



DECISION-SUPPORT INDICATORS FOR SIMULATION-BASED EVALUATION OF INDIVIDUALIZED LEVODOPA DOSING IN PARKINSON'S DISEASE

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ABSTRACT. This paper presents a simulation-based decision-support framework for evaluating individualized levodopa dosing strategies in Parkinson's disease. Building on pharmacokinetic–pharmacodynamic simulation, the study organizes model outputs into interpretable decision indicators that compare alternative schedules under patient variability. The pharmacokinetic–pharmacodynamic component describes gastrointestinal absorption, central and peripheral distribution, elimination, effect-site exposure, and nonlinear therapeutic response. Representative dosing schedules are evaluated using peak–trough fluctuation, mean effect-site exposure, time within a therapeutic reference window, response deviation, exposure variability, and an overall decision score. Numerical simulations illustrate how changes in dose size, dosing interval, and dose fractionation may alter exposure–response patterns and decision-indicator profiles. Under the selected parameter setting and equal-weight decision score, the standard four-hour schedule gives the lowest overall decision score among the three representative schedules. The framework is intended for scenario-based interpretation and hypothesis generation rather than direct clinical prescription. It provides a computational basis for future model-informed and data-driven approaches to personalized Parkinson's disease treatment.

Keywords. Parkinson's disease, levodopa dosing, PK–PD modeling, decision support, individualized therapy, numerical simulation.

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1. INTRODUCTION

Parkinson's disease is a progressive neurodegenerative disorder characterized mainly by dopaminergic neuronal degeneration and motor impairment, including bradykinesia, rigidity, tremor, and postural instability [7]. Levodopa remains the most effective pharmacological treatment for improving motor symptoms because it acts as a metabolic precursor of dopamine and restores dopaminergic activity in the central nervous system [2, 10]. However, long-term levodopa therapy is frequently complicated by wearing-off phenomena, delayed therapeutic response, motor fluctuations, and levodopa-induced dyskinesia [3, 13, 4]. These complications make dose adjustment and treatment scheduling clinically challenging, particularly in patients with advanced disease or heterogeneous treatment responses.

A major difficulty in levodopa therapy is the substantial variability among patients. Individuals receiving similar dosing schedules may exhibit different pharmacokinetic profiles, effect-site exposures, and motor responses because of differences in gastrointestinal absorption, delayed gastric emptying, clearance, distribution kinetics, body weight, disease stage, and pharmacodynamic sensitivity [2, 10, 17, 16, 6, 15, 1, 5, 11, 12, 8]. As a result, fixed dosing strategies may not adequately reflect patient-specific

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exposure–response behavior. This motivates the use of quantitative and simulation-based approaches for comparing alternative dosing schedules before further clinical validation.

Pharmacokinetic–pharmacodynamic modeling provides a useful framework for linking drug administration, systemic exposure, effect-site concentration, and therapeutic response [17, 16, 6, 15, 1, 5, 11, 12]. Recent developments in model-informed precision dosing also suggest that computational models can support individualized treatment planning when combined with patient-level pharmacokinetic data, clinical response measures, and digital monitoring information [9]. In our previous work, a computational PK–PD framework was developed to simulate and compare individualized levodopa dosing strategies in Parkinson’s disease [14]. Building on that foundation, the present conference paper reformulates the problem from a decision-support perspective.

The objective of this study is to propose a simulation-based decision-support framework for evaluating individualized levodopa dosing strategies in Parkinson’s disease. The proposed framework uses PK–PD simulation outputs to compute interpretable decision indicators, including peak–trough fluctuation, time within a therapeutic reference window, response deviation, exposure variability, and an overall decision score. The aim is not to provide direct clinical prescriptions, but to support structured scenario comparison, mechanistic interpretation, and hypothesis generation for future individualized dosing studies.

This paper is organized as follows. Section 2 describes the simulation-based decision-support framework. Section 3 presents the PK–PD model and simulation design. Section 4 introduces the decision indicators, and Section 5 provides the numerical demonstration. The discussion and conclusion are given in Section 6.

2. SIMULATION-BASED DECISION-SUPPORT FRAMEWORK

The proposed workflow links patient-profile information, dosing assumptions, PK–PD simulation, decision-indicator computation, and scenario-based interpretation. Patient-profile inputs include representative characteristics such as body weight, disease stage, absorption variability, clearance, and pharmacodynamic sensitivity. Dosing inputs define possible schedules through dose size, dosing interval, administration timing, maintenance strategy, and candidate schedule. The PK–PD model then generates plasma concentration, effect-site concentration, and predicted therapeutic response profiles. These outputs are transformed into decision indicators for comparing candidate schedules. The complete workflow is summarized in Figure 1.

