Mathematical modelling of the synergistic effect of chemotherapy and immunotherapy across scales

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Abstract

Tumours are challenging to treat, and single-agent therapies often prove insufficient, particularly in advanced stages of disease. In this context, the combination of chemotherapy and immunotherapy represents a promising therapeutic approach. Tumour cells are heterogeneous and can adapt their level of chemoresistance under chemotherapeutic pressure, while chemotherapy-induced tumour cell death may also enhance the immune response through T cell recruitment. We present a stochastic agent-based model of tumour–T cell interactions under chemotherapy and anti-PD1/PD-L1 and anti-CTLA-4 immunotherapies, in order to capture their synergistic effects. We then formally derive the corresponding deterministic continuum counterpart as a system of nonlocal partial differential equations. In order to carry out a complete exploration of the model parameter space, we integrate the results of numerical simulations of the agent-based model with the results of asymptotic analysis and numerical simulations of the continuum model. The obtained results provide insight into the mechanisms underlying tumour control and tumour escape, while emphasizing the synergistic potential of combined chemotherapy and immunotherapy.

Biological assumptions

We study tumour-immune dynamics under combined chemotherapy and immunotherapy, where:

- tumour cells are characterised by a phenotypic state represented by their level of chemoresistance;
- tumour cells proliferate, die, and undergo phenotypic changes;
- chemotherapy-induced tumour cell death promotes T cell recruitment, while T cells become exhausted over time;
- T cell cytotoxic activity contributes to tumour cell death;
- anti-PD1/PD-L1 enhances T cell efficiency, while anti-CTLA-4 enhances T cell recruitment.

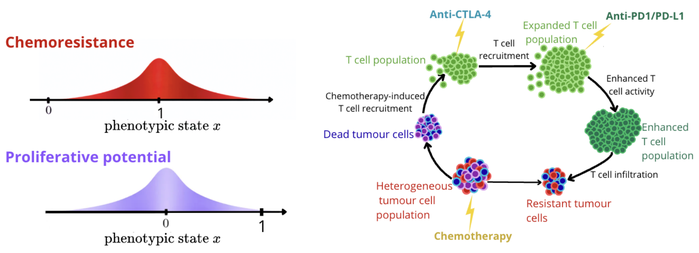

Figure 1: Left panel: tumour cell chemoresistance and proliferative potential depending on x. Right panel: interactions between tumour cells and T cells under chemotherapy, anti-PD1/PD-L1 and anti-CTLA-4 therapies.

Agent Based Model (ABM)

We model tumour-immune dynamics as a time-discrete branching random walk, with time-step τ and phenotypic-step size χ, where:

- $t_h = h\tau \in \mathbb{R}_{\geq 0}$: discrete time;
- $x_i = i\chi \in \Omega \subseteq \mathbb{R}$: phenotypic state of tumour cells;
- $n_i^h \geq 0$: tumour cell density in the phenotypic state x_i at time t_h;
- $\rho_n^h = \sum_i n_i^h \chi \geq 0$: total tumour cell population at time t_h;
- $\rho_I^h \geq 0$: total T cell population at time t_h.

Tumour cells

Division and death

At each time step h, tumour cells in phenotypic state x_i:

- divide at the net proliferation rate $b_i \equiv b(x_i) = \gamma - \eta\, x_i^2$;
- die due to intra-population competition at rate $d(\rho_n^h) = d\,\rho_n^h$;
- die in response to chemotherapy at rate $K_i(c) \equiv K(x_i, c) = \frac{c}{\alpha_c + c}(1 - x_i)^2$;
- die due to T cell action, enhanced by anti-PD1/PD-L1 immunotherapy, at rate $K_{immuno}(I_{P1}, \rho_I^h) = \frac{\xi}{1 + \frac{k}{1+b_p I_{P1}}} \rho_I^h$.

