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**PROFESSOR:** So today, what we want to do is we want to talk about two related topics. The first is going to this question of the evolution of virulence and how to model host-parasite interactions more broadly. That's kind of modeled on chapter 11 of Martin's book. We'll focus on the first half of it for the discussions today.

This is in the context of when a given host can only have one strain of the parasite or virus or whatnot inside that body. The model presented in Martin's book is very similar to classic models in epidemiology, which are the so-called SIR type models, where you divide up the host population into whether they are sensitive-- i.e., non-infected-- infected, or resistant.

And then, we'll draw the parallels of how we get from the model that you read about in Martin's book to the classic SIR models. But in both of these cases, the fundamental parameter that drives these things is this  $R_0$  parameter. It tells us about the expected number of new cases that will result when you introduce one infected member into the population.

**AUDIENCE:** Sorry, will you be taking about super-infections?

**PROFESSOR:** Only a little bit but, I would say, depending on time. But if you're interested in the super-infection discussion more, we can talk about it after class, maybe. All right. And so, for the second half of class, what we're going to do though is we're going to talk about the possible evolutionary benefits of sex.

And in particular, we'll talk about this hypothesis, which is one of the reigning hypotheses for why it might be that sex is as widespread as it is, which is the Red Queen hypothesis, from Lewis Carroll's novel. And we're going to discuss this paper that you guys read about, "Running with the Red Queen," which I think has a nice

discussion of this debate and, then, some nice experiments looking at experimental coevolution between the *C. elegans* worm and its infecting parasite, which is a *Serratia* bacterium. Any questions before we get going?

OK, what I want to do is start by discussing this model in Martin's book. But also, there's a little bit of this philosophical question. Any time, that you are modeling, you always had to make decisions about which of the details you want to try to model and which of the details you do not want to model.

And depending upon the situation, it may be that some assumptions are more or less appropriate than others. Now, in the model that Martin wrote down-- well, we'll try to figure out what the assumptions are here.

So we have what you might think of as some sensitive individuals. Plus, the infected individuals are going to interact at some rate,  $\beta$ . So this is how the sensitive become infected. And it results in, now, two infected individuals. Now of course, each of these individuals will, say, have some lifespan or die at some rate.

All right, so the sensitive or uninfected individuals die at rate  $u$ . Whereas, infected individuals, others-- an increase in the death-rate, described by some virulence,  $v$ . OK? OK. Now, the model as written-- what's going to be the fate of the population?

**AUDIENCE:** Everyone all dies.

**PROFESSOR:** Yeah. Everyone's going to die, right? And that's even true in the-- it's not even that the population's dying as a result of the infection. Because even in the absence of any infected individuals, you just have people dying. So you need to have some way of keeping the population going, so you can study it perhaps. What we're going to assume is that sensitive individuals, or uninfected individuals, will enter the population just at some rate,  $k$ .

Now, in terms of the philosophical question, in the beginning of the chapter, Martin talks a bit about this question of microparasites versus macroparasites. And I can somebody remind us, what's the distinction? and For what kind of parasite might this be intended to model? Yes?

**AUDIENCE:** Well, what I got from it is that microparasites are on the order of single-cellular organisms, generally things that have much shorter reproductive steps, I guess. They reproduce a lot more frequently.

**PROFESSOR:** That's right.

**AUDIENCE:** Whereas, macro-parasites are like the [INAUDIBLE] or the tapeworm or something, which would not necessarily reproduce a lot inside the host.

**PROFESSOR:** Mm-hm. Right. And I would say, that just given this distinction between the microparasites, that might be viruses and bacteria, as compared to the macroparasites, that are things like tapeworms and so forth, it's not obvious from that that you would have two different modeling frameworks.

But what is the argument that is made in Martin's book? Or can you think up an argument for why it is that it might be this kind of model you would want to use for microparasites? Yes.

**AUDIENCE:** Because we don't really care about-- he mentioned something that the microparasites reproduce in large numbers in infected individuals. So we don't have to keep track of the internal state of someone that's infected.

**PROFESSOR:** That's right. And some of it's, maybe, even a historical thing. There might be huge numbers of viruses-- a flu virus or so-- in an infected individual. And in some ways, maybe, the number of viruses that is in that host is not the most relevant thing. And it's certainly would be much more complicated to try to keep track of that.

And so, if you can get meaningful predictions-- rather than keeping track of the number of viruses, say, in each host, instead you just put the host into different classes-- sensitive and infected, for example. Later, we'll talk about what happens if you have a resistant type of class. But the idea there is that there's, maybe, even also some separation of time scales. Because you get infected. And kind of quickly, you're just sick and may be infective.

But at some rate, you get better. And it's not that you'll necessarily gain very much by keeping track of the precise number of viruses in the host. Of course, this is ultimately an experimental observational question of whether this sort of model provides you inside that you're going to need to make sense of these diseases, right?

**AUDIENCE:** And then it also seems like your method of transmission of macroparasites can be very different.

**PROFESSOR:** That's right. So the mechanism of transmission depends very much on the disease that you're studying. And the macroparasites, in many cases, they're transmitted not from direct interactions between the hosts, but through the environment or something else.

It's also, perhaps, just worth pointing out that parasites are just a ubiquitous aspect of life. So you can name an organism, and you can pretty much be guaranteed that there's going to be some notion of a parasite on that organism. And there can be multiple layers of this. So we certainly have many parasites. We're infected by many viruses and bacteria and other things.

But bacteria-- we think of them as being very small-- they're also preyed upon by these phage, which is a parasite that targets specifically bacteria. So it's not just that it's an incidental thing. But these are really viruses that have evolved specifically to divide in bacteria.

And we didn't really talk about this very much. But one of the classic models for cooperation and cheating is based on what you could think about as some sort of parasitic sub-population within phage. So this is a classic paper by Lin Chow where he showed that if you evolved phage and bacteria in a condition where many phage infect a given bacteria, then, you can evolve what you could think of as cheater strategies or cheater phage.

Because these are phage that maybe can't reproduce on their own, but have shorter genomes and can out-replicate the normal phage. So if both of these end

up in a single bacterial cell, then these cheater phage can spread by taking advantage of, say, the replication machinery from the rest of the phage. So in some ways, you might call that some sort of DNA parasite or so. So there's really parasites in many, many different levels.