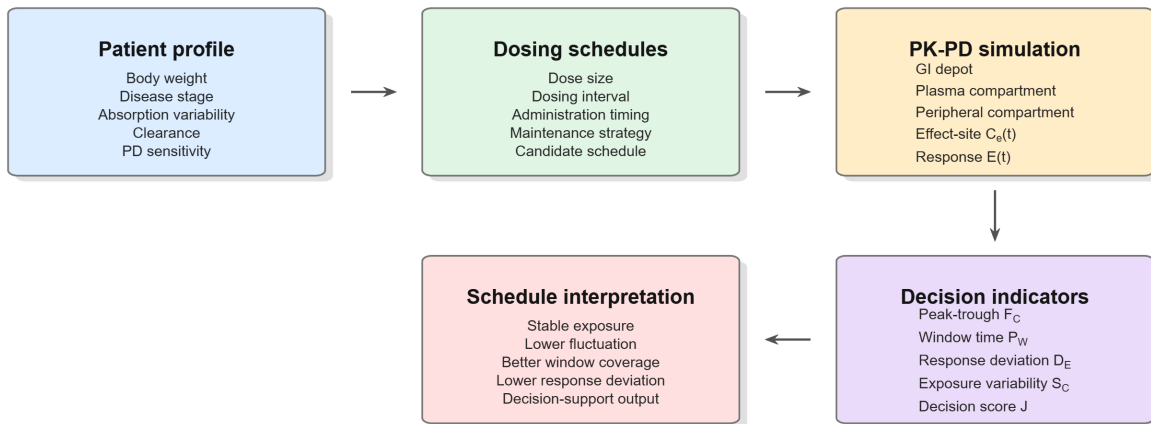


FIGURE 1. Simulation-based workflow for individualized levodopa dosing evaluation

A schedule is interpreted as more favorable in the simulation setting when it produces smoother effect-site exposure, longer time within the reference range, lower response deviation, and a smaller

overall decision score. Conversely, repeated underexposure, excessive peaks, high variability, or large deviation from a target response profile indicates a less stable simulated dosing scenario. The framework therefore converts pharmacological simulation outputs into decision-support information that can be used for mechanistic interpretation and future clinical study design.

The decision-support workflow also provides transparency. Instead of presenting a single optimal dose, it separates the simulation engine from the interpretation layer. This separation allows researchers to change the patient-profile assumptions, dose schedule, reference window, or indicator weights while keeping the overall comparison procedure reproducible.

3. PK-PD MODEL AND SIMULATION DESIGN

The computational core of the proposed decision-support framework is a pharmacokinetic-pharmacodynamic model for simulating levodopa exposure and therapeutic response in Parkinson's disease. The model is used to translate alternative dosing assumptions into simulated exposure-response profiles, which are subsequently evaluated using decision-oriented indicators. The model structure follows the main processes of oral levodopa therapy, including gastrointestinal absorption, systemic distribution, elimination, effect-site exposure, and nonlinear therapeutic response.

For oral administration, let $A_{gut}(t)$ denote the amount of levodopa in the gastrointestinal depot. The absorption process is described by

$$\frac{dA_{gut}(t)}{dt} = -k_a A_{gut}(t),$$

where k_a is the first-order absorption rate constant. This component represents the entry of levodopa from the gastrointestinal tract into the systemic circulation and is relevant because gastrointestinal variability can affect levodopa exposure and motor response.

Let $A_p(t)$ and $A_{per}(t)$ denote the levodopa amounts in the central plasma and peripheral compartments, respectively. The central-peripheral distribution dynamics are written as

$$\begin{aligned} \frac{dA_p(t)}{dt} &= R_{in}(t) + k_a A_{gut}(t) - k_{12} A_p(t) + k_{21} A_{per}(t) - k_{el} A_p(t), \\ \frac{dA_{per}(t)}{dt} &= k_{12} A_p(t) - k_{21} A_{per}(t), \end{aligned}$$

where $R_{in}(t)$ represents the dosing input, k_{12} and k_{21} are inter-compartmental transfer rate constants, and k_{el} is the elimination rate constant. For repeated oral dosing, $R_{in}(t)$ is determined by the assigned dose size, dosing interval, and administration timing.

