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Mathematical model of the effect of intercellular cooperative interactions in cancer during drug therapy

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Abstract

We present an agent-based model of head and neck cancer cell population dynamics that investigates the effect of cooperative interactions between individual cancer cells during the course of cytotoxic drug treatment. A model of cooperative behavior based on the Lotka-Volterra competition equations is combined with a model of drug resistance and response. Predictions regarding the individual and combination effects of cooperation and drug treatment qualitatively match experimental observations from the literature.

INTRODUCTION

Cancers are complex diseases involving the interactions of many different biological molecules and cell types. This diversity has encouraged recent research into the application of ecological principles for studying cancer development and progression [1]–[2]. In an ecological framework, the tumor and its microenvironment are described as a system consisting of cells with specific properties which participate in specific types of interactions. The role of cooperative interactions is particularly of interest in this framework, because they can promote the survival and proliferation of cancer cells.

Cooperative interactions are those in which one or more of the entities (e.g. cells) involved receive a fitness benefit and none experience a reduction in fitness. This contrasts with competitive interactions, which occur when multiple entities must allocate limited resources (e.g. space or nutrients) among themselves, and as a result, each entity may experience a reduction in fitness when the others are present. Several different processes through which cooperative behavior can occur among cancer cells have been identified. These include the mediation of angiogenesis, the production of growth factors, and tumor invasion and metastasis [3] [4] [5] [6]. The production of vascular endothelial growth factor (VEGF), which promotes angiogenesis and is involved in other processes related to tumor growth, is often provided as an example of a cooperative interaction. Cells which produce VEGF increase not only their own fitness but also that of neighboring cells, because recruited blood vessels supply nutrients to all cells in the vicinity, not just those which produced VEGF.

Recent mathematical modeling studies have investigated the role of cooperative behavior in cancer development and progression [7] [8] [9]. In particular, [7] developed an agent-based model to study how cooperative interactions between individual cells affect overall population growth patterns, and predicted that the final population size is directly related to the proportion of the initial cell population which exhibits cooperative behavior. However, these studies did not focus on how cooperation can affect the response of the population to therapeutic intervention.

In this study, we build upon the model of [7] to investigate the effects of cooperative behavior in the context of therapeutic intervention. In particular, we focus on intercellular cooperative interactions among head and neck cancer cells. Head and neck cancer is the 6th most common cancer in terms of worldwide incidence, and VEGF expression has been linked to disease prognosis [10]. We present an agent-based model of a head and neck cancer cell population in which some cells exhibit cooperative behavior, drug resistance, or both; Figure 1 describes the behaviors and processes associated with each agent (cell). We investigate how these properties can affect cancer cell population dynamics when a cytotoxic drug is administered.

METHODS

In this study, the processes of cell reproduction, non-drug induced cell death, and cooperation are directly adapted from the model of [7]. We extend the model by incorporating drug induced cell death and drug resistance. The probabilities of reproduction and non-drug induced death are inspired by the Lotka-Volterra competition model, in which the presence of neighbors is assumed to have a negative impact on a cell's fitness. The expected number of offspring (e.g. divisions) per simulation day for cell i , $E_{\text{divisions},i}$, is a function of three variables: (i) R_i (cell divisions. day⁻¹), the replication rate constant of cell i , (ii) α_j (unitless), the interaction coefficients between cell i and its j immediate neighbors within its Moore neighborhood, and (iii) K (unitless), the carrying capacity of the Moore neighborhood of cell i .

$$E_{\text{divisions},i} = R_i \left(1 - \frac{\sum_j \alpha_j}{K} \right) \quad (1)$$

The probability of death for cell i per simulation day considers both non-drug induced death and the effects of the cytotoxic drug. Non-drug induced death depends on three variables: (i) d_i (day⁻¹), the death rate constant of cell i , (ii) β_j (unitless), the interaction coefficients between cell i and its j immediate neighbors within its Moore neighborhood, and (iii) K . Drug induced death depends on two variables: (i) E (day⁻¹), the cell loss rate as a function of drug concentration, and (ii) r_i (unitless), the level of drug resistance of cell i , which is sampled from $U(0, 1)$. and interpreted as the probability of surviving any drug exposure.