**AUDIENCE:** [INAUDIBLE].

**PROFESSOR:** Yes?

**AUDIENCE:** [INAUDIBLE] ultimately think about is, k, is this really the number--

**PROFESSOR:** Yeah, you know, I would say that the k is, in some ways, not a very satisfying feature of this model. Because it makes it feel that the model is very special, right?

**AUDIENCE:** But I mean, in a natural population and rate at which people are born, is that the same change? Or--

**PROFESSOR:** Yes. That was the example I was going to give. It's not clear-- of course, it requires somebody to give birth to kids, right? So in that sense, modeling this as a constant number per unit of time-- which is what we're doing-- this rate k, is a little bit funny. Because then, what you'd really want to do is say, oh, maybe it's these guys that give birth at some rate or so, if you really wanted to be accurate.

So I'd say that this is, in some ways, just a mathematical simplification so that we can get at the heart of the dynamics. And what we'll see is that, in these SIR models, you don't invoke anything like this. But rather, what you do is you assume that, at some rate, infected individuals don't just die. But they become resistant. And then, maybe later, they become sensitive again.

So you need some way of being sure that it's not the case that everybody just always dies. So in some ways, this is more mathematical convenience. And the basic conclusions end up being very robust to these sorts of things.

All right, so in these models, it's always good to be clear about how we go from this framework to something that is more of a differential equation. And what we can do is we can think about these uninfected individuals, i.e. the S-es as compared to the

infected. And we're going to have these guys be  $x$ . And this  $S$  and  $I$ .

So the way that the  $x$  will be changing is that we're assuming that there's always some influx of individuals, which could be birth or migration or something else, that are just always entering. But then, there's going to be two ways that  $x$  is going to decrease. One is that there's just a death rate that is resulting in the absence of infection.

But then, also, there's going to be some rate of infection, which is going to be proportional to  $\beta$ . So this is the simplest way that you can imagine capturing this element that the infected individuals can transmit the infection to the sensitive individuals. So we're modeling them as a well-mixed population, just like in chemical reactions. And somehow, the rate of infection is proportional to the frequency that they hit each other. Certainly, the simplest kind of model you can imagine.

Whereas, the infected individuals-- well, we're going to have an increased rate of death. So this is a simplified way to write it. So this is really that there's a minus,  $u$  plus  $v$  times  $y$ . So this is just the death rate. But then, any individual that leaves the sensitive class-- this minus  $\beta xy$ -- enters the infected class. This makes a lot of sense, I think.

Now, the question is, can we make sense of what's going on? Now, you saw in your reading what this  $R_0$  parameter was. And you should always remember that it's defined as this thing of, if you introduce one infected individual into a population of sensitive individuals, what is the mean number of new infections that you get?

And it makes sense that the key thing is whether that  $R_0$  is greater or less than 1. Because if it's greater than one, that leads to this exponential explosion of the infected individuals. It doesn't mean that everyone's going to die, necessarily. We'll get into that. But if  $R_0$  is less than 1, then you expect that infection to die out.

So why is it that if  $R_0$  is greater than 1, and you introduce one infected individual, it doesn't necessarily lead to a wipe-out of the entire population? Or maybe it does. This model is a little funny. Because you always have an individual entering. But--

**AUDIENCE:** If the [INAUDIBLE] is really virulent, then only infected individuals die before--

**PROFESSOR:** Right. So if it's very virulent, then the infected individuals may die quickly. And this gets into this question of there may be some trade-offs in terms of virulence. And we'll talk more about, then, the evolution of virulence. But there's a wide variety of classes of models, not just the ones where you have  $k$  entering.

But the question somehow is-- just because  $R_0$  is greater than 1, that doesn't mean that the entire population will necessarily become infected. Because we have this idea of an exponential growth of the infected population if  $R_0$  is greater than 1. So why is it that it's not necessarily going to happen that the entire population is-- well, this question's a little bit ill-posed in this model.

**AUDIENCE:** Is it because the number of sensitive individuals becomes very low at some point and--

**PROFESSOR:** That's right. And I think this is the basic intuition. As more and more members of the population become infected, then that could, in principle, reduce to the possibilities for new individuals to be susceptible. And I'm using susceptible and sensitive interchangeably. And so eventually, this exponential growth of the population can be limited in some way.

We'll maybe look at this a little bit more in this SIR model. Because it's more clear.

**AUDIENCE:** So we basically collect a rate.  $R_0$  is a rate, right? [INAUDIBLE].

**PROFESSOR:** No. It's a number. It's the expected number of new infections that you get when you introduce one infected individual into the population. And we're--

**AUDIENCE:** It's like, period. So there's not, like, per-unit time or--

**PROFESSOR:** It's a number, period.

**AUDIENCE:** OK, so if you have  $R$  equal to 1, you expect that when you introduce an infected individual into a population of sensitive individuals, you will get one other infected individual.

**PROFESSOR:** That's right. So that's kind of the neutrally-stable situation. If  $R_0$  is 1, then you add one infected individual and you expect to get one other one, so you have a random walk and-- well, in general, it will randomly go extinct, eventually. Yes?

**AUDIENCE:** What is the lifetime of the infected--

**PROFESSOR:** So it depends. And so, that's what we're going to do right now is see if we can reconstruct what this  $R_0$  is equal to in this model.

**AUDIENCE:** Another quick question-- what's the distribution of the-- so--

**PROFESSOR:** Yes.

**AUDIENCE:** --a deterministic role--

**PROFESSOR:** Yes, exactly. So this is very interesting. The question is, what is going to the distribution of the number of infected individuals? And in this model, we're assuming that every infected individuals is the same. So we should be able to-- I wish that we just, on the wall somewhere, had our five different standard probability distributions, so that we could always go back to them.

So the question is, in this model, if you introduce one infected individual in the population, how many new infected individuals do you get?  $R_0$  tells you about the mean. But will you always get the mean? No.

So let's all think about this for 10 seconds. And we will verbally yell out what we think the distribution will be of the number of new infections from a single infected individual. OK? Verbally, ready! Five, (WHISPERING) four--

**AUDIENCE:** Poisson.

**AUDIENCE:** Piosson.

**AUDIENCE:** Exponential

**PROFESSOR:** All right, everybody thinks it's Poisson. Why would it be Poisson?



**AUDIENCE:** Because you have a rate--

**AUDIENCE:** It's not a rate.

**AUDIENCE:** It's not?

**AUDIENCE:** The initial population is much larger--

**PROFESSOR:** Right. OK, so the idea is that we imagine we're some infected individual. And there's some rate that we are infecting others. Now, if I ask you the question, how many individuals will I infect in the next 10 days? Or we could do 21 days if you guys like that. So all right, if I ask, how many do I infect in the next 10 days?

