Mathematical modeling of drug resistance due to KRAS mutation in colorectal cancer

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Introduction

- World Health Organization (WHO) declared colorectal cancer (CRC) the second most common cause of cancer mortality in Europe.
- Monoclonal antibody (moAb) was introduced as a promising treatment for CRC but a mutation in the KRAS gene complicates a lot personalized therapies, giving acquired resistance to moAb.
- In the paper a system of non-linear ordinary differential equations (ODEs) is developed, in order to model the impact of KRAS mutations on the moAb and chemotherapy combination treatment of colorectal cancer.

Monoclonal antibodies

Monoclonal antibodies are laboratory-produced molecules designed to mimic the immune system's ability to fight off harmful pathogens.

They kill tumor cells in three ways:

- by directly blocking the EGFR pathway,
- by enhancing the activity of chemotherapeutic drugs,
- by enabling antibody-dependent cellular cytotoxicity (ADCC) from natural killer cells.

KRAS mutation

- A small fraction of KRAS mutated cells within the majority of wild-type CRC cells is selected by moAb therapy but they will not be killed by the treatment so these cells survives, leading to acquired resistance.
- Patients with KRAS mutations frequently show no significant response to moAb treatment.
- For this reason KRAS mutational status is considered as predictive marker for determining the efficacy of anti-EGFR therapies.
- Only patients having wild type KRAS are eligible for moAb therapy.

Ordinary Differential Equations

Mathematical model based on differential equations that describe the dynamics of a set of chemical reactions.

ODEs are equations built for unknown function of one or several variables that relate the values of the function itself and its derivatives.

Since ODEs often cannot be solved analytically, numerical integration (or simulation) techniques are usually applied to find approximate solutions. The simplest numerical integration algorithm is Euler’s method.

Mass action kinetics

The ODE model of a set of chemical reactions contains one differential equation for each molecular species.

The rate of a reaction is proportional to the products of the concentrations of the participating molecules.

The law of mass action is an emprirical law giving a simple relation between reaction rates and molecular component concentrations.

Given knowledge of initial concentrations, the law of mass action provides a complete picture of the component concentrations at all future time points.

ODEs advantages

- ODEs offer tools for reasoning about the functioning of biological systems (validation of hypotheses, suggestions for new laboratory experiments, etc...),
- Models based on ODEs can be used to make predictions,
- ODEs can be also studied analytically the theory of ODEs is well-established (ODEs are the same in all books),
- a lot of rather efficient numeric solvers are available.

ODEs disadvantages

- When the complexity of the modelled system increases, ODE models become difficult to manage,
- ODEs are continuous and deterministic. This makes them unsuitable to describe systems in which components occur in small numbers and subject to stochastic events (e.g. systems involving interaction with the DNA).

Other models

Mass action kinetics may be too complex in some cases, adding unnecessary details, two simpler models are:

- The Michaelis-Menten kinetics: it describes the dynamics of irreversible enzyme-catalysed reactions
- The logistic function: used to describe the dynamics of something subject to an exponential growth combined with a saturation effect

Under certain conditions these approximated model are considered reasonable, making the models simpler and easier to be simulated.

The model used in the paper

- The purpose of the model is to monitor tumor growth with respect to KRAS mutational status during and after the moAb therapy.
- Tumor cells are represented using two equations, one for wild type KRAS cells and one for mutant KRAS cells.
- Other equations are used in order to represent natural killer (NK) cells, cytotoxic T lymphocytes (CTL), lymphocytes excluding NK and CTLs and medications.

Equations for tumor cells

- Tumor cells with KRAS wild-type nature go through natural clonal expansion process to form a tumor mass. The only two factors that interrupt the logistic growth of tumor cells are immune system and therapy.
- KRAS mutant cells behave differently from the KRAS wild-types by disturbing the triple action behavior of monoclonal antibody treatment. The monoclonal antibody is not able to directly kill KRAS mutant tumor cells.

