Introduction to Evolutionary Dynamics
Prof. Supreet Saini
Department of Chemical Engineering
Indian Institute of Technology, Bombay

Lecture - 39
Evolutionary games during weak selection

Welcome back everybody. We will continue our discussion from last lecture. We want to understand what is the probability of one mutant in a bacterial population of size N going to fixation and eliminating all other N minus 1 individuals, in terms of this game theoretic framework that we have developed. And the particular case, particular scenario we are interested in, that what is the relationship that this probability of this one mutant going to fixation have, what is the dependence of this probability on the population size n?

So, we had ended our last lecture by defining the transition probabilities P i to i plus 1, what is the chance that the system goes from i number of A individuals to i plus 1 number of A individuals? And those probabilities were defined using the Moran model that we have discussed earlier. And similarly we defined transition probability of the system going from i to i minus 1 and the probability that the system stays at i starting from i number of A individual. So, we have all of these.

And the one probability that we are very interested in is, what is the probability that this, the one probability that very interested in is, what happens when we start at i equal to 1? And what is the probability that this one individual goes to fixation?

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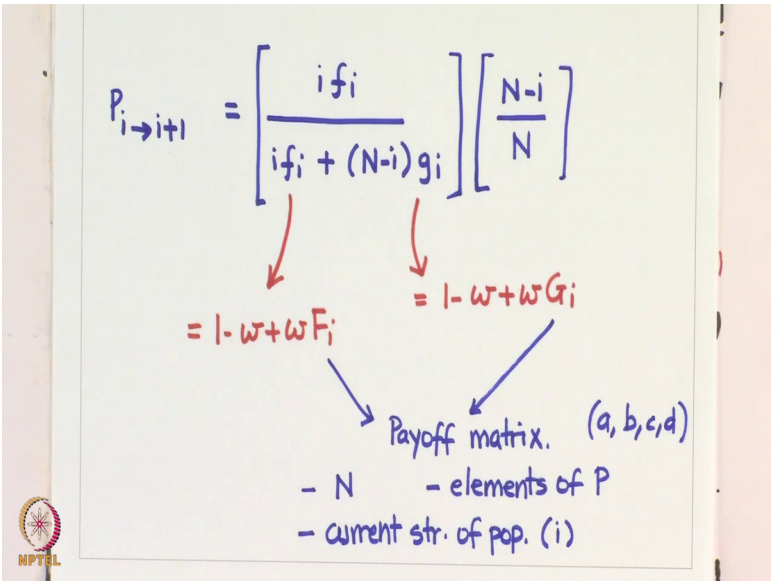

So, just to rewrite this that P i we had derived the transition probability as i to i plus 1 as i f i divided by i f i plus N minus ig i, this is the probability associated with the fact that we are selecting an a type individual for replication.

And this has to be paired with a probability that a b type individual gets selected for death and that is just given by N minus i upon N. And f the f and g variables are not, are not directly coming from the payoff matrix elements, but they are a function of the payoff associated with the matrix and this is just equal to 1 minus omega plus omega f i and g i similarly is just equal to 1 minus omega plus omega g i.

And depending on what value of omega do I choose that dictates how strongly or how weakly is the payoff associated with the payoff matrix linked with the fitness associated of these variables. So, we have these and we know that f i and g i come from the payoff matrix. So, we have these and we have already seen that f and g are going to be functions of N. So, both f and g are dependent on the population size N and also dependent on the current the current structure of the population, which is the variable i and it is also of course, dependent on f i and g i the elements of the payoff matrix.

Elements of P which are just a, b, c, d; so if we were to plug the expression for f here, and plug the corresponding expression of small f i into this transition probability we are going to get a expression which is going to be very involved in nature. So, without really going into that derivation we are just going to use a result. And we are going to use this

particular result in a very specific setting where we have seen that selection effects associated with the payoff matrices. Payoff matrix that we have is weak in nature and what that means, is that what we are implying that omega is very close to 0, it is not close to zero, but it is a small number which is very close to 0.

