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Modelling the Evolutionary Trajectory of Metastatic Cancer Treated with Modified Adaptive Therapy

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Abstract

Although cancer is recognized as an evolutionary process, cancer research lacks focus regarding the disease's evolutionary aspect. The focus of this study is on metastatic cancer as it is difficult to treat and control. COBWEB, an agent-based simulation software, was used to determine whether adaptive therapy could control the evolutionary trajectory of the tumor and reduce further metastasis in a patient. Initial results indicated that I. drug usage could serve as a selective pressure against aggressive and resistant cells in order to extrapolate selective advantages for the less aggressive cancerous cells and that II. primitive adaptive therapy, based on the oscillation of two drugs, could provide more control over metastasis rather than conventional treatments. Overall, further research is necessary to confirm whether adaptive therapy can increase median survival rates and the quality of life for patients with metastatic cancer.

Keywords: Adaptive therapy; Metastasis; Drug resistance; Cancer; Tumor

Introduction

As there are more than 100 variances of cancer, it is not considered a single disease, but a collection of related diseases [1]. As one of the leading causes of death in high-income countries, cancer causes an estimated 8.8 million deaths per year [2]. The five-year survival rate of cancer patients depends on the cancer type, ranging from 9% for pancreatic cancer to98% for thyroid cancer [1].

Cancer is the result of several factors including the environment and specific gene mutations where tumor suppressor genes or oncogenes mutate to become cancerous [1]. Within the body, cancer branches into varying subpopulations with different genetic traits. Specific conditions within the body can favour certain subpopulations of cancerous cells, which may lead to metastasis [3-7].

Targeted therapy is an innovation in cancer treatments. Targeted therapy interferes with specific molecules to reduce the growth of cancerous cells, which may result in complete remission for patients [8]. Some targeted therapy drugs include tyrosine kinase inhibitors and imatinib, also known as Gleevec. Before the usage of tyrosine kinase inhibitors, the median survival rate for chronic myeloid leukemia was approximately 3-5 years [9]. Since the introduction of tyrosine kinase inhibitors, the average five-year survival rate has increased to 89% [10]. A further follow-up study found the overall survival rate for patients using Gleevec over a time period of 8 years was 95.2% [11]. Targeted therapy has been proven to have higher success rates with treating metastatic cancer in comparison to other therapies, however, resistance is often observed promptly after the treatment commences [12].

Metastasis involves various stages in which cancerous cells leave the original tumor and travel to other locations in the body [7]. Once cancerous cells successfully infiltrate the bloodstream or lymphatic system, it becomes highly probable that the cancer will spread throughout the body [13,14]. The possibility of treatment being curative is greatly diminished once the cancer begins to metastasize [15]. Currently, most therapies attempt to rapidly eliminate cancerous cells, however, after susceptible cancer cells are eliminated, the tumor becomes resistant to the treatment [16-18]. Therefore, the evolutionary process of cancerous cells should be considered in order to understand the adaptive advantages for the subpopulations of cancerous cells [19,20].

Earlier treatments tend to target genes present in all cancerous cells in a tumor. While treatments attempt to target the origin of all cancerous cells, it is challenging to fully eliminate them. Introducing resistance to the most potent drugs during initial stages of treatment poses the risk of developing a more aggressive cancer [8,12]. In tumors there are subclones of cells with certain genotypes that provide specific advantages within their environment. Certain genotypes are associated with the aggressiveness of cancer, such as circumstances in which drug-resistant cells have been found in cancerous tumors prior to therapy [21-25]. The result of this study is comparable to other studies that have suggested drug-resistant genes exist before treatment [26-32].

As drug-resistant genes do not directly result from treatment and resistance is a recessive phenotype, there must be specific factors which elicit such a response. These drug-resistant genes are a part of a small subclone of cancerous cells prior to treatment [33]. If the treatment impedes and reduces drug resistance, in certain circumstances susceptible cells can outcompete resistant cells. As a result, drug combinations that limit the evolution of resistance in cancerous cells can render cancer as a chronic disease for many patients, thus increasing the median survival rate [29,33,34].

