Introduction to Evolutionary Dynamics
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Lecture – 40
Evolutionary dynamics of HIV

Hi everyone and welcome to the final lecture of the course, and what we hope to do today and finish the course of is we will continue the development of the model of this one example that we have started with which is of how does HIV infection propagate inside a host, and we want to model the dynamics and the interplay associated with the virus particles and the immune system in the body. Now we will develop this model and we will do that in a stepwise progression as in the sense that we will start with the simplest possible model associated with the infection, and we will keep building complexities which make the model more realistic and captures the actual physiology associated with HIV infection. With that example we will conclude the course and I will just to do a brief recap of what we have covered in the last 40 lectures or so ok.

So, in the last lecture we had seen that HIV infection, HIV specifically infects what are called c d 4 cells in the immune system and these c d 4 cells play a role in launching the immune system associated with the body, via activating c d 8 and b cells in the human host. And by targeting c d 4 cells HIV compromises the immune system that the host body can launch. Now it depends when you are starting any modeling exercise you can go up to any level of complexity and incorporate any amount of detail which is associated with this process. So, we can actually worry about how does HIV associated with c d 4 cells model that interaction then how does that interaction compromise the ability of the c d 4 cells to activate c d 8 cells model that interaction how does that compromise c d 4 cells in its ability to activate b cells and model that and so on and so forth.

But the very often the problem associated with this that one not all mechanistic details might be known of the process that you are interested in, this is just an example that we are working with, but mechanistically all details might not be available. The second problem is that even if the mechanistic details are known, the parameters which are associated with these interactions, dictate what is the dynamics that is going to be so.

Any model is going to have parameters and unless we have those we are not going to be able to accurately mathematically define what is going on.

So, what we are going to do is define a very course (Refer Time: 02:49) a very crude model of infection, where many many interactions are going to be lumped in a single term with a help of just one parameter. That is the way we will start our model and hopefully we will choose a particular value of that parameter which takes into account all the interactions which are associated physiologically, with the which are associated with the physiological process that that particular term represents. And that can be done with the help of limited data that might be available for cases like what we are going to model now, and using clinical data that might be available we might get estimates of what are those parameter values associated with the physiological process that we are going we are trying to represent through this term.

So, let us start this and in the most basic form, what we are going to assume is just 2 variables. One is what is the virus number and the second one is what is the immune system response associated with that amount of viruses being present inside the host; and lets represent those quantities by 2 variables.

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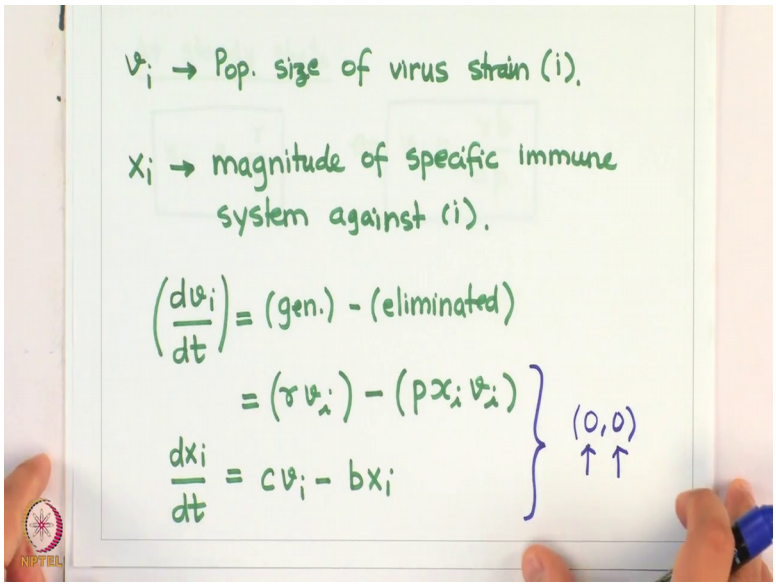

Let us call this v i which represents population size of one particular virus strain let us call thisi th strain and as we had discussed in the last lecture the virus has a very high mutation rate as and as a result new progeny with altered antigens exposed on them are

continuously arising in the system, but this v i variable represents just one type of a virus particle one particular genotype which has this one antigen associated with it, its numbers are represented by the variable v i. And I could take on any value which is equal to the number of different antigens associated with different virus particles.