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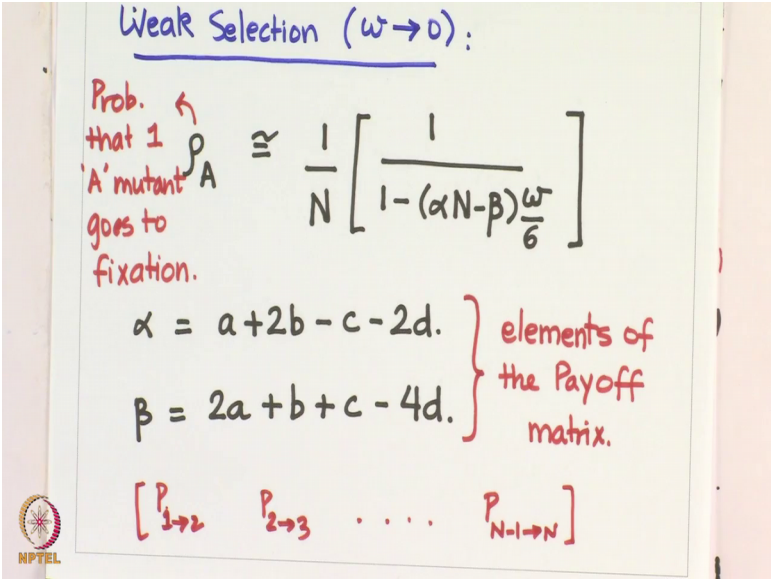

So, the limit under which we want to study this is called weak selection which implies that omega is close to 0. And what this means is that the payoff associated with the payoff matrix has a very weak effect on dictating the fitness associated with the 2 genotypes that we are talking about. The effect is not very strong, but it is not 0 either there is a small association between the payoff and the fitness associated.

With this in this setting what we get and remember we are interested in the probability associated with this one mutant going to fixation and eliminating all other N minus 1 individuals. And it can be shown that this probability it is called rho A is just going to be equal to, this is an approximation under the regime omega approaching 0.

Is just going to be equal to 1 by N times 1 minus 1 minus alpha N minus beta times omega by 6 where alpha is equal to a plus 2 b minus c minus 2 d. And beta is equal to 2 a plus b plus c minus 4 d. A, b, c, d are the elements associated with the payoff matrix and rho A is the probability, rho A is the probability that 1 A mutant goes to fixation. That in a population which was all b you have this one mutant that has arisen and this mutant now goes to fixation is defined by this variable rho A. What is important to realize is that we

are talking when we are talking of transition probabilities that, the probability that the system changes it is state from i to i plus 1. What happens is that when we are starting when the mutant has first arisen my i is equal to 1.

That means, the transition probability that I am interested in is telling me about what is the chance that this one mutant individual goes to 2 mutant individuals in the in the population. And that particular transition we will have a certain probability associated with it. As soon as I have 2 mutant individuals the transition probability that I am interested in terms of these numbers of mutants going to fixation is I becomes 2 now.

And I am interested in what is the probability that this system goes from i equal to 2 to i equal to 3. So, the transition probability I am interested in becomes P 2 to 3 and so on and so forth that I associated with the transition probability keeps on changing when I am interested in this particular mutant goes to fixation. And because each of the transition probabilities P i to i plus 1 is heavily dependent on i the probability of each of these transitions is going to be different in number. So, that changes as the number of individuals that belong to a particular genotype change, because these transition probabilities are the function of I themselves. So, we have we have this expression where these a, b, c, d are just elements of the payoff matrix.

And this particular rho A is obtained is the is the sum probability that that 1 A individual mutant that arose in the population goes to fixation. And while these mutants went to fixation all the steps associated with P 1 to 2, 1 to 2 and then P 2 to 3 and so on and so forth, going all the way up to P N minus 1 to N. All of these steps and their respective probabilities have been incorporated lead to this and under the regime that selection is weak this is the expression that we get. And that is the expression we want to work with and understand, understand that how does population structure have a role to play in dictating probabilities association with fixation of a particular mutant.

