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ISCI 330: Game Theory
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Prisoner's Dilemma or Snowdrift: Identifying The Evolutionary Superior Model in Viral Systems

Intracellular viral interaction is a system which is commonly modeled in evolutionary game theory. Current theoretical approaches are applying either the prisoner's dilemma or snowdrift games to model viral interactions (Doebeli, 2005). The problem with this approach is that it ignores the biological mechanisms which lead to the outcomes, thereby leading to conclusions of limited significance. Subsequently the strategies profiles are not linked to the biological processes. Through consideration of the biological mechanisms and subsequent assignment of it into a group, of either cooperating or defecting actions, a game matrix can be constructed which will provide a more realistic model for the viral interactions. This construct can further be analyzed to determine if the viruses that follow a prisoner's dilemma model or snowdrift model game are evolutionary superior.

The behavioral patterns, which are defined by the biological mechanisms of three common human viruses: Polio, Influenza and Human Immunodeficiency Virus (HIV) will be utilized in development of the model to describe some of the intracellular interactions which occur during co-infection of a host cell. A co-infection in this model will consist of two viruses of the same or different species infecting the same cell simultaneously. The specifics of the interactions amongst the viruses inside a cell will be discussed later.

Generally, the virus will adhere to one of two modes of replication, using either a lysogenic or lysolytic cycle. The resource consumption rate differs depending on which replicative mode the virus is employing. Different methods will be employed by the viruses to utilize the cell's ribosomes to produce new viral proteins. New proteins are critical in the production of progeny. Both the replicative mode and ribosome usage will be used to establish six models which will encompass all possible infection combinations separately. The constructed game matrices will then resemble either a Prisoner's Dilemma or a Snowdrift game matrix based on the payoffs of the viruses. The payoffs received by each virus will be determined by the theoretical amount of progeny produced. In the game matrices shown in Figure 1 & 2 the

numbers in the matrices refer to the viruses' preference for obtaining that outcome. The actions for each virus will be to either cooperate or defect. The strategy played by each virus will be based on the mechanism it uses in particular scenario. All the strategies utilized in the scenarios will be pure strategies since viruses which are used are just programmed units which respond to signals in the host cell and choose their mechanism based off of the environment.

	Cooperate	**Defect**
Cooperate	2, 2	4, 1
Defect	1, 4	3, 3

Figure 1. Prisoners Dilemma Game Matrix

	Cooperate	**Defect**
Cooperate	2, 2	3, 1
Defect	1, 3	4, 4

Figure 2. Snowdrift Game Matrix

Poliovirus belongs to the Enterorvirus subspecies which is a group of viruses capable of surviving in low pH environments (Kion, 2006). Poliovirus causes a disease known as Poliomyelitis, commonly known as Polio. While Polio has been eradicated in most of the developed world it is still an epidemic in many developing nations. Poliovirus is a lysolytic virus, which means that it will continuously replicate and produce progeny until a certain threshold level is reached (Kion, 2006). At the threshold point the host cell bursts releasing the viral progeny. Poliovirus has a single positive sense strand of ribonucleic acid (ssRNA (+)) as its genome as shown in Figure 3 (Campbell 2002). It is able to directly translate its RNA genome into proteins using the host cell's ribosomes without any modifications to the viral RNA because it contains a ribosomal binding site (Campbell 2002). To promote translation of the viral RNA over the host cell's, Poliovirus contains a protein complex which modifies a site in the ribosome which would recognize the host cell's RNA strand (Kion, 2006). Therefore, the host cell's RNA is not translated in the affected ribosomes since it can not bind to the ribosomes. This allows for near exclusive translation of the viral RNA.

