A Brief Review On Cancer Research And Its Treatment Through Mathematical Modelling

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Abstract
Mathematical models have been proposed in different aspects of disease dynamics over the last few decades. Mathematical modelling gives a better insight, which helps us to understand the biological process during disease period. In this review work, we have discussed some well-known research work on cancer dynamics performed by researcher for different aspects through mathematical modelling. We have found few significant works, which have been discussed by us in a systematic manner. Treatment of cancer is also a wide research area for medical sciences and health care systems. For these aspects, few works are discussed here based on the different treatment regimens. We have found that combination of two or more therapies may perform well in cancer eradication processes than a monotherapy.

Keywords: Cancer, Mathematical Modelling, Radiotherapy, Chemotherapy, Immunotherapy.

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Introduction
Cancer, the second largest health threat to human civilization, which arises due to uncontrolled growth of cancer cells, is usually caused by various sources from tobacco, chemicals, radiation, acquired transformations, hormones. Depending on size of the tumour and growth of abnormal cells in the body, we can define the stage of the Cancer. There are over 200 several types of cancer. A statistics conducted by American Cancer Society report - ed that prostate cancer in male, breast cancer in females are the most common type of cancer¹. The statistics also revealed that, deaths due to lung cancer are common in United States.

Designing a suitable treatment for cancer is a wide research area in medical science. At the first stage of solid cancer, surgery gives the better outcomes than the other treatments. By removing the tumours from healthy tissues, surgery stops the spread of cancer within the body. If the tumour found in large, also in a stubborn position then this treatment is not a good choice for oncologists. Radiotherapy is the treatment where a photon like energy delivers to a tumour side. The energy interrupts abnormal cells DNA (Deoxyribonucleic acid); hence, tumour cannot reproduce and regrow further. Chemotherapy is the widely used treatment for cancer cure in which chemically designed drugs are used mostly. The drugs kill the cells, which are growing rapidly. Now a days, researcher also practice with targeted chemotherapy to reduce the side effects on the healthy cells. Immunotherapy is the most effective treatment among the all cancer treatment as it has lesser side effects. The prime object of this treatment is to boost up the immune system to fight against cancer cells. Adoptive Cellular Immunotherapy (ACI), engineering genetic antibody called mAbs therapy, and IL-2 therapy are some classes of immunotherapy to improve or restore patients’ immune system. Oncolytic viruses are also used for treatment of cancer, which directly destroy the tumour site, replace the malignant cell, triggers the immune system to find and kill cancer cell, without harming normal cells or tissues. Reducing the side effects and duration of recovery of the patient, combining two or more treatment, finding optimal control strategies are also some on-going research areas in this field.

Development of cancer in human body involves a huge cell-to-cell interaction. Many research papers describe this complex interaction with the help of mathematical models. Out of these, some models deals with its treatment also. A mathematical model gives an appropriate insight into the interaction of cancer-immune-healthy cells and their dynamics in presence of drugs. The structure of the model is mainly based on their goals.
and perspective. Agent based model; Compartmental model; Continuous-time model; Discrete-time model; Deterministic model; Heterogeneous model and stochastic model are mainly used to describe tumour-immune-drug dynamics. Different methods are used to analyse the model by the researchers and for the parameter values, they can take theoretical values, values reported in the scientific literature, or estimate the parameters from data using methods from statistical modelling.

**Tumour and immune interactions**

A large number of cellular interactions occur in tumour immune interactions. Many cells participate in this phenomenon. A tumour originates from any part of the body through abnormal growth of a single cell. A tumour may have spreading tendency. Depending upon their spreading tendency, a tumour has three types. The tumours which has no spreading tendency and slow growth rate are called benign. They are not cancerous. There are some benign tumours, which may have the potential to become cancerous through uncontrollable growth of abnormal cells. Such tumours are referred as premalignant tumour. Malignant tumours are made up of cancer cells and grow rapidly. Hence, it has high spreading tendency.

Different types of immune cells are responsible for the elimination process of cancer at the various stages of cancer development. Cancer cells are developed through four stages: initiation, promotion, progression and malignant conversion. At the initiation stage, natural killer (NK) and CD8\(^+\) T cells are capable of eliminating more immunogenic cancer cells. Lesser immunogenic cancer cells are eliminated in the next stage of cancer development. Macrophages, which are tumour-infiltrating immune cells, can eliminate tumour cells in the tumour-promoting state. Various cytokines, chemokine, cytotoxic T cells, dendritic cells etc. are responsible for elimination of tumour in its progression and malignant conversion state.

