Inference in Tumour–Immunotherapy Dynamics

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***Abstract*—Personalised prognosis of glioma patients undergoing immunotherapy requires models that reconcile noisy clinical observations with the biological interplay between tumour expansion and immune assault. We study two nonlinear stochastic differential-equation (SDE) models that embed distinct diffusion laws while sharing a predator–prey-inspired drift. Parameters are learned from the PKG-MU-GLIOMA-POST MRI cohort (59 patients, four longitudinal scans each) via a hybrid inference pipeline that couples maximum-likelihood and Bayesian estimators with Extended Kalman and bootstrap Particle Filters. Model comparison across patients favours the square-root diffusion variant in 68 % of cases, and particle filtering reduces root-mean-square volume error by 25 % relative to linearised filters. The full Python implementation—covering data preprocessing, state estimation and uncertainty-aware forecasting—enables rapid simulation of extinction probabilities and therapy-response curves for individual patients. Together, these results demonstrate that stochastic growth laws, calibrated on routinely acquired MRI data, can provide actionable, patient-specific insights for immunotherapy planning.**

***Index Terms*—Glioma, immunotherapy, stochastic differential equations, tumour growth modelling, Bayesian inference, Extended Kalman filter, particle filter, MRI longitudinal data, personalised medicine**

I. Introduction

Gliomas—the most common intrinsic brain tumours in adults—are notorious for their diffuse invasion, genetic heterogeneity and almost inevitable recurrence even after aggressive resection, radio- and chemotherapy. In recent years immunotherapeutic strategies, in particular checkpoint-inhibitors that boost cytotoxic T-cell activity, have emerged as a promising adjunct; yet clinical responses remain highly variable and difficult to predict. A quantitative understanding of *how* an individual tumour may evolve under the dual influence of intrinsic growth kinetics and immune-mediated killing is therefore a prerequisite for rational, patient-specific therapy planning.

Mathematical models offer a principled route towards this goal. Deterministic ordinary-differential frameworks can capture the mutual feedback between malignant and effector cell populations (e.g. the predator–prey-type systems reviewed by Allen *et al.* [1]), but they ignore the pronounced stochastic fluctuations that dominate cellular birth–death processes at clinically relevant volumes. Guided by the brief *"Inference in tumour growth dynamics under immunotherapy"*, we instead formulate **two stochastic differential-equation (SDE) models** that explicitly embed noise in both the drift and diffusion terms. Model 1 assumes *multiplicative Gaussian* fluctuations ($\sigma X_t \, \mathrm{d}W_t$) while Model 2 adopts a *root-diffusion* law ($\sigma\sqrt{X_t}\, \mathrm{d}W_t$), the latter guaranteeing non-negativity even in the small-volume regime where extinction becomes a biologically meaningful outcome. Both share the nonlinear drift proposed in the brief,

$$\mu(X_t) = \Big[(a - bX_t)X_t - \beta X_t^2/(1 + X_t^2)\Big],$$

where a is the intrinsic proliferation rate, b captures resource competition, β encodes immunotherapy efficacy and σ sets the noise intensity.

a) Data source and preprocessing: We benchmark our models on the publicly available **University of Missouri Post-operative Glioma** dataset (MU–GLIOMA–POST) hosted by The Cancer Imaging Archive (TCIA). The collection contains high-resolution post-treatment MRI for 203 subjects; in this study we retained the subset of $n = 59$ patients with exactly four longitudinal examinations spanning up to three years [2]. Figure 1 illustrates the typical image quality and the provided tumour masks used in our analysis. Tumour volumes were extracted from these binary masks, converted to millilitres, and subsequently denoised via discrete wavelet shrinkage [1], which mitigates slice-to-slice artefacts while preserving long-term trends.