Now, I'm assuming that I stay alive. But let's say, assuming I stay alive, how many do I infect over the next 10 days? That's going to be distributed as-- that is Poisson. But the question you're asking is a different one. You're asking, what is going to be the distribution of the total number of new infections that I cause? And this is precisely the same situation that we've analyzed lots and lots of times. What does it look like?

**AUDIENCE:** Geometric distribution.

**PROFESSOR:** Hmm?

**AUDIENCE:** Geometric.

**PROFESSOR:** OK, yes. It's going to be a geometric distribution. But why?

**AUDIENCE:** Well, because you can have an infection and then another infection. And so then, it's, like, multiples of ten.

**PROFESSOR:** That's right. So we have an infected individual. There's two things that can happen. He's going to die at some rate. And there's this other rate, which is going to go as  $\beta$  times  $x$  or so, telling us about the rate of new infections. And we want to know, how many times do we go around this loop before we degrade, or die, or something, disappear from the population? Does this look at all familiar?

**AUDIENCE:** Mm-hmm.

**PROFESSOR:** All right. Were you guys the same students that were here for the first half of the class?

**AUDIENCE:** Ha.

**PROFESSOR:** Yeah? No.

**AUDIENCE:** And so,  $R_0$  is like the [INAUDIBLE]? It's like the number of--

**AUDIENCE:** It's the mean number for bursts.

**AUDIENCE:** You haven't evaluated when the population--

**PROFESSOR:** So  $R_0$  is the mean size of protein bursts, in the context of this other model, which was-- what was the situation? And this one's a really good one for you guys to know. It's going to be useful. So we saw this exact model in the context of gene expression. And what was the situation that we--

**AUDIENCE:** Production of [INAUDIBLE].

**PROFESSOR:** Production of--

**AUDIENCE:** --proteins from a single mRNA.

**PROFESSOR:** Yeah, the production of proteins from a single mRNA. Right? Because remember, we had this thing where we had the mRNA. And we said, oh, well the mRNA is going to be degraded at some rate. But also, it's going to be translated at some rate. So the distribution number of times that it's translated before it degrades is going to be geometric. Because we go around this loop some number of times. All right, so this is the same thing.

And the paper that I put as supplementary reading, by Jamie Lloyd-Smith? I always get his name and Jamie Lloyd Wright-- right? Something-- mixed up. But yeah, Jamie Lloyd-Smith. Smith. So he was studying the dynamics of infections when you

have this thing where there's intrinsic variation in, say, the infectivity of an individual. Because here, you get this geometric distribution, even though all the individuals are, in principal, identical.

Now, the question is, if there's some distributions of, say, infectivities, then you'll get an even broader distribution of resulting number of new infections. So there's this classic thing of Typhoid Mary. She's was a nurse-- OK, now I don't remember the story. Yeah?

**AUDIENCE:** She was a cook.

**PROFESSOR:** A cook. Oh, a cook, nurse--

**AUDIENCE:** [INAUDIBLE] so she cooked for a lot of people.

**PROFESSOR:** OK, so she was somehow resistant to typhoid. But then, she was cooking for other people and, so then, caused a bunch of infections. Is that--? OK. Yeah, so this would be an example of a very infective individual that's beyond the assumptions in this model. And as you can imagine, if you have variations in this infectivity, then what it does, for a given  $R_0$ -- so if you fix  $R_0$ , then you have a broader distribution of infectivity.

What it means is that a larger fraction of the infections will go extinct. But those that get going will be explosive. If you're curious about these sorts of ideas, you should look at this optional reading paper that I put out there. All right, so I just want to be clear. This is geometric number of new infections, distribution of new infections. Yes?

**AUDIENCE:** So is this just one cycle? Like, one--

**PROFESSOR:** So we're talking about the number of infections that result when you just add one infected individual to the population.

**AUDIENCE:** OK, so then, you don't think about, afterwards, what happens to those infected individuals and if they infect--

**PROFESSOR:** Well, we are not yet thinking about them. Although, in this case, those are also geometrically distributed. But what you expect is that the mean of those things will change. Because the number of susceptible or whatnot individuals-- that's going to change. So the mean number is going to change. But the distributions will still be geometric.

**AUDIENCE:** But in total, that won't be geometric anymore. Because if we're looking at the total number of infected individuals after learning about the geometric--

**PROFESSOR:** No. So just because each of these sub-steps is geometric does not mean that you end up with a geometric distribution. Indeed, let's say that I put in 20 infected individuals into the population. And I ask, what's going to be the distribution of the number of infections caused immediately from those 20? That's going to be what?

[INTERPOSING VOICES]

Yeah, and for 20, it's going to be basically Gaussian. OK, well if I said 100, well definitely Gaussian. It's a gamma distribution that looks very much like a Gaussian, in that case. All right? All right. So we've been talking about the definition of this  $R_0$ . But of course, we should figure out what it is.

We want  $R_0$  is equal to-- and what I'm going to tell you is that there's a  $1$  over  $u$  plus  $v$ . But then, there's some other terms. And I've unfortunately lost my notes. So you guys are going to have to help me figure this out. And what you're going to do is you're going to take advantage of your cards.

And again, put things in the numerators and the denominators, corresponding to how I'm supposed to fill out this equation. You can start thinking about it while I give you the options.

OK. So I guess you could recapitulate this by just putting B and C, although maybe you need it more than once. Do what you will. Do you understand the question? There's going to be something else I'm going to put right here. And I want to know-- there are going to be somethings in the numerator, somethings in the denominator. I'm going to give you 30 seconds to think about it. Because it's important to be able

to reason your way through this.

All right, do need more time? Yep, OK. I'll give you another 15 seconds. All right, let's go ahead and vote. Ready? Three, two, one. All right. I like it! We're really looking quite nice. So there's a claim that it's going to be  $\beta k$  over  $u$ . We should be writing a  $\beta k$  over  $u$ . All right.

Can somebody explain how they got there? Yes, please.

