Studying effects of competition on adaptive therapy

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# Introduction

## What is Cancer?

Cancer is a collection of disease that is usually caused by uncontrolled division of cells and that has potential to spread to other parts of the body . Cancer could be caused by various factors like tobacco usage, excess sun exposure, viral infection to name a few . Although, the underlying mechanism from these causes usually involves genetic mutations or epigenetic changes that alter the DNA. These alterations usually trigger a cascade of events that eventually leads to uncontrolled growth of cells .

Cancer is among the highest causes of death among human beings. In the year 2021, over 600,000 deaths are expected to be caused by cancer in the US alone . Cancer systems have been of research interest for several decades due to the massive impact it has on human lives. Through such research, we have been able to understand the causes and mechanism of how cancer arises and then develop new therapies and drugs that target them. Although, the mortality among some types of cancer have been reduced significantly, we were not so lucky among other types of cancers and, the overall mortality still remains pretty high.

## Conventional therapy against cancer

The most popular strategies to control cancer are radiotherapy, immunotherapy, surgery, and chemotherapy . Radiotherapy involves using ionizing radiation to kill cancer cells. The high intensity radiation damages the DNA beyond repair and this causes the cells to stop dividing and die. Normal cells are also affected by the ionizing radiation and hence the radiation needs to be focussed to reduce collateral damage. Surgery involves removal of the tumour by cutting open the patient. The tumour may be removed in its entirety if it is localised but partial removal may be required to relieve patients of burden when complete removal would be life threatening. Immunotherapy involves triggering the immune system of the body to fight and kill the cancer cells. Immune system on its own can detect and kill abnormal cells but cancer cells can evolve mechanisms to evade these immune suppression. Immunotherapy supplements the immune system to better target and fight against these cells. Chemotherapy involves administering drugs, usually cytotoxic to kill cancer cells. Among chemotherapy, there are different variations, hormone therapy which suppresses hormones required by some cells to survive, targeted therapy which inhibits specific enzymes or antigens produced by cancer cells, and combination therapy which uses multiple such drugs in combination. Depending on the type and stage of cancer, some of these strategies may not be effective.

Among chemotherapy, the standard clinical protocol, Standard of Care (SOC) followed for most cancer is to administer the cytotoxic drugs at the maximum tolerated dosage (MTD) . The aim of this method is to kill the maximum number of tumour cells as fast as possible. This minimises the tumour burden quickly and should give better standard of living if it’s the case.

However, evolutionarily thinking, a tumour would consist of cells with heterogeneous sensitivity towards a cytotoxic drug. Under normal conditions, that is, in the absence of therapy, these cells would compete with each other and keep the number of resistant phenotype in check. On administering the drug at MTD, the most sensitive cells are killed off first and this leads to a “competitive release" of the resistant phenotype . The resistant phenotype now grows without inhibition and takes over the population. These resistant phenotypes don’t respond to further dose administered and the therapy fails. This is illustrated in .

Competitive release could happen for other methods of therapy as well, if there are resistant phenotypes for that particular therapy method present in the population.

Illustration of competitive release under SOC

Illustration of competitive release under SOC

## Adaptive therapy

When competitive release happens, one could try to combat the cells with another drug or therapy method. However, these cells could potentially be resistant to the new drug as well and developing new drugs is research intensive. The best method would be to avoid such a competitive release in the first place. Research trend for cancer therapy has been towards development of new treatment protocols recently as a result.

Adaptive therapy (AT) is one such novel technique under development to avoid competitive release. In AT, the cytotoxic drug is administered at lower and fluctuating doses. This doesn’t kill off all the sensitive cells and the probability of a competitive release is minimised. The resistant cells cannot take over due to competitive pressure from the still remaining sensitive cells and the tumour burden is maintained under control due to further doses being able to kill the sensitive cells that grow back. This is illustrated in .

The dose administered at a given point is usually related to the tumour size at that given point . The challenge with designing AT regimens is to balance between the inhibition of resistant phenotype and the inhibition of the overall tumour size.

Even with this, AT may not be able to achieve control indefinitely. It’ll only attempt to maximise the survival time compared to other regimens. AT, however, ignores the possibility of a cure, where the standard of care method would yield the best results. The patient has to live with the tumour for the rest of their life and other complications could arise due to this. (put in discussion maybe?)

