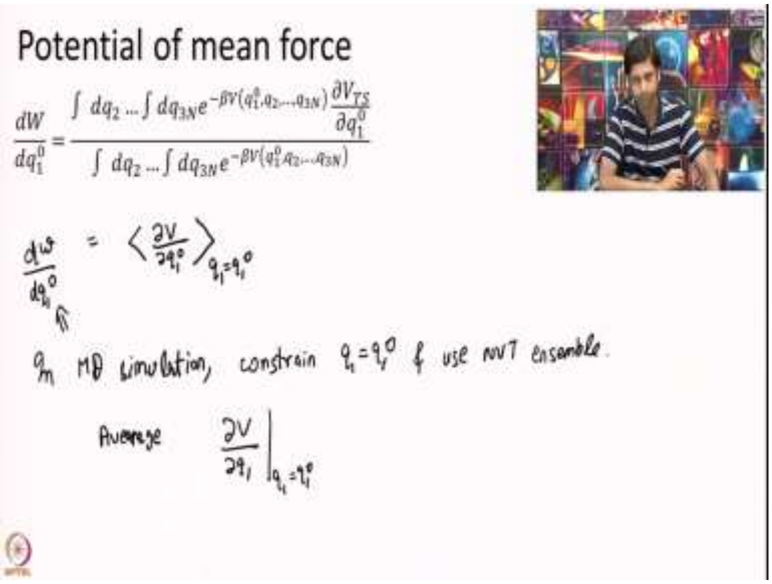
$$= + \cancel{k_B T \cdot \beta} \frac{\int dq_2 \dots \int dq_{3N} \, e^{-\beta V[q_1^0 q_2 \dots q_{3N}]} \cdot \frac{\partial V}{\partial q_1^0}}{\int dq_2 \dots \int dq_{3N} \, e^{-\beta V(q_1^0 q_2 \dots q_{3N})}}$$

So, W was defined earlier like this here and p I had already defined like this. So if I want to take del W over delta q1 naught this is nothing but minus kT into 1 over p of q1 naught into del p over del q1 naught. So I take, look at this p, q1 naught is only here. So this is equal to minus kT over p of q1 naught. And I write all these integrals now and I take the derivative of this term.

The derivative of this term is e to the power of minus beta V q1 naught q2 q3N into derivative of the exponential, so just differentiating by parts, nothing fancy, minus beta del V over del q1 naught divided by the denominator is independent of q1 naught. So I leave the denominator alone. Now, notice beta is nothing but 1 over kT so minus here and a minus here becomes plus, I have kT into beta divided by p.

So I take this p and write it again. So I get, let me write this term first. Sorry, for a little confusing statements. Till q3N into del V over del q1 naught divided by, you notice once I divide by the p here, if I am going to divide by p like this, this denominator is going to cancel. This integral dq1 to dq3N is exactly written here. So this exactly cancels and I am left with. And I noticed kT into beta is of course 1. Beta is 1 over kT. So kT into beta is 1.

(Refer Slide Time: 24:35)



Potential of mean force

$$\frac{dW}{dq_1^0} = \frac{\int dq_2 \ldots \int dq_{3N} e^{-\beta V(q_1^0, q_2, \ldots, q_{3N})} \frac{\partial V_{TS}}{\partial q_1^0}}{\int dq_2 \ldots \int dq_{3N} e^{-\beta V(q_1^0, q_2, \ldots, q_{3N})}}$$

$$\frac{dW}{dq_1^0} = \left\langle \frac{\partial V}{\partial q_1^0} \right\rangle_{q_1 = q_1^0}$$

In MD simulation, constrain $q_1 = q_1^0$ & use NVT ensemble.

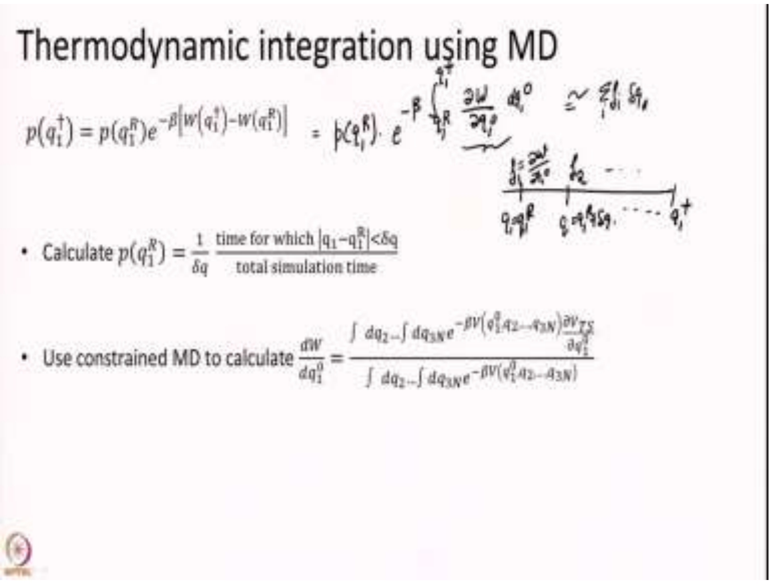
Average $\left. \frac{\partial V}{\partial q_1} \right|_{q_1 = q_1^0}$

So I am left with this integral. So this integral is actually called, that W is called a potential of mean force. What you have gotten is this is nothing but average of del V over del q1 naught at q1 equal to q1 naught. So I am taking a thermal average and I am fixing q1 equal to q1 naught both in numerator and denominator. Del V over del q1 naught is nothing but minus of force. So dW over dq1 naught is nothing but average thermal force at q1 equal to q1 naught.