**AUDIENCE:** Well, it's going to be-- these two--

**PROFESSOR:** OK, yeah. This helped, right? OK, good, perfect. So this thing is what? What is this term here?

**AUDIENCE:** That's the death rate.

**PROFESSOR:** Right. Which means that the one over it is the expected lifetime of an infected individual. So the definition of  $R_0$  is, you put an infected individual into a population of susceptibles. Now, we want to know, OK, well there's a expected lifetime of this infected individual, which is given by this.

And then, we have to think about, well, what's the rate that we're going to be infecting individuals? And that's going to be  $\beta x$ . But what we want to know is, is  $x$  before we add any infection? And without any infection, then we just have a rate of entry and, then, a death rate. So it's just  $k$  over  $u$ . OK?

Now, the key thing in all of these epidemiological models is whether this  $R_0$  is greater or less than 1. And that's going to tell us whether the disease becomes endemic or not, whether, at steady state, we have a population of infected individuals. So  $R_0$ , greater than one, means it's in an endemic population.

Now, in this model, we can then ask--

[LAUGHTER]

**AUDIENCE:** That really is really funny.

**AUDIENCE:** That is the hard part.

**PROFESSOR:** All right. So do you like A, donuts, B, cupcakes, or C, carrots?

[INTERPOSING VOICES]

Yeah, it's quite nice. Does anybody have any notion of why somebody might have-- so Sam likes cupcakes. That's good to know. Yeah, they're so pretty that I actually feel bad erasing it. OK, well, we'll leave it up there --

[LAUGHTER]

--for a little bit longer. Everybody can just smile, because they know that the drawing is back there.

[INTERPOSING VOICES]

All right. So in this model, the fact that  $R_0$  is this parameter that tells us about whether there's going to be an epidemic and then, indeed, whether later the disease will be endemic, does that already tell us that  $R_0$  is what's maximized by selection?

No. Right? What was the key thing that Martin does in the chapter in order to try to understand something about what strain is selected for? Yes?

**AUDIENCE:** Are you thinking of when he introduces [INAUDIBLE]?

**PROFESSOR:** Right. Yes, although, the part of the chapter your thinking about is, I think, the second half. It's talking about super-infection, where there's all these different types, and craziness, and so forth.

But the initial insight about what is going to be selected for comes from a simpler model than that. So you don't have to think about all those many parasites and those triangles and all the craziness. Instead, there was a simpler model that-- yeah?

**AUDIENCE:** If you have multiple parasites, then study states only that one parasite exists.

**PROFESSOR:** That's right. And so, what he does is he just writes down this model of where he now allows two different parasites to be spreading the population. And at the beginning-- well, we'll write it down. And we want to be clear. There's a very important assumption that he makes.

What he's going to find is that selection maximizes  $R_0$ , the basic reproductive ratio. And it's going to be in this model that I'm writing down now. So there's this  $x$  dot. And things look very similar.

All right. Now, the question is, what is the key assumption that we're making in writing down these equations? Thought?

**AUDIENCE:** One cannot have more than one type of--

**PROFESSOR:** That's right. A host cannot be infected by more than one type of strain. So that's very, very important. So there's no super-infection, as they say. And depending on the disease, this could either be a better or worse assumption. But then, what is it that is defining these two strains then? In what ways are they different?

**AUDIENCE:** In virulence.

**PROFESSOR:** Their virulence is different. And what is virulence again?

**AUDIENCE:** How likely it is that it could kill you.

**PROFESSOR:** That's right. It's the additional mortality that is caused by being affected by that strain. Is that the only way that they're different?

**AUDIENCE:** No.

**PROFESSOR:** No. What else is different?

**AUDIENCE:** The infectivity.

**PROFESSOR:** The infectivity, right. So the betas are also different. And it's imported to note that in

this model-- it's a very simple model-- but we're allowing the strains to be different in these two ways. And I think that it's very intuitive to just say that, oh, well, you want to have a larger beta, all other things equal. Because you would like to spread.

But I'd say, maybe, it's not as obvious what happens in terms of virulence. And then, of course, if you think about these two parameters-- in any biological context they may be coupled. In which case, things are more subtle.

**AUDIENCE:** So how reasonable is something of something of [INAUDIBLE] on the strain?

**PROFESSOR:** Yeah, I think that this depends on the disease.

**AUDIENCE:** [INAUDIBLE]. Is it that you're trading virulence and new response and--

**PROFESSOR:** Right, so that's somehow the argument. And I'd say that, depending on whether you're thinking about the host at the level of an organism or a cell, then this would correspond to very different worlds.

So certainly, in the context of viral infections and individual cells, there are various mechanisms where, if one strain gets in, then other strains have trouble getting in. Or if they do get in, they can't do anything. So I think, this really depends on the biology of the situation, whether this is a reasonable assumption or not.

So I'm not going to go through all of the math. Because it ends up being a little bit involved. But the condition for the mutual invasibility of the two strains is a little bit subtle. So I do want to talk about that a little bit. And so, in general, in this model there's some equilibrium,  $x^*$  and  $y^*$ . And indeed, there will generally be damped oscillations to this equilibrium.

So this is in the model where there's just a single strain that's described by some beta and some  $v$ . Of course, you can also think about the equilibria,  $E_1$  and  $E_2$ , that would result when you have-- so  $E_1$  is what would happen at the equilibrium when you have  $x^*$  evaluated for the particular parameters of strain one, i.e. evaluated for  $\beta_1$  and for  $v_1$ .  $x^*$ -- and that's also  $y^*$ .

Whereas, you would have a different equilibrium,  $E_2$ -- so this is a  $x^*$  and a  $y^*$



star-- evaluated at  $\beta_2$  and  $v_2$ . Do you understand what I'm saying? So these are the equilibria that you would have if this was the only strain that was present in the population or if this was the only strain in the population.

Now, it's not obvious that those-- the equilibria-- are the result when you have both strains present in the population. But that's what we want to try to figure out. But certainly, if you only added strain one and you didn't add strain 2, you would come to equilibrium,  $E_1$ .

So the question is, if we start out at equilibrium  $E_1$ , how is it we can determine what happens if we now add an infected individual, but infected by strain two? So what we want to know is-- strain 2 can invade.

And really, what we're thinking about is a situation-- these are the equilibria if it's the case that  $R_1$  is greater than 1 and  $R_2$  is greater than 1. Because in some ways, it's clear what happens. If both of the  $R_1$  and  $R_2$  are less than 1, then what happens?

