Good morning. My project is on the theoretical study of the implication of resource competition for adaptive therapy of castration-resistant prostate cancer.

How is Cancer usually treated? Conventional therapy against cancer aims to minimise the tumour burden as quickly as possible. With the standard of care regime of chemotherapy, this is done by administering cytotoxic drugs at their maximum tolerated dose that is the maximum dose of a drug that can be administered without any major toxic side effects. Tumours generally would consist of cells with heterogeneous sensitivity to these drugs. In the absence of therapy, the sensitive cells would compete with the resistant ones and keep them under control. But, with the high MTD dosage, the sensitive ones are eliminated and the tumour becomes resistant that don't respond to any further therapy

So, what can we do to avoid this? Adaptive therapy which is the application of drugs at lower and fluctuating doses so that the sensitive cells are preserved. During the drug holidays, the sensitive cells can compete with the resistant and keep them in check. As a result, the outcomes of adaptive therapy would depend on the competition playing out between the cell types arising mainly due to limited resources and we aim to study it explicitly via a mathematical model.

We have chosen the system of study to be the castration resistant prostate cancer which is thought to consist of three cell types: T+, Tp and T-. It is a specific type of prostate cancer that is particularly difficult to cure with current treatments. The system consists of cells that can be categorised into 3 major types: T+, Tp and T-. Prostate cells have androgen receptors that trigger proliferation when activated by testosterone. Some of these cells, given by T+, preserve this

mechanism and require testosterone for growth. Castration, either physical and chemical would remove the external source of testosterone and would lead to cure in a castration sensitive cancer. However, ours is castration resistant and this is brought by the Tp cells that produce testosterone by converting cholesterol with cyp17alpha enzyme. This testosterone can sustain both the T+ and Tp. T- on the other hand brings resistance by having androgen receptor mutations that make it proliferate independent of testosterone.

So, how do we model this?
We have modelled the system as coupled ordinary differential equations. The equation for cell population consists of cells growing at a rate r and dying at a rate delta with the growth following a logistic framework where it reduces as the total number of cells reaches the carrying capacity. The carrying capacity is dynamic and depends on the resources oxygen and testosterone through the function f. f ranges from 0 to 1 and takes a value of 0 when the resource is below the lower limit, signifying no growth, a value of 1 when the resource is above the upper limit, signifying saturated growth and varies linearly between the limits. We simulate varying levels of resource limitation by changing the lower and upper limits of the function f. For example by reducing the lower limit, the cells can grow at a lower resource level and be less limited and by reducing the upper limit, the cells can have a higher growth for the same proportion of resource. The equation for oxygen and testosterone involve production at a rate p, uptake by cells at a rate mu and decay at a rate lambda. With oxygen the production is external while with testosterone it is done by the Tp cells. It is also assumed that the cells don't mutate to the other cell type, doesn't have any spatial structure and all the cells and resources are well mixed. Additionally. the conditions a few conditions are imposed such that the equations are defined only for positive real values and a cell type is considered extinct when its population drops below 1 to

maintain biological relevance.

We have taken some parameters directly from literature of cell line data with T+, Tp and T- corresponding to LNCaP, 22Rv1 and PC3 respectively. When direct source weren't available, we derived these values from literature sources along with some constraints imposed by the system and some constraints. The resource limitations imposed by the lower and upper limits described as well as the initial seeding both in terms of ratios of cells as well as the total seeding hence became the study parameters.

Based on some initial findings with pairwise runs, we have gone with a case where all cell types would have the same limitations for a particular resource. Additionally, we found out that higher Tp seedings lead to more testosterone availability and we have chosen the 8:1:1 case to represent this. We should be looking for coexistence as the tumour with Tp and T+ would only respond to therapy. Testosterone has a drastic effect on coexistence as only Tp and T+ are affected by it. With moderate limitation and equal seeding they go extinct while a higher Tp seeding rescues it. Oxygen has a minor effect as its effect is only seen when the combined limitation is on the edge and can push the cells towards extinction.

Therapy is implemented as a boolean value where 1 represents dose at MTD and 0 represents no dose. Abiraterone, the main drug of interest works by blocking cyp17alpha enzyme and this reduces the production rate of testosterone. Abiraterone therefore can only target Tp and T+. Docetaxel, which was explored as a combination drug works by disrupting microtubule activity and this reduces the growth rate. Docetaxel can target all the three cell types are affected. Do note that these values were also derived from literature values. The standard of care protocol is to give the drugs at the maximum

tolerated dose from the beginning. For adaptive therapy protocol, a binary mode was considered where dose is applied at the maximum tolerated dose when on. The therapy is turned on when the population crosses the on threshold and stays on until it drops below the the off threshold, where it is turned off and the cycle continues.

So what happens with standard of care? Tp and T+ go extinct in all cases as testosterone levels are insufficient for their growth.

As mentioned earlier, adaptive therapy requires on and off threshold. With lower thresholds, T- dominates over and inhibits Tp and T+ and causes them to go extinct. With higher thresholds, Tp and T+ can effectively compete with T- and suppress it. This is in line with recent studies. However, increasing it further leads to no therapy being applied as the on threshold is never crossed. We have considered only the T+ and Tp population to control the switching, as when all three were considered, T+ and Tp go extinct before the therapy is turned off.

Will adaptive therapy lead to better results? Wherever Tp and T+ go extinct just by competition, there is no effect from adaptive therapy. With higher Tp and T+ in the population, the tumour is more responsive to the abiraterone doses and suppresses T- better. So as for the success of adaptive therapy, we have successfully prevented competitive release of the resistant T- in some cases. But, we haven't been able to reduce tumour burden as T- replace the space left by the dead cells on applying therapy and the total population remains high.

Can we do anything to make adaptive therapy better?
From the previous case we observerd that Tp and T+ increase in periods without therapy. So we speculated whether delaying treatment would lead to better balance between the Tp T+ and T-. However, we see no advantage even after 200 days of delay due to

similar temporal dynamics especially after application of the first dose.

For combination therapy, we have chosen to pair the hormone agent abiraterone with a generic cytotoxic drug docetaxel. They have different modes of action and would have minimal cross resistance. We have tried this out as a test of concept here with the same thresholds but with the population of Tp and T+ controlling abiraterone while all the three control docetaxel but extensive standardization required in future. From the limited testing we've done, we see that the negative effect on coexistence by reducing Tp and T+ outweigh the positive effect on coexistence by reducing of T-.

To summarise, this model shows that explicit resource limitations can be used as control knobs for strength of competition and balanced limitations between the cell types leads to coexistence. Standard of care increases the testosterone limitation on Tp and T+ and cause their extinction. While adaptive therapy has avoided the competitive release in some cases, this effectiveness depends on the population size of Tp and T+ which in turn depends on the resource limitations as well as the on and off thresholds. For the future of this work, the main goal would be to find a way to reduce the tumour burden with adaptive therapy. Dynamic thresholds could be explored where the thresholds are adjusted based on the tumour composition. Additionally, we haven't tested out the cases where different cell types have different limitations partially due to lack of time and this is especially interesting when we consider trade-off of a higher oxygen limitation with a lower doubling time and resistance.

I would like to thank my supervisor Prof. Sutirth Dey, my expert Dr. MS Madhusudhan, my mentor Vibishan, my PBL lab mates and my friends and family