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, chemotherapy, immunotherapy, and surgery. 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 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.

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

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.

## 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.

## 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 run 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 i &

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

&  
 & Population death rate of cell type i &

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

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

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

& ,

# 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 timeseries, 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 timeseries, 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 .

[fig\_Tpro-Tneg\_testlims]

Pairwise timeseries, 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 timeseries, 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

[fig\_Tpro-Tneg\_o2lims]

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 . This is visualised in .
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 . This is visualised in .
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. This is visualised in .

Lower limit of oxygen for

Lower limit of oxygen for

[fig\_Tpro-Tneg\_llo2Tp]

Lower limit of testosterone for

Lower limit of testosterone for

[fig\_Tpro-Tneg\_lltestTp]

Upper limit of testosterone for

Upper limit of testosterone for

[fig\_Tpro-Tneg\_ultestTp]

[fig\_Tpro-Tneg\_megarun]

From the above observations, the following cases were formulated as an exhaustive formulation of possible conditions. Three levels of testosterone limitation of pairwise competitive runs were done over varying initial cell seeding.

Table of cases for - pairwise

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
| AAA | normal | no | no |
| AAB | normal | no | moderate |
| AAC | normal | no | severe |
| ABA | normal | high | no |
| ABB | normal | high | moderate |
| ABC | normal | high | severe |
| ACA | normal | severe | no |
| ACB | normal | severe | moderate |
| ACC | normal | severe | severe |
| BAA | poor | no | no |
| BAB | poor | no | moderate |
| BAC | poor | no | severe |
| BBA | poor | high | no |
| BBB | poor | high | moderate |
| BBC | poor | high | severe |
| BCA | poor | severe | no |
| BCB | poor | severe | moderate |
| BCC | poor | severe | severe |
| [tab\_Tpro-Tneg\_cases] |  |  |  |

Here,

* For production: normal and poor correspond to min respectively.
* For limitation: no, high and severe correspond to respectively.
* For limitation: no, moderate and severe correspond to respectively.

normal production

normal production

[fig\_Tpro-Tneg\_cases\_normal]

poor production

poor production

[fig\_Tpro-Tneg\_cases\_poor]

[fig\_Tpro-Tneg\_cases]

The following were observed from the cases as visualised in :

1. Coexistence is observed only in cases AAA, AAB, BAA and BAB. All of them have low or moderate limitation of testosterone for and have no limitation of oxygen for . For low initial seeding, dominates over and causes it to go extinct, but as initial seeding increases the favour shift towards .
2. causes to go extinct for all initial seedings in cases AAC, ABC, BAC and BBC. is severely testosterone limited and even with a high initial seeding advantage, grows, overtakes and eventually causes to go extinct. At high initial seeding, also goes extinct in case BBC due to high oxygen limitation on it.
3. The outcome switches from going extinct to going extinct for higher initial seeding in cases ABA, ABB, ACA, ACB, ACC, BBA and BBB. As with cases AAA, AAB, BAA and BAB, for low initial seeding, dominates over and causes it to go extinct, but as initial seeding increases the favour shift 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. Case ACC has this switch only at the highest initial seeding as it is also severely testosterone limited.
4. goes extinct for all initial seedings in cases BCA, BCB and BCC. also goes extinct in the case BCC. The oxygen limitation on is too high and the oxygen levels never reach the levels required for a non-zero growth for . In the case BCC, is weighed down by both the testosterone limitation and density-dependent competition of the remaining cells and goes extinct as a result.

## 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. In the above case, the proportion of in the final population decreases as becomes more testosterone limited.
4. 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 timeseries, 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 timeseries, when is more testosterone limited than and when is more testosterone limited than . is more limited testosterone limited at and is limited more at .

[fig\_Tpos-Tpro\_testlims]

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

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

[fig\_Tpos-Tpro\_o2lims]

From the above observations, the following cases were formulated as representative and pairwise competitive runs were done over varying initial cell seeding.

Table of cases for - pairwise

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
| AAAA | no | no | no | no |
| AAAB | no | no | no | moderate |
| AAAC | no | no | no | severe |
| AABA | no | no | moderate | no |
| AABB | no | no | moderate | moderate |
| AABC | no | no | moderate | severe |
| AACA | no | no | severe | no |
| AACB | no | no | severe | moderate |
| AACC | no | no | severe | severe |
| ABAA | no | moderate | no | no |
| ABAB | no | moderate | no | moderate |
| ABBA | no | moderate | moderate | no |
| ABBB | no | moderate | moderate | moderate |
| ACAA | no | severe | no | no |
| BAAA | moderate | no | no | no |
| BAAB | moderate | no | no | moderate |
| BABA | moderate | no | moderate | no |
| BABB | moderate | no | moderate | moderate |
| BBAA | moderate | moderate | no | no |
| BBAB | moderate | moderate | no | moderate |
| BBBA | moderate | moderate | moderate | no |
| BBBB | moderate | moderate | moderate | moderate |
| BCAA | moderate | severe | no | no |
| CAAA | severe | no | no | no |
| CBAA | severe | moderate | no | no |
| CCAA | severe | severe | no | no |
| [tab\_Tpro-Tneg\_cases] |  |  |  |  |

Here,

* For limitation: no, moderate and severe correspond to respectively.
* For limitation: no, moderate and severe correspond to respectively.