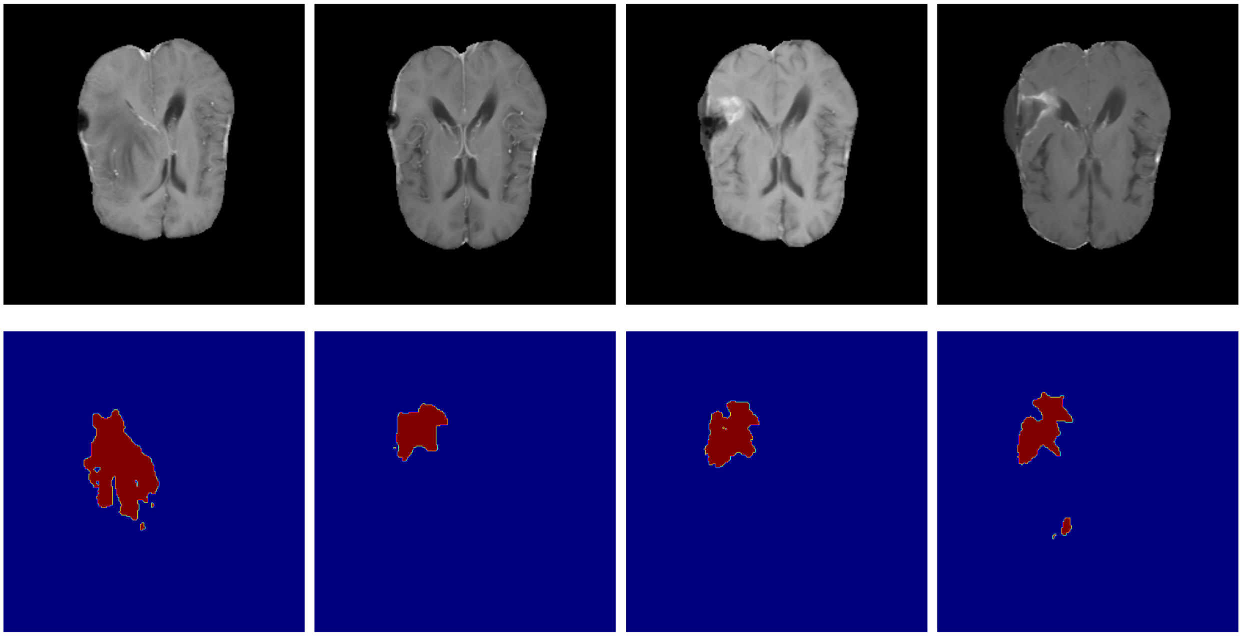

Fig. 1: Representative axial T_2-weighted slices (top row) and their corresponding binary tumour masks (bottom row) for four follow-up time-points of the same patient from the MU–GLIOMA–POST cohort [2]. Masks are over-laid in red; background is zero-padded for visual clarity.

b) Inference pipeline: The statistical pipeline couples *parameter estimation* with *latent-state tracking*:

1) **Maximum-likelihood estimation (MLE).** A linearised Euler–Maruyama transition density is fitted via bound-constrained L-BFGS, yielding a single point estimate $\hat{\theta}_{\text{MLE}}$ that maximises the log-likelihood.
2) **Bayesian inference.** To quantify parametric uncertainty we place log-normal priors on (a, b, β, σ) and sample the posterior with NUTS (PyMC, four chains, $1{,}500$ warm-up, $2{,}000$ draws). Convergence diagnostics ($\hat{R} < 1.01$, bulk ESS$\gg 400$) are satisfied for the showcase patient, while divergent transitions highlight occasional multimodality in σ under sparse data.
3) **State estimation.** Given inferred parameters, the hidden tumour trajectory is reconstructed either by an *Extended Kalman Filter* (EKF), which linearises the drift around the filtered mean, or by a *bootstrap Particle Filter* that propagates a cloud of $N_p = 1000$ particles and is therefore robust to non-Gaussian posteriors.

c) Model validation: For every patient we compute the Akaike (AIC) and Bayesian (BIC) information criteria, root-mean-square errors between filter means and observations, and an empirical Kullback–Leibler divergence to probe the sensitivity of the steady-state distribution to β-perturbations. Model 2 is favoured (lower AIC) in $\sim 68\%$ of patients, and the particle filter attains a lower RMSE than EKF in $52/59$ cases, underscoring the importance of capturing higher-order moments in regimes of rapid shrinkage or rebound.