So, let me just write the expression again we have rho A equals 1 upon N times 1 minus 1 minus alpha N minus beta times omega by 6.

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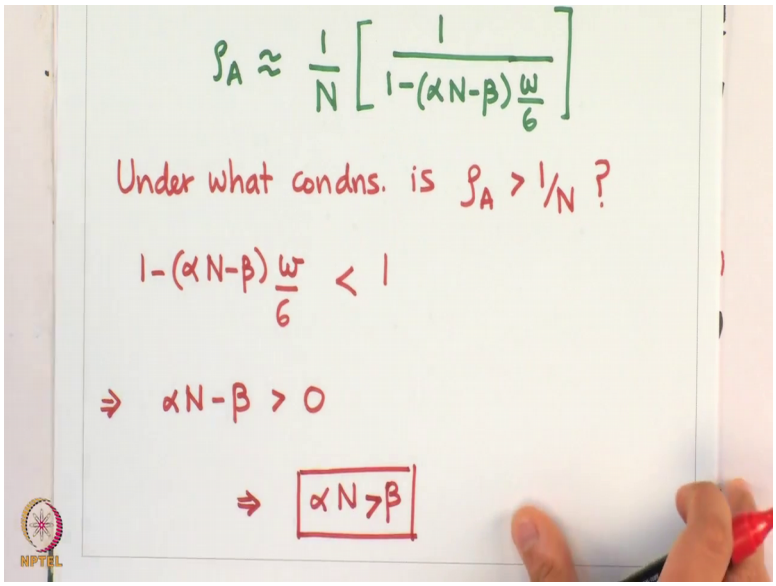

So, now you should ask the question, you should ask yourself the question that if the new mutant that has arisen had no fitness advantage or any fitness disadvantage over the parent genotype. If the new genotype was identical in terms of fitness compared to the parent genotype, what would rho A be? Remember rho A is the probability that this mutant goes to fixation. Suppose this mutant is different from the parent genotype in a characteristic which has nothing to do with fitness.

The mutant is growing identically as compared to the parent genotype, what is the probability that this mutant goes to fixation? Maybe pause the video for thirty seconds and try and think about this question for some time. The way you should think about this is that in a in a very long run, if there are N individuals in the population one of those N individuals will eventually go to fixation. That will just happen because of drift even if one no individual had any fitness advantage over any other individual in the population.

Drift would ensure that one of those N individuals goes to fixation. If that is the case then, then when I am working with the chance that the mutant has no fitness advantage or disadvantage associated with it compared to the parent genotype. In such a case the probability that this mutant will go to fixation is as good as any other individual which is present in the environment.

And if that is the case, then the probability that one of them will go to fixation is just going to be 1 by N, because some probability of any individual going to fixation is equal

to 1. And that 1 that probability equal to 1 is divided equally over N individuals in the population and hence the chance that my mutant will goes to goes to fixation, s just going to be equal to 1 by N. So, if there was no fitness advantage or disadvantage associated with mutant the fixation probability is 1 by n. But what happens here? Let us look at this expression and what we are interested in is under what conditions.

So, the question that we are interested in here is that under what conditions is rho A greater than 1 by N? Again the mutant that has arisen here had no fitness advantage or disadvantage compared to the parent genotype, then that rho A would just be equal to 1 by N and that comes from random chance. But we are interested in understanding conditions where this fixation probability is greater than 1 by N. Particularly greater than 1 by N because that tells us that under these conditions the mutant has a more than random chance of going to fixation. In addition to the random chance associated with every individual there is also some fitness advantage conferred on this mutant which gives it fixation probability of more than 1 by N.