$$P_{\text{death},i} = \min \left(1, \left[d_i \left(1 - \frac{\sum_j \beta_j}{K} \right) + (1 - r_i)E \right] \right) \quad (2)$$

Intercellular cooperative behavior is implemented by varying the interaction coefficients α_j and β_j . If there is no cooperation, $\alpha_j=1$ and $\beta_j=0$. If a cell j is cooperative, $\alpha_j \sim U(-1,1)$ and $\beta_j \sim U(0, 1)$. Thus, the presence of cooperative neighbors increases the fitness of cell i by promoting reproduction and suppressing non-drug induced death.

The model was parameterized using measurements reported in the literature for head and neck cancer. R_i , the replication rate, was based on the number of cell cycles per 24 hour period. The cell cycle duration was approximated by the doubling time of the HN-2 head and neck cancer cell line, which has been measured to be 48 hours [11], [12]. The estimated R_i was then 0.5 divisions per day. The death rate d_i was estimated as 0.01 per day, based on apoptotic index values of approximately 1% reported for head and neck tumors in [13], [14].

The input and removal of drug to the system was modeled using four different protocols, shown in Figure 2. Protocols a and c describe a constant level of drug exposure over time, while protocols b and d describe weekly dosing with clearance modeled by exponential decay. Protocols a and c are intended to mimic conditions in a cell culture exposed to a certain drug concentration, while protocols b and d are intended to mimic conditions that may be experienced by cancer cells *in vivo* under drug therapy. The efficacy of the drug in killing cancer cells $-E$ in the model – as a function of drug concentration was assumed to follow Michaelis-Menten (saturation) kinetics, as shown in Figure 3.

Simulations were carried out in MATLAB (MathWorks, Natick MA). An initial population of 100 cells was placed contiguously in an approximate square shape, on a square lattice grid with dimensions 50×50 . A percentage of the cells were randomly selected and initialized as cooperative, with $\alpha \sim U(-1, 1)$ and $\beta \sim U(0, 1)$. 10% of cells were randomly initialized as resistant, with $r_i \sim U(0,1)$. Individual cells could possess both resistant and cooperative properties. Cell properties were assumed to be inherited by daughter cells, without mutation. Five different initial percentages of cooperative cells were considered: 0%, 10%, 25%, 50% and 75%. The population was tracked over 168 simulation days (24 weeks). Because this is a stochastic model, simulations were repeated 100 times per each combination of the five initial percentages of cooperative cells and the five treatments (protocols a , b , c , d , and the case of no drug), and the distribution of results for each case was evaluated.

The effects of manipulating the treatment conditions and the initial percentages of cooperative cells were investigated by comparing the sizes of the simulated cell populations at an intermediate time step (simulation day 30). In these tests, the effects of protocols a , b and d were compared against the case of no drug, with the initial percentage of cooperative cells either 10% or 75% (protocol c was not included in these tests due to inhomogeneous variances). Because the cell population sizes across the 100 iterations for each combination of treatment and initial cooperative percentage were not normally distributed, the

comparison was conducted using the Kruskal-Wallis test followed by a post-hoc analysis using the Mann-Whitney U test with Bonferroni correction. The built-in MATLAB functions 'kruskalwallis' and 'ranksum' were utilized, respectively.

RESULTS

Simulation results are shown in Figures 4–9. Figure 4 describes how the cell population grows over time when no drug is present. As demonstrated by [7], the population growth varies as a function of initial cooperative percentage: greater initial proportions of cooperative cells lead to faster growth, and a slightly larger final population size. Figure 5 shows that the initial cooperative percentage has a similar effect when drug is administered. The presence of drug, however, is associated with slower growth and larger variations in population size. The drug protocols also affect the qualitative growth pattern; weekly dosing protocols *b* and *d* cause oscillations, as shown in Figures 7 and 9.