Similarly, we have a variable X i which is which represents the magnitude of specific immune system against i. So, remember I is the a particular virus strain and each and the immune system is only going to launch response to very specific strains of virus. So, when you have infections start with the first strain of virus you have v 1, the response that s launched through that particular strain is called x 1. Then after sometime via mutation you have another strain of virus that (Refer Time: 05:59) up inside the host let us call that strain v 2, and then the immune system is really going to recognize that and launch its appropriate response x 2 to this virus v 2, and then via mutation we have v three and immune system s response x 3 and so on and so forth that progression continues and the virus keeps producing these mutant progenies and the immune system keeps trying to catch up with the mutations and launch response against each particular variant that has a reason in the system. So, that s represented by v i and X i and these are not just 2 variables, but this is a just a set of variables associated with different viruses and immune system s response to those different viruses ok.

So, the 2 dynamics that we are interested in understanding is that, how does the virus dynamics of a particular type change with time and what is the immune is response dynamic associated with that virus. So, that 2 dynamics we are interested in are d v i by d t, how does this particular virus strain change with time and d x i by d t. So, we are going to try and give forms to these. So, first is the rate of generation. So, the virus numbers of this strain i are going to change by the rate at which this is being generated minus the rate at which it is being eliminated. And the way it is we are going to think about this is what is the rate at which virus particles of type i are being generated inside the host and one intuitive way to think about this is that the more the virus particles of a particular type inside the host the more is going to be its generation rate. So, this can simply be represented as r times v i, where v i is just the number of virus particles of the type whose rate of change we are interested in and r is the rate of is the rate at which the virus grows associated with that particular strain. Now virus particles are going to get eliminated because of the immune system and that rate can be had by this term called p x

i times v i which is obtained by multiplication of number of virus particles of which we are talking about here times the immune response against that particular type of virus strain.

So, if x i is equal to 0; that means, there is no immune response against this v i against this i strain of virus, then you have a case where viruses are not being eliminated because there is no immune response against that virus to eliminate it. On the other hand if v i is equal to 0; that means, there is no virus of this strain i, then also elimination is 0 because there is no virus to be eliminated. So, this is a basic model that we start with similarly d x i by d t can be modeled as times v i minus b times x i. C times v i represents the case that the immune system is launched with a strength which is proportional to the viral load associated with this strain i, and the second term b times X i represents the case that if there was no virus load associated with this the immune system would no longer need to launch this response and that response is just going to decay exponentially with a constant b associated with it. So, this is the basic model that we have and with these 2 equations the first thing that we should know is what is the steady state condition associated with this response; that means, we have put all the derivatives equal to 0 that is we are interested in what is the rate what is the value of v i and x I, at which the rate of change of these 2 quantities is equal to 0 we put the derivative terms equal to 0 and solve for them and we get at steady state.

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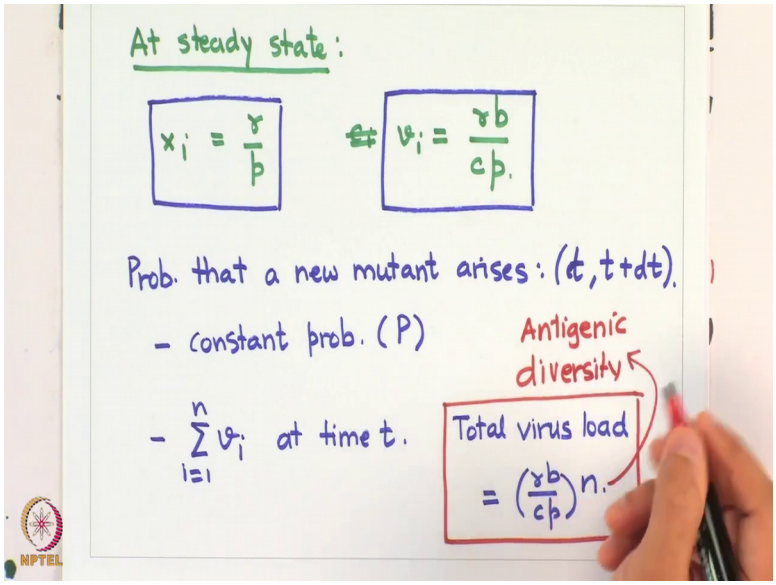

