PREVIOUS WORK

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From research [1], it has been investigated that in 70% of the cancer cases, the cancer cells suffer a distortion in the survival and features of the cells that are specialized to regulate/ eradicate the dead and degenerative cells – known as Macrophage [2].[3]. And it has been explored from following papers [4], [5] that the macrophage can be populated the antigens and the immune system can be rejuvenated once affected with cancer cells via therapies. In various resources, it has been illustrated that the therapies based on macrophage – and modelling based on equations – depict a method of using the process of diffusion after infiltrating the tumour with macrophage [6], [7], [8] using the mechanism of gliding motility but in using such therapies can also result in increasing the tumour size [7].

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As suggested and evaluated [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13] with the administration of drug dose along with the Chemotherapy is a healthy alternative to radio therapies which show side-effects and tends to destroy the healthy cells along with the cancer cells. Furthermore, the approach of optimal control therapy [9], [11], [13], [12] is required to have an optimal administration with the Chemotherapy [3], [2], which is observed by using a cost/ loss function to minimize the cost of model [6], [7] and resources for a favourable result with linear and quadratic modelling expressions.

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Pharmacokinetics is used for administration of drug using a linear model once, the intake of drug concentration is given. For the administration of a drug, the scheme suggest that the dose is infused followed with a low maintenance of drug dose at a stable infusion rate [1] which tends to be easy. But it holds the drawback that the administration of data is a rough approximation especially for the induction step and neither there is a sync between drug administration time and the pharmacodynamic phase, solution to this was given by synchronizing the time interval for the induction phase. A linear model also solves the problem of corresponding time intervals between a compartment and the management of drug within it [2]. The scheme of infusion can get more plausible using the Microprocessor Controlled Infusion for simultaneously infusion of drug with a programmed microprocessor.

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Another type of pharmacokinetic model which is based on physiological attributes is known as the Physiological-based Pharmacokinetic (PBPK) approach of modelling and make predictions on the chemical concentrations for the unexplored regions or for the regions without data based on ADME approach. [1]. [2] showcase the simulation for the PBPK modelling, and [3], [4], [5], [6] gives walk through over the influencing factors in pharmacokinetics.

1. Papers (Barton et al., 2007; Beaudouin et al., 2010; Bois et al., 2010; Fierens et al., 2016) gave the insights to make predictions with uncertainty and variability using the approach of Bayesian and Monte Carlo.
2. The following work also shows the work on the drug administration considering the environmental chemicals (Kenyon et al., 2016; Kim et al., 2007).
3. Even after the manifold of benefits of the PBPK (USEPA, 2006; WHO, 2010) approach and in reporting templates (EMA, 2019; Shebley et al., 2018; USFDA, 2018), it is not wholly accepted due to formal and informal factors (Chiu et al., 2007; McLanahan et al., 2012; Tan et al., 2018, McLanahan et al., 2012, Paini et al., 2017).

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To control of problem of closed loop in the administration of a drug, compartmental and non-negative model are found to be quite useful as they contain interconnected subsystems. [1] The following papers illustrate that the systems of non-negative adaptive control [8], [9], [10], [11].

Alternatively, the Adaptive algorithms shows a diverse behaviour in different subject due to a healthy correlation between the dose of the drug dose and the concentration of the blood as well as (pharmacokinetics) and between amount of blood and the physiological effect (pharmacodynamics). [6] Previously, based on Pharmacokinetic/ Pharmacodynamic models and on control algorithms for linear adaptivity and proportional-integral-derivative. [2], [3], [4], [5]. Previous model-based algorithms have assumed either a fixed pharmacokinetic model or a fixed pharmacodynamic model [4], [5].

In another approach, more flexible linear framework built on adaptive control compartment models is used with diverse implications from non-linear pharmacodynamic and pharmacokinetic criticalities of patients using compartmental model and non-negative model but in a non-linear environment. [This paper]. Quite similar approach can also be seen from the paper [11], [7].

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From the point of genomics to an extent the heterogeneity can be apprehend from the inheritance of cancer being directly synced with 2 elements:

* 1. the DNA sequencing now.
  2. Inception and the development (influencing factors) for structuring the cancer cells using Machine Learning on the past DNA sequencing pattern.

Another approach is by building the Cancer Inference pipeline from the cross-section of cancer cells from the genomic sequencing in order to fetch a mixed model [This paper].

Over past half a century, there has been revamping optimization in genetics algorithm, we have witnessed the pattern for cancer formation and its evolution [1], [2], [3]. Since, the mutation of cells is a natural and a biological process, the heterogeneity/ metamorphosis of tumour cells is also a natural phenomenon and assist a body for its survival. The growth and multi-step evolution from the cancer cells is given by [5], [6] which is still not studies completely but can be obtained at space-time scales because of complex interaction with genomics [7].

The inter-tumour and the intra-tumour are an important challenge to counter [22] because the prior is based on identification and treatment of patients possessing a similar form of cancer or it subtype [23] while the later one speaks for the variation within genomic cancer cell type and is pattern based on diverse history of natural selection within a patient [24]. The transformation in the cancer cells is cardinal due to unpredicted behaviours of it’s growth as it tends to vary throughout the body [4] and thus, large amount of genomic data is required and it can extracted through The Cancer Genomic Atlas [25], which contains highly populated genomic profiles from the biopsy of patients in hope that they might be indicating history of evolution of cells.

Therefore, to extract a patient-specific dataset different samples are taken corresponding to similar set of tumour [24] (and subtypes) along with sequencing dataset for a single cell [26]. But due to lack of suitable data with requisite features, even a simple application cannot be implemented [27].

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The first inhibiting compound to be used for anticancer therapy with the catalytic features is known as **tyrphostins, effective against the agents of anti-leukaemia and anti-tumour. Tyrosine kinase and molecular targeted inhibitor are used to treat the hematologic malignancy i.e., CML. [1] With reference to [6], [7], the second-generation of TKIs are also know be effective. From the statistics, it is released that almost half of the patients had 5-year survival with 89% and had 8-years survival with 85% but still the pondering point is impacting the of using typhostins on stem cells of leukaemia. [8], [9].**

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Keeping other approach aside, the Targeted Therapy [1] with the patient-specific drug administration [2], [3], [4] conceptual holds a firm grip but it is besieged with the complications that arise due to fluctuating tumour resistance and response to drug [5], [6], [7], [8], [9]. Higher dose can affect the healthy cell, while a low concentration can show limit the effectiveness of the drug thus, an optimistic integration is required between them. Thus, an optimal approach could be to aim to reduce the subcloning and subpopulation based on the characteristics, mathematical modelling and optimization for the resilient tumour cells.

[8] provided clinically proven dependency between the sensitivity of the used therapy approach and the tumour size with the drug management, bring the successful model of mathematics. [9] showed the relationship between the sensitivity of the approach with the resistant rate in the cancer cells at cell-separation level. The papers [10], [11] showed that the heterogeneity with the cancer cells is due to the mutation which occurs within a very small span after the intake of drug dose thus, to reduce the probability of the dependency between sensitivity and therapy, a quick administration is paramount and prevent mutation.

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