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ANALYSIS OF STOCHASTIC OPTIMAL THERAPEUTIC CONTROL FOR ENHANCING IMMUNE RESPONSE

[1]Savita, [2]Dr.Kapil Kumar Bansal

[1]Research Scholar [2]Supervisor

Sunrise University

Alwar, Rajasthan

ABSTRACT: Infectious microbes trigger a dynamic response of the immune system, in which potentially uncontrolled growth of the invader (or pathogen) is countered by various protective mechanisms. Initially, the innate immune system provides a non-specific tactical response, killing what pathogen it can, inducing inflammation and vasodilatation that aids the defense, causing blood coagulation that slows the spread of infection to other parts of the body, and raising the alarm for more complete response. In the process, a humoral response is initiated, signaling the presence of extra cellular "non-self" organisms and activating B cells to become plasma cells that are specific to the intruders' antigens.

KEYWORDS: Infectious, humoral response

INTRODUCTION

Many models of immune response to infection have been postulated [1–9], with recent emphasis on the human-immunodeficiency virus [10–15]. Norbert Wiener and Richard Bellman appreciated and anticipated the application of mathematical analysis to treatment in a broad sense [16, 17], and Swan surveyed early optimal control applications to biomedical problems in [18–20]. Optimal control theory was postulated as an organizing principle for natural immune system behavior in [21–24], and it is applied to HIV treatment in [25, 26].In the remainder, we consider therapy that enhances humoral immune response to a pathogen, such as a toxin or extracellular bacterium. The options available for clinical treatment of the infection are to kill the invading microbes, to neutralize their harmful effects, to enhance the efficacy of immune response, to provide healing care to organs that are damaged by the microbes, or to employ some combination of therapies.

In prior studies, we examined remedial treatments with differing hypotheses about the initial pathogen concentration. If the initial concentration is known precisely [1], the optimizing control history maximizes efficacy of the drug while minimizing its side effects and cost. For the second study [2], a feedback strategy based on a linear perturbation model of response dynamics is derived to account for variations induced by unknown initial infection. The therapy is modified as a function of the difference between the optimal and observed dynamic states over the entire treatment period, assuming that the difference is measured without error.

EVOLUTIONARY COMPUTING: GENETIC ALGORITHMS & MULTI-OBJECTIVE GENETIC ALGORITHMS

The concept of GA was developed by Holland and his colleagues in the 1960s and 1970s [12]. GA are inspired by the evolutionist theory explaining the origin of species. In nature, weak and unfit species within their environment are faced with loss by natural selection. The strong ones have greater opportunity to pass their genes to future generations via reproduction. In the long run, species carrying the correct combination in their genes become dominant in their population. Sometimes, during the slow process of evolution, random changes may occur in genes. If these changes provide additional advantages in the challenge for survival, new species evolve from the old ones. Unsuccessful changes are eliminated by natural selection. In a population-based

approach, GA are one of the best tool to solve multi-objective optimization problems.
A generic single-objective GA can be modified to find a set of multiple non-dominated solutions in a single run. The ability of GA to simultaneously search different regions of a solution space makes it possible to find a diverse set of solutions for difficult problems with non-convex, discontinuous, and multi-modal solutions spaces. The crossover operator of GA may exploit structures of good solutions with respect to different objectives to create new non-dominated solutions in unexplored parts of the Pareto front. In addition, most multi-objective GA do not require the user to prioritize, scale, or weigh objectives. Therefore, GA have been the most popular heuristic approach to multi-objective design and optimization problems.

