Computational Systems Biology
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Lecture - 91
Computational Modelling of Host - Pathogen Interactions

In today's video, we will move on to computational modelling of host-pathogen interactions. There are many, many methods to do it, and practically all the techniques studied in the course of ours such as constraint based modelling or Boolean networks or graph theory can be used to model host-pathogen interactions. So I will give you a brief overview of the methods.

Then go over to how we model Mtb-host interactions using Boolean networks, and I will talk about how we went about reconstructing this model. What is a pathogen? It is a disease causing organism and it interacts with a host. It basically infects a host. So what happens when a host is infected by a pathogen. There is an interplay of several processes. There is, if you are ill there is a host signalling, host regulation, host metabolism, a pathogen signalling, a pathogen regulation, a pathogen metabolism and they are all inter twined.

There is a lot of interaction that goes on, and what you think if you are talking about if the host is human, what you think is the most important component of this interaction. What is the one human system that is very important in this interaction, the immune system. So immune system is going to be extremely active, a major player orchestrating the entire response to any kind of host.

And today we will look at an example of tuberculosis and with a particular case study, but otherwise I will also try to outline some generic strategies to model host-pathogen interactions.

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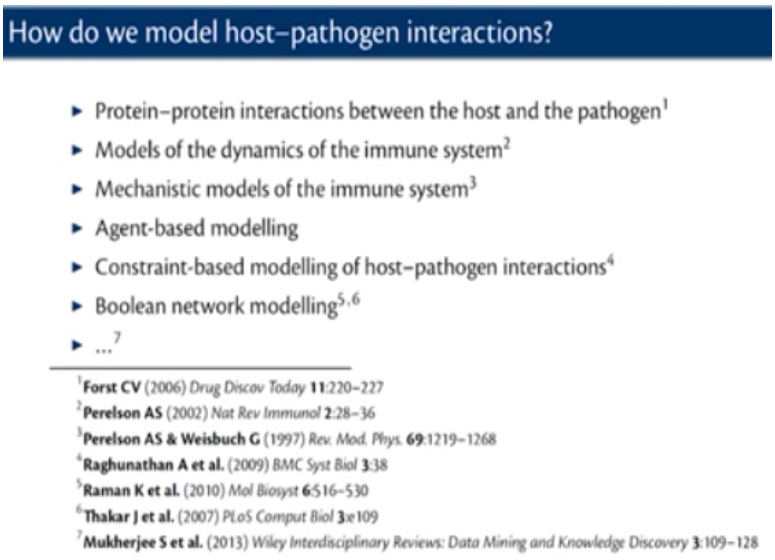

So how do we model host-pathogen interactions. There are people who have studied protein-protein interactions between the host and the pathogen. So there is a protein interaction network in the host. There is a protein interaction network in the pathogen. You can imagine there are some interactions that cross-over the organisms across the boundaries. There is a host-pathogen which interacts with the pathogen protein and vice versa.

There are very nice models of the dynamics of the immune system itself. This is somewhat similar to your SIR models as well, so you have differential equation based modelling of the immune system dynamics so on, very interesting models. Similarly, mechanistic models of the immune system various cells, what happens to B-cells, what happens to T-cells so on and so forth. Agent based modelling, again very powerful methodology for studying these kinds of cells.

So you model every single cell as an agent. So there are some rules governing its interaction with other agents, other species, other cells and so on. Of course constraint based modelling which obviously is going to underline mostly the metabolism of the interaction. There is some dependence between the host metabolism and the pathogen metabolism. This is actually very interesting. There are some organisms are really smart so when they infect a host they shut down some of their own metabolic machinery.

I am going to stop producing tryptophan, because now I can take it from the host. So they will start expressing transport of proteins from tryptophan rather than actually synthesising tryptophan themselves, much easier, much lesser energy expended that way. Of course

Boolean network modelling that we were seeing in the previous lecture. How can we explain Boolean network modelling towards understanding host-pathogen interactions?

There is a very nice review, that appeared in 2013 which covers a very large spectrum of these methods. You can imagine there are every technique that we have studied in the course so for could potentially be applied to the host-pathogen scenario, nothing stopping you from doing that. If you want apply networks, you want apply dynamics, you want apply constraint based modelling, you want apply Boolean networks.