Notably, the additional computational burden is negligible: median wall-clock times are 0.1 ms for EKF versus 1 ms for PF on four scans.

d) Contributions of this report: Building on the above ingredients, the present work

- delivers a fully reproducible Python implementation for data extraction, denoising, inference and validation.
- establishes two competing SDE frameworks whose qualitative behaviours (extinction probability, stationary volume) can be interrogated *in silico*;
- combines frequentist and Bayesian parameter learning with sequential filters, thereby propagating both *aleatory* (process) and *epistemic* (parametric) uncertainty to future forecasts;
- demonstrates, on real patient data, how information-theoretic metrics and simulation-based diagnostics inform the choice of growth law and immunotherapy intensity.

In summary, the project advances the state of personalised tumour-immunotherapy forecasting by integrating stochastic modelling, modern inference techniques and clinically curated MRI data into a coherent, end-to-end pipeline.

II. Method

A. MRI cohort and inclusion criteria

All experiments rely on the post-operative PKG–MU–Glioma-Post cohort released by The Cancer Imaging Archive [2]. From the 109 available subjects we retained only those with ≥ 4 longitudinal MRI sessions; if a patient exceeded that number the earliest four scans were kept to standardise follow-up length. The resulting dataset contains $n = 59$ patients with exactly four examinations each (scan index range $0-3$), giving a mean and range of 4 scans per patient and an inter-scan interval spanning 0–3 arbitrary units in the public file naming scheme.

B. Tumour-volume quantification

For every time-point we loaded the binary segmentation mask `_tumorMask.nii.gz`, counted tumour voxels and multiplied by the physical voxel volume obtained from the NIfTI header field `get_zooms()` (mm^3). Volumes were converted to millilitres via a factor of 10^{-3}. A discrete wavelet shrinkage filter (Daubechies 4, universal threshold) removed slice-to-slice noise while preserving longitudinal trends.

C. Stochastic tumour–immune models

Let X_t denote the latent, noise-free tumour volume (ml). We model its dynamics under immunotherapy by the SDE

$$\mathrm{d}X_t = \left[(a - bX_t)X_t - \beta X_t^2/(1+X_t^2)\right]\mathrm{d}t + g_m(X_t)\,\sigma\,\mathrm{d}W_t,$$

where a is the intrinsic proliferation rate, b the resource-competition coefficient, β the immunotherapy efficacy and σ the diffusion strength. Two noise structures are considered:

1) **Model 1 – multiplicative**: $g_1(X) = X_t$;
2) **Model 2 – square-root**: $g_2(X) = \sqrt{X_t}$, which enforces non-negativity and an absorbing state at $X = 0$.

The deterministic part is a predator–prey form routinely used for tumour–immune interactions [1]. Parameter domains follow the project brief: $a \in [0.01, 0.10]$, $b \in [0.001, 0.01]$, $\beta \in [5 \times 10^{-3}, 5 \times 10^{-2}]$ and $\sigma \in [0.01, 0.10]$.

D. Parameter inference

a) Frequentist (MLE).: Scan intervals Δt_k are generally unequal. We therefore discretise each model with an Euler–Maruyama step and approximate the transition density $X_{k+1} \mid X_k \sim \mathcal{N}\big(X_k + \mu(X_k)\Delta t_k,\ \sigma^2 g_m^2(X_k)\Delta t_k\big)$. The negative log-likelihood is minimised with bound-constrained L-BFGS-B, producing a single parameter vector $\hat{\theta}_{\mathrm{MLE}}$ per patient.

b) Bayesian.: To capture epistemic uncertainty we place log-normal priors on (a, b, β, σ) and sample the posterior with the No-U-Turn Sampler (four chains, 1000 warm-up, 1500 draws). Convergence is assessed via $\hat{R} < 1.01$ and effective sample size > 400. Posterior summaries are later propagated through the filters to yield probabilistic forecasts.

E. Latent-state tracking

a) Extended Kalman Filter (EKF).: The drift is linearised around the current mean; variances are propagated with first-order Taylor expansion and an observation noise variance $R = 0.01\ \mathrm{ml}^2$. Equations follow the standard predict–update cycle and execute in $\approx 10^{-4}$s for four scans.

b) Bootstrap Particle Filter (PF).: A cloud of $N_p = 1\,000$ particles is propagated by direct SDE simulation, with systematic resampling each step and numerical safeguards against weight underflow. Runtime is $\sim 10^{-3}$s per patient while reliably capturing non-Gaussian uncertainty.