So, we want to understand that when is what is the condition that this entire relationship is greater than 1 by N or we can say that when would it be that this term inside the bracket is more than 1, because of this is more than 1 then we have a number more than 1 multiplying 1 by N and hence the whole thing is more than 1 by N.

And this is 1 divided by something this would be the case if the denominator this whole expression in the bracket, will be more than 1 if the denominator is less than 1. So, this will be true if 1 minus alpha N minus beta times omega by 6 is less than 1. If the denominator is less than 1 then; that means, we have a number which is 1 divided by less than 1, So whole expression becomes more than 1. And this will be true if alpha N minus beta is greater than 0. Because omega is a number remember all of this is valid only in the regime where selection is weak omega is a positive number, but very close to 0. So, omega by 6 is always positive.

And if the term in this bracket alpha N minus beta is greater than 0 what that means, is that this whole expression will be negative and we have 1 minus a positive quantity and hence the denominator will be less than 1. And hence the whole expression will be more than 1. So, we have to ensure we have to find out the conditions under which this quantity holds. And if I substitute for alpha and beta So, this just implies that rho A is

more than 1 by N when alpha N minus beta, alpha N is greater than beta. That is the condition that I have to work under. And if I if I plug these expressions in I already have expressions for alpha and beta in terms of a, b, c, d the payoff matrix elements.

And if I plug those in I get an expression an inequality in terms of populations size N and the elements of the payoff matrix which help me comment on under what conditions is this mutant like, more than randomly likely to go to fixation.

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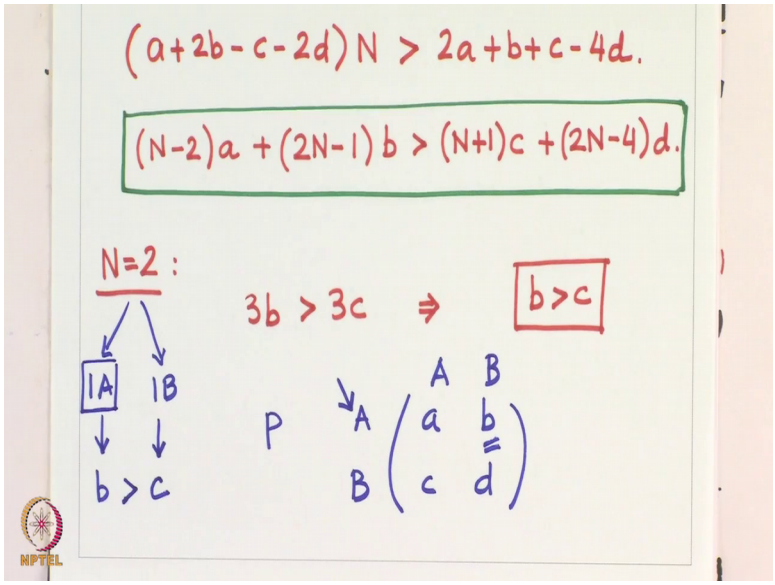

So, if I do that substitution, I get a relationship that a plus 2 b minus c minus 2 d times N should be greater than beta which is just equal to 2 a plus b plus c minus 4 d. This is the condition that has to be agreed to if my mutant has a fixation probability of more than 1 by N. And I can simplify this a little bit by clubbing all the terms associated with a, b, c, d and I get an expression equal to N minus 2 times a plus 2 N minus 1 times b should be greater than N plus 1 times c plus 2 N minus 4 times d.

So, that is the expression that I have in when I am computing the condition that the fixation probability associated with the mutant is more than 1 by N. So, as you can see that this is a interplay of this is a relationship which is of course, dependent on population size as well as elements of payoff matrix N. And depending on what is the population size that I have in my environment, this relationship is going to give me a different condition in terms of a, b, c, d for the for the likelihood that this one mutant goes to fixation is more than random is more than 1 by N.