All of these are potentially useful in the context of host-pathogen systems biology.

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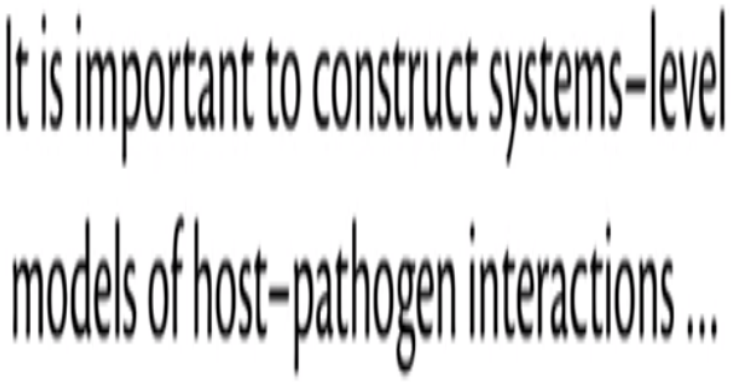

It is important to construct systems level models of host-pathogen interactions, because you cannot as we have discussed through the course, you cannot get sufficient insights from a very narrow model, by just looking at one pathway in the host or one pathway in the bacterium or pathogen and so on. Let us look at Boolean network modelling of human mycobacterium tuberculosis interaction. So how does the infection happen?

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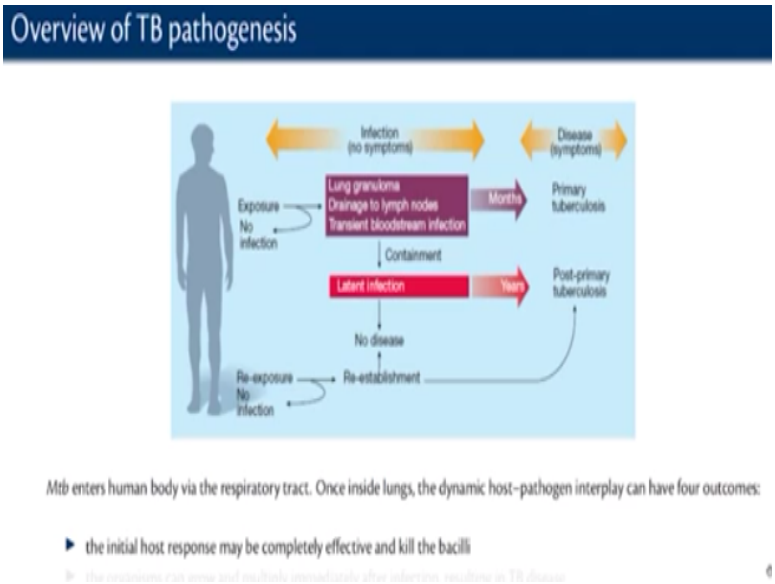

So TB organism enters the human body via the respiratory tract. Once inside the lungs there is a major interplay, it is a very interesting cat and mouse game that goes on. So there is the first immune response by the host. It is not necessarily the first immune response and so on, there is immune response by the host there is a defence by the pathogen. There is a counter response by the host and literally a counter response by the pathogen.

It is actually they keep exchanging blows, there are different molecules, different species and molecular species in both host and pathogen involved in this very interesting game. We will see how this goes on. So sometimes if you are very lucky you could have no infection, all is well. But then you can have infection and have no symptoms, and then you can have disease where you have all the symptoms of tuberculosis and so on.

This is a very common outcome of tuberculosis infection, so it is just in latent infection or what is known as persistence. The disease just persists; the organism just persists without causing active disease. It could manifest disease at some point. So the organism is in you but it does not like really cause all the symptoms. It does not, or in some sense it is only an infection but not a disease. You can see the difference between the 2.

Disease is like a state of being ill, infection is you have the organism in your body but it is not yet causing major damage. So the initial host response may be completely effective and get rid of the bacillus, which is the ideal outcome, or the organisms can grow and multiply immediately after infection resulting in active disease, serious disease. The bacilli may be dormant and literally not do anything at all.