We get the following condition that x i is equal to r by p, and c i I am sorry v i the viral load is given by r times p divided by c times p. So, these are my steady state loads associated with the immune response against the i th viral strain, and the number of the the number of the virus particles associated with strain i.

If you look at this condition if you look at these 2 equations again another solution steady state solution associated with these 2 equations when both the left hand sides re going to be equal to 0 is just 0 0, which just represents the case that when there is no virus particle there is no 0, when the individual is not infected with the virus there is no immune response. But that s not that is an uninfected agent and that s not the dynamics that we are trying to model. If there is a viral infection these are the steady states which are associated with viral numbers and the immune system response which is launched in response to this viral so, but the way the infection starts is it starts with just the just an individual being infected by just one genotype associated with virus and mutants are thereafter generated inside, the host when the virus particles are reproducing and producing more progeny. So, what we do is we say that the probability to incorporate the fact that viral load increases in terms of the number of genotypes are represented inside the host, by modeling that fact with this statement that probability that a new mutant arises, this can be modeled by either saying that that probability arises in time interval say to t plus d t, because mutation occurring of mutation is a random process every time a virus particle replicates you may have a mutation or you may not have a mutation, because there is randomness associated with that replication process, you capture that with the help of a probability.

So, you say that the probability that a new mutation arises in the time interval d t as you move from t to t plus d t, is either a constant probability and that s represented by a capital P, what you are saying by that and capital P might have a number associated with say let us say 0.1. Which means that what you are saying is that in moving from time t to t plus d t, there is a point one chance that a new type of virus has arisen in the system and you model that when you model that nine times of a 10 you will not have a new virus particle arisen in the system, but one time out of ten times on average, you would have a mutant virus enter the picture and grow from there.

A more representative physiologically representative way to capture this is you say that the probability that a new mutation arises is actually proportional to the total virus load

that is present at that particular instant at time t. And what this is saying is that the probability that a new mutant arises is actually proportional to the total number of virus particles which are present in the environment at that particular time.

Which makes more physiological sense because if you have more number of virus particles in the system then you have more divisions taking place in that d t interval of time that your interval d t interval of time, that you are interested in and if you have more divisions taking place, the likelihood that a mutant virus is going to arise also increases in proportion to the number of division events that are happening. Hence these are 2 ways of modeling of incorporating the fact that there are new virus particles new vs i is being generated in the system, as you move forward in time. So, the total virus load therefore, is a quantity that we are interested in which is the total sum of all virus genotypes which are present in the host, is just given by r b divided by c p times n.

Because each of these x i s and v i s will constitute dynamical equation for one particular virus, and if we do that for all the virus strains that are present then we get the total virus load as this where n is called the Antigenic diversity associated with this associated with the host at this particular time. So, that is the most basic model that we have available; now we want to incorporate 2 different features associated with HIV infection that are not present in the in the current model the first one is that immune system has a basal response against all virus particles.

So, a host does not need to launch immune response to every specific every new virus strain that arises in the host from a fresh, but it has a basal immune response which acts against all of these virus particles, irrespective of the specific immune response that the host launches against each of the new virus strains that arises in the population. And the second thing that we want to model is that HIV the model that we have developed so far, is actually very generic in the sense of in the sense that it captures every infectious agent that might infect an individual.

But what would make the model very HIV specific is the fact that if we were to incorporate the fact that when HIV infects, the ability of the host to launch an immune response is actually compromised. So, that facet of the infection has to be incorporated into the model, and that is what we will do we will make this model that we have started with slightly more complex and incorporate these 2 facets associated with infection.