So, that is where population size comes into picture. And depending on N you get very, very different conditions on a, b, c, d that is on the structure of your payoff matrix when you are trying to decide whether a mutant goes to fixation or not. So, we will just do 2 very simple cases let us do what happens in the case when N is equal to 2. This represents a case that there are only 2 individuals in the population and you have one mutant arise in the population.

So, just by random chance if this mutant had no advantage over the parent genotype then you would imagine from random chance that the probability that this goes to fixation eliminates the original the other individual which is still in the population and belongs to the parent genotype that probability is just equal to half, that happens by random chance. So, the, but the probability that this mutant is able to outcompete the probability, that this mutant is able to outcompete the parent genotype would be more than half, if we plug in N equal to 2 in this relationship and derive the relationship.

So, when we plug in N equal to 2 the a term drops out the b term becomes 3 times b this should be greater than 3 times c and the d term drops out. So, the condition that you get for N equal to 2 is simply that b is bigger than c. And now if you look at your payoff matrix what that means? What that means, is that b should be bigger than c. A is the new mutant that has arisen in the population and what does b bigger than c means b is the growth rate or fitness associated is a function of fitness.

B is how well does an A individual do in presence of b. And c is how well does a B individual do in the presence of an a. Now, because my population is such that there is only 1 A and 1 B individual- because there are only 2 individuals in the population; this A is always growing in presence of B and this B is always growing in this presence of A. So, B; that means, this A which is always growing in the presence of in the neighborhood of B A is going to grow at the rate which is decided by the element b of the payoff matrix. And the B individual which is growing in the neighborhood of A individual is according to the payoff matrix going to grow at a rate which is a function of c variable.

And if you have condition that b is greater than c; that means, an A individual is going to do better as compared to B individual. And hence there is a greater likelihood of this A individual going to fixation as compared to the B individual. So, you can see that there is a very nice connect between how you would anticipate growth rates when these growth

rates are plugged into this payoff matrix and eventually what you arrive at in terms of this analysis that we have just done.

We will finish this discussion by taking one more case associated with this with a different N and see that how varying the sizes of the population in the environment that we are talking about actually changes the result we get in terms of the relationship between payoff elements associated.

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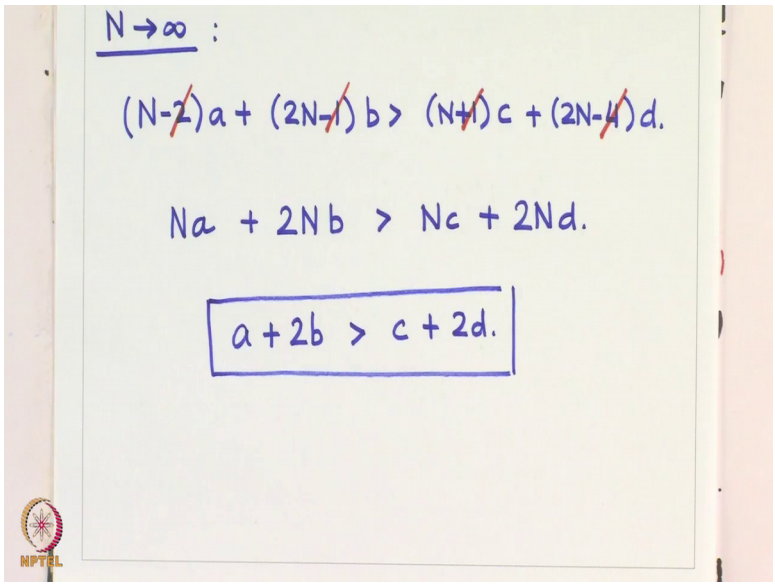

The elements associated with the payoff matrix. And the case that we take is N is very large or N approaches infinity. In that case remember we are working with a relationship N minus 2 times a plus 2 N minus 1 times b should be greater than N plus 1 times c plus 2 N minus 4 times d.