This is the case in very common scenario, especially for tuberculosis. In fact, there are people who have been suggesting strategies of trying to kick the bacterium out of persistence, so that it can actually be treated, in a sense cause disease. So that the disease may be treated, because the latent infection is just dormant and untargetable. This is something that can happen so the latent bacillus can actually become active later on and finally progress to the regular disease condition, stage 2, the condition 2.

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So how can we model the complex web of interactions that exists between TB and human. Essentially the bacterial metabolism and signalling verses human immune system. So human immune system is the major player here.

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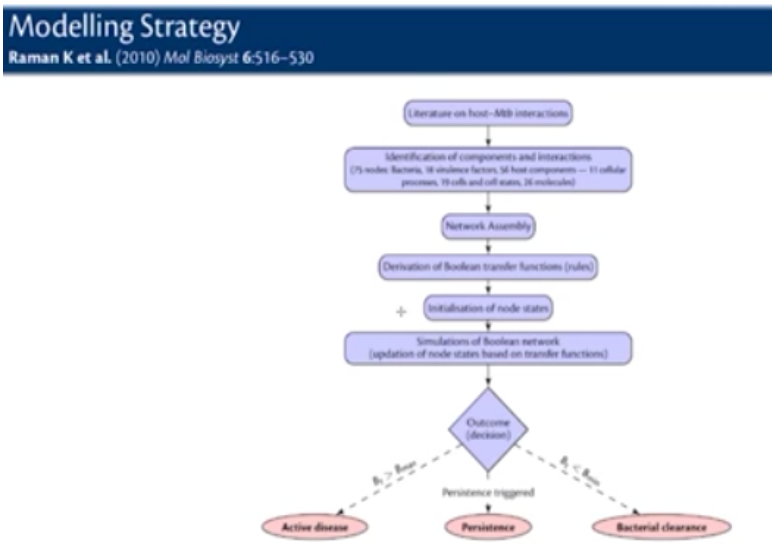

So this was a strategy that we have adopted. You always have to build this model from literature. So we went through a lot of literature on host mycobacterium tuberculosis interactions and identified several components and interactions. So we came up with 75 nodes with around including bacteria, 18 virulence factors, 56 host components including 11 cellular processors, 26 molecules, and 19 cells and cell states.

So this could be like T-cells and activated T-cells, B-cells and activated B-cells, they are all different states and build a network and then identify all the Boolean transfer functions as we discussed in the previous class, initialise the node states and then simulate the network. And we had some semi-quantitative variables as well, which helped us figure out what was the outcome.

We said if the amount of bacteria goes beyond a particular threshold, we say it is active disease, or if bacteria stay within a particular zone for a long time it enters persistence. Or if bacteria is like very low, you just have a few bacteria after a few days of infection, then it is essentially been conquered by the immune system.

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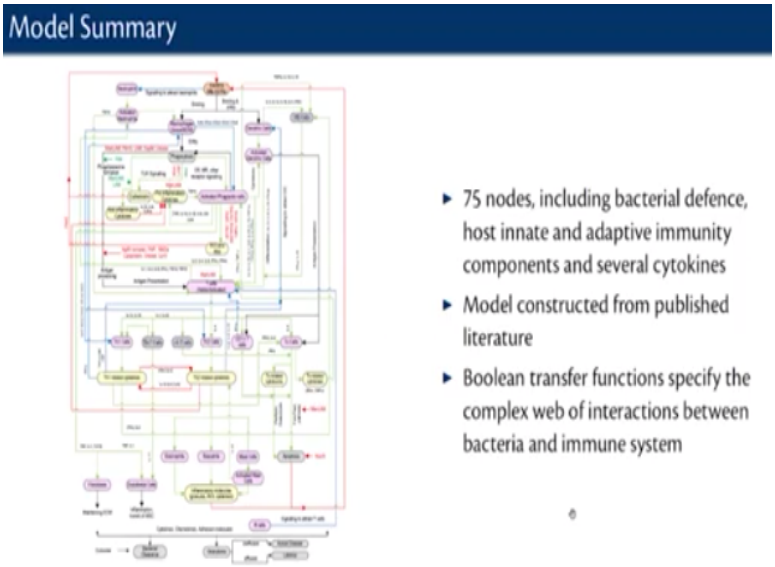