Phenotypic changes

Tumour cells undergo phenotypic changes to adapt to chemotherapy pressure and optimise survival. At each time step h, tumour cells in the phenotypic state x_i can:

- move x_{i-1} with probability $p_{l,i} \equiv p_l(x_i, c) = \frac{\lambda}{2} - \frac{\nu}{2} V_i(c)$
- move x_{i+1} with probability $p_{r,i} \equiv p_r(x_i, c) = \frac{\lambda}{2} + \frac{\nu}{2} V_i(c)$
- remain in x_i with probability $1 - p_{l,i}(c) - p_{r,i}(c)$,

where $V_i(c) \equiv V(x_i, c) = x_{grn}(c) - x_i$ encodes the impact of chemotherapy-induced phenotypic changes regulated by the gene regulatory networks.

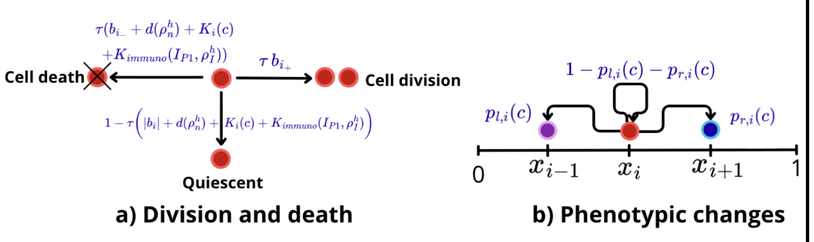

Figure 2: Probabilistic events of tumour division and death and phenotypic changes.

T cells

At each time step h, T cells can:

- enter the tumour microenvironment at rate $S_{basal} + S_{IC4} + S_n(n_i^h)$, where S_{basal} is the basal recruitment rate, S_{IC4} models anti-CTLA-4-induced recruitment, and $S_n(n_i^h) = \sum_i K_i(c)\, n_i^h\, \chi$ represents recruitment induced by tumour cell death;
- become exhausted at rate λ_I.

Corresponding continuum model

By letting $\tau \to 0$ and $\chi \to 0$ in such a way that

$$\lim_{\chi,\tau\to 0} \frac{\chi}{\tau}\nu = \alpha \quad \text{and} \quad \lim_{\chi,\tau\to 0} \frac{\lambda\,\chi^2}{2\,\tau} = \Gamma \quad \text{with} \quad \alpha, \Gamma \in \mathbb{R}_+^*$$

we formally derive a continuum model describing tumour-immune dynamics for the population density of tumour cells $n(x,t) \geq 0$ and for T cell population $\rho_I(t) \geq 0$, with $x \in \Omega \subseteq \mathbb{R}$ and $t \in \mathbb{R}_{\geq 0}$

$$\begin{cases} \dfrac{\partial n}{\partial t} = \Gamma \dfrac{\partial^2 n}{\partial x^2} - \alpha \dfrac{\partial}{\partial x}(V\, n) + \Big(b(x) - K(x,c) - d(\rho_n) - K_{immuno}(I_{P1}, \rho_I)\Big)\, n, \\ \dfrac{d\rho_I}{dt} = S_{basal} + S_{I_{C4}} + S_n(n) - \lambda_I\, \rho_I(t) \end{cases}$$

$$\text{with} \quad \rho_n(t) = \int_\Omega n(x,t)\,dx, \quad S_n(n) = \int_\Omega K(x,c)\, n(x,t)\,dx$$

We complement the above system of equations with suitable initial conditions. When $\Omega \subsetneq \mathbb{R}$, we impose zero-flux boundary conditions.

Main results

To simplify, let:

$$\beta_c = \frac{c}{\alpha_c + c}, \quad \eta_c = \eta + \beta_c, \quad \varsigma_{I_{P1}} = \frac{\xi}{1 + \frac{k}{1+b_p I_{P1}}}, \quad \gamma_c = \gamma - \frac{\eta\,\beta_c}{\eta_c}$$

Then $x_{fit}(c)$, denoting the phenotypic state that maximises the fitness function, is given by

$$x_{fit}(c) = \frac{\beta_c}{\eta + \beta_c}$$

Analytical results

We investigate the asymptotic behaviours of the system in order to characterise possible evolutionary outcomes of the tumour-immune dynamics.