And if N is very large you can think of N in terms of 10 power 8, 10 power 9 a typical bacterial population then what we are going to do is, we are just simply going to go drop this constant terms because as compared to N 2 is very, very small. So, N minus 2 is effectively just equal to N and we are going to drop all these terms because compared to the variables the terms which have N in them these terms are very, very small.

And the relationship we get is N a plus 2 N b should be greater than N c plus 2 N d. And then we can since all these terms have N we can drop N. And we get a plus 2 b bigger than c plus 2 d. So, what this shows is that by simply changing the size of the population

we can also change N to be an intermediate population size where N is not as small as to that we are not talking of a case where there are only 2 individuals.

And we are talking of a case where N is So larger again practically we treat it as infinite, we can tune intermediate we can plug in intermediate values of N and derive other relationships that must exist between the elements of payoff matrix for the probability that the for the probability that the mutation goes to fixation with a with a more than random chance. And hence population size is what I have tried to demonstrate through this is that the population size is play a very strong role in terms of what the likelihood associated with this mutations going to fixation.

And any analysis on evolutionary dynamics associated with a system like this must incorporate population sizes into the framework as well. So, that concludes our discussion on sort of evolutionary game theory and analysis associated with it the text book goes to some more detail associated with these phenomena. For our purposes we want to end the course with one particular example and what I want to discuss regarding that is an example associated with HIV evolutionary dynamics.

And what we will be discussing is how can we understand a very basic HIV phenomena inside a human host which is observed when somebody contacts this virus. HIV is a retro virus it has a RNA geno which gets transcribed into DNA when it enters the host organisms. And specifically HIV does not target any cell in the in the host which is human beings here, but it targets a very specific type of cells which are called CD4 plus cells which belong to the immune system.

So, the way HIV targets human cells is by targeting the immune system itself. And that of course, compromises the ability of an individual to fight back the virus and eventually the 2 the dynamics between or the fight between HIV and CD, and the immune system of the host dictates that who is going to go fast. But what happens is that CD4 plus cells the immune cells they play a specific role we will just discuss, that in the second keep continuously decreasing over time as the infection persists in the host. And eventually when the numbers, when the numbers associated with these CD4 plus cells get below a certain threshold that is when a certain that is when the individual is said to have it is which is the clinical manifestation associated with having HIV in a host.

So, we want to understand that why is it that it is very difficult to control these HIV infections. And what happens as during the interplay between the immune system and the virus itself.

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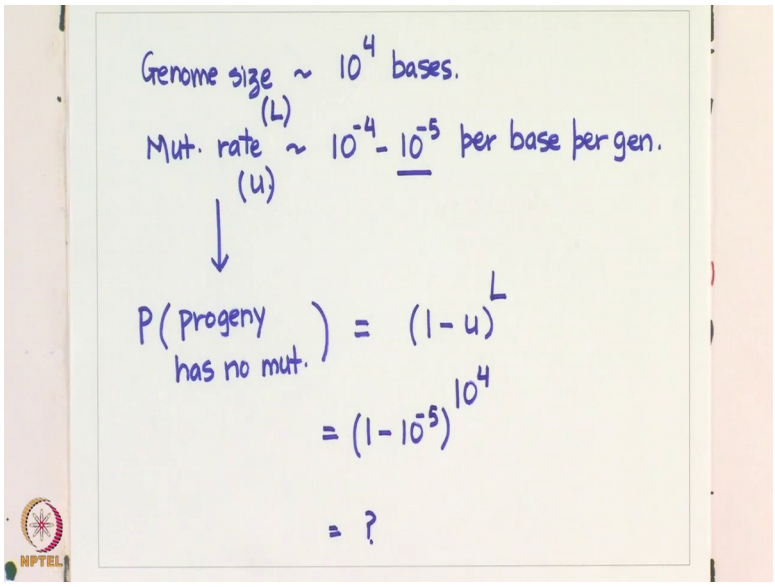

In order to do that what we will start with is a very a fact regarding HIV, I said it is a retro virus and it is genome size is around 10 to the power 4 bases. So, it is a it is a relatively small genome. The mutation rate associated with HIV is of the order of 10 to the power minus 4, 10 to the power minus 5 per base per geno, per base per generation. So, the first thing that you should check is when the virus replicates, what is the probability that the progeny has no mutations? This is something that we touched upon earlier in the course. And the probability that the progeny has no mutations is just going to be given by, if this is the mutation rate let us for our analysis, let us take the mutation rate to be 10 power minus 5.

