Optimizing FOLFOX

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***Abstract*—Adjusting timing and dosage of drugs involved in FOLFOX-6 chemotherapy treatment is crucial in order to maximize the degree to which the tumor will shrink while minimizing long-term damage to the patient's body.**

I. Introduction

FOLFOX-6 is a chemotherapy treatment used primarily to treat colorectal cancer. The treatment regimen is adjusted based on the patient's body surface area, the patient's overall health, the type of cancer, and the severity of the cancer, and may further be adjusted based on the patient's response to the current treatment. The standardized treatment plan follows a 2-week cycle: Starting from day 1, the patient is concurrently infused with 85 mg/m2 of Oxaliplatin and 400 mg/m2 of Leucovorin via IV over 2 hours, as well as a bolus of 400 mg/m2 of 5-fluorouracil (5-FU), followed by an infusion of 1200 mg/m2 of 5-FU which lasts for 2 days. The next 12 days give the patient time to recover for the next cycle of treatment, with 12 cycles as the upper limit.

Although there is time to recover in between drug infusions, the toxicity of Oxaliplatin gradually builds up over continuous exposure. With enough exposure, patients can show signs of peripheral neuropathy, which is damage to nerves outside of the spine and brain. Even further prolonged exposure can cause permanent and significant neuropathy, which will harm the patient's quality-of-life long after the treatment is finished. Another potential concern is neutropenia, or an abnormally low number of white blood cells called neutrophils. This can result from the drugs 5-FU and Oxaliplatin suppressing bone marrow function. While this condition is usually short-term, since bone marrow and neutrophils regenerate much more rapidly than nerves, significantly prolonged treatment or large enough doses can cause chronic neutropenia.

Thus an important factor of FOLFOX-6 chemotherapy is to find an optimal dosage and timing for infusing these drugs, which maximizes the amount of tumor reduction while minimizing the amount of long-term damage caused to the patient through neuropathy and neutropenia, expressed as quality-of-life.

II. Literary Survey

FOLFOX is a combination chemotherapy regimen composed of 5-fluorouracil (5-FU), leucovorin, and oxaliplatin. It is widely employed in the treatment of colorectal cancer, particularly in both adjuvant and metastatic settings. While this regimen has been associated with improved patient outcomes, it is not without significant toxicity concerns. Notably, grade 2 or higher neurosensory symptoms have been observed in nearly one-third of patients receiving FOLFOX, with a portion of these effects persisting beyond one year after treatment cessation [T. André et al]. The efficacy of FOLFOX was firmly established in the MOSAIC trial, which demonstrated that adding oxaliplatin to the standard 5-FU and leucovorin regimen significantly improved disease-free survival in patients with stage II and III colon cancer [T. André et al]. This pivotal finding helped solidify oxaliplatin's role in the standard of care. However, oxaliplatin is also known for its dose-dependent and cumulative neurotoxicity, which remains a limiting factor in prolonged treatment. As exposure accumulates, so does the likelihood of irreversible peripheral sensory neuropathy, often necessitating dose reduction or early discontinuation [M. W. Saif and J. Reardon].

Management strategies for oxaliplatin-induced neurotoxicity—such as dose reduction, cycle delay, or "stop-and-go" regimens—are largely empirical and reactive in nature. In contrast, 5-FU dosing has undergone a more analytical evolution. Traditional regimens relied on body surface area (BSA) as the basis for dosing, but pharmacokinetic studies have revealed up to a 10-fold interpatient variation in 5-FU clearance under BSA-based protocols, rendering such methods both imprecise and potentially hazardous [M. Fallahi-Sichani et al.]. In response, therapeutic drug monitoring (TDM) approaches—particularly those targeting plasma concentration integrals over time (i.e., area under the curve, or AUC)—have demonstrated improved consistency in drug exposure, leading to reductions in toxicity and improvements in therapeutic efficacy [M. Fallahi-Sichani et al.].