Illustration of control under AT

Illustration of control under AT

## Importance of competition in adaptive therapy

The only way of controlling the resistant phenotype for a fixed drug in AT is through competition by the sensitive cells. Therefore, the success of AT in containing the tumour depends on the effectiveness of competition between sensitive and resistant cells. Although, previously it was thought that resistant cells are required to have an inherent disadvantage for AT to be successful, even without it the survival time can be prolonged by competition between the cells .

Cells can use different strategies such as higher proliferation rate, better survival at suboptimal conditions or lower death rate to compete with each other, and several such strategies are seen to be acquired over the course of cancer progression, as shown by the “hallmarks of cancer" framework .

## System of Study

The metastatic castration resistant prostate cancer (mCRPC) was chosen to be the system of study. The mCRPC system already has a history of AT work done on it, although in different contexts .

Prostate cells express androgen receptors (ARs) that require testosterone or its metabolite, 5-dihydrotestosterone to activate. Activated ARs bind to promoters of genes responsible for proliferation . Without testosterone, proliferation is halted and the cells die of apoptosis. When cancerous cells evolve from prostate cells, the AR mechanism is preserved and such prostate cancer remains testosterone dependent.

This system is usually modelled as consisting of three different types of cells: , and . is the baseline population for prostate cancer which require testosterone for survival. The standard therapy for prostate cancer is castration or androgen deprivation therapy (ADT) which blocks external production of testosterone and would kill the cells in a normal castration sensitive prostate cancer. However, castration resistant prostate cancer soon develops, as the cells can produce testosterone and sustain the cells. cells are also dependent on testosterone, and they produce testosterone from cholesterol through upregulation of CYP17 . The cells on the other hand do not require testosterone as they have mutated ARs that remain active even in the absence of testosterone.

Abiraterone is a drug developed against mCRPC that inhibits the CYP17 and can be effective against both and , however, not against . And, this could lead to competitive release of the resistant cells if administered in the standard clinical protocol. Abiraterone is usually administered after ADT as the system develops into a mCRPC. For our study, we shall only consider AT protocols on abiraterone under ADT.

## Goal of the Project

The goal of the project is to:

1. Develop a model of the chosen system of study with their respective resource dependence.
2. Study the dynamics of the system under different conditions in the absence of therapy.
3. Compare the dynamics under effect of different therapy regimens.
4. Find the corresponding optimal therapy regimen that maximises the survival time for particular conditions.

# Methods

## System of Equations

The system of study was modelled using coupled Ordinary Differential Equations (ODEs). The model is based on a logistic framework modified with a dynamic carrying capacity that depends on the environmental conditions. The “environment" consists of the resources, oxygen and testosterone which have their own equations for production and consumption. We make the simplifying assumption that every other resource required by cells are present in non-limiting concentrations. Additionally, the cell types were assumed to not mutate and hence cannot change their types. No spatial structure is considered and the system is assumed to be well mixed and the resource available in bulk for all the cells.

The ODEs for population size of a cell type is given in . The equation is such that the population increases by a maximum growth rate and reduces by a maximum death rate . The effective growth rate decreases as the total population approaches a maximum limit while the effective death rate stays the same. This maximum limit for the total population varies between 1 to and varies depending on the resource availability as a function of the form as given in and visualised in .  
For

The functional dependence on resource . Below the lower limit, the function is 0, representative of no growth, and increases linearly above it upto the upper limit, and the function saturates to 1, representative of the maximum growth, for any resource levels above that.  
For

The ODE for oxygen is given in . This involves a term for external production that increase oxygen levels constantly at a rate , a term for uptake by all cells where they decrease oxygen levels at a rate and a term for decay where oxygen level decreases at a rate .

The ODE for testosterone is given in . The form is similar to that of oxygen, with the difference being production being done by cells at a rate here.

For implementation of therapy, production rate of testosterone and growth rate of the cells are governed by the dose of abiraterone and docetaxel respectively as given in and .

Note that these equations are defined only for positive values of cell count and resource level to be biologically relevant. To mitigate the problem of having a continuous variable for cell count, is defined as extinction of the cell type and in such a case.

## Therapy

Therapy is modelled as a boolen value, where represents dose at MTD and represents no dose. The dosing scheme for standard-of-care is given in . Here, the dose is applied at MTD at all times from the start of the simulation regardless of the population.  
For

The dosing scheme for adaptive therapy is given in . A binary mode of adaptive therapy is considered here, where dose is applied at MTD when the population size exceeds the threshold and stay on until the population size falls below threshold, after which it is turned off.