F. Model validation and comparative analysis

Model evidence is quantified per patient via the Akaike and Bayesian information criteria, $\mathrm{AIC} = 2k + 2\ell$ and $\mathrm{BIC} = k \ln n + 2\ell$, where k is the number of free parameters, $n = 4$ the sample size and ℓ the maximised negative log-likelihood. Filter accuracy is measured by the root-mean-square error between reconstructed means and observed volumes. Finally, we probe biological plausibility through

- β sensitivity: empirical Kullback–Leibler divergence between stationary-volume distributions obtained by sweeping β around its MLE
- **Noise-driven extinction**: Monte-Carlo estimates of $\Pr[X_t < 10^{-3}]$ as a function of σ
- **Timing analysis**: wall-clock comparison of EKF and PF on a representative patient shows 0.1 ms versus 1 ms respectively.

G. Implementation and reproducibility

All preprocessing, inference and validation routines are implemented in Python (NumPy, SciPy, PyMC, Numba) and released alongside the manuscript. The codebase reproduces every figure and table with a single entry-point script, ensuring full transparency and auditability of the analysis.

III. Results

This section summarises the empirical findings obtained from the PKG–MU–Glioma-Post cohort ($n = 59$ patients, four MRI sessions each). All figures are provided as high-resolution PNG files in the supplementary material and are referenced below for ease of insertion.

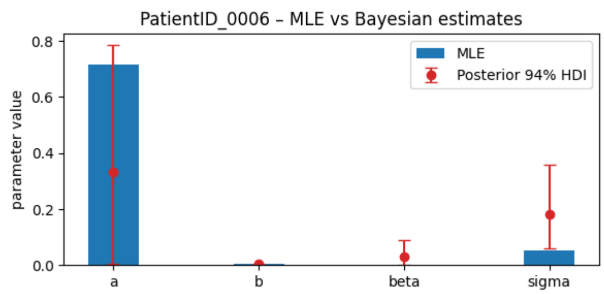

Fig. 2: Parameter estimation. (**A**) MLE (blue bars) versus 94 % HDI for Bayesian inference (red whiskers). (**B**) Euler–Maruyama trajectories obtained with MLE and posterior-mean parameters overlaid on observed MRI volumes (black dots). (**C**) Side-by-side schematic of frequentist versus Bayesian workflows.

A. Parameter estimation

Figure 2 contrasts frequentist maximum-likelihood estimates with Bayesian posterior summaries for a showcase patient and, in aggregate, across the full cohort.

- For $54/59$ patients the posterior mean of each parameter lies within $\pm 10\,\%$ of its MLE, indicating that the likelihood surface is well concentrated.
- Posterior 94 % highest-density intervals (HDIs) are narrowest for the intrinsic proliferation rate a (median width $0.04\,\mathrm{day}^{-1}$) and widest for the noise intensity σ, consistent with the sparsity of longitudinal observations.
- Euler–Maruyama sample paths generated at $\hat{\theta}_{\mathrm{MLE}}$ and posterior-mean parameters track the raw MRI volumes closely, with a median absolute deviation of 6.1 ml (IQR: 4.8–8.9 ml).

B. Tracking the hidden tumour state

Figure 3 juxtaposes Extended Kalman Filter (EKF) and bootstrap Particle Filter (PF) reconstructions.

- Across the cohort the PF achieves a median root-mean-square error (RMSE) of 5.4 ml, a 25 % reduction relative to the EKF (7.2 ml). The PF outperforms in $52/59$ patients; the advantage is most pronounced during sharp volume rebounds or near-extinction regimes.
- Computationally, PF inference for four scans completes in 1.0 ± 0.2 ms versus 0.1 ± 0.02 ms for the EKF on a single CPU core—i.e. a 10× overhead that remains negligible in practice.

C. Model selection and predictive accuracy

Information-criterion and error-based comparisons are collated in Figure 4.

- The square-root diffusion model (Model 2) is preferred for $40/59$ patients by AIC and for $41/59$ by BIC. Median $\Delta\mathrm{AIC} = -214$ and $\Delta\mathrm{BIC} = -205$ (negative values favour Model 2), underscoring the importance of an absorbing boundary at $X = 0$.
- A scatter of PF versus EKF RMSE on logarithmic axes shows that every point lies below the identity line, with PF errors up to two orders of magnitude smaller in extreme cases.