Despite these advances, most modeling efforts to date have addressed either 5-FU dose titration or oxaliplatin-induced toxicity in isolation. There remains a critical gap in comprehensive, integrative models that simulate the systemic and multi-dimensional nature of chemotherapy regimens. These dimensions include hematologic suppression, cumulative neuropathy, tumor progression, and economic or utility-based trade-offs. Some recent computational approaches, including

multi-objective optimization frameworks like the Two-Archive Multi-Objective Squirrel Search Algorithm (TA-MOSSA), attempt to mathematically optimize treatment schedules. However, these models often lack clinical interpretability and do not incorporate patient-specific toxicity feedback or dynamic disease state modeling [C. Jiang et al.], [M. A. Alafif et al.].

To address this unmet need, our work introduces a simplified but clinically informed simulation framework for FOLFOX optimization. It incorporates pharmacodynamic models of ANC (absolute neutrophil count) suppression, empirically grounded neurotoxicity thresholds for oxaliplatin, and tumor growth kinetics derived from longitudinal volumetric CT studies [J. R. Burke et al.]. In addition, the framework integrates cycle-level cost and utility scores, allowing the model to serve as a foundation for evaluating trade-offs between treatment efficacy, toxicity burden, and healthcare resource consumption. This simulation provides a platform for future extensions involving adaptive control strategies or reinforcement learning agents capable of optimizing treatment policies in real-time.

III. Methodology

A. Tumor Growth Models Evaluated

Modeling the tumor growth over time is very challenging as there are many different factors involved. We noticed one of the main factors was the stage of the cancer which for stage 2 colonorectal cancer had an average doubling time of 211 days. Although the standard deviation was very large. We compared three candidate models for growth—Exponential, Gompertz, and Simeoni—and ultimately selected the Gompertz model as by tweaking its variables we were able to reach the 211 day doubling time. Also the Gompertz model could realisticly predict how the growth rate would decrease as the tumor got larger due to lack of nutrients from blood.

1) Gompertz Model: **Formulation:** This model accounts for a carrying capacity K, slowing tumor growth as it enlarges.

$$\frac{dP}{dt} = \alpha\, P\, \ln\!\left(\frac{K}{P}\right) \tag{1}$$

- Captures saturation effects and biphasic growth (exponential early, decelerated later).
- Calibratable: α can be solved from a known doubling time.

B. Chemotherapy-Induced Tumor Kill Dynamics

In the selected Gompertz framework, the instantaneous rate of change of tumor volume $V(t)$ under drug exposure is given by:

$$\frac{dV}{dt} = \underbrace{\alpha\, V\, \ln\frac{K}{V}}_{\text{Gompertz growth}} - \underbrace{\left(k_{\text{ox}}\, C_{\text{ox}}(t) + k_{\text{fu}}\, C_{\text{fu}}(t)\right) V}_{\text{Chemotherapy kill}} \tag{2}$$

where:

- $V(t)$ is tumor volume at time t.
- α is the Gompertz growth constant.
- K is the carrying capacity (maximum tumor volume).
- $C_{\text{ox}}(t)$ and $C_{\text{fu}}(t)$ are the plasma concentrations of oxaliplatin and 5-fluorouracil, respectively, obtained from the optimization model.
- k_{ox} and k_{fu} are the drug-specific killing rate coefficients.

We represent the tumor as two interacting pools: proliferating cells and damaged cells. Proliferating cells follow Gompertz growth, with their instantaneous kill rate computed from the current concentrations of oxaliplatin and 5-FU. At each time step, the code subtracts killed cells from this pool and passes them into the first "damage" compartment, rather than removing them entirely.

To mimic the biological delay between cell damage and observable shrinkage, killed cells progress through a series of transit compartments in sequence. Each compartment empties into the next at a fixed rate, creating a built-in lag before dead cells are cleared from the total volume.

