Conventional therapy against cancer aims to minimise the tumour burden quickly. In the context of chemotherapy, this is done by administering cytotoxic drugs at their maximum tolerated dose. However, when looking at it from an evolutionary perspective, tumours would consist of cells with heterogeneous sensitivity to these drugs and the most sensitive cells are eliminated leading to a resistant population that doesn't respond to further therapy. Adaptive therapy aims to combat this by administering the drugs at lower and fluctuating doses so that the sensitive cells are preserved. During the drug holidays, the sensitive cells can compete with and keep the keep the resistant cells 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. Prostate cells have a androgen receptor pathway where testosterone interacts with these receptor and trigger a cascade of gene expression mechanisms that lead to proliferation. Typically, with prostate cancer cells this mechanism is preserved and as a result are affected by androgen deprivation therapy that blocks production of testosterone by testes and so. These cells are represented by cell type T+. But, some of these cells represented by Tp can evolve to express the enzyme cyp17alpha that convert cholesterol to testosterone and can sustain both itself and T+ cells. Abiraterone is a drug developed to target this enzyme and this can affect both these cells. However, some cells represented by T- can also gain mutations in their androgen receptors that can allow them to proliferate without testosterone and abiraterone has no effect on them.

We have modelled the system as coupled ordinary differential equations based on the logistic framework but with a dynamic

carrying capacity that depends on environmental conditions. This environment consists of the resources oxygen and testosterone, and all other resources are assumed to be in excess. The equation for cell population consists of cells growing at a rate r and dying at a rate delta. This growth reduces as the total number of cells reaches the carrying capacity and the carrying capacity depends on the functions f of o2 and test. 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. 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 testosterone the production 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. These equations are defined only for positive real values and a cell type is considered extinct when its population drops below 1.

We have taken a bottom up approach for exploring the system by first starting out with the pairwise competitive runs between Tp and T- and between T+ and Tp, then to competitive runs between all three cell types and finally to therapy. Pairwise between T+ and T- will trivially result in T+ extinction without testosterone and hence isn't explored. We simulate varying levels of resource limitation by changing the lower and upper limits of the function f that I mentioned previously.

For the Tp-T- pair, based on some preliminary runs we found out that Tp is most affected by limitations of testosterone whereas T- can only be affected by oxygen and that is explored in more detail here. The columns represent varying levels of testosterone limitations of Tp, the rows represent varying levels of oxygen limitation for T-. Additionally, we also added varying levels of oxygen production to check its effect

as well. Out of the cases tested, coexistence is possible only when there is no or moderate limitation of testosterone for Tp and low limitation of oxygen for T-. In other cases, the resource limitation is too high to push either of the cells, sometimes even both, to extinction. Poor production of oxygen just increases the limitation of oxygen and more so when T- is more oxygen limited. The initial proportion of initial seeding has a higher effect than the total population and the dominant population is favoured.

For the T+-Tp pair, the comparison can be made directly as both share the same resource. The two figures are for the two resources, the columns represent varying levels of limitations of Tp and the rows represent varying levels of limitation for T+. Generally, coexistence is observed when the resource are limiting by the same amount for both cell types and some of the cases when one of the cell is limited moderately relative to other. For combinations of limitations of both resources across both the cell types, the column represent varying levels of testosterone limits of T+ and Tp and the rows represent varying levels of oxygen limits for T+ and Tp. When the limitation is symmetric, that is, the first and last columns and first and last rows, the behaviour of the system remains similar although with a higher difference for testosterone. Just like Tp-T-, initial seeding has a higher effect than total population here as well.

Moving onto competition between all cell-types, we have gone with homogeneous limitations for all the cell-types as the combinations would increase exponentially. As a result, only Tp and T+ would be affected by testosterone limitations as it is a private resource. As a result, the no and moderate testosterone limitations have weaker and stronger inter-specific competition compared to intra-specific especially by T- and this affects coexistence. The effect of oxygen can be divided into three zones, one where there is no effect as the

combined effect of testosterone, seeding ratios and densities limit Tp and T+, driving them to extinction, the second where there is also no effect as the combined effect leads to saturating growth of Tp and T+, whereas the third one in the in-between where oxygen can push the outcome to either extinction or coexistence as seen here (test:no, 1:1:1, 1000) and here (test:mod, 8:1:1, 1000).

Therapy is implemented as a boolean value where 1 represents dose at MTD and 0 represents no dose. The effect of abiraterone is via the reduction of production rate of testosterone and that of docetaxel is via the reduction of growth rate of cells. With the standard of care, dose is applied at MTD from the start. With adaptive therapy, a binary mode is used where dose is turned on when population exceed an on threshold and stays on until it falls below an off threshold where it's turned off.

With, the framework of all cell type competition, on application of SOC protocol, Tp and T+ go extinct as testosterone limitation by abiraterone is insufficient for their growth.

As mentioned earlier, AT requires on and off threshold. Most AT literature use a 50% rule where therapy is turned at initial volume and turned off when the population drops below 50% of that. However, in the exploration we have done, lower thresholds including the 50% rule lead to strong competition by T- and Tp and T+ go extinct. In line with a few other literature we also found out that a higher threshold is better as Tp and T+ can suppress T- more strongly. However, increasing it further leads to no therapy being applied as they never reach such levels. We have also used the Tp and T+ population size to contribute to the switching of therapy as having all three was unfavourable.

Applying AT to the same framework, we see that higher Tp and T+ leads to more treatable tumour whereas there is no response when both of them go extinct just from competition. However on application of therapy, T- quickly replace the space left and as a result the total population remains high still.

Since we see that Tp and T+ increase and suppress T- in periods without therapy, we speculated that whether delaying treatment would be better. However, we see no advantage due to no variability even after 200 days from the case without delay. This however, only increases the physiological cost.

A hormone agent like abiraterone would pair well with a generic cytotoxic drug like docetaxel as they have different modes of action and would have minimal cross resistance. We have tried this out as a test of concept with the same thresholds but with the population of Tp and T+ controlling abiraterone while all the three control docetaxel. From the limited testing we've done, the negative effect on Tp and T+ outweigh the positive effect of reduction of T- on coexistence.

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. SOC increases the limitation on Tp and T+ and cause their extinction. The influence of AT on the other hand depends on the T+ and Tp available to start with which in turn is controlled by the resource limitations. In addition, a higher threshold for AT leads to increases its success with the caveat of a higher physiological cost. Our model just like every model has a lot of assumptions. A major one that is hard to justify is the assumption of an arbitrary limit of carrying capacity, especially since cancers are known to grow uncontrollably. Our model is a mechanistic approach rather than a data driven one. A data driven one could be

argued to be more realistic, however it lacks any insight of the system. One that achieves both would be ideal. This model acts as a foundation for future work that can be done with explicit resource dependence. An individual-based model would be suitable for building up on this through addition of features like spatial dynamics, phenotypic plasticity and heterogeneous response of the cells.