## Parameters Used

gives a brief description of the parameters from the above equations, the values used, and the sources for these values where applicable. Note that all the resource parameters are normalised to “Tissue levels of that resource" as obtained from the literature sources cited. The cell lines of LNCaP, 22Rv1 and PC3 were considered to correspond to the , and cells respectively when obtaining literature values.

Constraint equations given below were used to determine the values of some parameters for which direct sources were not available.  
is obtained from solving from to under the assumption that resources are not limiting and is small. This constraint along with doubling time and death rates obtained from literature can be used to get the growth rate.

is obtained from setting = 0 under the assumption that equilibrium is reached with only one cell type present and resources are not limited. This constraint along with an assumed equilibrium value of 10000 for the cells, growth and death rate obtained from above can be used to get the maximum carrying capacity for that cell type.

is obtained from setting = 0 under the assumption that equilibrium is reached with only cell type present. This constraint along with an assumed equilibrium value of 1 for oxygen and 10000 for the cells, and uptake and decay rates from literature can be used to get the production rate of oxygen.

is obtained from setting = 0 under the assumption that equilibrium is reached with only cell type present. This constraint along with an assumed equilibrium value of 1 for oxygen and 10000 for the cells, decay rates from literature can be used to get the production rate of testosterone.

is the same as with a lower equilibrium values of testosterone with abiraterone therapy.

is the rearranged version of with a lower equilibrium value for the cells with docetaxel therapy.

## Code Implementation

The code is written in Python 3 and with dependencies of numpy, scipy, pandas, matplotlib and seaborn libraries. The system of equations were solved numerically by the LSODA algorithm provided by the scipy.integrate.ode function. The code is designed to iterate over the different parameters of a set parallely over multiple threads, however, the actual solver is sequential and single threaded.

The code, at each time step checks if the values are non-negative and sets them to 0 if it is the case. This is since the equations are not defined in these range of values and numerical errors can give rise to negative values. A similar implementation is done for .

The source code along with the data is available at the following Github repository: <https://www.github.com/harshavardhan-bv/cancer-compe-strat>.

QR code for the Github repository

QR code for the Github repository

|l|p4.3cm|c|p2.3cm|

& & &

& No. of cells of cell type & N/A & N/A  
 & Population growth rate of cell type &

|  |  |
| --- | --- |
|  | min |
|  | min |
|  | min |

&  
 & Population growth rate of cell type under therapy &

|  |  |
| --- | --- |
|  | min |
|  | min |
|  | min |

&  
 & Population death rate of cell type &

|  |  |
| --- | --- |
|  | min |
|  | min |
|  | min |

&   
 & Maximum Carrying capacity, coming up through the environment/resources &

|  |  |
| --- | --- |
|  |  |
|  |  |
|  |  |

&  
 & Functional dependence of cell type on resource , normalised to 1 & & N/A  
 & Production rate of resource, either as bulk or by cells &

|  |  |
| --- | --- |
|  | 0.11 min |
|  | mincell |

& ,  
 & Production rate of under therapy & mincell &  
 & Uptake of resource by cell type &

|  |  |  |
| --- | --- | --- |
|  |  | mincell |
|  |  | mincell |
|  |  | mincell |
|  |  | mincell |
|  |  | mincell |
|  |  | 0 mincell |

& ,  
 & Decay rate of resource &

|  |  |
| --- | --- |
|  | 0.100 min |
|  | 0.004 min |

&   
 & Lower limit/threshold level of resource for carrying capacity of cell type & & N/A  
 & Upper limit/saturation level of resource for carrying capacity of cell type & & N/A  
  
 & Doubling time of cell type &

|  |  |
| --- | --- |
|  | hr |
|  | hr |
|  | hr |

&   
 & Equilibrium value of cell number in absence of competition & 10000 & assumed  
 & Equilibrium value of cell number in absence of competition under therapy &

|  |  |
| --- | --- |
|  |  |
|  |  |
|  |  |

&   
 & Equilibrium/Tissue levels of resource with one cell type present &

|  |  |
| --- | --- |
|  | 2.5 mmHg |
|  | 3.74 pmol/g tissue |

& ,  
 & Equilibrium/Tissue levels of testosterone with only cell type present under therapy & &

# Results

## Pairwise -

From the initial runs where two parameters were changed at a time, the following were observed:

1. Only when is not severely testosterone limited ( is low), can coexist with or outcompete as shown in . In every other case, drives to extinction.
2. These competitive outcomes are also dependent on the initial proportion of , all the other parameters being the same as shown in .
3. When is strongly oxygen-limited () but is also limited by testosterone. In this case, wins out eventually as oxygen levels rise faster than testosterone through the external supply term, as shown in .
4. When is oxygen limited but with poor oxygen production (lower ), is able to drive to extinction as can grow and consume enough oxygen to keep the oxygen levels below those required for to grow as shown in .

