Computational Systems Biology
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Lecture - 92
Computational Modelling of Host-Pathogen Interactions

In this video, we will continue with the Computational Modelling of Host-Pathogen Interactions. So we already have Boolean model. Building the model is the hard part and now we will go about simulating this model and deriving interesting insights, even by deleting nodes perturbations, as usual and so on. To understand the important components of this host-pathogen interaction machinery. How do you simulate?

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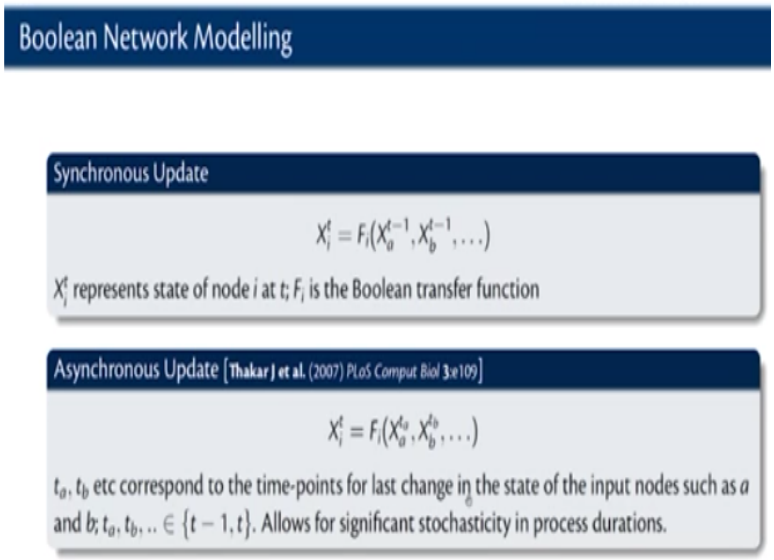

As we studied in the previous class, we can either go in for a synchronous update or an asynchronous update. When does one go in for a synchronous update versus asynchronous? So asynchronous gives you a lot more stochasticity in process duration. You can have processes that are relatively more fast. Synchronous assumes that everything takes one time step to happen, be it antigen presentation or the macrophage binding to some cell, whatever.

All that takes exactly one-time step, whereas the asynchronous allows for some more stochasticity. You can even have like longer term memory. You can even depend on something that was like 5 steps previously, 3 steps previously and all that, although we did not really do that here.

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Semi-quantitative Model

We hacked the Boolean model to account for

- Delay in the onset of adaptive immunity
- Initial bacterial load
- Persistence interval
- Bacterial clearance efficiency
- Delay in phagocytosis
- Delay in apoptosis
- ...

So we also tweet the Boolean model to account for delay in the onset of adaptive immunity. You have an adaptive immune system, but that never kicks off on day 0. It kicks off only after some punishment has been received from the bacterium. What is the initial bacterial load, then when does persistence set in, how efficient are we clearing the bacterium, this can depend on drugs and so on?

Is there a delay in phagocytosis, apoptosis and so on and so forth? So we made essentially a semi-quantitative model for this.

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Growth and Clearance of Bacteria

If the growth rate of the bacterium is taken as λ, for exponential growth,

$$B_t = B_0 e^{\lambda t} \quad (1)$$

The updates of bacterial population are effected at the end of each time step, as

$$B_{t+1} = (1 + \alpha) B_t \quad (2)$$

Solving these, α can be seen to be $e^{\lambda} - 1$.
α thus represents the incremental change in the bacterial population, in each time-step. At each time step, where bacteria is not cleared, it grows as shown in Eq. 2.
If cleared,

$$B_{t+1} = (1 - \eta) B_t \quad (3)$$

If the growth rate of bacterium is taken as lambda for exponential growth, we can think of a simple equation like this. So Bt is B0*e to the lambda t. We can update the population in this fashion so we can say Bt+1 is 1+alpha*Bt and solving this, you can say that alpha is nothing

but e to the lambda-1. This is very simple. So we essentially used alpha as an input parameter to the model.

So alpha is nothing but the incremental change in the bacterial population at each time step. If conditions are good for bacterial clearance, so what is bacteria growing and clearing mean, as far as the Boolean model is concerned? True and false. If bacteria star evaluates as true, I will try to use this equation to grow the bacterium. If bacteria star evaluates as false, I will use this equation to basically clear out the bacterium.