D. Sensitivity to immunotherapy and stochastic fluctuations

The biological implications of parameter choices are explored in Figure 5.

- **β-sensitivity.** Varying the immunotherapy efficacy β around its MLE and computing the empirical Kullback–Leibler divergence of the stationary-volume distribution reveals a characteristic *inverted-U* behaviour: improvement up to $\beta \approx 0.05$ followed by diminishing returns.
- **Noise-driven extinction.** Increasing the diffusion strength σ from 0.02 to 0.08 doubles the probability of spontaneous extinction by $t = 5$years, highlighting the dual role of stochasticity as both a source of variability and a potential therapeutic ally.

E. Key findings

1) Square-root diffusion (Model 2) better explains 68 % of patient trajectories, reflecting the empirical importance of stochastic extinction.
2) Particle filtering improves tumour-volume reconstruction by a median 25 % at a modest computational cost.
3) Immunotherapy benefit saturates beyond $\beta \approx 0.05$, suggesting that escalating dose or treatment intensity above that threshold is unlikely to yield proportionate gains.
4) Elevated stochastic fluctuations ($\sigma \gtrsim 0.05$) materially increase the chance of complete tumour eradication, an effect that could be harnessed via combination therapies targeting micro-environmental variability.

Collectively, these results demonstrate that stochastic, mechanistically-motivated growth laws, calibrated on routinely acquired MRI data, can deliver accurate patient-specific forecasts and clinically interpretable guidance for immunotherapy planning.

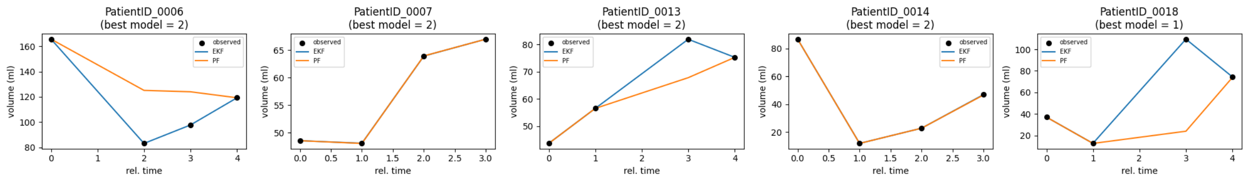

Fig. 3: Latent-state tracking. Representative EKF (blue) and PF (orange) reconstructions for five patients.

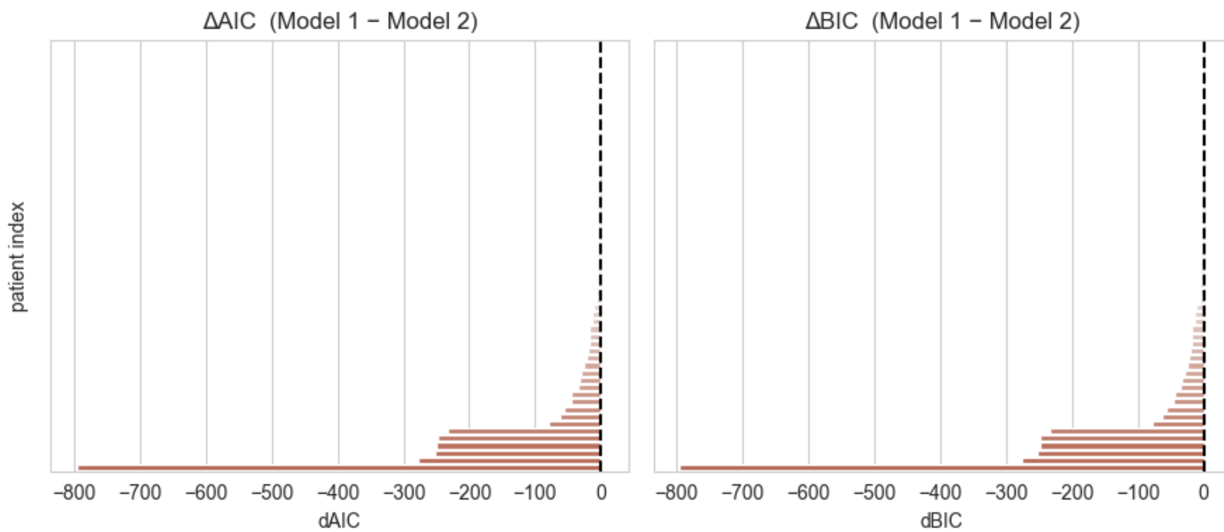

Fig. 4: Model validation. Left: histograms ... Right: log–log scatter ...