**AUDIENCE:** It would die out.

**PROFESSOR:** They both die out. If one of them is greater than 1, one is less than 1. Then, right, the strain that's below 1 goes-- so the only interesting or the only the only non-obvious question, somehow, is what happens if they're both larger than 1?

What that means is that, for example, if you had a population of susceptible individuals, and you had one infected by strain one, one infected by strain two, then, in the deterministic differential equation limit, they would both spread. So they're both exponentially growing. Does that already tell us that you're going to have coexistence of the two strains?

No. It means that they're both exponentially spreading. But who knows what's going to happen later? And indeed, what you can show is that only one of the two strains is going to win. And it's the strain with the higher reproductive ratio, the higher  $R_0$ , or in this case, here.

So how is it that we can determine if strain two can invade equilibrium one? It's if-

and-only-if something. Does anybody remember what this condition ended up being?

**AUDIENCE:**  $y_2$  dot at  $E_1$  has to be positive?

**PROFESSOR:** All right,  $y_2$  dot at  $E_1$  has to be positive. Yes. And this ends up being equivalent, I think, to what he writes. So let's write. I'll write and tell you. So the way that he wrote it, is that it's  $y_2$  dot, with respect to  $y_2$ .

But I think that this is really equivalent to what you said. Because you said, OK,  $y_2$  dot has to be something, right? But then,  $y_2$  dot evaluated what? And you would say, evaluated at  $E_1$ . But then, at  $E_1$ -- what is  $y_2$  dot evaluated at  $E_1$ ?

**AUDIENCE:** 0.

**PROFESSOR:** 0, right? Because at  $E_1$ , there is 0  $y_2$ . So then, of course,  $y_2$  dot is 0. So it's almost what you want, but not quite. So this condition, which looks very weird, is really saying that, if we are at  $E_1$ -- so there's no infected type-two infections-- what we want to do is add a little bit of  $y_2$ .

And then, we want to ask, what is  $y_2$  dot? And this derivative, evaluated at  $E_1$ , somehow allows you to do that. And do we want this to be greater than 0? Or less than 0? We're going to do verbal answer. Ready? Three, two, one.

**AUDIENCE:** Greater.

**PROFESSOR:** Greater, right. Because if it's saying you add a  $y_2$ , you want  $y_2$  to start growing. So you want this thing to be greater than 0. And this looks really crazy. But it's actually pretty easy to do. Because you take the derivative of this thing, with respect to  $y_2$ . And you just get the thing in parentheses, right?

But you evaluated it at  $E_1$ . So it's  $\beta_2$ . And this is  $x$  star at  $E_1$ , minus  $u$ , minus  $v_2$ . And this thing has to be greater than 0. But this is  $x$  at  $E_1$ . That's  $u$  plus  $v_1$  divided by  $\beta_1$ . So what we have is  $\beta_2$ , then,  $u$  plus  $v_1$  divided by  $\beta_1$ . And this thing has to be greater than-- we'll move this over to the other side--  $u$  plus  $v_2$ .

OK, so this is not so horrible, right? There's a  $u + v_1$ ,  $\beta_1$ , right? I just want to make sure I write-- (WHISPERING)  $u + v_1$ . (NORMAL VOICE) OK, we have to these in the denominators now, somehow. So we'll put divide by both of these things. So we have a 1 divided by a  $u + v_2$ . 1 divided by  $u + v_1$ . So we put these things in the denominator.

And now, the  $\beta_1$  is going to come up here. So we have a  $\beta_1$  and a  $\beta_2$ . And there still is a greater-than sign. Did I screw anything up yet? Maybe? No? All right. Now, we can do something wonderful, which is we can just multiply by  $k$  divided by  $u$ . And so what does this say?

**AUDIENCE:**  $R_2$  is greater than  $R_1$ .

**PROFESSOR:**  $R_2$  is greater than  $R_1$ , right? And what were we trying to calculate? How did we get started on this math?

**AUDIENCE:** What can [INAUDIBLE] the strains.

**PROFESSOR:** Right, we wanted to ask, strain two can invade the equilibrium one, if and only if  $R_2$  is greater than-- now, that's interesting, right? So that's saying that, if you start out with the endemic strain one and you add the strain two in there, it's going to be able to invade if it's  $R_2$  is greater than  $R_1$ . That's not obvious.

Because  $R_2$  and  $R_1$ , that was telling us about a different situation. That was telling us about what happens when you add those infected individuals into a population of susceptibles. But this also ends up telling us about what happens when the strains are competing against each other.

So this is so simple that it feels trivial. I'm sure that if you understood it well enough, it would be trivial. But you'd have to think about it more than I have. So I think this is surprising.

Now, you can also ask the same question, which is about whether strain one can invade strain two. And that is kind of the same thing. So it all comes down to the orderings of  $R_2$  and  $R_1$ . And what you find is that, if this condition is satisfied, strain

two will drive strain one out of the population.

**AUDIENCE:** What if they strains are the same?

**PROFESSOR:** So if they're the same, then you can get coexistence. But as Martin says, it's non-generic, in a sense that it's kind of a coincidence, or it's of measure 0, the situations in which the two will have the same R parameters.

But of course, you could imagine-- just like we talked about all this neutral evolution business-- things are nearly neutral and so forth, da-da-da-- you can kind of invoke similar ideas. Because you can imagine that, as these two become closer and closer to each other, it's going to take longer and longer for the more-fit strain to out-compete the less-fit strain.

Now, even though this is such a simple condition and the R parameters have such a simple physical origin or mathematical origin, the actual expression for the Rs is kind of complicated. But again, it's a combination of all of these different parameters, whether it's the  $\beta_1$ ,  $B_1$ , or  $\beta_2$ ,  $v_2$ .

Which board do you think is least useful? Well, I don't want this one anymore.

But in particular, we want to say something about the evolution of virulence in this model and what the expectation is. So what we're going to do is I'm going to give you some different situations, in terms of how the infectivity depends upon the virulence. And then, you guys will get to tell me how the virulence will evolve.

Now, this is virulence,  $v$ . All right, so the first situation is if  $\beta$  as a function of the virulence-- so the infectivity as a function of virulence is, we'll say, some  $\beta_0$ . So first, the question is, if the infectivity does not depend upon the virulence, where will virulence go to? You have equation, various places that'll help you.