The actual value is somewhere between the two, but the probability that 1 base is correctly copied is 1 minus u, where this is the mutation rate u associated with replication. So, this is the probability that 1 base is copied correctly and the probability that the entire genome is copied correctly and the progeny has no mutation will be 1 minus u to the power l, which ensures that every one of these bases is copied correctly where l is the genome size.

So, we are looking at a value of 1 minus 10 to the power minus 5 raise to power 10 to the power 4. I will leave this as an exercise for you to compute, which tells you that what is the likelihood that every time HIV generates a progeny inside the host; what is the chance that this progeny is identical in genotype? And what you will find when you plug these numbers in that actually HIV has a HIV s mutation rate is very high which ensures that the probability that there is a mutation in the progeny s genotype is actually going to be very, very high. And when you consider the fact that the number of progenies produced of this virus particle inside the host is so large the number of variation that is generated by this replication and mutation process inside the host even in a very, very short time is going to be very, very large.

And that is the that is the particular challenge that is posed by HIV that the antigenic variation associated with the virus particles is So large that the immune system is always trying to catch up with the virus and act against a new a new antigenic form that is produced by just mutations happening in the system. So, as I had mentioned that the target something called CD4 cells in the system and if you look at the particular viral dynamics associated with infection, it would typically look like this.

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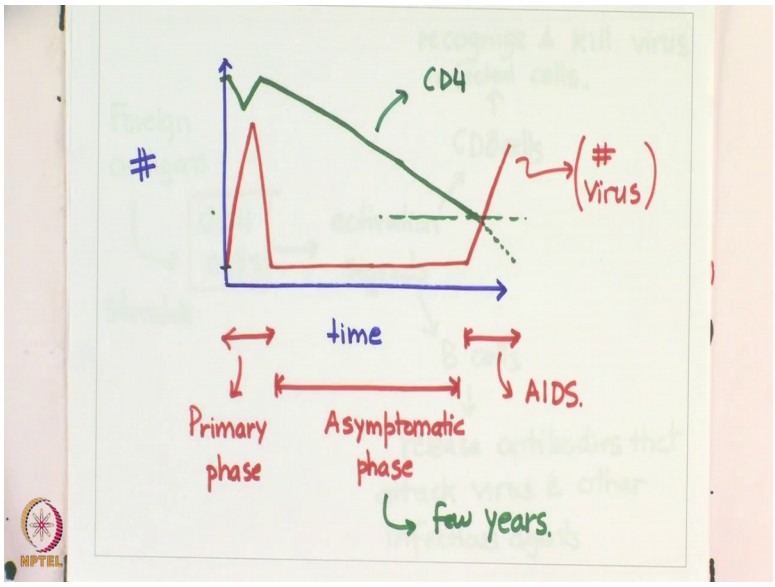

This is time and on we want to plot numbers of CD4 cells and the number of virus particles. And upon infection the virus particles increase and they are suddenly they are rapidly brought down by the immune system and there is a very long asymptomatic

phase where the virus particles do not increase very much. And eventually you would have a large increase in virus particles take place. So, this is the dynamics of number of virus particles associated with the system that takes place over time. And this phase of the infection is called the primary phase, this phase of the infection where the immune system is able to keep the numbers in control is called asymptomatic phase.