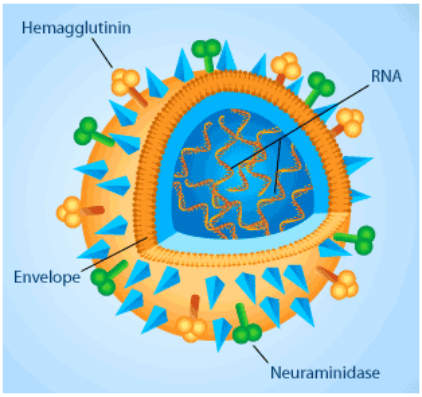

Figure 3. Poliovirus Structure

Influenza is a member of the orthomyxovirus family and causes a disease commonly referred to as 'the flu'. Its genome is comprised of eight single stranded ribonucleic acid negative sense strands (ssRNA (-)) as shown in Figure 4 (Kion, 2006). Initially, Influenza is a lysogenic virus, so it does not destroy the cell like Poliovirus. Instead the progeny is released from the cell through the cell membrane. However, Influenza is capable of switching replication modes and can become lysolytic depending on environmental factors (Kion, 2006). If Influenza co-infects with another lysolytic virus in these scenarios it will enter a lysolytic cycle. Influenza contains its own ribonucleoprotein complex (RNP) which allows it to replicate its genome autonomously (Kion, 2006). Hence, it does not require any of the host cell's RNA genome replication machinery. The Influenza RNA genome does not contain ribosomal binding sites, therefore to translate the RNA into viral proteins it uses the host cell's ribosomal binding site recognition sequence (Kion, 2006). When replicating the genome the RNPs take host cell's RNA and remove the ribosome recognition site from it (Campbell, 2002). Then the RNPs begin sequencing the viral RNA and attach it to the ribosome recognition sequence. This allows for near exclusivity of viral RNA translation, since the host cell's RNA sequences have been disrupted.

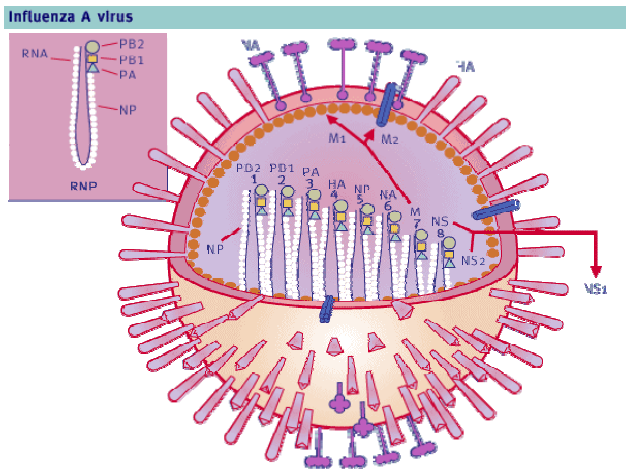

Figure 4. Influenza Virus Structure

Human Immunodeficiency Virus (HIV) is a member of the Lentivirus family which is a collection of retroviruses (Kion, 2006). Retroviruses transcribe their RNA genome into DNA and insert it into the host cell's genome. This allows HIV to use the cellular machinery to construct copies of its genome and produce viral proteins. HIV's genome consists of two positive sense ribonucleic acid strands (dsRNA (+)) as shown in Figure 5 (Campbell, 2002). One of the viral RNA strands is reverse transcribed into deoxyribonucleic acid (DNA) using the reverse transcriptase protein which is contained in the capsid of the virus. Another protein, Integrase, also located in the viral capsid subsequently integrates the new viral DNA into the host cell's genome (Kion, 2006). The virus's DNA is then preferentially transcribed into new viral RNA and translated into new viral proteins by the host cell's machinery. Additionally, HIV is a lysogenic virus and can not become lysolytic which is considered to be a defective action in the proposed game model (Campbell, 2002). However, if HIV is modified by another virus during co-infection it will morph into the virus which causes autoimmune deficiency syndrome (AIDS). The AIDS virus is capable of entering the lysolytic cycle and therefore can perform a defective action (Kion, 2006).