The plasma concentration is defined by

$$C_p(t) = \frac{A_p(t)}{V_p},$$

where V_p is the apparent central volume of distribution. To represent the delay between plasma levodopa exposure and therapeutic effect, an effect-site compartment is incorporated:

$$\frac{dC_e(t)}{dt} = k_{e0}(C_p(t) - C_e(t)),$$

where $C_e(t)$ is the effect-site concentration and k_{e0} is the effect-site equilibration rate constant. The effect-site compartment is interpreted as a functional pharmacodynamic compartment that captures the temporal dissociation between systemic exposure and motor response.

The predicted therapeutic response is linked to the effect-site concentration using a sigmoidal $E_{\max}$ -type function:

$$E(t) = E_0 + \frac{E_{\max} C_e(t)^\gamma}{EC_{50}^\gamma + C_e(t)^\gamma},$$

where E_0 is the baseline response, $E_{\max}$ is the maximum achievable drug effect, EC_{50} is the effect-site concentration producing 50% of the maximum effect, and γ is the Hill coefficient. This formulation allows the model to represent nonlinear response saturation and differences in pharmacodynamic sensitivity among simulated patient profiles.

In the simulation design, each dosing scenario is defined by dose size, dosing interval, and administration timing. Representative schedules are simulated over a fixed time horizon to generate plasma concentration, effect-site concentration, and predicted therapeutic response profiles. To reflect individualized variability, selected pharmacokinetic and pharmacodynamic parameters, including absorption rate, clearance, distribution volume, body weight, disease severity, and pharmacodynamic sensitivity, are varied within plausible ranges. The same dosing schedules are then applied across virtual patient profiles to examine whether a schedule produces stable or unstable exposure–response patterns under heterogeneous patient conditions.

The main simulation outputs used in the proposed framework are $C_e(t)$ and $E(t)$. These outputs are not interpreted as direct clinical dosing recommendations. Instead, they are transformed into decision indicators in the next section, allowing alternative dosing schedules to be compared in terms of exposure stability, target-window coverage, response deviation, and overall decision score.

4. DECISION INDICATORS FOR SCENARIO COMPARISON

Decision indicators are used to summarize simulated exposure–response profiles into interpretable quantities for comparing alternative levodopa dosing schedules. The main simulation outputs considered in this study are the effect-site concentration $C_e(t)$ and the predicted therapeutic response $E(t)$. These outputs are evaluated over an interval $[T_1, T]$, where T_1 is chosen after the initial transient period. The indicators are designed to support scenario comparison rather than to provide direct clinical prescribing recommendations.

The first indicator is peak–trough fluctuation, denoted by F_C , which measures the difference between the maximum and minimum effect-site concentrations over the evaluation interval. A smaller value of F_C indicates smoother effect-site exposure and less concentration instability across dosing intervals. The second indicator is the mean effect-site exposure, denoted by $\bar{C}_e$, which summarizes the average simulated exposure. This quantity should be interpreted together with fluctuation and therapeutic-window measures, because higher average exposure does not necessarily imply a more favorable schedule.

The third indicator is the proportion of time within a therapeutic reference window, denoted by P_W . This indicator measures how long $C_e(t)$ remains within a predefined target range $[C_L, C_U]$. A larger value of P_W indicates longer maintenance of the desired exposure range. The fourth indicator is response deviation, denoted by D_E , which measures the mean squared difference between the predicted response $E(t)$ and a reference response profile $E_{ref}(t)$. A smaller value of D_E indicates closer agreement with the desired response pattern. The fifth indicator is exposure variability, denoted by S_C , which measures the dispersion of $C_e(t)$ around its mean value. A smaller value of S_C indicates more stable exposure over time.

For overall scenario comparison, a normalized decision score J is introduced by combining the main decision indicators as follows:

$$J = w_1 \tilde{F}_C + w_2 (1 - P_W) + w_3 \tilde{D}_E + w_4 \tilde{S}_C, \\ w_1 + w_2 + w_3 + w_4 = 1, \quad w_i \geq 0.$$

where $\tilde{F}_C$, $\tilde{D}_E$, and $\tilde{S}_C$ are normalized forms of peak–trough fluctuation, response deviation, and exposure variability, respectively. The parameters $w_1, w_2, w_3, w_4 \geq 0$ represent decision weights. A

smaller value of J indicates a more favorable simulated dosing scenario because it reflects lower exposure fluctuation, longer time within the therapeutic reference window, lower response deviation, and lower exposure variability.