Selective pressure can be applied to subpopulations of cancerous cells [35] to create competition between susceptible cells and resistant cells [32,34,36]. However, cells with metastatic tendency or drug resistance are naturally selected during treatment [12,33,36,37]. Therefore, an environment that selects against metastatic tendency or drug resistance has to be synthetically established. Drugs can be used as a selective pressure against aggressive and resistant cells in order to infer

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selective advantages for less aggressive cancerous cells. However, no attempts have been made to target phenotypes and genotypes that are known for being non-aggressive. By using adaptive therapy to control the subpopulations of cancerous cells with specific genotypes, it is possible to reduce the population of aggressive cancer cells.

Adaptive therapy can select for subpopulations of cancerous cells that are less likely to metastasize by applying multiple treatments utilizing different combinations of drugs to select against aggressive cancer genotypes [29,32-34]. Less aggressive cells are therefore selected to become the dominant phenotype of the tumor. In addition, adaptive therapy can create more competition between different subpopulations of cancer. In metastatic cancer, the possibility of further metastasis decreases, and the aggressiveness of the tumor may decrease over time, potentially increasing the median survival rate for patients. A model of this scenario was developed with the COBWEB software to observe whether modified adaptive therapy could be used to alter the evolutionary trajectory of a metastatic tumor, thus improving median survival rate as well as the quality of life for patients.

Research Methodology

The properties of cancerous cells in tumors as well as their interactions with different drugs were modeled with the software Complexity and Organized Behaviour Within Environmental Bounds (COBWEB). Utilizing the simulations in COBWEB, issues regarding treatment for metastatic cancer could be identified and further research could be conducted to reaffirm results. The model in COBWEB is not be limited to a specific type of cancer. For the first part of this study, a model was created to determine whether less aggressive cancerous cells could out-compete aggressive cells in order to become the dominant population. A simple initial model of the metastatic tumor with two different agents representing two different subpopulations of cancerous cells was created using COBWEB. For more details, please refer to the Appendix.

Generating metastatic tumours using COBWEB

In COBWEB metastatic tendency was defined as having a higher fitness level within a specific microenvironment. When running the model, Agent 1 was found to be more resistant to drugs in comparison to Agent 2. Modifying the parameters of the 1600 unit^2 grid could generate a more complex and realistic model than Figure 1. For more information on the generation of the tumour, refer to Appendix B.

Simulating adaptive therapy

Aggressive genotypes were associated with higher reproductive rates and higher efficiencies in resource uptake. The adaptive therapy model which simulates two oscillating drugs selecting against aggressive genotypes, while alleviating the selective pressure for less aggressive genotypes. A 6400 unit^{2}grid was used to represent the body. Seven horizontal bands in two abiotic factors were used to simulate two microenvironments, representing different parts of the body. The metastatic tumor, as described above, was inserted into the upper region of the grid. Food 1 represented resources for the tumor. Food 2 and Food 3 represented different types of drugs. The effects of the drugs represented Food 2 and 3 were represented as a change in step energy (the energy penalty for taking one step), different for each drug. Another option for Food 3 was an increase in breed energy (the energy required for breeding). The mode was set up to allow the effect of the two drugs to oscillate during the experiment. Refer to Appendix C for more information on generating the simulation of adaptive therapy used in this paper.

Results

COBWEB could generate different types and different stages of tumors

Different models of metastatic cancer were generated by changing different COBWEB parameters. The model was created based on the physical characteristics of the tumor. In Figure 2a, a simple primary tumor of 1 cm^3 was generated. Assuming that each agent represents 650,000 cancerous cells, a simple 1cm^3 primary tumor constructed in COBWEB contained approximately 1×10^9 cells. In Figures 2b and 2c, subclones of the tumor escaped from the primary tumor and began to colonize other parts of the body. After migrating from the primary tumor, the dominant genotype in the secondary tumor was different from the genotype in the primary tumor, as seen in Figure 2d.

Drugs could select for less aggressive phenotypes

Using Figure 2b, a stage II metastatic tumour model, different drugs could be used to affect the dominant subpopulation of the tumor. As seen in Figure 3, cancerous cells with aggressive phenotypes were the dominant phenotype outside of the primary tumor. By using treatments that affected both reproduction and step energy, a normal, less aggressive phenotype without a metastatic tendency could become the dominant phenotype.

