METHODOLOGIES

The first and the most common therapy that is used to treat cancer patients is radiotherapy, which uses the UV radiations to degenerate the cancer cells, but the problem is not just kills the cancer cell but also the normal cells thus, a healthy alternative was required to treat the cancer patients and Chemotherapy comes into action. Chemotherapy is a type of cancer treatment therapy that follows standardized regimen using one or many anti-cancer drugs to treat the cancer cells. This therapy is effective because it puts aggressive constrains on cancerous cells from growing, mutating, and breaking into more cells.

To decipher the mechanism of drug administration of Chemotherapy, the therapy can be considered as blend of two approaches namely, Pharmacokinetic (PK) and Pharmacodynamic (PD). In this therapy, the pharmacokinetic model is defined as the drug dosage administration with respect to the models built and the dosage considered. On the other hand, the model of pharmacodynamic is coined at the analysis of the effect of drug and the mechanism of drug action. These two models basically form a simultaneous compartment model which can explained as, when the drug is taken, the PK model is considered for examination and when the drug starts its action on the body of the patient or on the cancer cells, the PD model takes the lead.

\*Add Image: PK and PD Compartment model

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The approach of mathematical modelling is become more proficient with time in medical research using quantitative approach and a suitable mechanism. Growth of cancer cells is a part of a genetic disease progressed due to consistent process of evolution. [1], [2]. And throughout the process of evolution and the mutation, it spread via cancer cells or the pre-malignant cells. [3] With accumulation and mutation over time [1], [4] makes them more pungent and sensitive to sustain within the tissues [5] Consequently, to comprehend and analyse the growth, behaviour, and properties of cancer cell [3], we need micro-level observations within tissues [6]. [7].

To acknowledge the structure of the cells, make predictions and to suggest expected development of tissues or cells [14], [15], models based on mathematics play a dominant role [16-27]. These models help to get insights with an abstract view of the equations and thus, helps to extrapolate, quantitative descriptions and predictions as well as to analyse the association within the system for investigation and interpretations. Mathematical modelling taken into consideration must represents degeneration and generation of cells, their mutation and to consider age-specific impact on the cell growth. [28], [29], [30]. Furthermore, a process known as the Branching process considering the probabilistic approach for the cell growth can also be considered as the influence of the events at the cellular level are assumed to show a similar behaviour for simplicity [37].

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But the key challenges modelling a mathematical framework has been to have a:

* + 1. Patient-specific administration, to give the correct treatment individually and independently to a cancer patient.
    2. Disease-specific data, to have right pattern of drug dosage with right knowledge on disease.
    3. Building adaptive model based on a patient’s demographics or medical record.

Therefore, in this research a mathematical framework for modelling and optimization for medical/ healthcare system is divided into following components:

* 1. Build models, optimize parameters, and test build models.
  2. Simulating the PK models and using cost function for optimization
  3. Collecting significant patient-specific attributes.
  4. Making hybrid method for modelling and optimization

Considering these points for analysis over distinct values and influencing factors, [1] it is crucial to understand the influencing of changing parameters based on observations and interpretations to analysis the behaviour and biological of the characteristics within the body. [2], [3], [4], [5]. It is complex to decipher the impact of dose within a biological body and the further implications but with the study of personalized medication possible from getting deeper insights of protein and molecules in a large-scale help in gaining precise, cost-effective, and patient-specific diagnostic details. [6].

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Ordinary Differential Equations

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When we model or form differential equations for a cell population that contains the degrading cell and the healthy cells that can transition towards unhealthy cell, it is known as delay differential equation with the change rate being dependent on life cycle time for each cell. [9]

With context to the work of [10], [11], [12] gave a more detailed balanced model based on the multi-staging. The susceptibility and the growth of tumour cells is influenced by the metabolism of cells existing in the cancer spread region, which is modelled using an advanced analysis and framing the model mathematically based on the metabolism of cell as given by [13]. And it helps to find the precise correlation for the cell cycle using the process of selection, detection, and quantification.

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For the oral administration with the PK model using the ODE, following are the equations:

Equation1: shows the rate of change in the amount of Imatinib in gastrointestinal track at time is given as:

and Equation 2: illustrates the rate of change in the amount Imatinib in blood at time is represented as:

In equation 1, is the amount of Imatinib in the gastrointestinal track at time t, ka is a rate constant or the first order absorption or simply, the rate of absorption and negative sign here, indicates the decrease in the amount of drug with time as it starts dissolving in the gastrointestinal track.

In equation 2, is the amount of Imatinib in the blood at time t with volume v and the rate constant CL also known as clearance which determines the rate of elimination of drug. Thus, the second equation can also be framed as the rate of change in amount of Imatinib in gastrointestinal track being equal to the difference between the rate at which it is absorbed from the gastrointestinal track and the rate at which is it removed. In this equation, the value of is known as the concentration of Imatinib in blood.

For the analysis, the initial value of in the equation 1 is the product of D i.e., drug dose and f i.e., bioavailability where the bioavailability determines the proportion of the drug that goes into circulation (for initial analysis, value of f is 1 which signifies a complete circulation) and D is the drug dose given to a cancer patient (initially, a random value of D is taken to be 400 mg). While for equation 2, the initial value of is 0 which explains the fact that since, the drug dosage is not taken, the rate of elimination of drug is 0.

Optimization

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Chemotherapy Optimization help in the acquaintance with the optimized structure of the PK model assists in achieving a patient-specific and scheduled dose interval. [7]

So, basically, the Pharmacokinetics (PK) model determines the propagation and the metamorphosis once the drug – a specific concentration of drug - reaches the blood stream, different organ system with different absorption rate (f) and thus, is based on mass balance. And due to generation, degradation, and regenerations of cells, it becomes crucial in Chemotherapy to reflect the same in the drug equation with point of action.

\*Pharmacodynamic (PD) model.

It is paramount to balance the proportion of drug impact on the cells at the time of degeneration of healthy cells and that of cancer cells thus, based on the profile for the corresponding concentration of the drug, the inputs are feed to the PD model from the PK model. Therefore, for modelling the kinetic of the cells, a sequence of Ordinary Differential Equations is used [8] as showed from equations 1 and 2. And once the equations and designed and built

\*Attach Images: Personalized Chemotherapy Protocol

To have optimal patient specific model, the used cost function is the integral of the Euclidean distance between the optimal target concentration and the steady state concentration with time, the relation is represented as by:

Where, is the penalty function also known as the cost function, is the concentration of Imatinib, is the target concentration with t1 as the initial observation time and t2 as the final observation time.

\*Gradient Descent Optimization

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1. In order to opt for the most suitable therapy to treat the cancer cells, a model of precise medication is opted which says that the biological attributes of a patient are linked to the mode/ pattern of treatment and dose requirement to be cured due to presence of patient-specific genomics [1], [3]
2. Using the identification of a biomarker will be not just assist in providing the right medication but will also refrain the patients from being injected with unwanted chemicals with respect to the low cost and DNA sequence analysis of the cancer cells. [3]
3. Extracting the details using assay will help in building a cost-effective framework for the biomarker via testing the detection limits, calculating precision and validating (through true-positive and true-negative values) to have the unaltered genomics expression and the quality proteins, RNA and DNA. [2], [4].

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DATA

1. [12] showed that the kinetic of a cell is a vital component to measure for a complicated and complex analysis and it focussed on
   1. Span of a cell life cycle before regenerating or degrading.
   2. Influencing factors of the surrounding environment that tend to affect the metabolism of leukaemia cells.

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