So that is why it is called potential of mean force. You are taking a mean force and you are converting a potential out of it. So this dW over dq1 naught actually can also be computed using an MD simulation. So the point is in MD simulation there is another trick I can do that I am not covering in this course, I can put constraints, constrain q1 equal to q1 naught and use NVT ensemble. So if you download any of these popular softwares like GROMACS or LAMMPS which can run MD, they all will be able to do these tricks for you.

So once that happens, you can basically run MD simulation with constraint q1 equal to q naught and that can be any value, that can also be the transient state value. And once you have done that, you can calculate average force. So you calculate this derivative with respect to q1, run your simulation and fix q1 naught, q1 equal to q1 naught and just run the simulation and just find this average and that will give you dW over dq1 naught.

(Refer Slide Time: 27:10)



Thermodynamic integration using MD

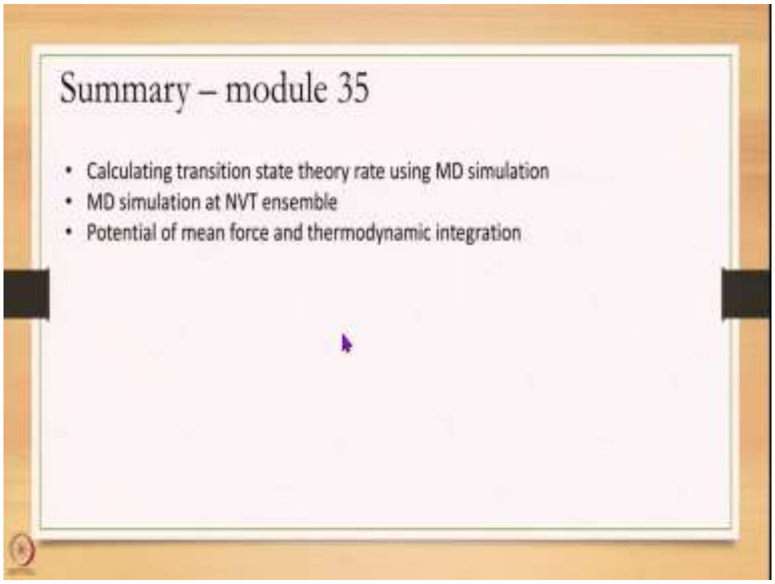
$$p(q_1^\dagger) = p(q_1^R)e^{-\beta\left[W(q_1^\dagger)-W(q_1^R)\right]} = p(q_1^R)\cdot e^{-\beta\int_{q_1^R}^{q_1^\dagger}\underbrace{\frac{\partial W}{\partial q_1^0}}\,dq_1^0} \simeq \sum_i f_i\,\delta q_1$$

- Calculate $p(q_1^R) = \frac{1}{\delta q}\frac{\text{time for which } |q_1 - q_1^R| < \delta q}{\text{total simulation time}}$
- Use constrained MD to calculate $\frac{dW}{dq_1^0} = \frac{\int dq_2 \ldots \int dq_{3N} e^{-\beta V(q_1^0, q_2 \ldots q_{3N})}\frac{\partial V_{TS}}{\partial q_1^0}}{\int dq_2 \ldots \int dq_{3N} e^{-\beta V(q_1^0, q_2 \ldots q_{3N})}}$

So now we have a full prescription. Pq1 dagger we had shown was pq1R into this exponential and we had written this exponential as an integral. So this I have written as pq1R into e to the power of minus beta integral from q1R to q1 dagger del W over del q1 naught, dq1 not. Pq1R I can calculate directly from an MD simulation by using this kind of a trick. And I do this integration numerically. I start at q1 naught equal to q1R. I calculate this value.

I shift q1 to q1R plus some dq. I recalculate this. So this integral itself now can be calculated numerically at, using small grids of q1. So what I am again doing is, I am setting q1 equal to q1R here. I calculate dW over del q naught then I shift q equal to some q1R plus some del q and I recalculate this function here and I keep on calculating it till q1 dagger and this integration then is nothing but just f into del q, sum over f into del q. So this integral is nothing but sum over i fi del q. And again this dW over dq I can calculate using a constraint NVT MD simulation.

(Refer Slide Time: 29:03)



Summary – module 35

- Calculating transition state theory rate using MD simulation
- MD simulation at NVT ensemble
- Potential of mean force and thermodynamic integration

So this was a quick summary today of how we can use an MD simulation to calculate a transition state theory rate. So this is useful when partition functions are not easily available, when you cannot separate, let us say, rotation and vibration or if the vibrations are harmonic. Then what do you do, then you do this kind of potential of mean force. Thank you very much.