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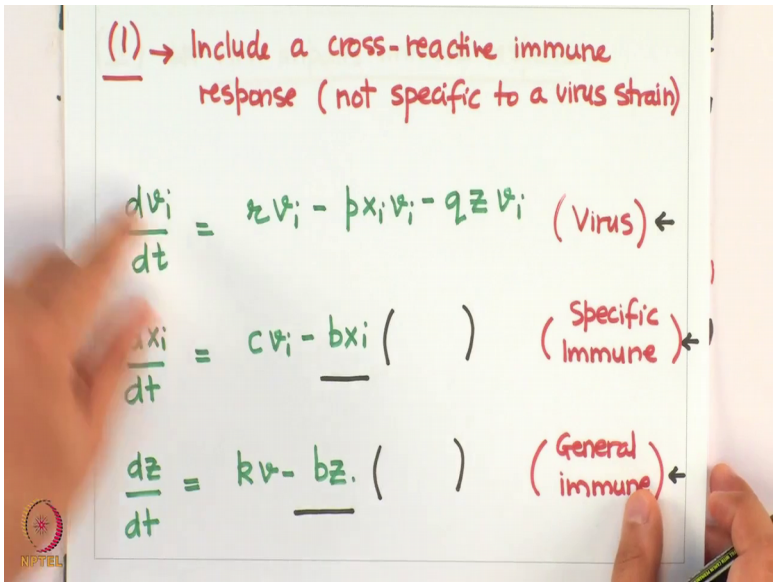

So, the first facet that we want to incorporate in our model is that we will that we wish to include a cross reactive immune response which is not specific to a particular virus strain. And the way we do that is we slightly edit our equations to incorporate this fact we say d v i by d t is just equal to r times v i minus p times x i v i minus q times z v i. Second d x i by d t is just equal to c times v i minus b times x i and last d z by d t k times v minus b z ok.

So, what this captures is the first equation is just capturing the virus dynamics, the second is just capturing the specific immune response. And this is capturing the general immune response and what we mean by that is that x i is the immune response which only acts against the v i virus particles and its very specific in nature x 1 would only act to control virus particles, which are of type x 1. On the other hand z represents the general immune response which acts against all virus particles irrespective of their particular type, and this general immune response are generated which is in a strength which is proportional to the rate of change of launch of this response, is proportional to the total viral load associated with this.

So, the v here is the total virus load associated with all different strains of the virus and it decays exponentially if there were no if there were no viruses inside the host. It is quite similar to the wavy model the x I, the only difference being that this is non specific and acts against all virus types where as the x i response acts only against the against the very

specific virus strain that that is present in the host. So, that s the first facet associated with the system, lets include the second one second aspect that we want to capture in our model and which makes the model more HIV specific and that s the fact that upon infection the ability of the individual to launch the immune response actually gets compromised; and that that is very representative of what happens in HIV and any model that captures HIV dynamics should incorporate that. So, that is.

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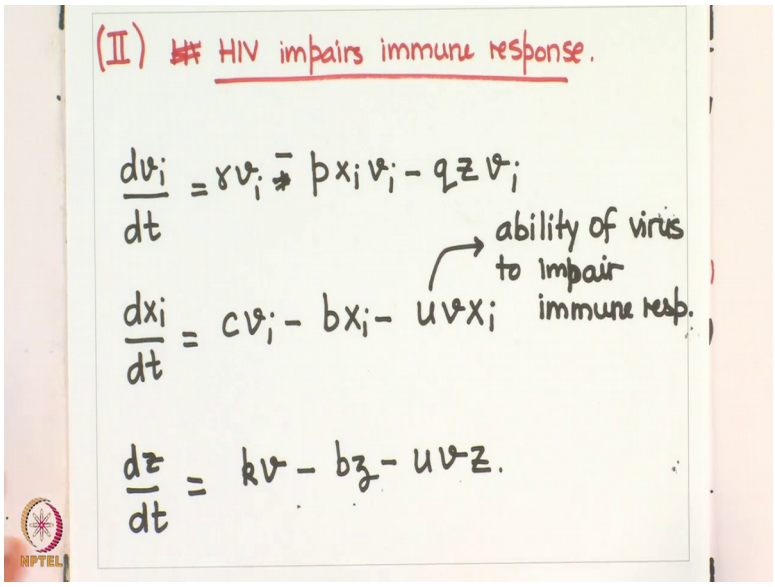