Pairwise time-series, when is testosterone limited and not testosterone limited (columns) and at different initial proportions of (rows). is testosterone limited at and not testosterone limited at .

Pairwise time-series, when is testosterone limited and not testosterone limited (columns) and at different initial proportions of (rows). is testosterone limited at and not testosterone limited at .

Pairwise time-series, when is oxygen limited and at different oxygen production (column). is oxygen limited at and is testosterone limited at . The normal and poor production of oxygen are 0.11 and 0.0675 min respectively

Pairwise time-series, when is oxygen limited and at different oxygen production (column). is oxygen limited at and is testosterone limited at . The normal and poor production of oxygen are 0.11 and 0.0675 min respectively

Additionally, a brute force parameter space exploration was done over a large combination of parameters. Due to the large parameter set, interpreting the results is difficult and only a few generalised observations were found, as listed below.

1. drives to extinction when , regardless of the other parameters, in other words, shouldn’t be limited by oxygen to compete with .
2. drives to extinction when , regardless of the other parameters, in other words, needs to be able to grow even on the smallest amount of testosterone to compete with .
3. drives to extinction when and but not when , in other words, shouldn’t be testosterone limited when is not oxygen limited to be to compete with . The required for to not go extinct also increases with increased , that is, can afford to be more testosterone limited as becomes more oxygen limited.

From the above observations, the following cases were formulated as an exhaustive formulation of possible conditions. Three levels each of limitation: no, moderate and severe corresponding to respectively, three levels each of limitation: low, high and severe corresponding to respectively, and two levels each of production: normal and poor corresponding to min respectively were considered and pairwise competitive runs were done over all combinations of these given in with varying initial cell seeding.

Table of cases for - pairwise

|  |  |  |
| --- | --- | --- |
| **production** | **limitation** | **limitation** |
| Continued on next page |  |  |
| normal | low | no |
| normal | low | moderate |
| normal | low | severe |
| normal | high | no |
| normal | high | moderate |
| normal | high | severe |
| normal | severe | no |
| normal | severe | moderate |
| normal | severe | severe |
| poor | low | no |
| poor | low | moderate |
| poor | low | severe |
| poor | high | no |
| poor | high | moderate |
| poor | high | severe |
| poor | severe | no |
| poor | severe | moderate |
| poor | severe | severe |
|  |  |  |

The following were observed from the cases as visualised in :

1. Coexistence is observed only when there is no or moderate limitation of testosterone for and low limitation of oxygen for . For low initial seeding, dominates over and causes it to go extinct, but as initial seeding increases the favour shifts towards .
2. causes to go extinct for all initial seedings when is severely testosterone limited. Even with a high initial seeding advantage, grows, overtakes and eventually causes to go extinct. also goes extinct in this case if it is limited by oxygen under poor oxygen production. Despite this is weighed down by both the testosterone limitation and density-dependent competition of the remaining cells and goes extinct as a result.
3. The outcome switches from going extinct to going extinct for higher initial seeding when is highly limited by oxygen under either poor or normal oxygen production and when is severely limited by oxygen under normal oxygen production. Similar to the cases with coexistence, for low initial seeding, dominates over and causes it to go extinct, but as initial seeding increases the favour shifts towards . However, in this case the oxygen levels don’t go above the levels required for to grow before it goes extinct and only remains.
4. goes extinct for all initial seedings when it is severely oxygen limited under poor oxygen production. The oxygen limitation on is too high and the oxygen levels never reach the levels required for a non-zero growth for .
5. Additionally, total population size has a weaker effect than initial proportion for the dynamics and outcomes for each particular case.

normal production

normal production

poor production

poor production

## Pairwise -

From the initial runs where two parameters were changed at a time, the following were observed:

1. When limited by testosterone more than (), can consume and grow on the limited testosterone present, and this is enough for the density-dependent competition to drive to extinction. Without to provide testosterone, subsequently goes extinct.
2. When is weakly limited by testosterone relative to (), both cells coexist. Due to weaker testosterone limitation, can grow faster initially and secrete enough testosterone for without being negatively affected by . This is visualised in .
3. When both are severely testosterone limited but not oxygen limited, causes to go extinct. However, in a special scenario when both are oxygen limited with being more limited, coexistence is observed. A balance of sort is achieved here, where, in the initial period of low oxygen, can grow more than and secrete enough testosterone to sustain both population but doesn’t grow as much as to drive to extinction. This is visualised in .