C. Toxicity Model

To account for chemotherapy-induced side effects, we implemented a multi-component toxicity model. This model simulates the biological response of the hematologic, neurologic, gastrointestinal, and systemic systems based on drug concentrations and cumulative exposures.

1) Hematologic Toxicity: Neutropenia Modeling: The dynamics of the Absolute Neutrophil Count (ANC) are governed by a Friberg-Karlsson-type turnover model:

$$\frac{d\,\text{ANC}}{dt} = k_{\text{turn}}(\text{ANC}_{\text{base}} - \text{ANC}) - (\alpha_{\text{ox}} C_{\text{ox}}(t) + \alpha_{\text{fu}} C_{\text{fu}}(t)) \cdot \text{ANC} \tag{3}$$

where:

- $\text{ANC}(t)$: circulating neutrophil count.
- ANC_{base}: baseline neutrophil count.
- k_{turn}: neutrophil turnover rate (homeostatic restoration).
- $C_{\text{ox}}(t), C_{\text{fu}}(t)$: plasma drug concentrations.
- $\alpha_{\text{ox}}, \alpha_{\text{fu}}$: toxicity coefficients for oxaliplatin and 5-FU.

To maintain biological plausibility, a lower bound is enforced:

$$\text{ANC}(t) \geq 1 \times 10^9 \text{ cells/L}.$$

2) Neuropathy Severity: Neuropathy is modeled as a quadratic function of cumulative oxaliplatin exposure:

$$\text{neuropathy\_severity} = \min\left(1.0, \left(\frac{\text{cum}_{\text{ox}}}{\theta_{\text{neuro}}}\right)^2\right) \tag{4}$$

where cum_{ox} is the cumulative oxaliplatin dose and θ_{neuro} is the neuropathy threshold.

3) Gastrointestinal (GI) Toxicity: GI toxicity is modeled as a combination of instantaneous and cumulative exposure to 5-FU:

$$\text{GI\_severity} = \min\left(1.0,\ \gamma_{\text{imm}} C_{\text{fu}}(t) + \gamma_{\text{cum}} \cdot \text{cum}_{\text{fu}}\right) \tag{5}$$

where γ_{imm} and γ_{cum} are weighting factors for immediate and cumulative effects respectively.

4) Other Toxicity Metrics:

- **Fatigue:** Modeled as a function of total systemic drug exposure over time.
- **Hypersensitivity:** Severity increases with cumulative oxaliplatin exposure, with stepwise thresholds.

5) Composite Toxicity Score: A weighted maximum-based composite toxicity score is computed:

$$\begin{aligned}\text{toxicity\_score} = {} & w_{\text{neuro}} \cdot \max(\text{neuropathy}) + w_{\text{gi}} \cdot \max(\text{GI}) \\ & + w_{\text{heme}} \cdot \max(\text{neutropenia}) \\ & + w_{\text{fatigue}} \cdot \max(\text{fatigue}) \\ & + w_{\text{hyper}} \cdot \max(\text{hypersensitivity}) \end{aligned} \tag{6}$$

D. Optimization Algorithm

1) Initial Guesses: To improve the chances of finding a global optimum and to explore other regions of the solution space, the optimization process is initialized from multiple seed schedules:

- **Base Diverse Schedules:** Eleven different regimens, including:
  - Standard FOLFOX (all drugs on day 0 at full dose).
  - Intensified early treatment (higher initial doses).
  - Dose-dense approaches (lower per-cycle dose with varied intra-cycle timing).
  - Delayed toxicity strategies (staggered spacing in later cycles).
  - Alternating high/low dose patterns.
  - Minimal oxaliplatin strategies (prioritize 5-FU intensity).
  - Randomized dosing and timing patterns.

2) Optimization Methods: The objective function is minimized using Sequential Least Squares Programming (SLSQP) via `scipy.optimize.minimize`:

- **Decision bounds:** All timing and dose fractions constrained to [0,1].