Do you need more time? No? All right, ready, three, two, one. OK, we've got many A's. That's great. So if it's the case that the parasite, regardless of how rapidly it's killing the individual, has the same rate of getting to other individuals, then we want to make the  $R_0$  to get as large as possible. So then, we make  $v$  go as small as

possible. That's the mathematical thing you can look at. And why does this make sense?

**AUDIENCE:** You're killing people off, and you're infecting most people. But--

**PROFESSOR:** Yeah. So from the standpoint of the parasite, in this situation where the infectivity doesn't depend on the virulence, well in that case, you don't want to kill your host. Because the longer that the host lives, the more other individuals you can infect.

And this is the basic statement underlying the statement you often hear that a well-adapted parasite does not harm its host. And I think this is one of those things that you can write down a simple model and convince yourself it should be true. You can maybe find a few case studies where it seems to be true.

But then, you always have to be careful about how strongly you should believe such a statement based on those kinds of evidence. Because it's a very simple model. It's making an assumption that is very likely not true and, actually, many assumptions that are very likely not true.

And there are counterexamples. So Martin talks about malaria, which humans have had for millions of years, and still causes a lot of problems.

And so you might imagine, what would happen if the infectivity is a function of the virulence? Maybe it's just proportional to the virulence. And this kind of would make sense. Because you say, oh well, let's imagine that the number of viruses in the host-- that somehow, the virulence is proportional to that number. And also, the infectivity is proportional to that number.

In that case, infectivity will just scale linearly with  $v$ . It's kind of another reasonable world. So in this situation, where does the virulence evolve to? We'll think about this for 10 seconds. Ready? Three, two, one.

All right, so now we actually have votes that are pretty distributed around. OK, I'm just going to write down the expression. Just because I think we can do it quickly.

So now, the  $R_0$  is going to be given by-- we're going to be thinking about a 1.

There's a  $u + v$  down here. But beta-- we're going to put beta here. This is an  $a$  times  $v$ , and then a  $k$  over  $u$ . Right? So if we plot this as a function of  $v$ , what does it look like?

**AUDIENCE:** It monotonically increases.

**PROFESSOR:** Monotonically increases. This is a Michaelis-Menten type form where the  $R_0$  is a function of  $v$ . It starts out linear and, then, saturates. Oops, this is not  $v$ . This is  $R_0$ . If we want to maximize  $R_0$ , then  $v$  goes to infinity, right?

There was one other model that Martin talked about, which was the situation if the infectivity itself. It had a kind of Michaelis-Menten type form. And we still have an  $a$  there. So it's some  $a, v, c$  plus  $v$ . So this would be the situation where, initially, the infectivity increases with virulence. But beyond some virulence, you no longer get an increase in infectivity.

So for example, if it's the case that every time you sneeze on somebody you're going to infect them, then it doesn't matter if you double the number of viruses you have. You've still saturated the infectivity. Now, I'll just tell you that, in this case, there ends up being some intermediate infectivity that you evolve to, which comes here.

And indeed, this makes sense. As  $c$  goes to infinity, so if  $c$  is very large, then it just looks like this. It's divided by something large. But in terms of the scaling with  $v$ , it's just linear in  $v$ . And that means that the evolved virulence goes very large. Does that make sense? No?

OK. So I guess what I'm saying is that, if you're in the region where  $c$  is somehow very large, then you end up with the infectivity just being proportional to the virulence. Because the virulence, the  $v$  here in the denominator, doesn't really contribute very much.

And that means that it's going to be the same kind of functional form as this. Except if it's  $a$  divided by  $c$ . But it's still proportional to the virulence. And that leads to a

larger and larger evolved virulence. OK? Yep? Yes?

**AUDIENCE:** Is it possible to say something in actual infection, what the data is? Is it virulence? Or can you [INAUDIBLE]--

**PROFESSOR:** Yeah.

**AUDIENCE:** --other than just these verbal--

**PROFESSOR:** Yeah, right. So I think, from real data, I think people do argue about it. But I think it seems to be there is some sense that it does plateau. But it's an increasing function of  $v$ , but sub-linear. And the question is how strong of a statement you can make there.

Because also, in many cases, there is super-infection. And super-infection tends to lead to even higher virulence than what you would expect from this. Because you're competing against viruses in the same host. So you have to out-compete the other parasite in the host, as well as go on. And you don't pay the full cost associated with keeping the host alive.

So when you have super-infection, there's this notion that the better strategy, from the standpoint of the parasite, can be to just evolve very high virulence. So you're going to kill the host. But you can get out quickly. So then, you can imagine that the less-virulent strain was kind of stranded in that host that died.

So from that standpoint, you can think about, in some cases, for a parasite, evolving low-virulence is somehow like some cooperative behavior. Because you're keeping this host alive. You're using the resources in a wise way, so that you can infect other individuals.

But then, that kind of strategy is susceptible to these cheating strategies that just have high virulence and kill the host and, then, get on to a new host.

Yeah, so I think there are enough of these issues that it's hard to take any of this too seriously. I would say that, perhaps, where this field has had the biggest impact is in the context of vaccinations. Because you can really measure  $R_0$  for many

different diseases.

And I think that's somehow easier to measure than many other things. Because you can try to do tracing of infections. So if you think about somebody that gets infected and moves to a new city or lands in a new city, you can try to figure out who they infected. So then, you can go and measure these  $R_0$  parameters.

And of course, the diseases that we worry about tend to have  $R_0$ s larger than 1. And how large they are tells you about how difficult the vaccination will be in order to be successful and to remove the disease from the population.

So if you're curious, after class, you can come up. And there's a nice table that I have here for smallpox, measles, whooping cough, German measles, chickenpox, diphtheria, scarlet fever, mumps, and poliomyelitis. Estimates of  $R_0$ s-- and they kind of range 5 to 15, to give you a sense.

And so, if you want to remove the disease from the population, what is it that changes? --in terms of vaccination, in order to remove the disease. Yes?

**AUDIENCE:** In  $R_0$ , then, the [INAUDIBLE] for  $u$ , as the population available [INAUDIBLE].

**PROFESSOR:** That's right. So by vaccinating you're removing susceptible individuals from the population and making them resistant somehow. And the  $R_0$  parameter tells you about what fraction of the population you have to vaccinate in order to remove the parasite from the population. And so, basically, you have to vaccinate a fraction, a percentage,  $p$  that's greater than  $1 - 1/R_0$ .

