**First question: how do you think modelling can be applied to practice? (The endgoal question)**

I think there’s a lot of uses right now. There are many ranges of modelling, from the network level to the molecular level, structural based modelling. I think most of drug discovery heavily in use in pharmaceutical industry has mainly been in the molecular level. The practical applications look like drug inhibitors you can model using physics-based approach, where you can see the drug binding to a given protein in a given pathway and as a result leads to cell death or angiogenesis. In my opinion, this seems to be most direct method of modelling. Dan’s been doing a lot of papers on adverse drug effects using cancer-genome modelling, especially carcinogenic drugs. He can tie that to actual pathway behavior, and there you can start getting into practical applications. If you know the possible side effects of the drugs, if it leads to cell growth or cell death, you can start developing therapeutics to address that.

**Do you foresee any limitations in modelling using AMBER?**

We looked at the effects of SNPs in human proteins on drugs and how they might influence drug metabolism, and if certain people can’t take certain drugs because of their SNPs to it. Workflow: look at the WT protein and look at the mutation and study not only the changes in the structure of the protein that is due to the SNP, but also the changes in that amino acid will affect BOTH drug binding and metabolism binding. The limitations would be sampling long enough the conformational space the protein needs to explore. For example, if you have the crystal structure as the starting point, you have to manually mutate the residue mutation. It is well known a single mutation has the possibility to alter the protein, whether it be stability or the binding affinities. Using molecular dynamics is good for where we know the perturbations are relatively minimal. We need long enough time sampling to know if the protein really unfolds. Also, if it doesn’t alter the structure but, let’s say, the protein undergoes large scale conformational changes which affects drug binding (for example HIV protease has two flaps that you can basically sample the conformational space of when the drug comes in and out and the opening and closing of the flaps).

**AMBER** with kinetic modelling

We have a way of formulating molecular dnamics to constraint based molecules. We can asses differences between wild type nad mutants and we can see how they affect kinetic parameters and see how it works. It seems trickier with constraint based modelling. But you can take the ratio of the Kms and determine how much of a flux difference the protein will feel. For instance, you can talk about kinetic changes in turnover rate of metabolites for your project.

**Where’s the applicability of modelling**

let’s say we have mutations in this protein, which we saw in experiments. When we knock out another gene in the PPP we see a lot of mutations accrue in this protein. If you look across different species of bacteria we see a lot of mutations on the other side of the protein. We can start to see how these mutations affect the flux. This is called flux-omics where we feed the cell labelled glucose so we really know the flux. This can be easily applied to a cancer problem. Let’s say there’s a mutation and it affects a binding site, and it starts to bind to NAD cofactors instead of NADP. Thus you get a change in flux.

People are starting to understand that we can’t only extract data from statistics, and thus have placed a stronger emphasis on modelling.

This lab focuses more on the fundamental understanding. On the applications side, Dr. Palsson is the CEO on metabolic engineering community sustainability center and that’s probably the closest application work on it. If you want to engineer an organism, how would you engineer the pathways to do so.