Oscillation of two drugs could control metastasis

Figure 2d, a more complex metastatic cancer model was inserted into a 6400 unit^{2}grid in COBWEB. As shown in Figures 4 and 5, the oscillation of two different drugs could control further metastasis. In Figure 4, the oscillation between two different drugs increased the time for further metastasis. The time required for further metastasis in the body with two different drugs increased by 269% when compared with

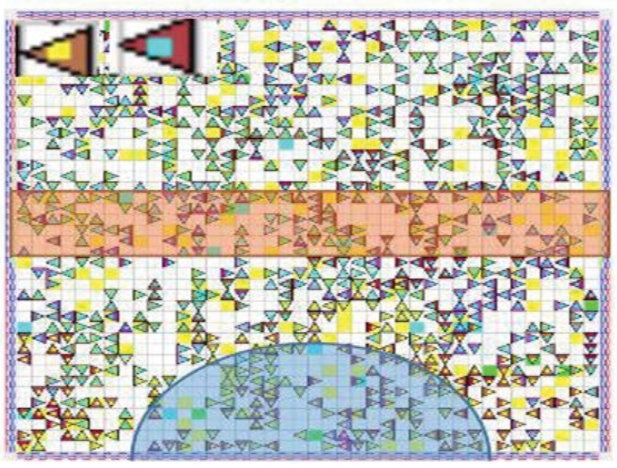

Figure 1: Model of Metastatic Cancer (Stage IV): This model represents a metastatic tumor made in COBWEB. To obtain results, the simulation was run for 5000 ticks. The colour of the agents represent their genotype while the colour of the agents' inscribed circle represent the type of agent. Agent 1 represents cancerous cells with metastatic tendency while Agent 2 represents cancerous cells with the normal phenotype. An example of Agents 1 and 2 are shown in the upper left corner of the figure. The blue circular overlay represents the location of the primary tumor. The orange overlay represents the blood and lymphatic vessels. The area above the orange overlay represents the secondary tumour site. The solid coloured blocks below the orange overlay represent cells surrounding the primary tumour. The solid coloured blocks in the orange overlay represent blood cells. The solid coloured blocks above the orange overlay represent other cells in the body.

no treatment. Compared to one drug, the time required for further metastasis with oscillation between two drugs increased by 30%.

The number of cells in a tumor treated with one drug and two drugs are similar, however, most of the cancerous cells were in the primary tumor for tumors treated with two oscillating drugs as shown in Figures 5b, 5c, and 5d. Further migration of cancerous cells into another part of the body was slower when the tumor was treated with two drugs compared to the tumor treated with one drug.

In Figure 6, the primary tumor for the metastatic cancer undergoing oscillation of two drugs has 31% more agents compared to the primary tumor undergoing one drug. There were 313% more agents in the blood for the metastatic cancer undergoing oscillation of two drugs compared to the metastatic cancer undergoing treatment with one drug. The number of agents in the secondary tumor for metastatic cancer undergoing one drug treatment was 420% higher compared to the metastatic cancer undergoing two drug oscillation at 2700 ticks.

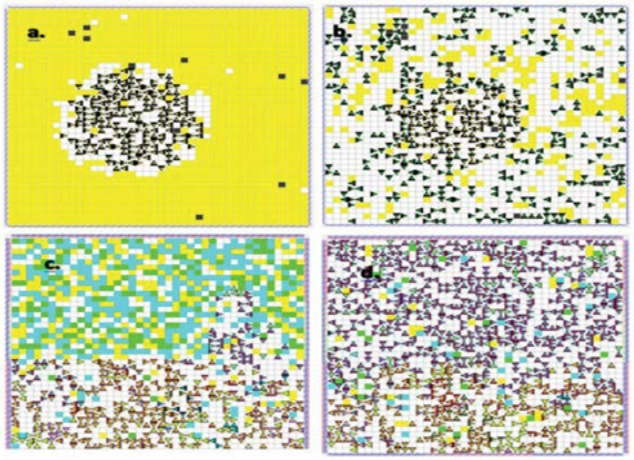

Figure 2: Models of a tumour: This model represents four different types of tumours. Model a represents a 1 cm3 primary tumor. Model b represents a stage II, primary metastatic tumour that is starting to invade local tissue. Model c represents a primary tumor beginning to metastasize. Model d represents a metastatic tumour comprising of primary and secondary tumours.