So as  $R_0$  gets very large, it means that you have to vaccinate, essentially, everybody. So if you have  $R_0$  of, say, five-- which is typical of many of these diseases-- it's saying you have to vaccinate 80% of the population. You can never get to 100%. And that's why it's very difficult to get rid of these diseases with large  $R_0$ s.

And incidentally, they note that smallpox has an  $R_0$  of 3 to 5. And this always depends on the environment. But in the case where they measured, smallpox  $R_0$  is



3 to 5. And this is sort of small, as compared to many of these diseases.

And this is telling us that smallpox is easier to get rid of via vaccinations than many of these other diseases. And indeed, the vaccination procedures have been more successful in smallpox than the others.

**AUDIENCE:** Do you know what is 3, 4?

**PROFESSOR:** I don't. But maybe in the next 20 minutes, somebody can Google this. We can estimate this right now, though. We've had, what? --five Ebola patients come to the United States. And we've gotten two or three infections. So I'll say, 3/5.

[LAUGHTER]

It obviously depends on the environment, right?

**AUDIENCE:** Yeah.

**PROFESSOR:** Yes.

**AUDIENCE:** I mean, I guess that was my question. You're not going to take someone with Ebola and throw them in New York City and just measure how many people they infect.

**PROFESSOR:** That's right.

**AUDIENCE:** So--

**AUDIENCE:** That would be [INAUDIBLE].

**AUDIENCE:** Like--

**AUDIENCE:** [INAUDIBLE].

**PROFESSOR:** Yeah, but the thing is, you don't have to do anything that's so immoral. Because what you're interested in is the R0 for individual in an actual environment that they're actually going to be in. So this is a situation where the doctor comes back from Africa after working with Doctors Without Borders. In this day and age, he knows that he has to watch out for a fever, da-da-da. And then, if he gets a fever,

he calls in. And he's brought to the hospital.

And that's the world that we're interested in of what the  $R_0$  is. It's not the world in which there's fevers everywhere and nobody knows. So the  $R_0$  in the United States is going to be much lower than the  $R_0$  somewhere else. Yeah?

**AUDIENCE:** Is there enough of  $R_0$  for a disease that you don't transmit between people? You get malaria or the plague--

**PROFESSOR:** Yeah, right. So I think that you could try to generate a similar kind of  $R_0$  for those to diseases. Although, it's going to be very muddled, in the case of where you have all the vectors and so forth. Because it's not even clear-- yeah, I'm hesitant to say too much. Because I don't know anything.

**AUDIENCE:** According to Wikipedia, it's like 1.5 to 2.5.

**PROFESSOR:** For Ebola?

**AUDIENCE:** Yeah.

**PROFESSOR:** Here? Or in--

**AUDIENCE:** It says the 2014 West Africa aggregate.

**PROFESSOR:** Ah, so this is in West Africa then.

**AUDIENCE:** Apparently.

**PROFESSOR:** Right. Yeah And it has obviously spread exponentially, which means it had to have been larger than 1. And I think it's important to remember that, just because you have a chart with a bunch of  $R_0$ s, this is not set in stone. Public policy, hygiene, and everything changes this. And we'd like to drive it down. Was there a question in the back?

**AUDIENCE:** I just was going to say about two.

**PROFESSOR:** Same thing, about two. OK, so that means that we could actually, in principle,

vaccinate against Ebola. We'd only have to get over 50% of the population vaccinated in West Africa. And then, we can maybe make it so it cannot spread and become an epidemic. Of course, we need to have a vaccine first.

**AUDIENCE:** [INAUDIBLE].

**PROFESSOR:** So I think I'm going to skip the discussion of SIR models. Because you are going to play with some of them in the context of your problem set. And if you just Google SIR, you can find it. And a very similar kind of intuition that you get from this model.

Because I do want to spend the last 15 minutes, at least, talking about the evolution of sex. Because it is an interesting topic. And I think the paper is a nice discussion of it. So can somebody say why it is that this is a puzzle at all? Yeah?

**AUDIENCE:** In almost all the situations we imagine and things that can be [INAUDIBLE] introduce much faster, even violating the [INAUDIBLE]--

**PROFESSOR:** That's right.

**AUDIENCE:** --80% [INAUDIBLE] right?

**PROFESSOR:** So sex is costly, and in particular, if you have this obligate bi-parental sex. In particular, there's the so-called twofold cost of males. Because you can imagine comparing these two populations, one of which has both males and females. And one of them is just, maybe, reproducing asexually, or parthenogenetically, or hermaphroditically, or what not.

And so, if you have a male and a female, then on average, if they have two kids, you end up with another male and a female. And of course, this could be many different males and females. So you don't have to have any sibling anything. But if, every generation, each female is giving birth to two progeny, then you end up with a constant population size.

Whereas, if you started out in a population with just two females and they were reproducing hermaphroditically, then you end up with-- whatever-- more. 8. So you can see that you get a factor of 2 in the rate of exponential growth of the population.

Yeah?

**AUDIENCE:** Well, it seems to me the question is not why sex, but it's why males. Right, I mean--

**PROFESSOR:** Yes. So I think this is the most extreme cost of sex. But then, also, you can think about even just horizontal gene-transfer among bacteria. It's a costly behavior in some way or another. It's not as costly as this.

But if you're going to think about bacteria in their competence state, when *B. subtilis* kind of pulls in DNA, it stops dividing. And then, it enters a state where it reels things in. And it can pick up DNA that may be harmful in some cases. So there are various costs for, if you want to call it, horizontal gene-transfer sex.

So the key thing of sexual reproduction is it somehow is the sharing of the DNA. And I'd say that this can either be relatively low cost or relatively high cost. But this is the most extreme version of it. And I'd say, as a species that reproduces with obligate bi-parental sex, then I'd say that, not only humans, but almost all animals have this form of reproduction.

I would say it's sort of surprising, given that this is a huge cost. But it's not that all species that engage in any sort of gene-transfer bear this large of a cost. But they bear more modest costs.

**AUDIENCE:** Well, although, other species do-- even with this [INAUDIBLE], it's like having multiple children per sex.

**PROFESSOR:** You're saying that they can just have more kids.

**AUDIENCE:** Yeah, I mean--

**PROFESSOR:** Yeah, although the basic statement is still true. Let's say that these females all have three kids. They get to grow exponentially. But then, these guys grow faster. And ultimately, there's going to be competition for resources. And these ones will still win.