Pairwise time-series, when is more testosterone limited than and when is more testosterone limited than . is more limited testosterone limited at and is limited more at .

Pairwise time-series, when is more testosterone limited than and when is more testosterone limited than . is more limited testosterone limited at and is limited more at .

Pairwise time-series, when both cell types are testosterone limited and not oxygen limited at and is oxygen limited and moderately at .

Pairwise time-series, when both cell types are testosterone limited and not oxygen limited at and is oxygen limited and moderately at .

From the above observations, the following cases were formulated as an exhaustive formulation of possible conditions. Three levels each of and limitation: no, moderate and severe corresponding to respectively, Three levels each of and limitation: low, moderate and severe corresponding to respectively were considered and pairwise competitive runs were done over some combinations of these as given in with varying initial cell seeding.

Only two levels of limitations were considered for each resource when combinations of both or limitations were done to reduce the number of combinations for better interpretability. Similarly, different levels of or production is not considered in these cases for the same reason. Production terms will ultimately affect resource availability, and we’re doing something roughly similar by adjusting the response function of the cell instead of actual resource concentrations.

Table of cases for - pairwise

|  |  |  |  |
| --- | --- | --- | --- |
| **limitation** | **limitation** | **limitation** | **limitation** |
| Continued on next page |  |  |  |
| low | low | no | no |
| low | low | no | moderate |
| low | low | no | severe |
| low | low | moderate | no |
| low | low | moderate | moderate |
| low | low | moderate | severe |
| low | low | severe | no |
| low | low | severe | moderate |
| low | low | severe | severe |
| low | moderate | no | no |
| low | moderate | no | moderate |
| low | moderate | moderate | no |
| low | moderate | moderate | moderate |
| low | severe | no | no |
| moderate | low | no | no |
| moderate | low | no | moderate |
| moderate | low | moderate | no |
| moderate | low | moderate | moderate |
| moderate | moderate | no | no |
| moderate | moderate | no | moderate |
| moderate | moderate | moderate | no |
| moderate | moderate | moderate | moderate |
| moderate | severe | no | no |
| severe | low | no | no |
| severe | moderate | no | no |
| severe | severe | no | no |
|  |  |  |  |

The following were observed from the different cases. For better visualization, the figures are divided into testosterone limitations in , oxygen limitations in and combinations of the limitations in .

1. Severe limitation of either oxygen or testosterone for relative to causes it to go extinct. In a special case, when numbers are high enough to produce an excess of testosterone, a small fraction of survives regardless of the strength of test limitation. Conversely, when neither resource is limiting, coexistence occurs at all seeding densities and proportions of , which suggests that competitive exclusion of either cell type is strongly dependent on environmental conditions and resource limitation. When is moderately oxygen limited relative to , can coexist at low initial density of but goes extinct at higher initial densities.
2. is driven to extinction in every case where limitation of either oxygen or testosterone is more severe relative to limitation of the same resource. Extinction of then leads to extinction of trivially. Such is the case for the most part with moderate limitation of testosterone for relative to . However, this extinction is seen to be rescued for higher initial density of relative to as this allows the former to overcome competition, leading to coexistence.
3. In very broad terms, coexistence is more common when the strength of limitation of either resource is the same for both cell types-these are the main diagonals in and . However, under severe limitation of testosterone for both cell types, increasing relative proportion gives a competitive edge to presumably by increasing net availability of testosterone in the system. This increased availability also has limits beyond which further increase in proportion is marginally detrimental to success.
4. With moderate limitation of oxygen for relative to , still requires testosterone from for survival which could weaken the growth inhibition of , despite the lower oxygen limitation of compared to . Interestingly, this is also the case with coexistence at lower final proportions than any other case. Coexistence here is therefore driven by the dependence on by for testosterone, which overrides any advantage from a better oxygen use strategy.
5. Coexistence is also observed when is moderately testosterone limited relative to . However, in this case, a lower initial proportion of favours and leads to a dip in the plot. At a low initial proportion of , being limited by testosterone dies out until sufficient testosterone is established and this might give an advantage for to establish a larger population before has the capacity to compete.
6. The behaviour of the system is very similar if the resource limitatation is symmetric across the two cell types. This can be seen from the first and last columns or from the first and last rows respectively of . Although, with the higher testosterone limitations of , a higher initial seeding is required to have overcome suppression by . Additionally, when is moderately limited by oxygen relative to , the higher testosterone limitation of leads to higher required for the testosterone.
7. When both testosterone and oxygen are moderately limiting for a cell type relative to the other, the combined overall limitation is severe and that particular cell type is driven to extinction similar to when only one resource was severely limiting.
8. When is moderately limited by oxygen relative to and moderately limited by testosterone relative to , a balance is achieved. can outcompete due to the excess oxygen but soon is limited by testosterone and has to allow a sizeable population of to grow to maintain the required testosterone levels. However, with the inverse case where is testosterone limited and is oxygen limited, the outcomes are unstable and it switches from driven to extinction at low initial proportion to going extinct for higher initial proportion.
9. Additionally, total population size has weaker effect than initial proportion for the dynamics and outcomes for each particular case.