Proposition

Assume $\Omega \equiv \mathbb{R}$ and $x_{grn} = x_{fit}$. The continuum system subject to the initial conditions

$$n(x,0) = \frac{\rho_{n,0}}{\sqrt{2\pi\,\sigma_0^2}} \exp\left(-\frac{(x-\mu_0)^2}{2\,\sigma_0^2}\right),$$

admits the solution

$$n(x,t) = \frac{\rho_n(t)}{\sqrt{2\pi\sigma^2(t)}} \exp\left(-\frac{(x-\mu(t))^2}{2\,\sigma^2(t)}\right),$$

where $\rho_n(t)$, $\mu(t)$, $v(t) := \frac{1}{\sigma^2(t)}$ and $\rho_I(t)$ satisfy the Cauchy problem

$$\begin{cases} \rho_n'(t) = \Big(\gamma_c - \frac{\eta_c}{v(t)} - \eta_c\,(\mu(t) - x_{fit}(c))^2 - \varsigma_{I_{P1}}\,\rho_I - d\,\rho_n(t)\Big)\,\rho_n(t), \\ v'(t) = 2\big(\eta_c + \alpha\, v(t) - \Gamma\, v(t)^2\big) \\ \mu'(t) = (\alpha + 2\,\frac{\eta_c}{v(t)})\big(x_{fit}(c) - \mu(t)\big) \\ \rho_I'(t) = S_{basal} + S_{I_{C4}} + \rho_n(t)\,\beta_c\,\big(\frac{1}{v(t)} + (1-\mu(t))^2\big) - \lambda_I\,\rho_I(t) \\ \rho_n(0) = \rho_{n,0}, \quad \rho_I(0) = \rho_{I,0} \quad v(0) = \frac{1}{\sigma_0^2}, \quad \mu(0) = \mu_0 \end{cases}$$

Moreover, under assumptions $c(t) \equiv c$, and $I_{P1}(t) \equiv I_{P1}$, the solution satisfies,

$$\big(\rho_n(t), \rho_I(t), \mu(t), v(t)\big) \xrightarrow[t\to+\infty]{} \big(\rho_n^*, \rho_I^*, \mu^*, v^*\big)$$

where

$$\rho_n^* = \max\left(0, \frac{A_\infty}{d + Y}\right), \quad \rho_I^* = \frac{S_{I_{C4}} + S_{basal} + \rho_n^*\,\beta_c\,\big(\frac{1}{v^*} + (1 - x_{fit}(c))^2\big)}{\lambda_I},$$
$$\mu^* = x_{fit}(c), \quad v^* = \frac{\alpha + \sqrt{\alpha^2 + 4\,\Gamma\,\eta_c}}{2\,\Gamma}.$$

with

$$A_\infty = \gamma_c - \frac{\eta_c}{v^*} - \frac{S_{I_{C4}} + S_{basal}}{\lambda_I}, \qquad Y = \varsigma_{I_{P1}}\,\frac{\beta_c}{\lambda_I}\left(\frac{1}{v^*} + (1 - x_{fit}(c))^2\right)$$

- As $t \to +\infty$, $\mu(t) \to x_{fit}(c)$: the phenotypic state of tumour cells concentrates around the most advantageous one.
- Tumour survival depends on the balance between tumour proliferation, immune efficacy, and treatment intensity.
- T cells proliferate following tumour death and help control the tumour, but may not eliminate it completely.
- Chemotherapy and immunotherapy reduce tumour growth and enhance T cell efficacy.

Comparison between the ABM and its continuum counterpart

We compare the tumour and T cell dynamics obtained from numerical simulations of the ABM and its continuum counterpart under different initial conditions. For certain parameter values, the asymptotic analysis predicts convergence of the continuum model to a tumour-survival steady state independently of the initial conditions. However, the initial conditions can substantially affect the transient dynamics before convergence.

In particular, for some initial conditions, the tumour population remains close to zero for a prolonged period. In this regime, stochastic effects in the ABM may drive tumour extinction, whereas the continuum model still predicts eventual tumour regrowth.