Equations for immune response

- Natural killer (NK) cells are a fundamental part of host first-line defense system.
- Cytotoxic lymphocytes are part of cell-mediated immunity. They kill target cells by releasing into them specialized granules that program them to go under apoptosis.
- Lymphocyte count is the most important parameter to be considered while modeling tumors undergoing chemotherapy. Reduction in lymphocyte count means weakening of immune system, which makes the body more vulnerable.
- Interleukin-2 is a major regulatory factor of immune responses. It belongs to a immune signaling group of cytokines. Interleukin-2 works as an immune response system by increasing the activity of cytotoxic T-cells.

Equations for treatments

- The activity of chemotherapy depends on the concentration of drug present in body at a specific time. This can be understood by the rate of excretion of drug from body.
- Monoclonal antibodies bind to the epidermal growth factor receptors (EGFRs) present on the surface of tumor cells. The loss of moAb molecules due to their binding with the tumor is an important factor to be considered while modeling moAb drug treatment to tumor.

Patient immune strength formula

- Immune strength: the effectiveness of CD8 + T-cells.
- The formula uses the lymphocyte count L and total tumor mass along with other parameters to compute immune strength.

Note: in the simulation the formula’s parameters have been varied to generate three types of immune strength values: strong, moderate and weak.

Equation examples

$$\frac{dT_w}{dt} = aT_w(1 - b(T_w + T_m)) - \left(c + \xi \frac{A}{h_1 + A}\right) NT_w - DT_w - (K_t + K_{at}A)\frac{T_w}{\alpha T_m + T_w}(1 - e^{-\delta TM})T_w - \psi A T_w$$

KRAS wild-type tumor cells count

$$\frac{dC}{dt} = \alpha - \beta C - K_C(1 - e^{-\delta CM})C$$

Lymphocytes count

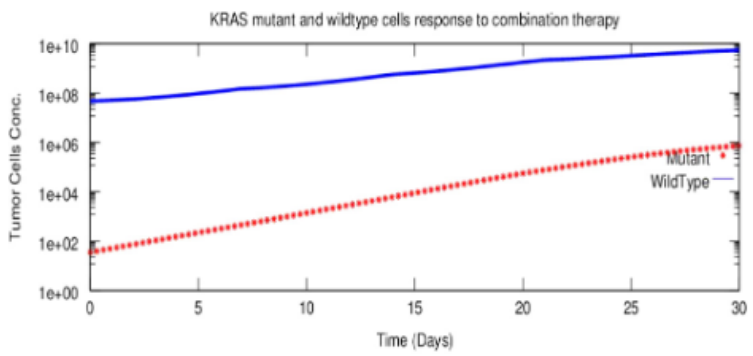
$$\frac{dM}{dt} = -\gamma M + V_{M(t)}$$