limitations. Columns: limitation, Rows: limitation.

limitations. Columns: limitation, Rows: limitation.

limitations. Columns: limitation, Rows: limitation.

limitations. Columns: limitation, Rows: limitation.

Combination of and limitations. Columns: limitations, Rows: Columns: limitations.

Combination of and limitations. Columns: limitations, Rows: Columns: limitations.

## All 3 cell-types

With all three cell types, the number of combinations and permutations increase combinatorially, and sifting through such a massive pile of data is a daunting prospect. So, we are starting with a simpler case of the same strategy for all three cell types. The corresponding lower and upper limit for the different resources are listed in .

Table of limits corresponding to limitations for different resources of all three cell-types

|  |  |  |  |
| --- | --- | --- | --- |
| **Resource** | **Limitation** | **lower limit** | **upper limit** |
| Continued on next page |  |  |  |
|  | no | 0.0 | 1.1 |
|  | moderate | 0.0 | 1.0 |
|  | high | 0.4 | 0.1 |
| Testosterone | no | 0 | 0.1 |
|  | moderate | 0 | 0.3 |
|  |  |  |  |

Competitive runs were done over all the six combinations of limitations for two different ratios of seeding and three initial total seeding. The following were observed from the different cases as visualised is . The time-series of the same is given in .

1. Moderate limitation of testosterone leads to a stronger interspecific competition relative to intraspecific competition as and numbers cannot increase enough to produce self-inhibition. In these cases, inhibition by is much stronger and they are driven to extinction, which is in contrast to when and coexisted when seeded without . However, consistent with the results, coexistence can be recovered between all three cell types when is seeded at a much higher proportion than the other two presumably by increasing net available testosterone in the system. Therefore, when testosterone is a strongly limiting resource, it also leads to strong positive dependence on density for coexistence due to the fact that it is produced by .
2. No limitation of testosterone leads to weaker interspecific competition relative to intraspecific competition above a threshold proportion of that is required to produce the minimum amount of testosterone for survival. Again, we see that self-production of testosterone by leads to a progressively lower limitation of the hormone, both across runs with increasing number of cells, and within a given run with increasing time. Additionally, in the moderate testosterone limitation cases, it can be seen that simultaneous lower oxygen limitation reinforces this positive feedback on to further, leading to coexistence that is further biased towards the combo.
3. At higher limitations of testosterone, the addition of oxygen limitation only drives it down further, whereas at lower limitations of testosterone, the limitations are overcome and hence it has no further effect. The only place where oxygen limitations have an impact is where the testosterone limitation is just on the edge and the outcomes are pushed to either coexistence or extinction of and by the oxygen limitation. Therefore, limitations of oxygen seem to have a much less of a direct impact on competition and instead supplements the competition imposed by testosterone.
4. Testosterone then acts as a private resource and the primary limitation between and that serves to produce positive feedback above some minimum concentration, thus leading to coexistence between all three cell types even though has a significantly shorter doubling time.