E. User-Configurable Parameters

The following parameters can be set by the user via `config.yaml` or command-line:

- `cycles`: Number of treatment cycles.
- `tumor_threshold`: Surgical volume threshold (cm^3). We considered the cancer ready for surgery if it is below this threshold, meaning we have finished the simulation.
- `ox_max_cum`: Maximum cumulative oxaliplatin dose (mg/m^2).
- `anc_min`: Minimum acceptable ANC (10^9 cells/L).
- Weighting factors: $\{w_1, w_2, w_{\text{thr}}, \dots\}$ for objective components.

F. Optimization Problem Formulation

1) Decision Variables: For each cycle $c = 1, \dots, C$ we optimize:

$$\begin{aligned} x^{\text{ox}}_{c,\text{day}} &\in [0,1], \quad x^{\text{ox}}_{c,\text{dose}} \in [0,1], \\ x^{\text{bolus}}_{c,\text{day}} &\in [0,1], \quad x^{\text{bolus}}_{c,\text{dose}} \in [0,1], \\ x^{\text{inf}}_{c,\text{day}} &\in [0,1], \quad x^{\text{inf}}_{c,\text{dose}} \in [0,1]. \end{aligned}$$

2) Objective Function: We minimize

$$J = w_1\, B + w_2\, T + P_{\text{thr}}\,, \tag{7}$$

where

- $B = \frac{1}{T_{\max} V_0} \int_0^{T_{\max}} V(t)\, dt$ is the normalized tumor burden.
- T is the composite toxicity score.

3) Tumor Burden Calculation:

$$B = \frac{1}{T_{\max} V_0} \int_0^{T_{\max}} V(t)\, dt\,,$$

with V_0 the initial volume.

4) Toxicity Score:

$$\begin{aligned} T = {} & w_{\text{neuro}}\ \max(\text{neuropathy}) + w_{\text{gi}}\ \max(\text{GI}) \\ & + w_{\text{heme}}\ \max(\text{neutropenia}) + w_{\text{fatigue}}\ \max(\text{fatigue}) \\ & + w_{\text{hyper}}\ \max(\text{hypersensitivity}) \end{aligned} \tag{8}$$

5) Constraints:

a) Minimum ANC:

$$\text{ANC}_{\min} > 0.2 \times 10^9 \text{ cells/L},$$

b) Maximum Cumulative Oxaliplatin:

$$D_{\text{ox}} < 1200 \text{ mg/m}^2,$$

IV. Results

All simulations were carried out over a fixed course of 20 treatment cycles. In the subsections that follow, we present the key outcome metrics—tumor volume, neutrophil dynamics, dosing schedules, cumulative exposures, and toxicity severities—for both the optimized and standard FOLFOX regimens.

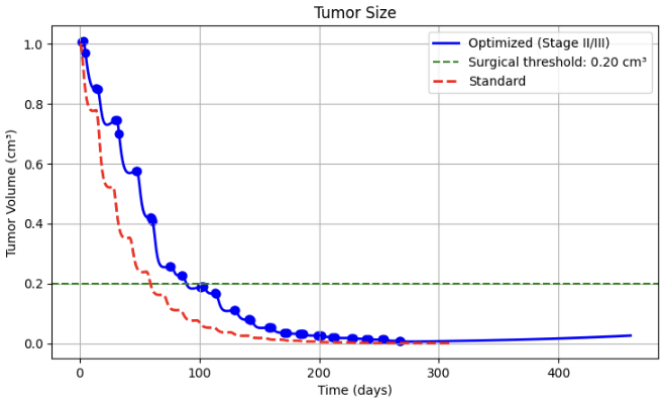

Fig. 1. Tumor volume over time for a simulated stage II/III colorectal cancer patient (70kg, 175cm). The optimized FOLFOX schedule (solid blue) produces stepwise declines in tumor size—each "step" corresponds to a drug administration followed by regrowth—reaching a final size of 0.04 cm^3 by day 139, below the 0.20 cm^3 surgical threshold (green dashed). The standard regimen (red dashed) also crosses the threshold but with a faster initial decline.

