A novel framework for parameter estimation and senstivity analysis in colon cancer

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1 Mathematical model

We use a mathematical model that describes tumor growth and response of various immune cells. This model is modified from the model given in the paper by dePillis [1]. The following are the variables associated with different types of cell populations whose evolution we track over time.

1. $T(t)$- the total tumor cell population.
2. $N(t)$- the concentration of Natural Killer (NK) cells per liter of blood (cells/L).
3. $L(t)$- the concentration of cytotoxic T lymphocytes ($CD8^+$) per liter of blood (cells/L).
4. $C(t)$- the concentration of lymphocytes per liter of blood, not including NK cells and active $CD8^+$ T cells (cells/L).

The governing system of ordinary differential equations (ODE), representing the dynamics of the above defined cell populations are given as follows:

$$
\begin{aligned}
\frac{dT}{dt} &= aT(1-bT) - cNT - DT,\ T(0) = T_0\\
\frac{dN}{dt} &= eC - fN - pNT,\ N(0) = N_0\\
\frac{dL}{dt} &= j\frac{T}{k+T}L - qLT + (r_1N + r_2C)T,\ L(0) = L_0\\
\frac{dC}{dt} &= \alpha - \beta C,\ C(0) = C_0
\end{aligned}
\tag{1}
$$

where $D = d\dfrac{(L/T)^l}{s+(L/T)^l}$. The unknown parameters that needs to be determined are the patient specific parameter vector $\boldsymbol{\theta} = (d, l, s, p, k, q)$ defined as follows:

1. d- day^{-1} of cancer.
2. l- immune system strength coefficient.
3. s- the value of $(L/T)^l$ required for half-maximal $CD8^+$ T cell effectiveness against tumor.

4. p- rate of NK cell death due to tumor interaction.

5. k- tumor size for half-maximal CD8$^+$ T cell lysed tumor debris CD8$^+$ T cell activation.

6. q- rate of CD8$^+$ T cell death due to tumor interaction.

2 Tasks

The project is divided into the following steps:

1. Build a forward solver to solve the ODE system (1).

2. Given values of T, N, L, C at specific time instants $t_1, \cdots, t_N$, find the optimal parameter set $\boldsymbol{\theta}$ by solving the following optimization problem

$$\begin{aligned}\boldsymbol{\theta}^* = \underset{\boldsymbol{\theta}>\mathbf{0}}{\arg\min}\, J(\boldsymbol{\theta}) := \sum_{i=1}^{N} \Bigg[& \frac{\alpha_T}{2}(T(t_i) - T_i)^2 + \frac{\alpha_N}{2}(N(t_i) - N_i)^2 \\ & + \frac{\alpha_L}{2}(L(t_i) - L_i)^2 + \frac{\alpha_C}{2}(C(t_i) - C_i)^2 \Bigg] \\ & + \|\boldsymbol{\theta}\|_{L^2}^2,\end{aligned} \tag{2}$$

subject to the ODE system (1). For this purpose, we will first build an adjoint solver to solve the corresponding adjoint equations. Next, we will use either variable inertial proximal methods [2, 3] or non-linear conjugate gradient methods [4] to solve for $\boldsymbol{\theta}^*$.

3. Perform sensitivity analysis of the parameter vector $\boldsymbol{\theta}$ with respect to the tumor size k with a novel Latin hypercube sampling-partial rank correlation method that uses a Weibull distribution based on [4].

References

[1] L.G. dePillis, H. Savage and A. E. Radunskaya. Mathematical model of colorectal cancer with monoclonal antibody treatments, *British Journal of Medicine and Medical Research*, 4(16):3101-3131, 2014.

[2] M. Gupta, R. K. Mishra and S. Roy. Sparse reconstruction of log-conductivity in current density impedance imaging, *Journal of Mathematical Imaging and Vision*, 62:189-205, 2020.

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[4] S.Pal and S. Roy. A new non-linear conjugate gradient algorithm for destructive cure rate model and a simulation study: Illustration with negative binomial competing risks, *Submitted*, arxiv:https://arxiv.org/abs/1905.11379, 2020.