How does this look, this is how the complex the system looks? So we have a whole lot of different cells, cell states, species, molecules and so on, I will try to zoom into a part of it. So this is the bacterium out here, and it interacts with macrophages, neutrophils, activated neutrophils, dendritic cells, activated dendritic cells, activated phagocytic cells, pro-inflammatory cytokines, these are chemical, reactive oxygen and nitrogen intermediates, T-

cells that could be either naive or activated, Th1 cells, Th17 cells, gamma delta T-cells, the whole battery of immune system components, really very interesting set of interaction.

All these are bacterial proteins and so on, SodA, SecA2, SodC, BpoB, ManLAM. ManLam is an important polysaccharide which is secreted by lipoarabinomannan, LAM stands for and this interacts with, this helps the organism trick the host and so on and so forth, and all this IL stuff you see here there are all interlucants. They are signalling molecules used in the human systems.

So essentially there are about 75 nodes including bacterial defence, host innate and adaptive immunity, do you know what is innate and adaptive immunity. So innate immunity is sort of the de-factor response to any infection and adaptive is more tailored response, usually happens once you have, in a sense, loosely speaking calibrated to the infection. So what happens when you have a vaccine.

You already surmount an adaptive response, which is why your vaccines work, when they work. You already have seen this organism before, most of us must had those BCG shots, which is actually the TB vaccine. You have now seen a weaker version of TB, so you can respond adapted to the TB infection. The adapted immune machinery has more different components that come into play and so on.

You can read about this, this is really quite interesting. We essentially built the model from published literature and using this picture which is essentially a condensation of all the knowledge that is contained in about 100-120 papers, you now have to frame the transfer functions. So when is bacteria active, when does phagocytosis kick in, when does antigen presentation work out so on and so forth.

There is an element of chance in some of these as well, which we basically take care by using a random variable, and you will see that all this works very nicely with BooleanNet that we saw in the previous lab.

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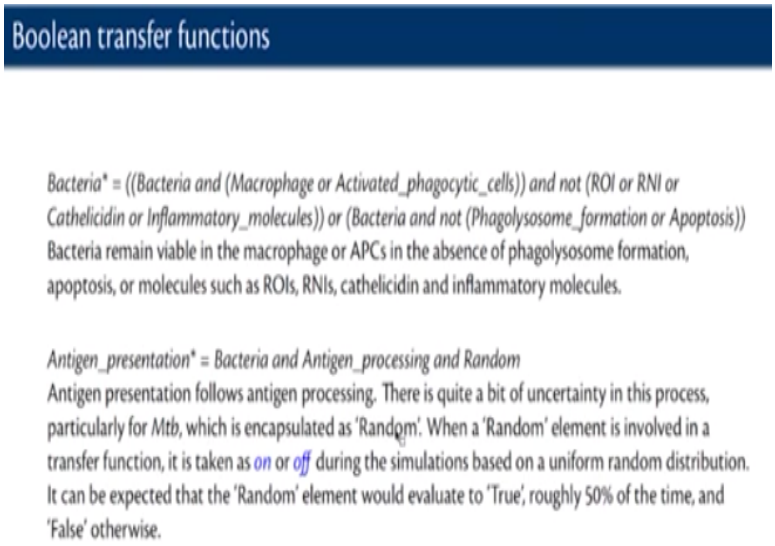

This is a sample of our transfer function, how does it look like. So bacteria update rule is bacteria and bacteria resides only in macrophage or activated phagocyte cells, but it should not be exposed to ROI or RNI or catholicidine or other inflammatory molecules. Or bacteria and, phagolisosome formation or apoptosis should not have set in, so things like that. So basically the text is given below.

So bacteria remain viable in macrophage or antigen present in activated phagocyte cells, in the absence of phagolisosome formation, apoptosis, or molecules such as ROIs, RNIs, catholicidine and other inflammatory molecules. Antigen presentation follows antigen processing and there is a bit of uncertainty in this process which is encapsulated as random. So random element is basically true or false 50% of the time.