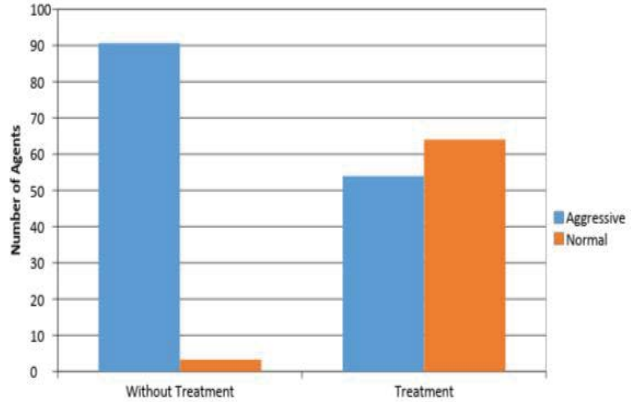

Figure 3: Number of cancer cells with aggressive or normal phenotypes with or without treatment: To obtain the data in this graph, the cancer cells were represented by agents, with each agent representing approximately 650,000 cancerous cells.

Discussion

For the majority of cancer treatments, the objective is to reduce the population of cancerous cells as quickly as possible. When curative treatment is not possible, chemotherapy or radiotherapy is utilized to control the growth of cancerous lesions before other curative treatments are considered. While treatment is initially effective, the subclones of cells post-treatment are resistant to the applied drug [32,33]. As a result, the aggressive cancerous cells become more likely to metastasize and repopulate in other locations of the body. Drug resistance becomes the dominant paradigm of treatment and the original curative treatment is often no longer effective [32].

In adaptive therapy, a minimal amount of multiple drugs is used to control the size of the tumor while granting time for susceptible cells to recover and compete for resources with resistant cells [32,34]. As per a principle of adaptive therapy, in order to control cancer indefinitely, the genetic diversity in tumors should decline and the competition between different populations of cancerous cells should increase [32]. Two or more drugs in minimal doses should be used simultaneously in each round of treatment to control the total population of cancerous cells. The number of drugs needed to maximize the effects of treatments and minimize resistance depends on the death rate, mutation rate and the genetic diversity of the tumor [27,32,37]. By applying selective pressure on a subpopulation of cancerous cells in each round of treatment, non-dominant and non-resistant cancer cells are able to grow and become the dominant phenotype. The timing and the dosage of administered drugs used to create competition between susceptible and resistant cells can help control tumour growth [32]. This model aims to determine whether the following is possible: I. whether adaptive therapy can affect the evolutionary trajectory of metastatic cancer, II. whether it is possible to create competition between different subclones of the tumor, and III. whether the tumour can be affected to become less aggressive. However, an accurate simulation of adaptive therapy cannot be fully replicated in COBWEB. Therefore, two different models have been created: I. a preliminary model of adaptive therapy where two drugs are oscillated, and II. a simple metastatic cancer model to demonstrate competition between different subclones of a tumor. By using COBWEB, the evolutionary trajectory of a metastatic tumour can be predicted and influenced by targeting specific genotypes or phenotypes of cells within the tumour

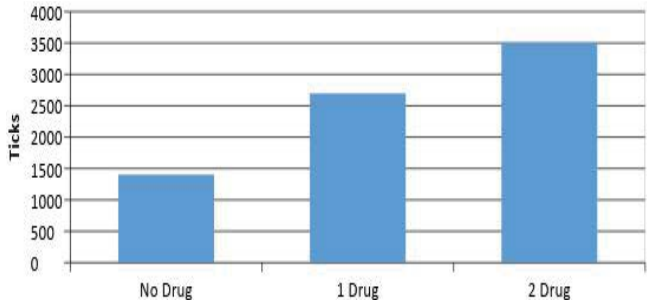

Figure 4: Comparison of time of metastasis with different treatments: To obtain the data in this graph, time was measured by tick number, a unit of time in COBWEB. Metastasis was defined as when the agent migrated to the lower half of the model, representing another part of the body. Using the metastatic cancer model, 1300 ticks were needed for further metastasis with no treatment, 2700 ticks with one drug, 3500 ticks with two drugs. The metastatic cancer model in Figure 1 was used for this simulation.

Adaptive therapy can increase competition between different subpopulation

As seen in Figure 3, competition between different subclones can be increased through the artificial selection of less aggressive cells. Figure 3 demonstrates that it is possible to select for less aggressive cancerous cells if a specific genotype was conferred with selective advantages. Aggressive genotypes were defined as genotypes that allowed the agent to have a higher level of fitness in a particular microenvironment. The model simulates selective pressure against aggressive genotypes while alleviating the selective pressure for less aggressive genotypes. The simulation demonstrated the great potential for less aggressive cancerous cells to out-compete aggressive cells and eventually become the dominant subpopulation (so long as an artificial environment can be created to favour the less aggressive phenotype).