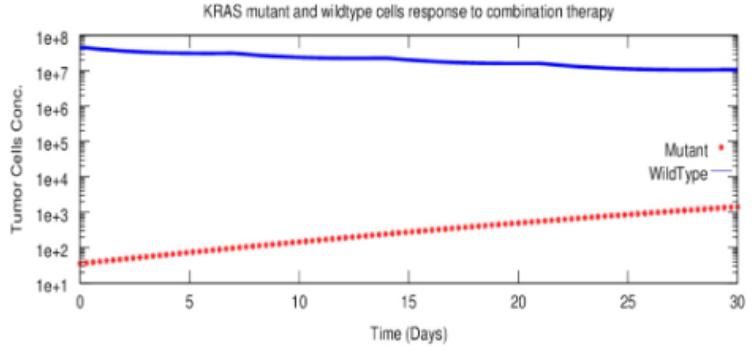
Chemotherapy / irinotecan

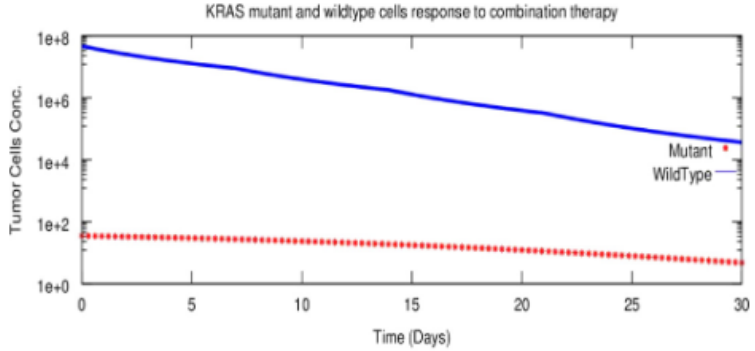
Results

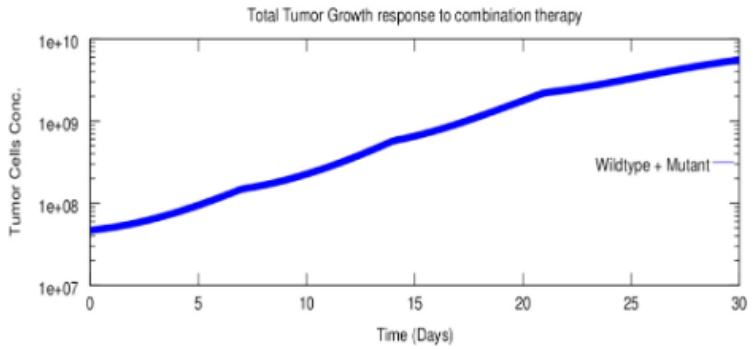
- A small number of mutated cells can have an influence on whole tumor for making it refractory to the therapies.
- Chemotherapy may work effectively only at the beginning of the treatment but then, with the increase of KRAS mutant population, it starts to loose its strength.
- There is no correlation between immune strength and combination treatment for KRAS mutated patients.
- Cetuximab and irinotecan combination therapy is proved to be very effective as first-line therapy for colorectal cancer but this is true only for KRAS wild-type patients.

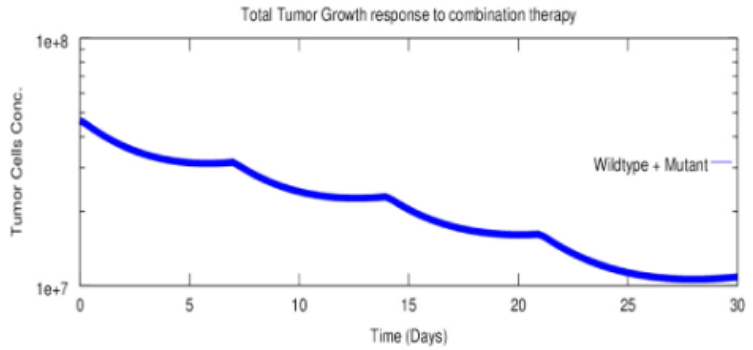
Response to combination therapy

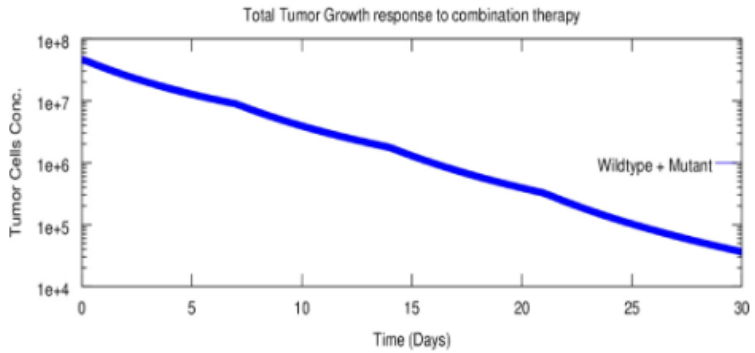












Comparison: immunity response with and without KRAS mutation