The effector lymphocytes NK cells are central components of the natural immune system. They are present in human bone marrow and lymphoid tissue. NK cells are capable to prevent and kill several types of tumours growth without the need for prior sensitization. Within a short period, NK cells are activated and proliferated quickly into human immune system during tumour development. NK cells transfers the signals from inhibitory receptors through activating NK cells receptors to the targets cells. By secreting IFN-\(\gamma\), Natural Cytotoxic Receptors (NCR) and by up-regulating MHC-I molecules, NK cells are capable to killed tumour cells.

CD8\(^+\) T cells are primarily activating the immune system by targeting tumour surveillance. During first phase of malignancy, CD8\(^+\) T cells response the tumour by secreting primary cytokines TNF-\(\alpha\) and IFN-\(\gamma\). By releasing cytotoxic granules in the direction of the tumour cells, CD8\(^+\) T cells are able to serial killing of tumour cells. CD8\(^+\) T cells are also responsible for destruction of tumour cells. At the Fas / FasL interaction, these cells are capable of fighting against tumour by contributing excess of immune response.

CD4\(^+\) T cells are one kind of T cells whose role is cardinal in production of antibody during malignancy. It is also responsible for activation and expansion of CD8\(^+\) T cells. Hence, sometimes these cells are referred as helper T cells. Besides the helping role, CD4\(^+\) T cells also give a negative effect on tumour regrowth by developing cytotoxic activity, mediating MHC-II molecules, producing antiangiogenic chemokines.

Interleukin-2 (IL-2) is a key cytokine, which promotes the activity and programming of CD8\(^+\) T cells, NK cells, and CD4\(^+\) T cells against the tumour. IL-2 binds to its three receptors IL-2R\(\alpha\) (CD25), IL-2R\(\beta\) (CD122), and IL-2R\(\gamma\) (CD132) at different energy and builds a better signal pathway for activation, survival, proliferation, differentiation of the different immune cells. Dendritic cells are developed in bone marrow and tissue like skin, lung etc. They are working as a bridge between innate and adaptive immune responses. These cells have highest potential to activate an anti-tumour response of CD8\(^+\) T cells. Apart from these, there are various types of cells, chemokines, cytokines, proteins produce an anti-tumour response for tumour suppression directly or indirectly.

**Mathematical Modelling**

For better understanding of biological processes, cellular interactions, dynamics of specific cell during malignancy, mathematical modelling is a key tool. A perfect model can help to understand the development of a particular disease and its spreading tendency. Modelling can also be used to measure the rate of drug administration and scheduling a treatment in a proper way.

A lot of research has been done in cancer research through the mathematical modelling aspect in the last few decades. Out of them, few are based on clinical data and few are based on only assumptions of theoretical observations. To describe the interaction of tumour cells and cytotoxic T lymphocytes Kuznetsov and Knott developed a deterministic model. Kolev presented a model, which describe how the antibodies can help the immune system to fight with cancer. To understand the complex phenomenon of cancer evolution and eradication Robertson-Tessi et al. describes a model by considering different cells and cytokines, which are more sensitive to tumour. de Pillis et al. investigated dynamics of tumour and other healthy cells with the use of optimally administered chemotherapy drug. There are several works that has been done by de Pillis and his collaborators in the filed cancer modelling.
A work by Subiyanto et al. suggested that bio-chemotherapy could be an effective treatment than immunotherapy and chemotherapy. Their model primarily focused on effect of TIL, IL-2, and IFN-α on tumour cells under the influence of immunotherapy, chemotherapy and bio chemotherapy. Focusing on the accounts of biological and clinical factors, which regulate the interaction rates of CTL cells on the surface of the tumour mass Frascoli et al. has done an analytical study of a proposed model [26].

Belostotski et al. prescribed a treatment schedule of radiotherapy with different control regimens to fight cancer [27-29]. Sharma et al. described the interaction between tumour-normal-immune cell under periodically pulsed chemotherapy and they observed that the prescribed therapy is much more effective in controlling tumour growth [30]. In another work Sharma et al. showed the combined effect of immunotherapy and chemotherapy in a cancer patient in which resultant of combined therapy has lowered the tumour burden in patients’ body [31]. By subdividing the tumour cell population into its inter phase and mitosis phase Awang et al. have tried to analyse the role of NK cells and CD8+T cells under tumour influence [32].

As use of more drugs in treatment of cancer is harmful to the patient, so the controlling of drug is also a new research area in this field. Some research already has been done using optimal control strategies [33-35].

In the next section, we discussed some significant research work in a systematic manner in the recent years (Table 1).