The weights can be adjusted according to the decision emphasis. For example, when stable symptom control is prioritized, larger weights may be assigned to P_W and D_E . When avoidance of peak–trough instability is prioritized, larger weights may be assigned to F_C and S_C . In this way, the decision score provides a flexible summary measure for comparing dosing schedules under different clinical or simulation priorities. Table 1 summarizes the indicators and their preferred directions.

TABLE 1. Decision indicators used for schedule-based evaluation

Indicator	Symbol	Preferred direction	Interpretation
Peak–trough fluctuation	F_C	Lower	Smoother effect-site exposure
Mean effect-site exposure	$\bar{C}_e$	Context-dependent	Average simulated exposure
Time within reference window	P_W	Higher	Longer maintenance of desired exposure
Response deviation	D_E	Lower	Closer agreement with target response
Exposure variability	S_C	Lower	More stable exposure over time
Overall decision score	J	Lower	More favorable simulated scenario

Overall, these indicators form the interpretive layer of the proposed framework. They transform PK–PD simulation outputs into quantitative summaries that can be used to compare alternative dosing schedules across virtual patient profiles. A schedule is interpreted as more favorable when it provides smoother effect-site exposure, longer target-window coverage, lower response deviation, and a smaller overall decision score.

5. NUMERICAL DEMONSTRATION

Representative simulations were performed to demonstrate how the framework compares alternative dosing schedules. Three schedules were considered: a standard repeated-dose schedule, a shorter-interval schedule designed to reduce fluctuation, and a fractionated-dose schedule in which the daily input is distributed into smaller and more frequent doses. These schedules illustrate common trade-offs in levodopa therapy, including maintaining adequate exposure, reducing peak–trough variability, and avoiding excessive response fluctuation. The aim is not to declare one schedule clinically superior, but to show how the same computational workflow can organize competing criteria into an interpretable comparison. The three schedules are summarized in Table 2.

TABLE 2. Representative dosing schedules used to demonstrate the decision-support workflow

Schedule	Dosing idea	Decision question
Standard schedule	Repeated dose at conventional interval	Does the baseline schedule provide adequate stability?
Shorter-interval schedule	More frequent administration	Does reduced interval increase target-window coverage?
Fractionated schedule	Smaller and more frequent doses	Does dose distribution reduce peak–trough variation?

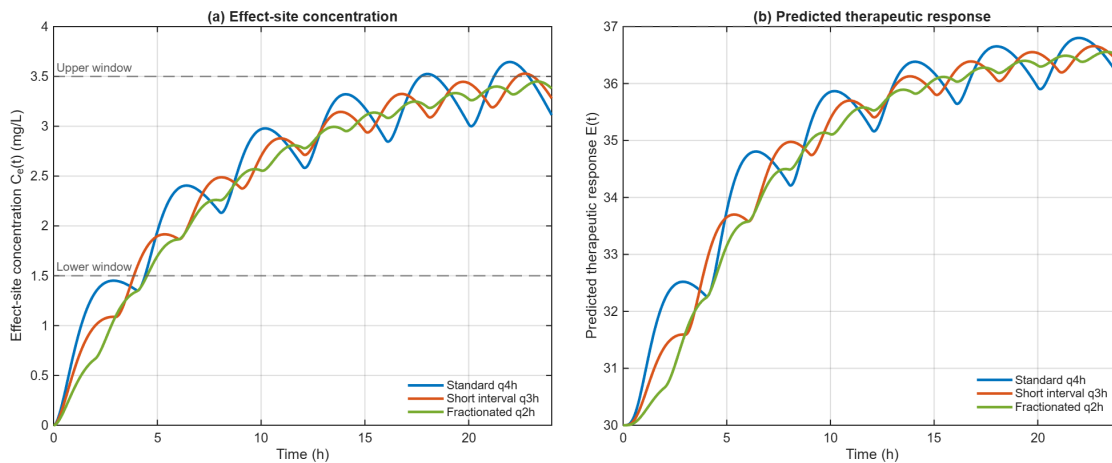


FIGURE 2. Simulated effect-site concentration and predicted therapeutic response under representative dosing schedules

The simulated effect-site concentration and predicted therapeutic response profiles are shown in Figure 2. The standard schedule produces visible oscillations in effect-site concentration because concentration increases after dose administration and declines before the next dose. The shorter-interval and fractionated-dose schedules reduce large peak–trough differences by distributing input more evenly over time. Because the pharmacodynamic response is nonlinear, increases in effect-site concentration do not produce proportional increases in therapeutic response when the exposure–response curve approaches saturation. Conversely, low trough concentrations may be associated with reduced predicted response. These results show why dosing interval and dose distribution should be evaluated using several decision indicators rather than a single concentration profile.