Equal Seeding - :: 1:1:1

Equal Seeding - :: 1:1:1

High seeding- :: 8:1:1

High seeding- :: 8:1:1

## Therapy

### Standard of care

With standard-of-care, the therapy is applied from the beginning at the maximum tolerated dose for all the cases as mentioned in the all 3 cell type competitive run. The following were observed from the different cases as visualised is .

1. and go extinct in all the cases, regardless of the limitations of either of the resources, seeding proportion or initial total seeding.
2. Competitive release of happens and the total population reaches its maximum effective carrying capacity. Further treatment doesn’t lead to any reduction of cell number.
3. The extinction of and is immediate as the testosterone levels are reduced below required levels on administration of abiraterone.

Equal Seeding - :: 1:1:1

Equal Seeding - :: 1:1:1

High seeding- :: 8:1:1

High seeding- :: 8:1:1

### Adaptive Therapy

For adaptive therapy, on and off thresholds are required. Different such carrying thresholds were tried out for the case where oxygen limitation is low and testosterone limitatation. The following were observed and some are visualised in .

1. For low thresholds, the and populations are so low and the competition by drives them to extinction. This includes the rule of having the on threshold at initial population and off threshold at of the initial population.
2. A higher threshold would be better for and to survive the competition by as well as to suppress . However, increasing it further, leads to no therapy being applied for the entire duration as the levels don’t go above the on threshold. Although, not administering drugs may be a viable solution in a clinical situation, it is hard to justify it when exploring adaptive therapy. The threshold of On:6000 and Off:4000 seems like a reasonable middle ground for further exploration.
3. This increased effectiveness of a higher threshold seen here has also been shown in .
4. The and cell types are only considered for the thresholds for therapy. This might be difficult to measure in a clinical scenario as it will be hard to differentiate the cell types easily and non-invasively. The case where all the three cell types are considered for the thresholds for therapy were also tried out as visualised in . However, all the cases led to competitive release in the initial few days and hence the former choice was made.

Standardization of threshold for adaptive therapy, Columns: On-Off threshold, Rows: Seeding

Standardization of threshold for adaptive therapy, Columns: On-Off threshold, Rows: Seeding

With the on and off thresholds of 6000 and 4000 respectively, the following were observed from the different cases as visualised is .

1. Tumours with higher numbers of and would be more responsive to abiraterone and hence more treatable. Coexistence is of importance here as extinction of and would lead to no response.
2. For cases when testosterone is moderately limiting and testosterone levels below the requirement of and , these two cell types go extinct just by the competition from and produce no response from abiraterone naturally. Therefore, abiraterone efficacy depends strongly on seeding densities and total population, as with coexistence.
3. In cases where coexistence is achieved, the cells quickly replace the space left by dead and cells on applying therapy. In periods of no therapy the and cells compete with and replace the cells but are soon met with therapy on exceeding the on threshold. So the total population size remains high for most of the duration except for a sliver during therapy.
4. As noted earlier, higher the amount of available testosterone, weaker the interspecific competition relative to intraspecific competition and therefore, better the coexistence. Since coexistence is tied strongly with the effectiveness of therapeutic outcomes, it stands to reason that the window of population sizes of and that are used in adaptive therapy must be chosen to allow for sufficient numbers of and to remain in the population.
5. Applying this idea specifically to the case with no limitation for both oxygen and testosterone, and population fractions increase monotonously with time without treatment. It is therefore possible that early treatment could be detrimental to coexistence and cause early competitive release of . Choosing a higher therapy window for control negates this possibility. This may even correspond to some of those cases in the clinic that are largely left untreated.
6. A related idea to the above finding is whether delaying the onset of treatment could improve therapeutic outcomes by allowing for a better balance of and . The conditions that we have tested here shown in do not show such an advantage to delay since we do not see much variability in the population fractions of each cell type within the delay time periods considered here.
7. Although we may expect that there are potential spaces where docetaxel could be used to alleviate some of the pressure on and , especially where they’re driven to extinction, initial data visualised in show that the direct negative effect of docetaxel on and outweigh any positive effect from reduction of competition. Results so far suggest that the scope for docetaxel application is highly limited in this system as it disrupts the sensitive balance of numbers between the three cell types. Nevertheless, more extensive testing is warranted.