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 limitiations in .

1. causes to go extinct for all initial seedings in cases CAAA and CBAA. is severely oxygen limited and quickly utilized the intial period to grow to a large population and suppress from further growth.
2. A similar situation to above happens for cases AACA and AACB, but for high initial seeding of , a very small population of is able to survive due to the excess testosterone produced by .
3. Both the cell types go extinct for cases AAAC and AABC. is severly limited by testosterone and consumes the limited amount produced by and denies it of growth. goes exctinct and soon followed by due to non availability of testosterone.
4. A similar behaviour to above happens for cases ACAA and BCAA, but for high initial seeding of with low total population, there is coexistence. Both the cells manage to survive until the oxygen levels reach above the levels required for growth and they can recover from it. For higher total populations, the density-dependent suppression is too high and they go extinct before oxygen levels can reach it.
5. In case AACC, at low initial seeding, it follows a similar behaviour to cases AAAC and AABC and both go extinct while at high initial seeding, it follows a similar behaviour to cases AACA and AACB, where there is extinction of at medium seeding and coexistence at high seeding.
6. Both coexist for all initial seeding in cases AAAA and AABA. Here, can grow unhindered by , secrete testosterone, which can grow on. Case AABB is similar, but both go extinct at low initial seeding as dominates over through number and prevents it from growing due to the higher testosterone limitation.
7. Case AAAB is the opposite of the above as only at high initial seeding can both coexist. can grow better than for the same amount of testosterone present and can outnumber and cause to go extinct. At higher seeding, has a numbers advantage from the begining and can produce enough testosterone to sustain both.
8. Case BBAA is exactly the same as Case AAAA as both are limtied by the same amount.
9. is driven to extinction in all but the low initial seeding in Case BAAA. At low seeding, can use the number advantage to stay alive and then use the testosterone produced by to grow but at higher seedings, is limited by oxygen.
10. In case ABAA, at low initial seeding, the higher number can cause to go extinct and eventually both the cell types. Whereas at higher initial seeding, despite growing faster than due to lowered oxygen limitation, stops at a point due to requirement of testosterone produced by and this maintains a balance between the two cells.
11. Cases BBAA, BBAB, BBBA and BBBB were exactly the same as cases AAAA, AAAB, AABA and AABB respectively as the two corresponding cases are limtied by oxygen by the same amount with all else being the same.
12. In a similar manner cases ABBB and BABB are similar to cases ABAA and BAAA. Due to the higher testosterone limitations of , a higher initial seeding is required have overcome suppression by . Additionally in case ABBB, the higher testosterone limitation of leads to higher required for testosterone and a higher final population.
13. Case ABAB gives a double disadvantage to due to both testosterone and oxygen limitiation and it goes extinct along with in all seedings. Similarly, case BABA gives a double disadvantage to and goes extinct for all seedings.
14. Case ABBA is similar to case ABBB, but can coexist at lower initial seeding as well since is not testosterone limited.
15. At low initial seeding, both cells go extinct due to higher testosterone limitation of . However at higher initial seeding, is able to push to extinction due to the higher oxygen limitation of .

limitations. Columns: limitation, Rows: limitation.

limitations. Columns: limitation, Rows: limitation.

[fig\_Tpos-Tpro\_cases\_test]

limitations. Columns: limitation, Rows: limitation.

limitations. Columns: limitation, Rows: limitation.

[fig\_Tpos-Tpro\_cases\_o2]

limitations. Columns: limitations, Rows: Columns: limitations.

limitations. Columns: limitations, Rows: Columns: limitations.

[fig\_Tpos-Tpro\_cases\_combi]

[fig\_Tpos-Tpro\_cases]

## All 3 celltypes

### Efficiency

To simplify things, the resource limitations as described in the previous sections can instead be considered as efficiencies of the cell types in utilization of a particular resource. Although many possible combinations are there, all the cell types are assumed to have the same efficiencies for the respective resources.

1. When the testosterone efficiency is high, all the three cell types can coexist in all the oxygen efficiency cases as shown in .
2. At lower oxygen efficiency, is able to have a larger final population as the turn over is slower in the case of .
3. The difference between null oxygen efficiency and high oxygen efficiency is small, where high oxygen efficiency has a slightly higher and and a lower final population.
4. The same holds when the initial seeding is at ratio but the final population of is much higher in this case.
5. At null oxygen efficiency, all three cell types can coexist in all the testosterone efficiency cases only when the initial seeding is at ratio as shown in .
6. At lower testosterone efficiency, is able to have a larger final population due to no effect of the efficiency changes on .

All 3 cell types timeseries, at different oxygen efficiency (columns) and at different initial proportions of (rows).

All 3 cell types timeseries, at different oxygen efficiency (columns) and at different initial proportions of (rows).

[fig\_all3\_o2eff]

All 3 cell types timeseries, at different testosterone efficiency.

All 3 cell types timeseries, at different testosterone efficiency.

[fig\_all3\_testeff]