MATHEMATICAL MODELING OF IMMUNE SYSTEM RESPONSE

We are considering here, the mathematical model as employed in [1, 2] which is the idealize model of a generic humoral immune response. The model consisting of four components: the concentration of a foreign pathogen (y_1), concentration of plasma cells (y_2), concentration of antibodies that bind to the antigen (y_3) and a measure of the health of an organ (y_4) that may be damaged in infection attack. The model presented in [1, 2] has not been accounted for therapy. We have modified the original model by adding active and passive immunotherapeutic control agents, μ_i (Active immunotherapy strengthens natural immune response, as by enhancing plasma cell and antibody production, while passive immunotherapy addresses the effects of infection directly, as in killing the pathogen or healing the infected organ) and an exogenous input, υ_i, to the model: pathogen killer (μ_1), plasma cell booster (μ_2), antibody booster (μ_3), and organ healing booster (μ_4). The dynamic system can be represented by the following set of ordinary differential equations:

$$y_1' = (q_{11} - p_{12}y_3)y_1 + q_1\mu_{11} \quad (1.1)$$

$$y_2' = p_{21}(y_4)p_{22}y_3y_1 - p_{23}(y_2 - y_2') + q_2\mu_2 \quad (1.2)$$

$$y_3' = p_{31}y_2 - (p_{32} + p_{33}y_1)y_3 + q_3\mu_3 \quad (1.3)$$

$$y_{4'} = (p_{41}y_1 - p_{42}y_4 + q_4\mu_4 \quad (1.4)$$

The parameters used for this study are:

$p_{11} = p_{12} = p_{23} = p_{31} = p_{42} = q_2 = q_3 = 2;$

$q_1 = q_4 = -1;$

$p_{33} = p_{41} = 1.5$

$p_{22} = 5;\ p_{32} = 2.5$

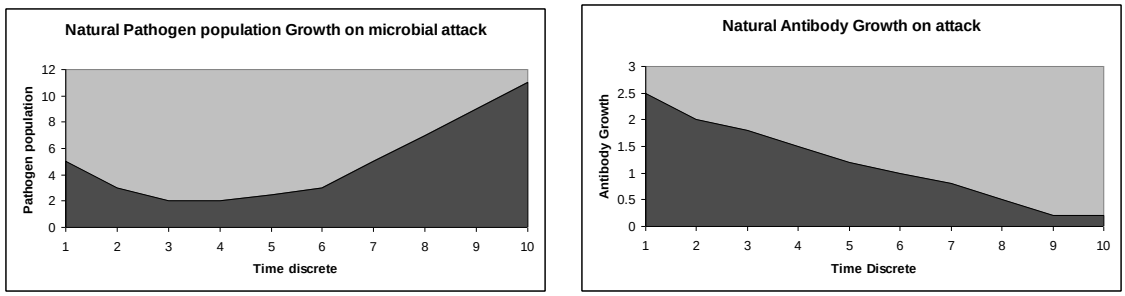

Figure 1.1: Pathogen and antibody response on microbial attack

Figure 1.1 shows typical uncontrolled response to increasing levels of pathogen concentration at the start of the time domain. We may assume some initial period of microbial infection and growth prior to beginning the simulated immune response at zero time.

1.3 STOCHASTIC OPTIMAL THERAPEUTIC CONTROL MODEL & ITS SOLUTION WITH GA

The optimal therapeutic protocol is derived by minimizing a treatment cost function, *TH* that punishes large values of pathogen concentration, poor organ health, and excessive application of therapeutic agents. This multi-objective, positive-definite scalar cost function of many variables allows tradeoffs between important factors to be adjusted through the relative weighting of individual components. Systematic responses tend to reinforce each other while conflicting responses compete in the development of an optimal regimen. The cost function is evaluated over the fixed time interval $[t_i, t_f]$ and can be given as,

$$TH_i(y) = \frac{1}{2}(a_{11}y_{1_f}^2 + a_{44}y_{4_f}^2) + \frac{1}{2}\int_{t_i}^{t_f}(b_{11}y_1^2 + b_{44}y_4^2 + c_{11}u_1^2 + c_{22}u_2^2 + c_{33}u_3^2 + c_{44}u_4^2)dt \qquad (1.5)$$

The cost-function elements are squared to amplify the effects of large variations and to de-emphasize contributions of small variations. Each squared element is multiplied by a coefficient (a_{ii}, b_{ii}, or c_{ii}) that establishes the relative importance of the factor in the treatment cost. These coefficients could reflect financial cost of treatment, or they could represent physiological 'cost' such as virulence, toxicity, or discomfort. The resulting treatment protocol balances speed, efficacy, and cost of treatment against implicit side effects.