So this is like a clearance efficiency and so on, which depends potentially on any drugs that are being taken and things like that.

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Simulation Parameters

Description	Parameter	Default value	Possible range
Initial bacterial load	B_0	5	0–25
Threshold for active disease	B_{max}	10^5	—
Threshold for clearance	B_{min}	1	—
Persistence interval	$[P_{min}, P_{max}]$	[5, 100]	—
Persistence time	δ_{per}	14	7–21
Delay in onset of adaptive immunity	δ_{AI}	14	7–21
Incremental bacterial growth	α	0.7	0.4–0.8
Bacterial clearance efficiency	η	0.4	0.4–0.8
Delay in phagocytosis	δ_{PH}	7	7–14
Delay in apoptosis	δ_{AP}	7	7–14
Simulation time	t_{max}	105	—

- Asynchronous updates of states
- Ranks for Boolean transfer functions to enforce updates of certain nodes before others

So we used an asynchronous update and we also had ranks for the Boolean functions to enforce update of certain notes before others. We saw that how that works in BooleanNet in the previous lab. These are all the parameters that we used. So we looked at an initial bacterial load and this is the possible range that we determine through a study of literature and so on. What is the maximum bacteria for infection to be irreversible in some sense?

What are the threshold for clearance and how long should it persist? How long should it stay in the body within a zone, before it enters persistence. This is the number of bacteria that should be there. This is the time, 14 is 14 days or two weeks. This is onset of adaptive immunity, which is again 2 weeks. Then, some default values for bacterial growth and clearance and delay in phagocytosis, apoptosis and so on and so forth.

We simulated for 15 weeks. It is a sort of macromodel. It is not a very cellular model. In some sense the model, it takes into account the cellular components and so on, but then overall looks at the concentration of bacteria in the whole human sort of thing.

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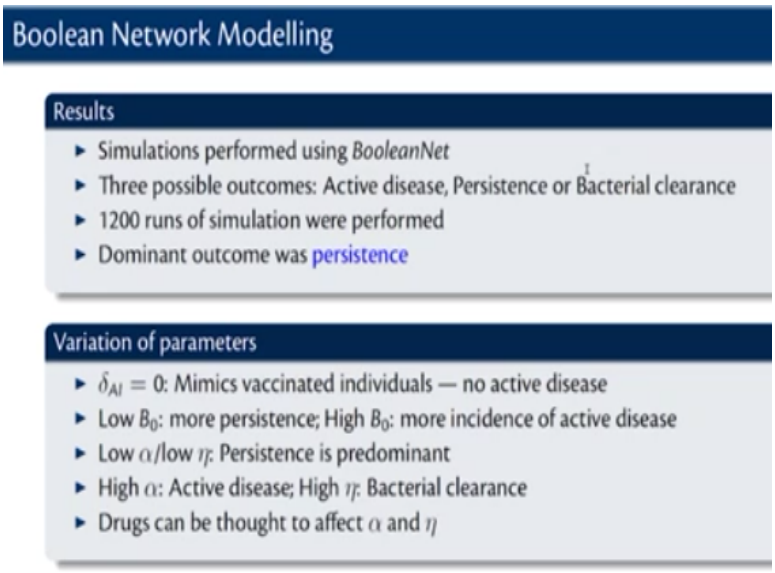

So we performed the simulations using BooleanNet and we had 3 possible disease outcomes. So it could be either active disease, persistence or bacterial clearance and we performed 1200 runs of the simulation and the dominant outcome we found was persistence, which is actually what happens in reality. Most people are just careers of TB without actually even manifesting.

What we found, for example we did that we can sort mimic vaccination by putting delta Ai is 0. That is the adaptive immunity delay, so what does it mean when data Ai is 0, it means you have already been exposed, which is what happens during vaccination. We find that in almost all case, they do not go towards active disease. This is reasonable observation, but sometimes you do find that vaccinated individuals in reality can contract disease.