Simulating different stages of cancer with COBWEB

It took approximately 40 doubling of cancer cells for the tumor to be considered lethal. In this model, we were trying to simulate the later stages of the growth of the tumor, which was the last 10-20 doubling of cancer cells. In Figure 2c, the initial tumor model, there are approximately 100-150 agents with each agent representing approximately 650,000 cancer cells. In Figure 2d, there are approximately 2000 agents, which represent approximately 1.3 x 10^9 cancerous cells in the tumor. This is approximately 32-35 doubling of the cancerous cells.

Treatment can be used to affect the evolutionary trajectory of tumor

Targeting part of the genetic tree enabled cancer to regrow and genetically diversify as certain genes were unique to certain subpopulations of cancerous cells. As different drugs target different types of cancerous cells, there was potential for various results. As shown in Figure 5, the tumor was less aggressive and less likely to move into another part of the body by oscillating between two drugs that targeted a particular phenotype. The secondary tumor undergoing one drug treatment had 420% more cancerous cells compared to the tumor undergoing two drug oscillation at 2700 ticks.Since this primitive adaptive therapy could control metastasis, adaptive therapy should yield better results since it can control the types of cells that are conferred the maximal selective advantage by using more than two drugs with more flexibility. By artificially selecting against subpopulation of cancerous cells, it is possible to affect the evolutionary trajectory of the cancerous cells in the tumor as shown in Figure 3. Adaptive therapy can use this principle to control the growth of cancerous cells.

A new chapter for personalized medicine

Genomic information can be used to improve the diagnosis and treatment of the patient. As genomic sequencing becomes more affordable and feasible, we are more likely to use genomic sequencing to get a detailed genetic profile of tumors before initiating treatment. However, the current resources and tools available for usage are limited, especially in predicting the evolutionary trajectory of the tumor while undergoing different types of treatment. Despite possessing the necessary information, we do not yet have the tools to provide a holistic analysis of the data. An approach known as co-clinical trial can be used, where mouse trials occur in parallel with human trials [38]. The result from the mouse trials can be used to improve clinical outcome of the human trials [39]. By integrating COBWEB with data from co-clinical trial as well as the genomic sequence of the tumor, we can integrate the data to improve the accessibility of treatment and create a more holistic approach to cancer treatment (Figure 7). There's potential for the usage of computers to analyze information from the clinic and provide new insights for new treatment directions. We can predict and quantify the possible evolutionary trajectory of the tumor when undergoing different types of treatment and adjust the treatment plan accordingly [40].

Challenges of this model

The comprehensive microenvironment of the tumor was not completely replicated with the current model. We have not yet devised a model containing the lymphatic system, which is an essential defense mechanism against cancer. In the current model, the lymphatic system and other mechanisms of the body were simulated as different abiotic factors in COBWEB. However, an enhanced representation of the lymphatic system can be provided through the use of agents or stones.

Another issue was that the oscillation of drugs was difficult to reproduce in COBWEB. While attempts were made to oscillate between two groups of two drugs in the model, only two drugs successfully oscillated for this model. The potential of adaptive therapy is not optimally realized nor represented. A more accurate representation may be constructed by manually injecting the various rounds of different drugs into the model.

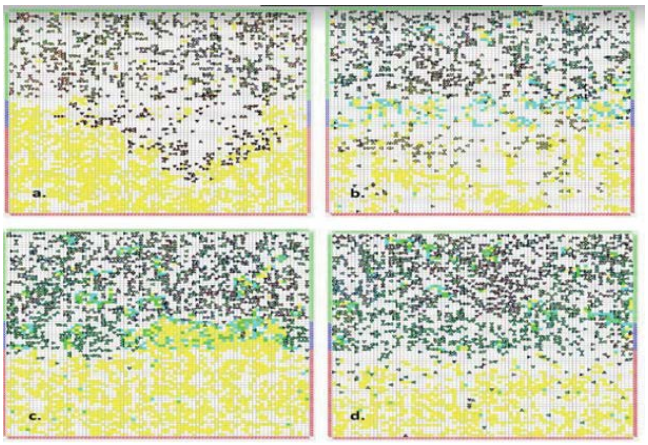

Figure 5: Comparison of different treatments in controlling further metastasis (a) No treatment at 1300 ticks (b) One drug at 2700 ticks (c) Two drugs oscillating at 2700 ticks (d) Two drugs oscillating at 3500 ticks.