Equal Seeding - :: 1:1:1, Initial Total seeding: 1000

Equal Seeding - :: 1:1:1, Initial Total seeding: 1000

High seeding- :: 8:1:1, Initial Total seeding: 1000

High seeding- :: 8:1:1, Initial Total seeding: 1000

Equal Seeding - :: 1:1:1, Initial Total seeding: 2000

Equal Seeding - :: 1:1:1, Initial Total seeding: 2000

High seeding- :: 8:1:1, Initial Total seeding: 2000

High seeding- :: 8:1:1, Initial Total seeding: 2000

Equal Seeding - :: 1:1:1, Initial Total seeding: 4000

Equal Seeding - :: 1:1:1, Initial Total seeding: 4000

High seeding- :: 8:1:1, Initial Total seeding: 4000

High seeding- :: 8:1:1, Initial Total seeding: 4000

Equal Seeding - :: 1:1:1, Initial Total seeding: 2000

Equal Seeding - :: 1:1:1, Initial Total seeding: 2000

High seeding- :: 8:1:1, Initial Total seeding: 2000

High seeding- :: 8:1:1, Initial Total seeding: 2000

Equal Seeding - :: 1:1:1, Initial Total seeding: 2000

Equal Seeding - :: 1:1:1, Initial Total seeding: 2000

High seeding- :: 8:1:1, Initial Total seeding: 2000

High seeding- :: 8:1:1, Initial Total seeding: 2000

# Discussion

Mathematical modelling is a really powerful tool in biology which helps in understandanding a system without use of an actual system for the main experimentation. This can be very useful when experimenting on the actual system or biological model is not possible due to ethics, health risks, etc. However, one must keep in mind that all biological models are simplifications and involve a lot of assumptions. Quoting “All models are wrong, but some are useful".

There are no objective criteria for what makes a good model, or a fair set of prior assumptions. Every model makes assumptions that are manifestations of constraints inherent to the mathematical framework and data availability. What is more important is how these assumptions are structured to enable meaningful study of at least one aspect of the system’s behaviour. What makes this a difficult enterprise is the fact that all these choices and assumptions also involve subjective values and judgement that is only accumulated with time and can go wrong at any point of time.

One of the largest assumption made in this model is the effective carrying capacity of each cell type, that is the equilibrium values, in . Every other assumption is linked in someway to this assumption due to the unavailability of data for them. The concept of carrying capacity in a Logistic or Lotka-Volterra system is a debated topic and even more so in the cancer systems . We tried to build a model without an explicit carrying capacity, where the resource limitations affect the growth rate instead. However, the exponential nature of the model made it very sensitive to the parameters and suitable parameters were not available from literatures we searched.

Our modelling approach has been more mechanistic in nature than data driven. We have started with parameter from fundamental processes governing the system for the overall behaviour to emerge out of it. A data driven model on the other hand, fits the parameters to clinical data. One could argue that such a data driven model refelects closer to reality since it follows the same dynamics, however, such models don’t give valuable insight into these fundamental processes and act as black boxes.

In the end, all the therapy strategies we tried have been a failure. Even though we avoided competitive release in some cases by maintaining a non-zero population of the responsive cell types and , total tumour burden is very high and very close to the maximum effective carrying capacity. This might be attributed to either the assumptions made in the model or it could be fundamental to the system.

# Supplementary

Equal Seeding - :: 1:1:1, Initial Total seeding: 1000

Equal Seeding - :: 1:1:1, Initial Total seeding: 1000

High seeding- :: 8:1:1, Initial Total seeding: 1000

High seeding- :: 8:1:1, Initial Total seeding: 1000

Equal Seeding - :: 1:1:1, Initial Total seeding: 2000

Equal Seeding - :: 1:1:1, Initial Total seeding: 2000

High seeding- :: 8:1:1, Initial Total seeding: 2000

High seeding- :: 8:1:1, Initial Total seeding: 2000

Equal Seeding - :: 1:1:1, Initial Total seeding: 4000

Equal Seeding - :: 1:1:1, Initial Total seeding: 4000

High seeding- :: 8:1:1, Initial Total seeding: 4000

High seeding- :: 8:1:1, Initial Total seeding: 4000

Equal Seeding - :: 1:1:1

Equal Seeding - :: 1:1:1

High seeding- 8:1:1 ::

High seeding- 8:1:1 ::

![Standardization of threshold considering all three cells for adaptive therapy, Columns: On-Off threshold, Rows: T^p:T^+:T^- Seeding](data:application/pdf;base64,)

Standardization of threshold considering all three cells for adaptive therapy, Columns: On-Off threshold, Rows: Seeding