Being a population-based approach, GA are well suited to solve multi-objective optimization problems. The classical approach to solve a multi-objective optimization problem is to assign a weight w_i to each normalized objective function $TH_i(y)$ so that the problem is converted to a single objective problem with a scalar objective function as follows,

$$\min TH(y) = w_1TH_1'(y) + w_2TH_2'(y) + w_3TH_3'(y) + \ldots\ldots\ldots\ldots\ldots + w_kTH_k'(y) \qquad (1.6)$$

where $TH_i'(y)$ the is the normalized objective function $TH_i(y)$ and $\sum w_i = 1$. This approach is called the priori approach since the user is expected to provide the weights. Solving a problem with the objective function (1.7) for a given weight vector $w = \{w_1, w_2, w_3, \ldots\ldots, w_k\}$ yields a single solution, and if multiple solutions are desired, the problem must be solved multiple times with different weight combinations. The main difficulty with this approach is selecting a weight vector for each run. To automate this process; Hajela and Lin [12] proposed the WBGA for multi-objective optimization (WBGA-MO) in the WBGA-MO, each solution y_i in the population uses a different weight vector $w = \{w_1, w_2, w_3, \ldots\ldots, w_k\}$ in the calculation of the summed objective function (6). The weight vector w_i is embedded within the chromosome of solution y_i. Therefore, multiple solutions can be simultaneously searched in a single run. In addition, weight vectors can be adjusted to promote diversity of the population.

PROCEDURE RWGA:

E =external archive to store non-dominated solutions found during the search so far;
n_E = number of elitist solutions immigrating from E to P in each generation.
Step 1: Generate a random population.
Step 2: Assign a fitness value to each solution $y \in P_t$ by performing the following steps:
Step 2.1: Generate a random number u_k in [0,1] for each objective k, k =1,…..,K.
Step 2.2: Calculate the random weight of each objective k as $w_k = \frac{1}{u_k}\sum_{i=1}^{k} u_i$.
Step 2.3: Calculate the fitness of the solution as $f(y) = \sum_{k=1}^{K} w_k z_k(y)$
Step 3: Calculate the selection probability of each solution $y \in P_t$ as follows:

$$p(y) = (f(y) - f^{\min})^{-1} \sum_{y \in P_t} (f(y) - f^{\min}) \text{ where } f^{\min} = \min\{f(y) : y \in P_t\}$$

Step 4: Select parents using the selection probabilities calculated in Step 3. Apply crossover on the selected

parent pairs to create *N* offspring. Mutate offspring with a predefined mutation rate. Copy all offspring to P_{t+1}.Update E if necessary.

Step 5: Randomly remove nE solutions from P_{t+1} and add the same number of solutions from E to P_{t+1}.

Step 6: If the stopping condition is not satisfied, set $t = t + 1$ and go to Step 2. Otherwise, return to E.

The main advantage of the weighted sum approach is a straightforward implementation. Since a single objective is used in fitness assignment, a single objective GA can be used with minimum modifications. In addition, this approach is computationally efficient. The main disadvantage of this approach is that not all Pareto-optimal solutions can be investigated when the true Pareto front is non-convex.

CONCLUSION

The model presented here having active and passive immunotherapeutic control agents, and pathogen killer, plasma cell booster, antibody booster, and organ healing booster to model enhanced immune system response. For a strong enough attack, the combination of immune response and nominal therapy is insufficient, and the pathogen grows without bound, killing the organ. The therapeutic protocol must be adjusted to accommodate the change, either through continued reevaluation of the stochastic optimal policy or through a simpler mechanism for modifying the policy in proportion to deviations from the expected response history.

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