PK/PD Model

S1 Appendix for “Optimal dynamic regimens with artificial intelligence”

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Model equations

The equations of the PK/PD model we use are given below.

\[
\begin{align*}
    \dot{y}_1 &= -k_a y_1 + u(t) \\
    \dot{y}_2 &= -k_e y_2 + \frac{k_e}{V} y_1 \\
    \dot{y}_3 &= -a_1 \exp(-b_1 y_3) y_3 + (y_2 - c_1) H(y_2 - c_1) \\
    \dot{y}_4 &= -a_2 \exp(-b_2 y_4) y_4 + (y_2 - c_2) H(y_2 - c_2) \\
    \dot{y}_5 &= \lambda y_6 \log \left( \frac{K}{y_5} \right) y_5 - \exp(-r y_7) u_1 y_3 y_5 \\
    \dot{y}_6 &= 1 - (1 + u_2 y_4) y_6 \\
    \dot{y}_7 &= (y_2 - c_1) H(y_2 - c_1) \\
    \dot{y}_8 &= H(K_D - y_2) \cdot \left( r_{\max} - (r_{\max} - r_{\min}) \cdot \left( \frac{y_{11}}{y_{11} + K_m} \right) \right) - k_1 y_8 \\
    \dot{y}_9 &= k_1 y_8 - k_2 y_9 \\
    \dot{y}_{10} &= k_2 y_9 - k_3 y_{10} \\
    \dot{y}_{11} &= k_3 y_{10} - k_{el} y_{11}
\end{align*}
\]

We use the following initial conditions.

\[
\begin{align*}
    y_1(0) &= y_2(0) = y_3(0) = y_4(0) = y_7(0) = 0 \\
    y_5(0) &= 30 \\
    y_6(0) &= 1 \\
    y_{11}(0) &= K_m \left( \frac{r_{\max} - k_3}{k_1 - r_{\min}} \right) \\
    y_{10}(0) &= k_{el} y_{11}(0) / k_3 \\
    y_9(0) &= k_3 y_{10}(0) / k_2 \\
    y_8(0) &= k_2 y_9(0) / k_1
\end{align*}
\]

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\[H\] denotes the Heaviside function (i.e., \(H(x) = 1\) for \(x \geq 0\) and 0 otherwise). Other variables have the following meaning:
• $y_1, y_2$: one-compartment model for the PK modelling of temozolomide;
• $y_2$ is the temozolomide plasmatic concentration;
• $y_3$ to $y_7$ model the PD for efficacy;
• $y_3$ models the effect of temozolomide on cancer cells;
• $y_4$ models effect of temozolomide on endothelial cells;
• $y_5$ is the tumor size in grams;
• $y_6$ models temozolomide anti-angionic effect; the effect is present when $y_6 < 1$ and absent when $y_6 = 1$;
• $y_7$ represents the area under the curve of plasmatic concentration $y_2$ with a threshold $c_1$;
• $y_8$ to $y_{11}$ model the PD for toxicity;
• $y_8$ is the proliferating cell count in the bone marrow (all types combined);
• $y_9$ is the non-proliferating cell count in the bone marrow in early maturation stages (metamylocytes);
• $y_{10}$ is the non-proliferating cell count in the bone marrow in later maturation stages (bands and segmented);
• $y_{11}$ is the neutrophil count (in % of the beginning-of-treatment neutrophil count).

Model calibration

S1 Table 1 gathers the parameter values we consider.
S1 Table 1: Parameters’ values

| Parameter | Value | Parameter | Value |
|-----------|-------|-----------|-------|
| \(a_1\)   | 0.7   | \(r\)     | 0.07  |
| \(a_2\)   | 0.27  | \(r_{\text{max}}\) | 0.13/h |
| \(b_1\)   | 0.31  | \(r_{\text{min}}\) | 0.0445/h |
| \(b_2\)   | 0.31  | \(k_1\)   | 0.046/h |
| \(c_1\)   | 3.7   | \(k_2 = k_3\) | (2./9.2)/d |
| \(c_2\)   | 0.3   | \(k_{\text{el}}\) | (1./6.8)/h |
| \(\lambda\) | 0.00551/d | \(K_D = K_m\) | 0.009 |

Authors of [1] have set the parameters of the left column (except \(\lambda\)) to physiologically plausible values that enable to reproduce some stylized facts about the MTD protocol. However, these parameters have not actually been estimated based on clinical trials. The parameters in the right column, as well as the parameter \(\lambda\), have been estimated in [2] on to match the outcomes of a clinical trial.

The population pharmacokinetics parameters are gathered in S1 Table 2. All parameters follow a log-normal distribution \(\mathcal{LN}(\mu, \sigma^2)\) and we report for each parameter the distribution parameters \(\mu\) and \(\sigma^2\) (the mean and variance of the logarithm of the parameter, respectively). We also report the mean and the standard error of the parameter. These latter quantities come from Panetta et al. [3], who have estimated population variability in temozolomide pharmacokinetics using results of a clinical trial.

S1 Table 2: Population parameters’ values

| Parameter | \(\mu\) (mean of log) | \(\sigma^2\) (variance of log) | Mean | Standard error |
|-----------|-----------------------|-------------------------------|------|----------------|
| \(k_a\) (day\(^{-1}\)) | 4.053 | 10\(^{-4}\) | 57.6 | 0.58 |
| \(k_e\) (day\(^{-1}\)) | 2.218 | 0.036 | 9.36 | 1.80 |
| \(V\) (L) | 2.629 | 0.021 | 14.0 | 2.04 |

The population of 3,200 patients that we consider in the paper differs along the values of their pharmacokinetic parameters. We have randomly drawn these values using the log-normal distributions that are specified in S1 Table 2, assuming that patients are independent from each other and that the different parameters of a given patient are also independent from each other. Because of space constraints, we cannot report here the 9,600 parameter values that we have drawn. However, they are not mandatory for replicating our study.
Indeed, given the size of the population, any other draw of 3,200 patients would enable to very closely replicate our results.

Finally, for the simulations with no variability, we use the parameter mean values.

References

[1] Faivre C, Barbolosi D, Pasquier E, Andre N. A mathematical model for the administration of temozolomide: comparative analysis of conventional and metronomic chemotherapy regimens. Cancer Chemother Pharmacol. 2013;71(4):1013–1019.

[2] Panetta JC, Kirstein MN, Gajjar AJ, Nair G, Fouladi M, Stewart CF. A mechanistic mathematical model of temozolomide myelosuppression in children with high-grade gliomas. Math Biosci. 2003;186(1):29–41.

[3] J. C. Panetta, M. N. Kirstein, A. Gajjar, G. Nair, M. Fouladi, R. L. Heideman, M. Wilkinson, and C. F. Stewart. Population pharmacokinetics of temozolomide and metabolites in infants and children with primary central nervous system tumors. Cancer Chemother. Pharmacol., 52(6):435–441, Dec 2003.