We find that low initial bacterial load, we have more persistence and high initial infection, you have more active disease and again if you have low clearance or low growth, persistence is predominant and high growth disease and high clearance efficiency, you have bacterial clearance and so on and all these are like sort of fictitious parameters in a model. You can think of alpha and eta to be influenced by any drugs that are being taken and so on.

If you are taking rifampicin, that would have a particular influence on alpha and eta. If you are taking isoniazide, it may have different influence on alpha and eta and so on.

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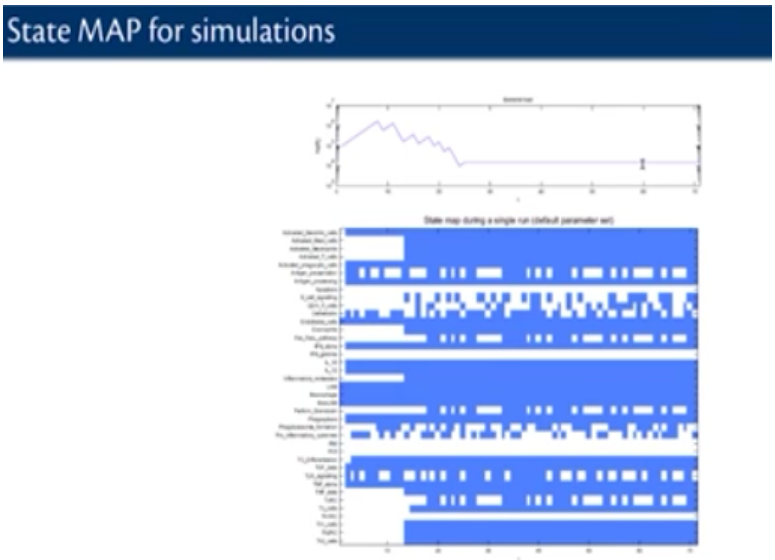

This is like a state map for simulations. So this lists several of the simultified states that we have. So blue is on and white is off and so on and if you see I am not showing bacteria here, because it makes more sense to look at bacteria as the load because we have a discrete update for bacterial population after each time step. So this is how the bacterial population varies. So after this point of time, it basically goes into persistence.

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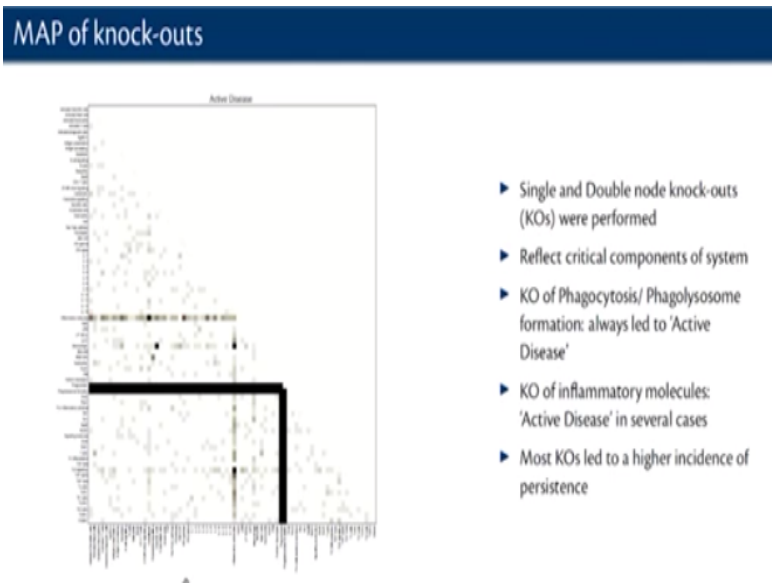

We also as in any systems biology experiment, 1 wants to do perturbations. What happens when there is some defect in the system, if there is a bacterial protein that is not working perhaps because of a drug or there is immune defect or so on, for whatever reason or even

without going into the physiological significance of these experiments, it helps us understand what are the key players in these systems. What are the key drivers of these interactions?

So this is the map of knock outs, which shows what fraction of simulations resulted in active disease. If I knocked out some formation or phagocytosis it always resulted in disease, you see a completely dark band there and if inflammatory molecules are not present in the human body, it means your defence is too weak. So in a lot of cases, it was leading to active disease. This is a double knock out, this matrix.