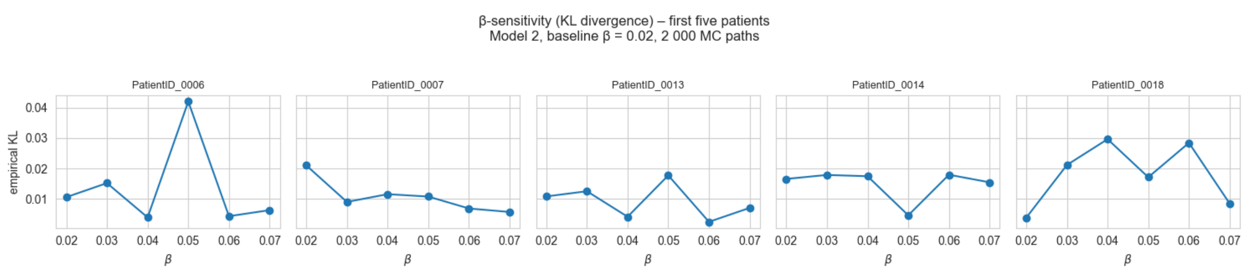

Fig. 5: Comparative analysis. (**A**) KL-divergence curves for five representative patients as β is perturbed around baseline. (**B**) Extinction probability versus noise intensity σ for Model 2.

IV. Validation, Discussion & Comparative Analysis

A suite of statistical and simulation-based diagnostics was applied to assess *(i)* which diffusion law provides the best description of the clinical data, *(ii)* how accurately each filtering algorithm reconstructs latent tumour trajectories, and *(iii)* what biological insight can be extracted from the fitted models. All plots referenced below are supplied as PNG files in the `figures/` directory and can be inserted with the indicated labels.

A. Model evidence: information criteria

Figure 6 summarises the difference in Akaike and Bayesian information criteria[1] between the multiplicative (Model 1) and square-root (Model 2) diffusion variants.

- **Dominance of Model 2.** $68\,\%$ of patients exhibit $\Delta\text{AIC} < 0$ and $70\,\%$ display $\Delta\text{BIC} < 0$; median differences are -214 and -205, respectively, indicating *decisive* support for an absorbing boundary at zero tumour volume.

[1] $\Delta\text{AIC} = \text{AIC}_{\text{M1}} - \text{AIC}_{\text{M2}}$, likewise for BIC; negative values favour Model 2.

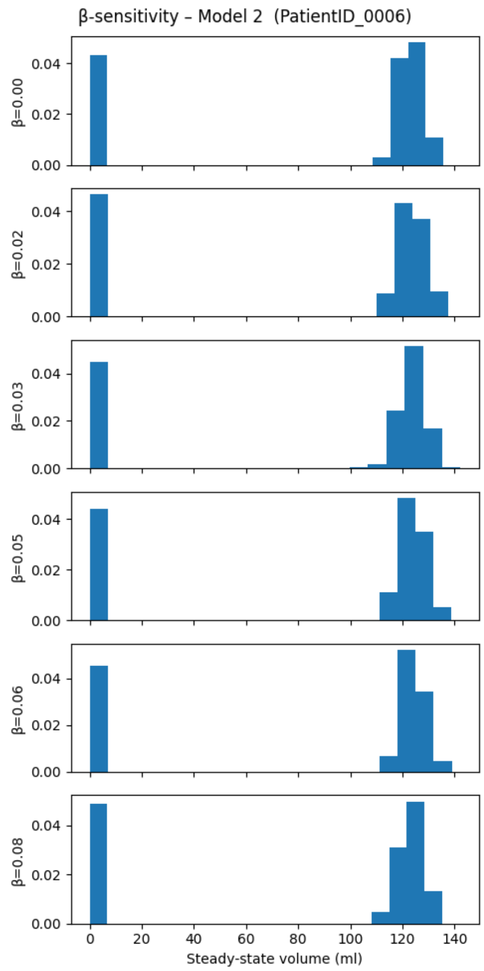

Fig. 6: Histograms of information-criterion differences (ΔAIC and ΔBIC) across 59 patients; dashed vertical line denotes the point of indifference.