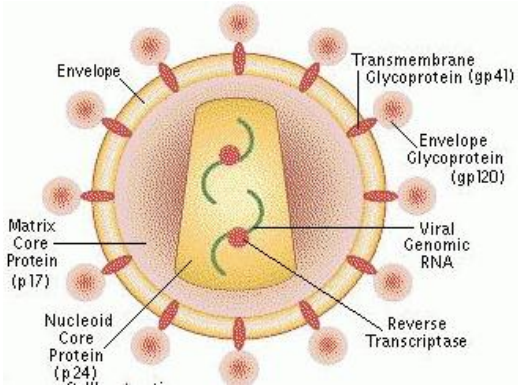

Figure 5. HIV Virus Structure (Kion 2006)

Game 1. Poliovirus vs. Poliovirus

Poliovirus being a lysolytic virus will play with a strategy of always defecting. If it co-infects with another polio virus the outcome will be mutually damaging. Since both viruses will be replicating at high levels and consuming cell resources at a high rate both will be competing equally for all the shared cell resources therefore the worst possible outcome will be attained for both viruses in this situation. Since the only action profile is mutual defection additional games will need to be modeled to determine which game type Poliovirus conforms to.

Poliovirus uses an enzyme which modifies the host cell's ribosome which causes the ribosome to only translate the viral RNA into proteins. With both viruses performing the same action it causes a mutually beneficial affect since both viruses are capable of using any modified ribosome regardless of which of the two viruses modified it.

Game 2. Influenza vs Influenza

Influenza is primarily a lysogenic virus remain in this cycle throughout the duration of this co-infection. Neither virus would normally enter a lysolytic cycle due to the lack of a trigger signal. Both viruses will replicate at a rate which is sustainable by the host cell, since they are playing their cooperative action. If a trigger was present and caused one of the viruses to enter the lysolytic cycle, a signal cascade would be created which would trigger the other virus to also enter a lysolytic cycle. This would be the second most destructive outcome for the viruses since the second lowest amount of progeny would be

produced in this situation. If one of the viruses was not triggered it would replicate at a reduced rate and when the cell was destroyed its progeny may not be assembled yet or too few to survive. This would provide the worst payoff for the cooperative virus and the best for the defecting virus. This scenario is analogous to the prisoner's dilemma.

The Influenza virus utilizes the host cell's ribosomes by taking preexisting cellular RNA and removing the ribosome recognition site. Because both viruses are utilizing the same mechanism the amount of cell RNA will decrease and reduce the amount of available copies that can be used to make new viral RNA. Consequently, this will reduce the amount of viral protein made and both viruses will have a reduced rate of replication. If one enters the lysolytic cycle it will exponentially increase the amount of viral RNA being produced by that virus since it will make more RNP complexes. The other virus's replication rate will be reduced further which would cause it to have a very low payoff. If both viruses enter a lysogenic cycle it will cause a very rapid decrease in cell RNA and both viruses will get the lowest possible payoff since they were only able to reproduce for a very limited amount of time. This is analogous to a snowdrift model. For both viruses the payoffs received from cooperating while the other defects is better than the payoff received from the mutual defection outcome.

Game 3. HIV vs HIV

HIV is a lysogenic virus so it will always cooperate and can not become lysolytic and defect. HIV viruses can not activate themselves or each other so it can not mutate into AIDS. Furthermore, the use of ribosomes will use the same mechanism of relying on the host cell machinery. This situation will result in a detrimental affect for both viruses since they will be competing for a shared resource. In this situation the only action set possible for the modes of replication is mutual cooperation so to fully model HIV interactions it must be modeled with different viruses since a specific game type can not be specified from this action profile alone.

Game 4. Poliovirus vs. HIV

Poliovirus a lysolytic virus and HIV is a lysogenic virus. The Poliovirus will have a strategy of always defecting and HIV will always cooperate due to the limitations of the individual viruses. In this case

the ribosomal interactions are also similar. HIV uses the host cell to make its RNA and Poliovirus disables the ribosomes so they can not translate cell constructed RNA. Yet again Poliovirus is playing an always defect strategy while HIV is playing a cooperative strategy. Additionally HIV can not be activated by Poliovirus, and consequently it can not become AIDS and employ a defect strategy by entering a lysolytic cycle. It is unnecessary to determine which type of game is played in this scenario since the only outcome possible is for HIV to cooperate and attain a low payoff, while Poliovirus defects and receives a high payoff. In this type of co-infection Poliovirus is determined to be evolutionary superior to HIV since it has a relatively higher payoff in all outcomes.