It shows you what happens when the inflammatory molecules and catholicised. So 2 major inflammatory molecules are out, disease always sets in and so on. Again as I was mentioning reflect the critical component of the system, so any time you knocked out phagolisosome formation and phagocytosis together, it always led to active disease and we also found that most knock outs lead to a higher incidence of persistence, that is not visible from this figure.

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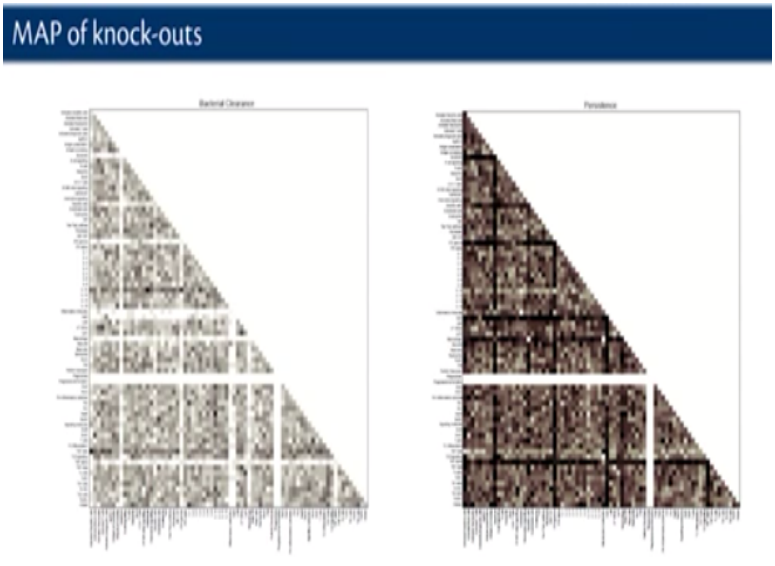

Whereas it is visible from this figure. The figure on the right shows, you can see it is a very dark plot compared to the others. So darker the square is more fraction of simulations ended in that outcome, which in this case is persistence. So except you see a full white band for phagolisosome because all of this is in the previous slide, where it all went to active disease. If you see this, whenever CAT-G is knocked out, almost goes into persistence.

Similarly, whenever apoptosis is knocked out, persistence is more common and so on and so forth. So you can study what are all, when IL-10 is knocked out along with it. There is some

flow inflammatory and anti-inflammatory cytokines. There is a delicate balance between these 2 in the body. So you see that sometimes it can result in clearance a lot of times when this is knocked out.

In many cases when apoptosis is knocked out, there is no clearance at all or when interferon gamma is not there, there is practically no clearance at all. These are very interesting insights that one can obtain by studying knock outs or perturbations on these kinds of models.

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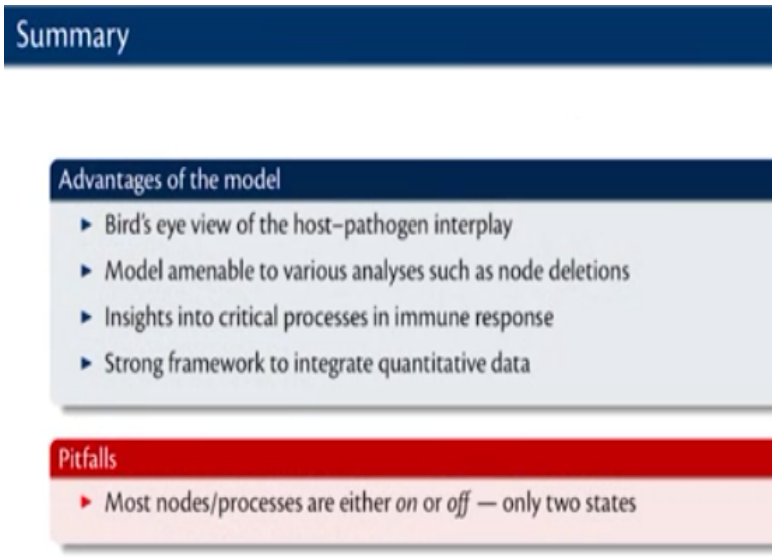

To summarize, this gives you a bird's eye view of the host-pathogen in to play. It is a far more complex network that underlies this. This is just a small, very high resolution or high level view of what happens, but the model is amenable to various analysis, which has no deletions and so on. It gives you good insights into critical immune processes. That is a very strong framework for integrating quantitative data.