Table 1  A Systematic Reviews of Previous Research Work on Cancer.

| Authors | Model Types | Considered Cell Population | Types of Treatment & Strategy | Analysis & Results |
|---------|-------------|----------------------------|-------------------------------|--------------------|
| Kuznetsov et al. (1994)[36] | Deterministic (ODE type) | Tumour Cells, Effector Cells, Effector cells-Tumour cells conjugates, Inactivated Effector cells, lethally hit tumour cells. | No treatment. | Local and global bifurcations for realistic values of the parameters are calculated and a relation between the process of immune-stimulation, sneaking through and dormant state of tumour growth is established. A threshold value is predicted for which uncontrolled tumour growth occurs and for which disease is persisted with periodic behaviour for every 3–4 months. |
| Kirschner & Panetta (1998)[37] | Deterministic (ODE type) | Effector cells, Tumour cells, Concentration of Interleukin-2 (IL-2) | External LAK or TIL treatment (ACI treatment), External IL-2 treatment. | Parameters are estimated from the realistic patients’ data. For a low antigenicity tumour and without any treatment, a periodic behaviour is observed and bifurcation analysis is carried out. Combination of both ACI and IL-2 treatment can clear the tumour without any effect on patients’ immune system. |
| Sherratt & Chaplain (2001)[38] | Spatial Model (PDE type) | Proliferating cells, Quiescent cells, Necrotic cells, Generic Nutrient. | No treatment. | Proposed an appropriate model of avascular tumour growth by considering continuous cell densities, contact inhibition of migration and nutrient effect. |
| Szymanska Z. (2003)[39] | Deterministic (ODE type) | Cancer cells, NK cells, LAK lymphocytes, Helper T cells. | Vaccine therapy, Adoptive Immunotherapy, Active Immunotherapy. | Adoptive immunotherapy has an advantage over Active immunotherapy. During Adoptive immunotherapy there is a smallest increase in lymphocytes whereas Active immunotherapy is highly depend on vaccine activity and proper time of it implementation. |
| Sarkar & Banerjee (2005)[40] | Deterministic (ODE type), Stochastic (ODE type), Prey-predator type | Tumour cells (Prey), T-lymphocytes and cytotoxic macrophages/natural killer cells (Hunting predator and Resting predator). | No treatment. | A threshold rate of destruction of tumour cells by hunting cells is determined, which help to control the malignant growth. |
| Tse et al. (2007)[41] | Compartimental (ODE type) | Tumour cells is divided into eight subpopulation based on drug sensitivity and resistant capability. | Optimal Combination of three drugs Chemotherapy. | Determined an optimal treatment schedule through multidrug administration. |
| Bunimovich-Mendratzitsky et al. (2007)[42] | Deterministic (ODE type) | Infected Tumour cell with BCG, Uninfected Tumour cells, Effector cells. | BCG immunotherapy. | Predicted that the stage of tumour eradication through BCG therapy. It may be effective for cancer patient if it is administered in a continuous manner. |
| Mukhopadhyay & Bhattacharyya (2009)[43] | Deterministic (ODE type), Stochastic (ODE type) | Uninfected Tumour cells, Infected Tumour cells, Virus specific CTL cells. | Oncolytic Virus Therapy. | High concentration of CTL cells and high rate of virus replication performs a significant impact on tumour eradication. |
| Freedman & Belostotski (2009)[44] | Deterministic (ODE type) | Healthy cells, Cancerous cells. | Perturbed control Radiotherapy | Radiotherapy may be an effective treatment for eradicating cancer if it affects only the cancerous cells not healthy cells. |
| Authors               | Type of Model | Description                                                                 | Methodology                                                                 |
|----------------------|---------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| de Pillis et al.     | Deterministic (ODE type) | Tumour cells, NK cells, CD8$^+$ T cells, Lymphocytes, Concentration of Interleukin-2 (IL-2). | Developed an updated model and estimated unavailable parameter from clinical data. CD8$^+$ T cells taken from peripheral blood are effectively killing tumour cells. Established that rather than other treatment immunotherapy may comparatively help to eliminate tumour cells from low immunity patients’ body. |
| Rihan et al.         | Deterministic (ODE and DDE type) | Effector cells, Tumour cells, Concentration of Interleukin-2 (IL-2). | Developed a new treatment schedules based on existing clinical schedules, which is more efficient than existing treatment schedules for reducing tumour size. |
| Mamat et al.         | Deterministic (ODE type) | Tumour cells, NK cells, CD8$^+$ T cells, Circulating lymphocytes cells, IL-2 cytokine, Interferon alpha (IFN-α) cytokine. | Proposed an extended model and have showed the effect of cytokines TIL, IL-2, IFN-α on cancer cell dynamics under treatment based on clinical data. |
| Pinho et al.         | Compartmental (ODE type) | Normal cells, Cancer cells, Endothelial cells. | Both the therapies alone are not able to reduce tumour burden effectively from the body. But, combination of both is able to promote the body to reduce tumour. |
| Dong et al.          | Deterministic (bilinear ODE type), Prey-predator type | Tumour cells (prey), Effector Cells (predator), Helper T cells. | Role of Helper T cells (HTC) in a long term oscillating behaviour of tumour-immune interactions is established. Using treatment through HTC tumour can be eradicated. |
| Ghaffari et al.      | Deterministic (ODE type) | Healthy cells, Cancer cells. | Used of vaccine therapy and chemotherapy push the system optimally to the domain of attraction of the healthy state. |
| Rihan et al.         | Deterministic (DDE type) | Tumour cells, Effector cells, Normal cells. | Optimal strategies of chemo-immunotherapy is better than mono-therapy in reducing tumour cell and increasing effector cells. |
| Khajanchi & Ghosh    | Compartmental (ODE type) | Effector cells, Tumour cells. | Combination of both therapies showed better effect than single therapy in reducing tumour burden. For the case of single therapy, ACI is more acceptable therapy than IL-2 therapy. |
| Ku-Carrillo et al.   | Deterministic (ODE type) | Tumour cells, Immune cells, Normal cells, Fat stored in adipocytes. | Showed an obesity effect on chemotherapy treatment. During chemotherapy, gaining of weight of a patient can cause a problem in tumour reduction. |
| Liu & Yang           | Deterministic (ODE type) | Cancer cells, Healthy cells. | A relationship between the radiation dose, chemotherapy dose and the treatment time is established. |
| Guiraldello et al.   | Spatial (PDE type) | Tumour cells, Normal cells, Endothelial cells. | Metronomic chemo-treatment protocol is more effective than maximum tolerated dose (MTD) protocol. Also, metronomic protocol along with uniform drug delivery process reduce tumour amount within a short period. |
| Pang et al.          | Deterministic (ODE type) | Tumour cells, CTL cells. | An effective treatment regimen of mixed immunotherapy and combination chemotherapy to treat a tumour is established. |
| Ghosh & Banerjee     | Deterministic (ODE type) | Cancer cells, Large B cells, Plasma cells, Antibodies. | Established that antibody may kill cancer and hence monoclonal antibody therapy is a key treatment for cancer patients. |
| Arabameri et al.     | Compartmental (ODE type) | Tumour cells, Effector cells, Th1 cells, Treg cells, LM-matured Dendritic cells, CPG-matured Dendritic cells. | Successive time injection dendritic cells based vaccines are capable for effective suppression of tumour cells. |
Researchers have proposed a huge number of mathematical frameworks to explain the complex phenomenon of cancer evolution, its interaction with other cells, and eradication through treatment. Usually, these models can help to explain the dynamics of cancer cells within the body in presence of immune system and process of eradication through a theoretical manner. So, for better outcomes of these models clinical and experimental verification fitting with real time data must be needed.