So, this is the second feature that we want to include in our model and that says that HIV impairs the immune response and clearly what should happen.

If we look at the equations that we just derived what should happen is that if we think about it that how do we incorporate a fact such as that into our models. Now what we want to capture is that these virus particles do not permit the host do not permit the immune response to get activated as it would in a normal circumstance. So, if we look at our equations this equation represents the virus dynamics, and these 2 equations represent the immune response dynamics. And what we want to capture is the fact that the virus particles should somehow limit this response. Both these responses if the virus acts to control only the immune response the specific immune response then there should be a term which captures that fact here, and if the presence of virus also compromises the general immune response then there should be a term which captures these 2 responses.

So, the second facet that we are interested in that the virus compromises the immune response should be captured via terms in these 2 equations, and the way we do that is again lets write down our three equations again the first one is just the virus dynamics which is d v i by d t, and this is r times v i plus p this should be minus x i v i minus q z v i. So, this is the growth rate the specific and the general immune response acting against the virus which gives me the viral dynamics for the specific immune response dynamics I have d x i by d t equals c times v i its launched in proportional to the virus load, it decays exponentially in the absence of virus and we add another term which says u v x I, and uv is the factor which represents the ability of virus to impair immune response.

And similarly for the general immune response we have d z by d t equals its launched in proportional to the total virus load, unlike this one which is launched in proportional to the virus associated with that specific of that specific strain. Decays exponentially in the absence of virus and again is compromised u is the factor which decides a sensitivity of this compromise of the immune system by the virus and it is also proportional to v which is the total virus load associated with the host at any at that particular instant.

So, this now captures the dynamics associated with virus the specific immune and the general immune response associated with the host at any particular instant. And if you were to solve these equations they actually tell us a lot about the viral dynamics that are happening inside this host. So, if you solve these equations for steady state, what we would get.

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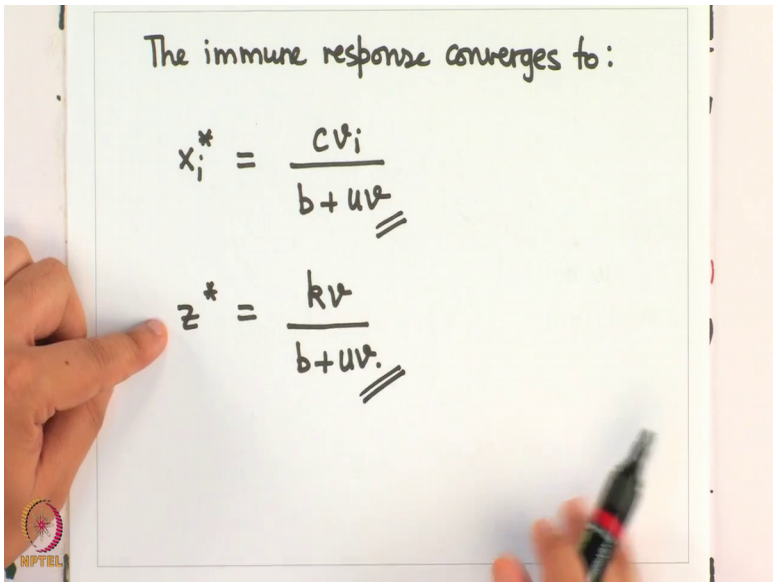

So, if we solve these the immune response converges to the specific viral load associated with the strain converges to this value, and the general immune response which is non strain specific converges to as you can see this is proportional to the specific viral load viral load this is proportional to the total viral load, but these are also normalized by the total viral load. So, this represents the fact that the specific virus load actually is going to converge to 0, if the total virus loads becomes very very high. Specifically in addition the general viral load also saturates if the virus loads keeps on increasing and that saturation value will be given by k by u.