And this phase where the virus particles grow and are uncontrolled is when the patient is said to have AIDS. Along with this if we take a look at the CD4 cells numbers in the cell they go down are able to recover, but then in the asymptomatic phase there is a constant decrease in CD4 cells over time. And when they cross a threshold which is this threshold of they cross a certain threshold that is when the virus is able to just grow practically uncontrolled and go to very, very large numbers in the in the host.

So, that is those are the 3 steps associated with an HIV infection. And particularly what is curious about this is that there is a very long asymptomatic phase associated with HIV infection. And typically this could last up to a few years. And what is sort of we want what we want to understand is just interplay between these CD4 cells and a HIV particles, which tells as why should there be this such a long asymptomatic phase associated with the infection which lasts, such a long time and what happens at the end of it that triggers the uncontrolled explosion associated with virus particles inside the host. So, to understand that let us let us understand the role associated with CD4 cells In the immune system.

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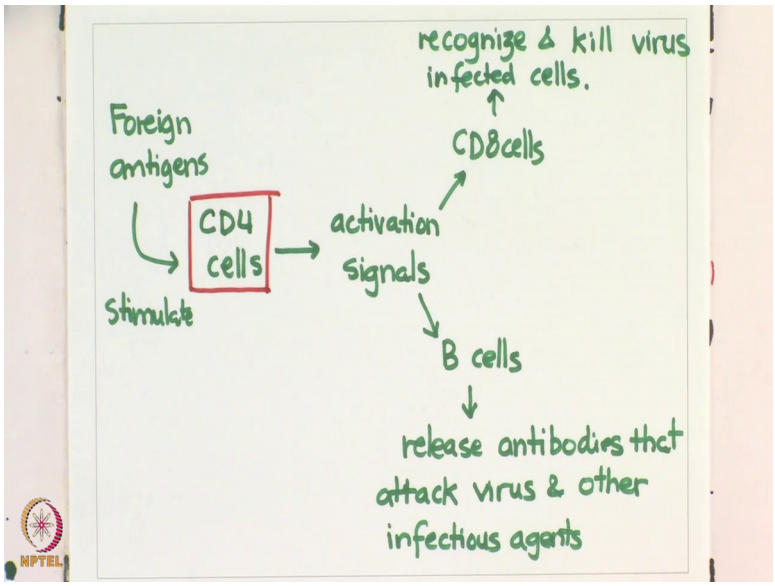

And what these cells do is, we have CD4 cells and when there are foreign antigens, these antigens stimulate CD4 cells. CD4 cells then send activation signals to what are called CD8 cells and B cells of the immune system. The role of B cells is to release antibiotics, I am sorry antibodies that attack the virus particles and other infectious agents in the body.

Whereas the role of the CD8 cells is to recognize and kill the virus infected cells inside the host. So, that is a dynamical relationship that are that is present in the body between foreign antigens and the immune response. And of course what HIV targets is CD4 cells itself, So it breaks the link that exists between antigens and the immune response associated with the body. So, what we want to understand through we want to develop a model to understand this dynamics between this interplay between the virus particles and the immune response.

And on first glimpse if you look at this graph of dynamics of numbers associated with the players, here the green here refers to the CD4 numbers, what happens is that initially in this phase of the response the virus particles that are getting selected are those which have the highest growth rate associated with them, that is what selection is acting against. But then once these numbers grow the immune system is able to launch a response in A is able to launch A response to the viruses and then these viruses which are growing very fast are able to be controlled by this immune system response.

But in that phase of the infection what now gets selected for is those viruses which have a capability to evade the immune system response and still survive. So, the selection that is happening which controls the virus particles at any given instant varies in the in the sense that initially it is the virus particles it is that sequence which is able to grow fastest, but very soon the immune system launches the response and you are selecting for those virus particles or those sequences now which are able to evade the immune system. And these mutants are now generated because of the mutation rate associated with the virus particles which we have seen is actually very, very high.

So, in the final lecture of the course we will work towards development of a model which captures this dynamics, and see what that tells us whether that can explain the very long asymptomatic phase of infection which is associated with HIV.

Thank you.