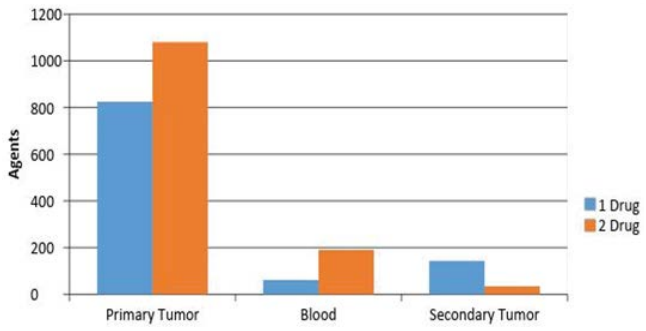

Figure 6: Comparison of number of cancer cells in primary tumour, blood, and secondary tumour: To obtain the data in this graph, two oscillating drugs were measured by 2,700 ticks. The cancer cells were represented with agents, with each agent representing approximately 650,000 cancerous cells.

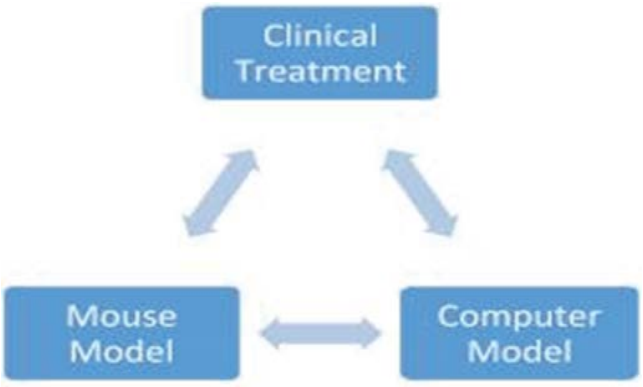

Figure 7: Relationship between clinical treatment, mouse model and computer model. Computer model can generate data for better decision-making in clinical treatment. Data from mouse model as well as from the clinical setting can be integrated into computer model for a more precise quantification of the tumor.

Conclusion and Future Directions

Clinical usage

This model would be useful as an educational tool for physicians, patients, and researchers seeking familiarization with the evolution of cancer. In the clinical setting, apprehensible engagement between the physician and the patient is crucial in improving the patient's health and well-being. Presenting active exchange without medical jargon will result in an increased understanding for the patient, and subsequently improve the patient's compliance to the treatment plan. In previous studies, cancer patients did not fully understand how the application of the treatment plan would lessen metastasis; hence, the amount of psychological stress was high. By using a simplified model, a clinician could demonstrate the effect of treatment, which could alleviate the psychological and physiological stress of the patient.

Personalized medicine in prevention

The concept of personalized medicine is not only limited to curative medicine. By providing accessibility to more information, it becomes easier for patients to take initiatives in their own health care and aid with disease prevention. [40]The current model can be modified to simulate various conditions before the formation of a detectable primary tumor based on the lifestyle habits, family history and genomic sequence of the patient. Predisposing factors can be quantified and predicted to prevent the advancement of cancer from the pre-clinical stage to the clinical stage. Various factors can be determined beforehand to influence the growth or shrinkage of the tumor during this stage. This information enables clinicians and patients to intervene before the disease worsens. The prevention of metastatic cancer not only pertains to improving conditions of patients, but it also alleviates the pressures placed on the healthcare system.

Research and education

This model can be utilized as a tool for researchers, patients and clinicians for education and planning. New data from research can be easily integrated into the existing model. Unique models for specific experimental and educational purposes can be customized using personalized data as well.

Modelling novel treatment

The genetic diversity of the cancer cells after treatment can be modelled in the future. If genetic diversity is low, it is possible to target the entire tumor by rapidly changing the environment to prevent further adaptation. A model of this scenario can be developed with COBWEB to observe whether modified adaptive therapy with an ecological approach can eliminate cancerous cells in the patient.

Finally, the model can be modified to simulate the interaction between modified adaptive therapies with other novel treatments. Novel treatments could potentially cause cancerous cells to revert to the normal state, so the model can simulate whether adaptive therapy can provide a complementary role to improve efficiency and prevent further resistance to introduced novel treatment. These models can demonstrate whether the evolutionary trajectory of the tumor can be affected by existing treatment and whether metastatic cancer can be treated differently.

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