Figure 2 shows the simulated Absolute Neutrophil Count (ANC) over the 10-cycle treatment course. Each trough corresponds to a cycle's chemotherapy doses, with recovery between cycles. Although we initially enforced a hard constraint

$\text{ANC}(t) \geq 1.0 \times 10^9/\text{L}$, no feasible solution existed under that restriction within 20 cycles. Therefore, we relaxed the constraint to permit dips below the minimum ANC, enabling the optimizer to converge on a clinically reasonable dosing schedule. You can also see that the ANC goes back up to the baseline once the chemo treatment is over.

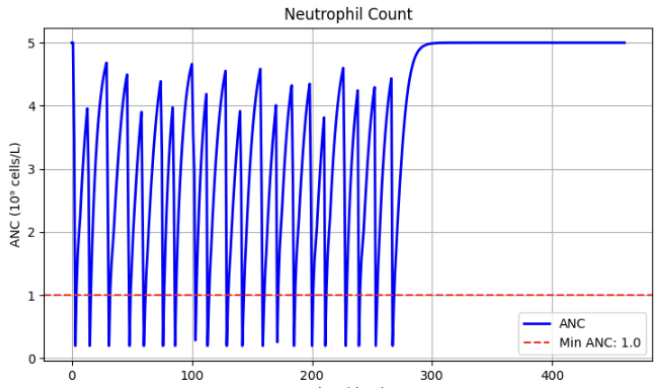

Fig. 2. Simulated ANC during 10 FOLFOX cycles for a 70kg, 175cm stage II/III colorectal cancer patient. Although the dashed red line indicates the minimum acceptable ANC of 1x 10^9/L, we change this to 0.2 x 10^9/L for the sake of feasebility. Oscillations reflect neutrophil depletion and recovery with each cycle.

Figure 3 shows the per-cycle dosing of oxaliplatin and 5-FU under the optimized schedule across 20 cycles. Oxaliplatin doses (blue bars) vary modestly between 30 and 55mg/m², avoiding both extreme peaks and sustained low levels (this will be explained in the next graph).

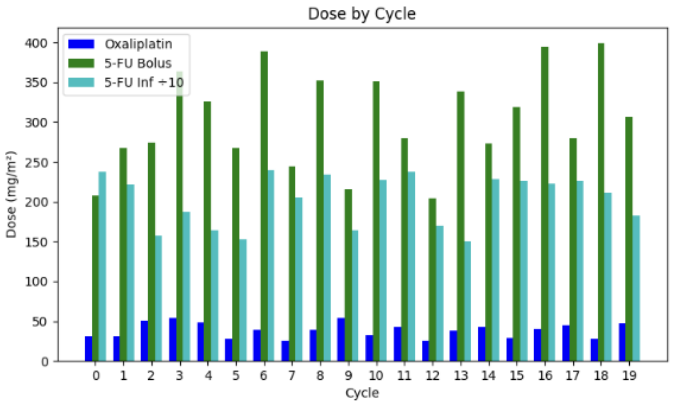

Fig. 3. Optimized per-cycle doses for oxaliplatin and 5-FU (bolus and continuous infusion). Oxaliplatin (blue) remains within 30–55mg/m²

By capping cumulative oxaliplatin just under the 800mg/m^2 neuropathy limit, the optimizer balances effective tumor kill against the risk of severe peripheral neuropathy like shown in figure 4 where the blue line is right below the dashed blue line. This dosing strategy explains why per-cycle oxaliplatin remains relatively low compared to 5-FU.