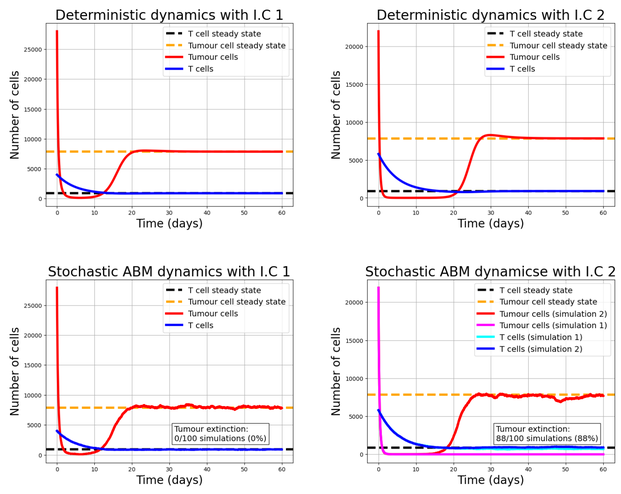

Figure 3: Comparison between the ABM and its continuum counterpart under different initial conditions.

The ABM therefore captures possible extinction events that cannot be described by the continuum model when tumour cell number becomes very small.

Sensitivity analysis

We perform a Sobol sensitivity analysis of the asymptotic *tumour ratio* $\frac{\rho_n^*}{\rho_n^* + \rho_I^*}$ to identify the parameters with the greatest influence on tumour control.

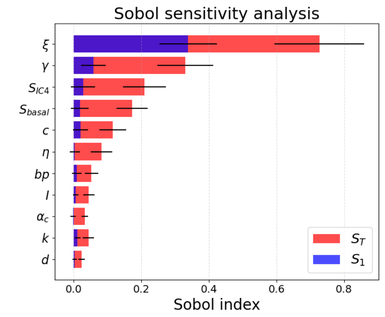

Figure 4: Sobol sensitivity analysis on the continuum model parameters.

The dominance of ξ over S_{basal} and $S_{I_{C4}}$ indicates that T cell efficacy, rather than T cell recruitment, is the main driver of tumour control. On the tumour side, sensitivity analysis shows that tumour aggressiveness, captured by the proliferative parameter γ, is also a key determinant of tumour outcome.

Impact of treatment strategies

We compare three treatment strategies using the same asymptotic *tumour ratio* $\frac{\rho_n^*}{\rho_n^* + \rho_I^*}$ for different values of γ (maximum tumour net proliferation rate) and S_{basal} (basal immune recruitment), identified as key parameters of tumour control. High values (in red) correspond to tumour persistance, while low values (in green) indicate tumour control.

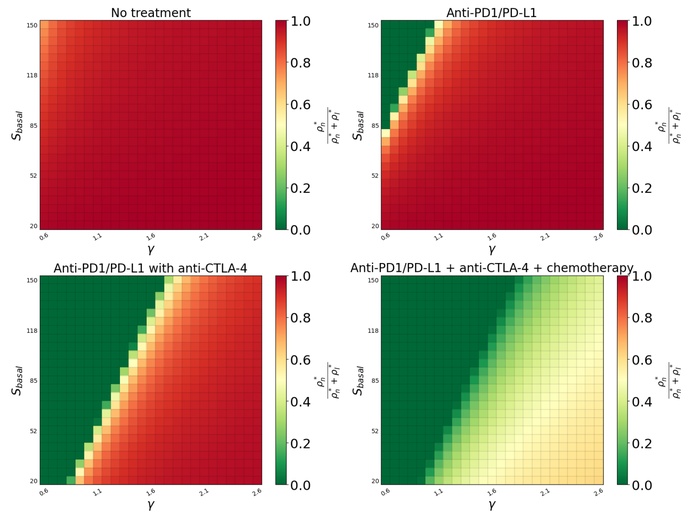

Figure 5: Asymptotic tumour ratio under different treatment strategies.

- Without treatment, T cells fail to control tumour growth, leading to tumour dominance.
- Anti-PD1/PD-L1 therapy becomes effective for high T cell recruitment and low tumour proliferation.
- Anti-CTLA-4 increases the T cell population, leading to a multiplicative effect on tumour control when combined with anti-PD1/PD-L1 therapy.
- Chemotherapy further improves tumour control and enables eradication where immunotherapy alone fails.

These results highlight a strong synergistic effect of the three combined therapies.

References

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