At this junction when the immune response has converged to a steady state values, at that point the viral dynamics can represented as the following.

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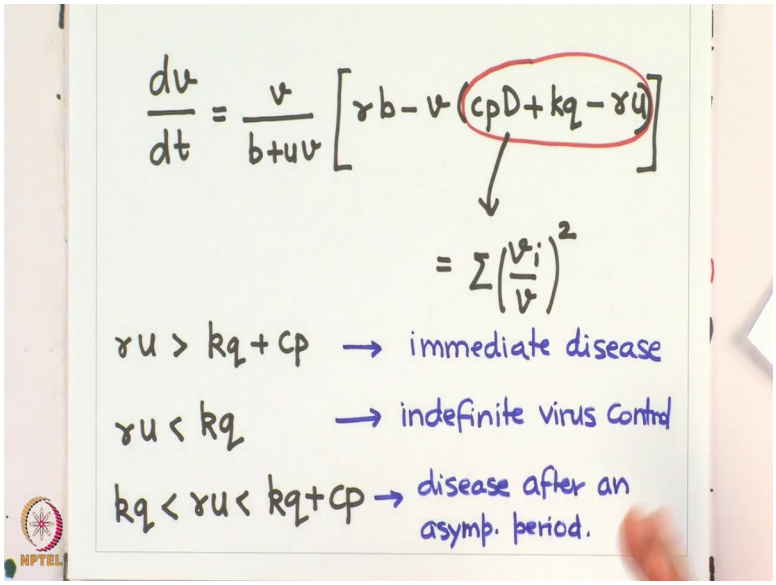

The total virus loads is then represented by this. Where D is just defined as sigma v i upon v square, which is just an inverse measure of the diversity associated with the viral infection. If you have lots of virus particles which together make up the total number v, then d is going to be very small and indicate that there is a high amount of variability associated with various virus particles on the other hand if all the virus particles are represent in the host belong to one particular strain; that means, v i is equal to v in that case d is just going to be equal to one indicating that there is a very low variability that exists between the virus particles, that are present in the host. D is an inverse measure of the variability associated with this, this variability is important because what the virus by continuously generating these new particles is doing instead of tiring the immune system that s associated with the host.

So, once you have this the critical the variable that becomes critical in dictating the dynamics of the viral load is actually represented by this quantity here. Depending on what is the value associated with these you get a different type of a response dictates the dynamics of this thing. And specifically I leave this as an exercise, but you can show that if r u is greater than k q plus c p, or you can have a case where r u is less than k q r you can have a case where k q is less than r u is less than k q plus c p.

Depending on which of the regimes you currently or an individual who is infected with HIV falls in, you can have immediate disease, you can have an indefinite virus control or

you can have disease after an asymptomatic period. So, I leave this as an exercise to work out the details which lead you to this conclusion, but this is very interesting because this tells us that what the HIV is typically doing is operate in this regime, where you lead to disease aids after a long asymptomatic period. And any strategy that works towards treatment of this should work such that we move from this regime to the regime where r u is less than k q, where you are indefinitely able to control the virus load associated with this.

So, what this tells you is that you can play with these parameters and hopefully move in a direction which allows you to control, the viral load associated with the individual. So, with the help of this simple example what we have tried to show is that how you can model (Refer Time: 30:43) phenomena as complex as HIV dynamics inside a host, and from this very basic simple models you can gain insights of that. And that sort of brings us to the closure of this course and hopefully through the through these 40 lectures 20 hours of lectures that we have gone through, what I have tried to communicate is that how can we approach biology evolutionary biology using simple mathematical models which allow us and give this give us this framework in which we can put biological phenomena and building of this framework allows us to quantitatively define biological phenomena and gain some insight via these mathematical models.

Thank you very much.