If you know what is going to be the effect of a particular drug and a particular component, you can easily include that and so on, but obviously the body is limiting in the sense, you currently have only on and off states for practically everything, we did put something for the bacterial population and so on, but it is just either on or off, but this you can imagine, as a sort of strong way to look at, a nice way to study host-pathogen interactions.

You can study metabolism as well, but the good thing is that you can study metabolism and integrate it into this model because this model presents you a lot of opportunities to integrate as I was mentioning even in the previous class, the Boolean framework or the discrete

framework gives you an opportunity to integrate from other kinds of modelling techniques. You can like solve an ODE to decide the outcome of a particular state.

You can solve an FBA model to predict the outcome of some other state and so on.

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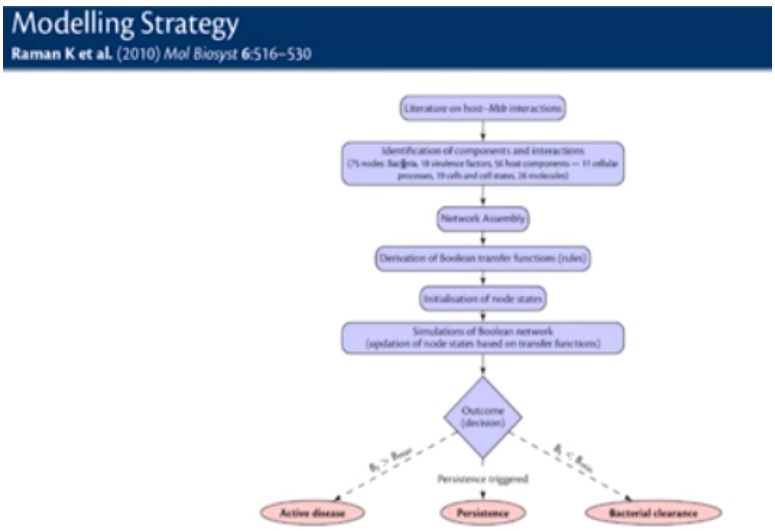

There are 75 nodes including bacteria 18 virulence factors. These are actually from the bacteria. These are bacterial cell bacterial molecules inside the bacterial cell, 56 host components including 11 cellular processes, 9 cells and cell states and 26 molecules themselves.

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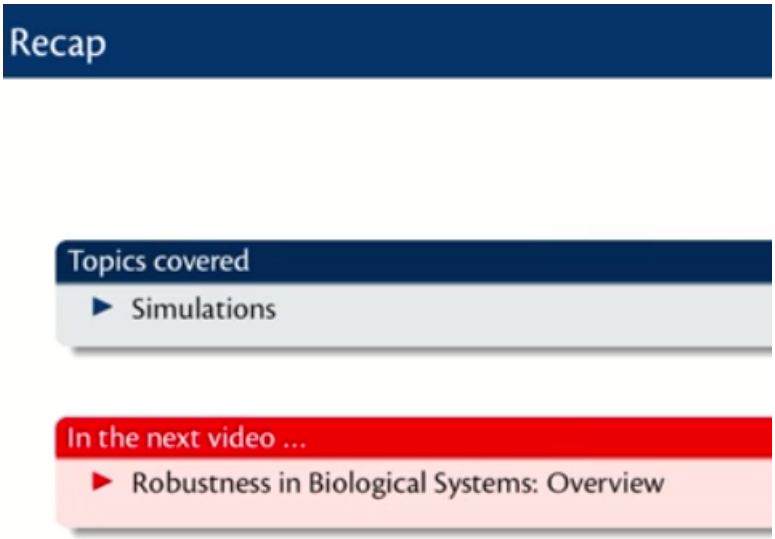

In this video, we looked at simulations of the Boolean Network model that we built for studying MTB human interactions. It is not a pure Boolean model, but we also had some nice

hacks to include how the bacterial load changes and the efficacy of a drug and so on. In this next video, we will switch gears and we will start looking at some advanced topics. We will first look at robustness in biological systems. I will give you a brief overview of robustness in biological systems.