**Conclusion**

However, researchers have tried to propose perfect model for mechanisms of cancer cells. But, due to the complexity of cancer evolution process, researcher still not clearly understood the dynamics of cancer cells. Also, dynamics and response of immune cells and cytokines not clearly have understood. For example, in many research works CD4+T cells have considered as helper T cells. They considered these cells are responsible for only activation of CD8+T cells and other cytokines. Practically it has been proven that these cells are also responsible for killing cancer cells directly. So, model has to be improved by taking such kind of clinical results for real scenario of cancer cells.

A well-organised combination therapy can cure a cancer patient. But, for this, one should make a good fit model with realistic data. Also, with the use of different mathematical terms, that can express the real biological processes one can make a better model for this area of research.

**List of Abbreviations:**

- ODE: Ordinary Differential Equations
- PDE: Partial Differential Equations
- DDE: Delay Differential Equations
- TIL: Tumor Infiltrating lymphocytes
- CTL: Cytotoxic T-Lymphocytes
- LAK: Lymphokine Activated Killer
- BCG: Bacillus Calmette-Guerin
- IL-2: Interleukin-2
- mAbs: Monoclonal Antibody
- IFN-α: Interferon-α
- IFN-γ: Interferon-γ
- MHC-I: Major histocompatibility complex-I
- MHC-II: Major histocompatibility complex-II

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