Game 5. Poliovirus vs. Influenza

Poliovirus and Influenza will both act as lysolytic viruses and will use strategies of always defecting. Since Influenza is initially a lysogenic virus it will have a lag period while it begins to enter a lysolytic cycle. Poliovirus has an advantage in this scenario since Influenza is slower in defecting; consequently when both defect it is not the worst outcome. The worst outcome for Influenza would be not to enter the lysolytic cycle and continue in the lysogenic cycle. This would be equivalent to Poliovirus defecting and Influenza cooperating. A plethora of Poliovirus progeny would be made and then the cell would burst while Influenza would have a relatively low number of replicates at this time. This is analogous to the prisoner's dilemma model in which the worst possible situation is for one virus to cooperate and the other to defect; secondly, the next most unfavorable outcome is mutual defection.

The ribosomal mechanism for Poliovirus as previously discussed is to modify the host cell ribosomes. Influenza utilizes the ribosomal binding site from host RNA and attaches it to the viral RNA. In this situation Poliovirus is defecting while Influenza is cooperating since Poliovirus is inhibiting Influenza from creating its viral proteins. Influenza would be triggered to enter a lysolytic cycle by this and it would attempt to use any ribosome which had not yet been modified by Poliovirus. Nevertheless Polio would have a higher amount of progeny produced since it would eventually modify all the ribosomes in the cell. Once more a prisoner's dilemma is created since the worst outcome for influenza is to cooperate, whereas through defecting it would obtain a higher payoff.

Game 6. Influenza vs HIV

HIV a lysogenic virus will cause Influenza to also be lysogenic, since naturally, HIV and Influenza will both play cooperative actions. Influenza could be triggered by another factor causing it to enter a lysolytic cycle such as HIV activating and becoming AIDS. If this occurred HIV would receive the worst possible payoff and Influenza will receive the highest possible payoff since it would produce a large number of progeny and then destroy the cell. If HIV morphed into the AIDS virus and Influenza stayed in the lysogenic cycle, HIV would receive the highest possible payoff and Influenza would be receive the lowest possible payoff, due to the number of progeny produced. If both AIDS and Influenza were in lysolytic cycles, which is equivalent to mutual defection, they would both receive better payoffs compared to the previous situations where one cooperated while the other defected. This is analogous to the prisoner's dilemma game since mutual defection is not the worst possible outcome. Cooperating while the other virus defects results in the worst possible payoff.

At the ribosomal level HIV uses the cell to make its RNA while Influenza uses the host cell RNA to make its RNA. As a result, Influenza is using HIV RNA to make its own RNA. This is a strategy of defection while HIV is cooperating. So overall Influenza would have a higher level of progeny produced if both viruses were in lysolytic or lysogenic cycles. If HIV was in a lysolytic cycle it would be producing copious amounts of its RNA so the lysogenic Influenza would not impact the translation of HIVRNA into proteins as drastically. Alternatively, the same would be true if Influenza was in a lysolytic cycle while HIV was in a lysogenic cycle. Yet again, a prisoner's dilemma is created in this situation due to the payoffs in each of the possible outcomes.

Overall, lysogenic and lysolytic viruses have different payoffs depending on which type of virus they co-infect with. Lysogenic viruses can be considered cooperative viruses since they do not consume large amounts of resources. Alternatively, lysolytic viruses use defective actions because they replicate at a relatively rapid rate thereby consuming significantly more cell resources. Poliovirus always defects, because it has evolved mechanisms which enable it to inhibit the cell from producing innate or viral proteins. Poliovirus preferentially creates matrices which resemble a prisoner's dilemma. Thus, by destroying its host it is not able to persist. This causes it to be an evolutionary unstable organism as it will rapidly exhaust its

supply of host cells.

Influenza and HIV have evolved to survive with few host cells because they can exist in a more symbiotic relationship with their host. They consume resources at a slower rate and they do not destroy the cell to release their progeny. However, Influenza disrupts the production of HIV proteins. The mechanism employed by Influenza to produce viral proteins is more sophisticated compared to HIV. Therefore, Influenza is evolutionary superior to the HIV virus. In all co-infection cases involving Influenza and either of the other two viruses, a prisoner's dilemma model system was constructed. Hence, viral interactions which create a situation that results in a prisoner's dilemma are evolutionarily stable and consequently superior to an interaction which would result in a snowdrift model.

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