These results were further evaluated through statistical analysis of the set of simulation runs for the different cases. The results of the Kruskal-Wallis and Mann-Whitney U tests indicated that several of the differences between the treatment cases at different initial cooperative percentages are statistically significant ($p < 0.01$). For protocols *a* and *d* all difference pairs except one were significant. The exception is that of 10% initial cooperative cells with no drug compared with 75% initial cooperative cells with drug; these two cases are represented by the green and blue curves in Figures 6 and 9, respectively. This indicates that reducing the initial cooperative percentage, administering the drug, or doing both all led to significant differences in the cell population size compared to the control, and that administering both treatments led to a significantly different cell population size than doing either alone. Similarly for protocol *b*, the post-hoc test for all pairs was significant, indicating that all treatment cases differed from the control and from each other.

The model can be evaluated by comparing its predictions with experimental observations from the scientific literature. Ricker and colleagues evaluated the effect of paclitaxel and 2-methoxyestradiol (2ME2), an agent with anti-angiogenic activity, on five head and neck squamous cell carcinoma cell lines [15]. As one of the proposed mechanisms for cooperation among cancer cells is through VEGF and promotion of angiogenesis, it is possible to interpret an anti-angiogenic drug as being 'anti-cooperative.' In [15], the cell growth inhibition resulting from treatment with paclitaxel only, 2ME2 only, or both was compared for each cell line. In three cell lines, similar growth inhibitions were observed for paclitaxel only and 2ME2 only, followed by the greatest inhibition for the combination. Similar trends are shown in Figures 6 and 9, indicating that the model predictions under corresponding conditions qualitatively match this observed response. Under protocols *a* and *d*, (i) administering the drug while maintaining the same level of initial cooperative cells, and (ii) decreasing the percentage of initial cooperative cells without administering drug, both decrease the cell population size compared to the control case of no drug and 75% initial cooperative cells. The greatest decrease in total population size is observed when both the percentage of initial cooperative cells is reduced and drug is administered. Figure 7 shows that under protocol *b*, the greatest decrease in total population size is again seen for the combination, but (ii) yields a greater decrease in cell population than (i). In the other two

cell lines in [15], the greatest effect was for the combination, followed by paclitaxel only, and then by 2ME2 only. This trend – the greatest response for the combination, followed by (i) and then by (ii) – was predicted in the mean cell populations for the higher constant drug concentration in protocol c, as shown in Figure 8, but is associated with larger variation within the drug treatment cases.

DISCUSSION

We present a mathematical model of the effects of drug treatment and intercellular cooperative interactions on the dynamics of a head and neck cancer cell population. Several model predictions qualitatively agree with experimentally observed trends of response to individual and combination therapeutic interventions.

The mechanisms underlying drug response in cancer cell populations, and the molecular biology of head and neck cancer, are complex and active areas of research. The current model is limited because it is phenomenological, and does not describe cooperative interactions in terms of specific underlying bio-molecular processes. This presents an obstacle in terms of applying models to predict how and why certain trends occur in experimental systems. The development of models which examine cooperation and other ecological interactions in the context of specific biochemical pathways could help to develop effective strategies for modulating the behavior of the cancer ‘ecosystem’ through combination therapies.

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Fig 1.
Agent diagram describing cell properties and life processes.

Fig 2.
Four alternative protocols of drug administration over time.

Fig 3.

The effect of drug exposure on cells as a function of drug concentration.

Fig 4.
Model predictions under different initial percentages of cooperative cells when no drug is administered.

Fig 5.
Model predictions under different initial percentages of cooperative cells when drug is administered under protocol a.

Fig 6. Model predictions under different initial percentages of cooperative cells for the cases of no drug and drug under protocol *a*,

Fig 7.
Model predictions under different initial percentages of cooperative cells for the cases of no drug and drug under protocol *b*,

Fig 8.
Model predictions under different initial percentages of cooperative cells for the cases of no drug and drug under protocol c,

Fig 9.
Model predictions under different initial percentages of cooperative cells for the cases of no drug and drug under protocol d