If we had a better idea, if we knew a probability you could encode it to. So this as I said goes back to the strength of a discrete modelling framework. You can just easily integrate whatever function you want here and so on.

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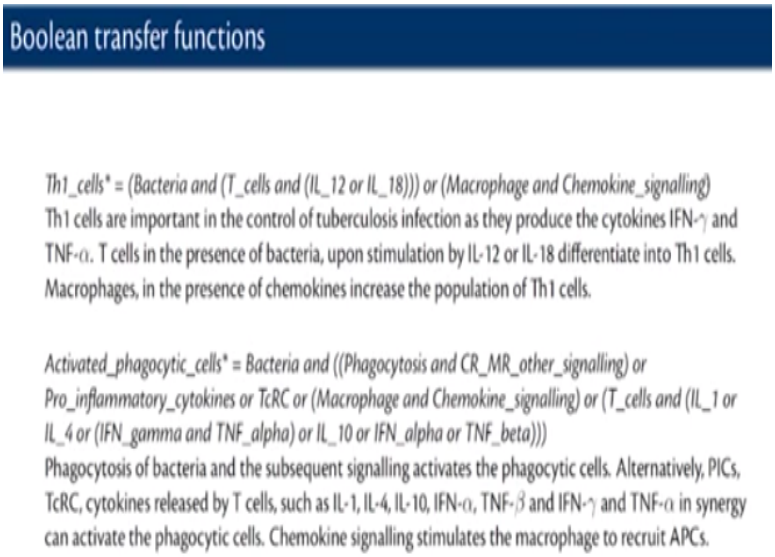

So Th1 cells are important in the control of TB infections as they produce a cytokines, interferon gamma and tumour necrosis factor alpha. And T-cells in the presence of bacteria upon simulation by interlucant 12 or 18 differentiate into these Th1 cells and macrophages in the presence of chemokines further increase the population of Th1 cells. So if you see here, Th1 cells will be true if macrophages and chemokine signalling are there.

If bacteria and T-cells and these interlucants are present and so on. So this basically tries to encapsulate all the biology that you see here, in terms of a Boolean function. One more example, so phagocytises of bacteria and subsequent cells activates the phagocyte cells alternatively there are pro-inflammatory cytokines and TRC and cytokines released by the T-cells, such as Il1 and so on which in synergy can activate the phagocyte cells.

Chemokine signalling also stimulates macrophage recruit activated phagocyte cells. If you see, this is actually quite easy, if somebody is given you this. So the model construction, reconstruction happens in this part, and this is hard work involves lot of literature, mining and reading and so on.

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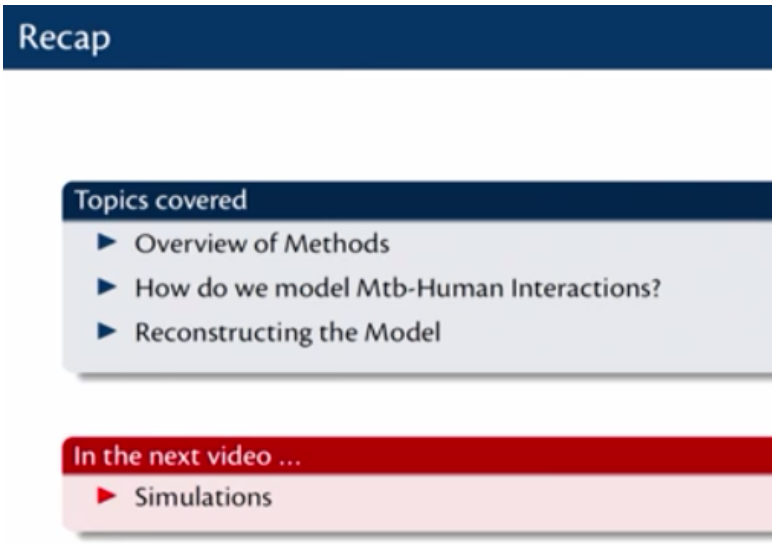

So in this video, we had a brief overview the methods for modelling host-pathogen interactions, and we also looked at how we construct a Boolean model of the interactions between mycobacterium tuberculosis and the human host. In the next video, we will look at how to go ahead performing the simulation with this model and derive interesting conclusions.