**AUDIENCE:** Yeah.

**PROFESSOR:** So the question is-- you can imagine you have a population that's reproducing sexually-- if one female has a mutation that leads her to start reproducing parthogenetically, that mutation you'd expect should spread throughout the population very rapidly.

And indeed, there are these cases of, for example, sharks held in captivity where a female held in captivity for years eventually gives birth to daughters. So this sort of virgin birth is possible. I'm not aware-- well, I'm not going to talk about--

[LAUGHTER]

But in some animals, it is at least possible, I'll say. So then, you have to ask, well, what kind of selective advantage could sexual reproduction have that could possibly compensate for this so-called twofold cost of sex or twofold cost of males? And what is the argument that's made in this paper? Anybody? Yes?

**AUDIENCE:** The recombination favors genetic diversity.

**PROFESSOR:** That's right. This recombination is favoring genetic diversity. So there are a number of different mechanisms. I'd say that at the heart of this idea of the Red Queen hypothesis is-- let me see if I can find the actual quote for you guys. Maybe not. So it's from a Lewis Carroll novel, *Through the Looking Glass*. The quote was something-- run-- oh, shoot. Never mind, I can't remember what the quote was.

But the idea is that sexual reproduction may allow a population to adapt against, say, changing environments more rapidly. And this has a couple of reasons. Because you generate genetic diversity. You don't have the same clonal interference effects that we talked about earlier.

So if you have asexual lineages, then, if you have two beneficial mutations, they cannot both fix. So the more fit version is going to fix. And then, you have to wait for the next one. Whereas, in sexually reproducing populations, those genes can spread throughout the population, sort of as genes, rather than being tied to a

particular individual.

So that means that, if you find yourself in a new environment, it may be the case that sexual reproduction can allow for the population to adapt more rapidly. But on one hand, you might say, well, the environment's always changing. So that can always favor the sexually reproducing populations.

But then, there's a feeling out there that maybe that's not enough, in the sense that the environment is not changing rapidly enough and dramatically enough to force the population to reproduce sexually as compared to asexually.

And so, the proposal from the Red Queen Hypothesis is that the constantly changing environment is a result of co-evolution between hosts and their parasites. Because parasites are always trying to target common host genotypes. Because they can spread on those.

So the parasites are evolving. And then, the host populations or genotypes are kind of being chased away by those parasites that are targeting them.

So the notion is that parasites, as a result of this co-evolution, can be the source for the constantly changing environment that may be driving the evolution of sex.

Yeah?

**AUDIENCE:** And this, proportional with [INAUDIBLE], bacteria also get parasites [INAUDIBLE].

**PROFESSOR:** That's right.

**AUDIENCE:** So--

**PROFESSOR:** Yes, so is the question is why--

**AUDIENCE:** Why only in multi--

**PROFESSOR:** Right. So I can give you my best guess on this. First of all, not everybody agrees that the Red Queen Hypothesis is the true explanation, if a true explanation even exists. But within this framework, you definitely want to try to explain why it is that

large life forms seem to have a lot of obligate sexual reproduction. Because this is a very strong pattern that you see.

And I guess what I would say is that there's certainly a correlation between physical size and generation time. And generation time tells you something about the typical time scales over which you can evolve. So my sense of this is it just maybe that, in general, large animals, by their nature, will evolve rather slowly as compared to their parasites.

And so, that means that they are the populations that are most in need of speeding up their evolution. And it's hard to know how convincing that argument should be.

But-- yes?

**AUDIENCE:** What's the difference in reproductive productive time between phage and bacteria? Like, how fast does phage--

**PROFESSOR:** Right. So bacteria can-- as we've discussed, division times are order hour. And phage-- when you get a phage infection, what happens is that the phage you can infect as a single phage. And then, they will divide within the bacterial cell and then burst out as a population of 100, 200-- typical of phage.

And I think that that might take four or five hours, is kind of my sense. And then, they go off and they find new bacteria. So in that sense, it's a little bit faster than the bacteria, I'd say.

So can somebody say what the core experiment was that they did in this experiment? Yes?

**AUDIENCE:** [INAUDIBLE] and one time, it was reproducing asexually when they always produce sexually. And the other time, it was dividing.

**PROFESSOR:** That's right. So this worm, *C. Elegans*-- sort of a millimeter in size-- and there are going to be three different conditions. One is the wild type that can out-cross, can have males mate. Then, there's the obligate out-crossing, which means they have to mate with males.

And then, there's the-- what did they call it? --obligate selfing. OK. And then, what they do with those worms?

**AUDIENCE:** They put them right back to [INAUDIBLE] more typical.

**PROFESSOR:** That's right. So then, there's a bacterial pathogen, *Serratia marcescens*. And they're going to have these three different conditions. For the SM, the bacteria, they're either going to allow for co-evolution, where they take the bacteria from each of the infections and propagate.

Or they're going to do the no evolution, where you just compete against the ancestor. And there's also a control. So there's co-evolution. There's this no evolution of the bacteria. And then, there's also control, where there's no bacteria. And what was the most striking thing that they saw in this experiment?

**AUDIENCE:** I guess I would say that the obligate-selfing population died in evolution.

**PROFESSOR:** That's right. So if you allowed the bacteria to be evolving, against this obligately selfing population, this killed the worms. And what was the other thing that was, maybe, very striking about their experiment? Yeah.

**AUDIENCE:** The worms that did the out-cross or self increased. [INAUDIBLE]--

**PROFESSOR:** Yeah, so this was kind of amazing. So they saw, as a function of time, if you look at out-crossing-- the rate of mating with the males-- this started out at, like, 0.2. And then, in the presence of the co-evolution, it went up. And it goes up to, maybe, 80%. And for co-evolution, it stayed up high.

Whereas, if the wild-type worms continued to be just challenged by the ancestral bacteria, it initially came up. But then, it came back down. So this is the co-evolution. And this is the ancestral SM. So there was a sense that that wild-type population had initially evolved to out-cross more. But then, once it had solved this problem of how to handle the ancestral *Serratia*, the out-crossing rate went back down.

So we are pretty much out of time. But I don't know if you guys noticed the last



sentence of the paper. It is amazing that they got this through the publication process. All right, so they say, "taken together, the results demonstrate that sex can facilitate adaptation to novel environments. But the long-term maintenance of sex requires that the novelty does not wear off."

[LAUGHTER]

It's one of those things that you read and you think-- OK. So I will leave that sentence with you. And then, we'll meet on Tuesday, OK?