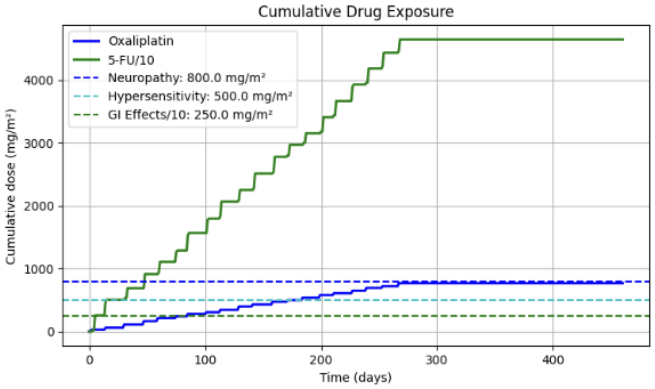

Fig. 4. Cumulative doses of oxaliplatin (blue) and 5-FU infusion (green/10) versus toxicity thresholds (dashed lines).

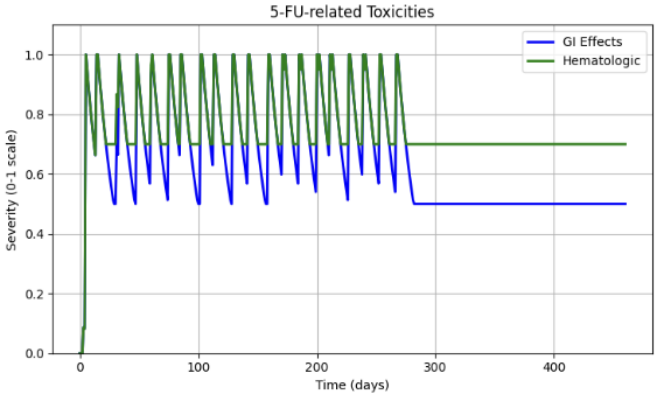

Fig. 5. Gastrointestinal and hematologic toxicity severity from 5-FU across treatment time. Scaled for 0 to 1. As you can see the effect are at maximum intensity during treatment and slowly decrease over the rest period.

V. Limitations

First, tumor-growth parameter uncertainty: literature reports for stage II/III colorectal cancer doubling times varied widely, making it hard to choose a single growth constant α. We addressed this by trying to pick data more specific to our problem, such as focusing on colorectal cancer only and looking only at human trials.

Second, the multi-objective problem—balancing *tumor kill* against *toxicity penalties* required careful tuning of weight parameters. There were many trials where the optimizer would just pick one drug and avoid the rest.

Third, it was very challenging to make the simulation realistic to actual medical data. There are many factors which can influence how a person reacts to chemo and it is simply impossible to capture all of them.

VI. Conclusion

In this project, we developed a clinically motivated simulation framework to optimize the FOLFOX chemotherapy regimen by adjusting dose timing and intensity. Through integration of pharmacokinetic modeling, tumor growth simulation using the Gompertz framework, and multi-dimensional toxicity metrics, we were able to demonstrate a way to personalize

treatment plans that trade off tumor reduction against long-term side effects like neuropathy and neutropenia.

VII. Contributions

- **Javad:** Conceived project. Wrote most of the code (simulation code, ANC toxicity simulation, PK/PD scheduling logic, optimization constraints) and researched how the body responds to tumors, and focused mainly on the methodology and results sections of the paper. Also joined team discussions and helped with the presentation.
- **Hans:** Scheduled/hosted group meetings. Gathered pharmacokinetic resources to ground our model with realistic associated values and interplay of somatic elements. Helped with code specifically how the tumor is affected by chemotherapy (the rate at which the tumor's size is to decrease based on the current state and the dose of medicine). Worked on the literature review.
- **Eric:** Put together the majority of the presentation slides. Worked on the introduction and the abstract part of the final paper. Researched costs relating to ongoing FOLFOX treatments. Helped with the code (specifically the fine tuning of optimization parameters regarding symptoms felt from the chemotherapy)
- **Mahammad:** Helped with the code (specifically the tumor growth (Gompertz model) and simulation plots). Participated in discussions and worked on the presentation. Helped get the plots for the results section of the final paper.

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