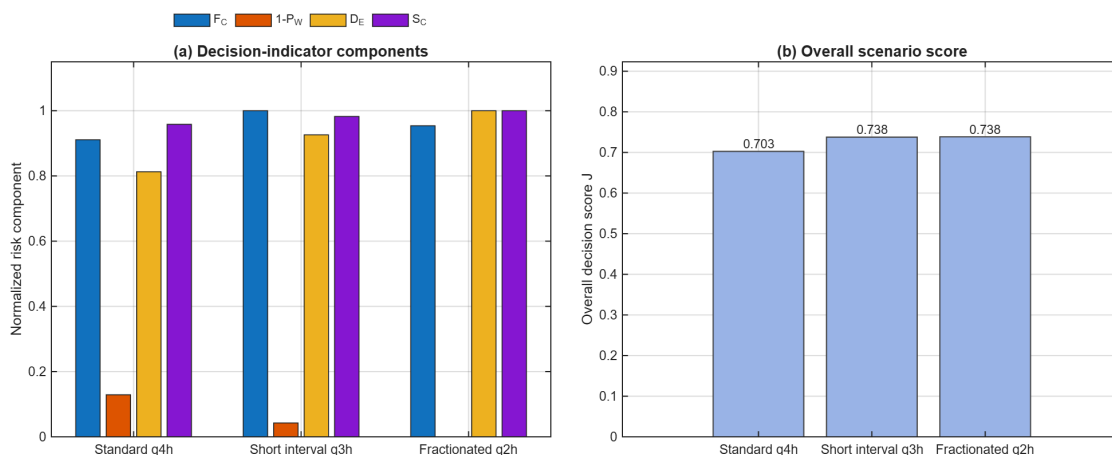


FIGURE 3. Normalized decision-indicator components and overall decision score for the representative schedules

Figure 3 presents the normalized decision-indicator components and overall scores. Under the selected parameter setting and equal-weight decision score, the standard q4h schedule gives the lowest overall decision score among the three representative schedules. Although the shorter-interval and fractionated-dose schedules increase the time within the therapeutic reference window, this benefit is partly offset by changes in response deviation and exposure variability. Therefore, increasing dosing

frequency does not automatically improve the overall simulated outcome when multiple indicators are evaluated simultaneously. The numerical example demonstrates the main purpose of the framework: to reveal trade-offs that may be hidden when dose size or dosing interval is considered alone.

6. DISCUSSION AND CONCLUSION

The proposed framework provides a structured approach for comparing levodopa dosing schedules under patient variability. It does not attempt to identify a universal optimal schedule. Instead, it evaluates which candidate strategy may generate a more stable exposure–response pattern for a given simulated profile. This is important because patients may differ in absorption rate, clearance, distribution volume, disease severity, gastrointestinal function, and pharmacodynamic sensitivity. A schedule that appears favorable for one profile may generate excessive peaks, underexposure, or unstable response in another profile.

The main contribution of this paper is the organization of PK–PD simulation outputs into decision-support indicators. Peak–trough fluctuation and exposure variability evaluate exposure stability, time within the reference window evaluates maintenance of desired exposure, response deviation evaluates agreement with a target profile, and the overall decision score combines these components into a compact comparative measure. This decision-support perspective may help design future individualized dosing studies and may also support integration with clinical rating data, wearable monitoring, and model-informed precision dosing systems.

Several limitations should be emphasized. The simulations are illustrative and based on representative parameter assumptions. The framework has not yet been prospectively validated using patient-level pharmacokinetic measurements, motor scores, or wearable-derived symptom measures. Gastrointestinal variability and formulation-specific effects are represented only in a simplified manner. Therefore, the results should not be interpreted as patient-specific medical recommendations or clinical prescriptions. Future work should incorporate real patient-level data, clinical motor assessments, gastrointestinal variability, digital biomarkers, and prospective validation. In conclusion, simulation-based PK–PD modeling can be extended beyond concentration–response prediction toward a practical decision-support approach for comparing individualized levodopa dosing strategies in Parkinson’s disease.

STATEMENTS AND DECLARATIONS

The authors declare no conflict of interest. The data generated during the current study are available from the corresponding author upon reasonable request.

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