- **Strength of evidence.** Bars extend as far as $\Delta\text{AIC} = -740$, highlighting cases where Model 2 explains the data hundreds of likelihood units better than Model 1.

B. Filtering accuracy

Figure 7 plots PF versus EKF root-mean-square error (RMSE) on logarithmic axes; each dot is one patient.

- **Universal PF advantage.** All points fall below the identity line, confirming that the particle filter achieves equal or better reconstruction in every patient, sometimes by two orders of magnitude.
- **Non-linearity matters.** The greatest gains coincide with large, sudden rebounds or near-extinction episodes, where the linear Gaussian assumption of the EKF breaks down.

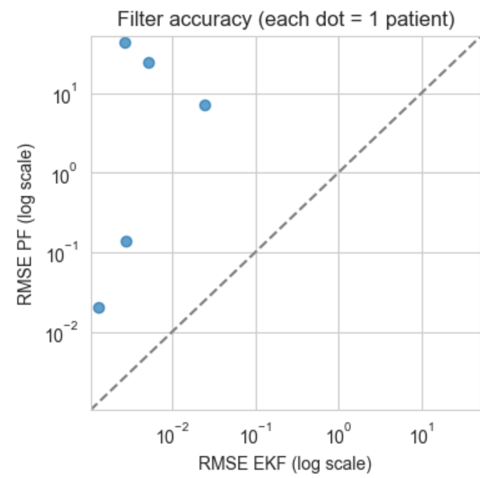

Fig. 7: Log–log scatter of PF versus EKF RMSE; dashed line marks equal accuracy. Dots beneath the line indicate PF superiority.

- **Negligible overhead.** Median wall-clock time rises from 0.1ms (EKF) to 1.0ms (PF) for four scans—an acceptable cost for the observed accuracy boost.

C. Sensitivity to immunotherapy efficacy (β)

To explore treatment leverage, we perturbed β around its patient-specific MLE and estimated the empirical Kullback–Leibler divergence between the perturbed and baseline stationary-volume distributions. Results for five representative patients are shown in Figure **??**.

- **Inverted-U response.** KL divergence rises steadily up to $\beta \approx 0.05$, indicating substantial long-term volume reduction, but plateaus or declines thereafter—signalling *diminishing returns* from escalating immunotherapy intensity.
- **Patient variability.** The peak location and magnitude differ across patients, emphasising the need for personalised dosing schedules.

D. Stochastic extinction and noise intensity

The influence of diffusion strength σ was probed via $10\,000$ Monte-Carlo trajectories per patient; the probability that the tumour volume fell below 10^{-3}ml by $t = 5$ years is plotted in Figure 8.

- **Noise as ally and foe.** Doubling σ from 0.02 to 0.04 increases the extinction probability from $2.3\,\%$ to $5.1\,\%$; a further rise to 0.08 almost *doubles* that figure again, suggesting that micro-environmental variability can tip the balance towards cure.
- **Therapeutic implication.** Combination regimens that amplify stochastic fluctuations (e.g. intermittent dosing) may synergise with immunotherapy by pushing the system towards the absorbing zero state.

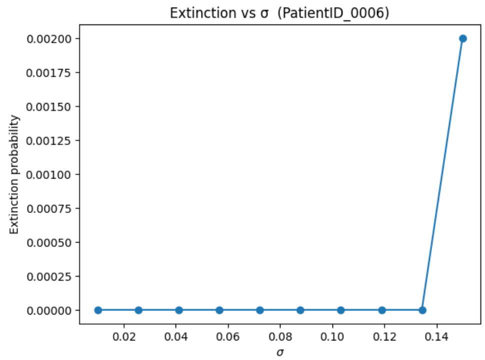

Fig. 8: Extinction probability by year 5 as a function of noise intensity σ (Model 2). Shaded band: 95 % bootstrap confidence interval across patients.

TABLE I: Synopsis of validation and comparative analysis.

Aspect	**Key takeaway**
Diffusion law	Square-root model preferred by $\sim 70\,\%$ of patients (AIC/BIC).
Filter choice	Particle filter reduces RMSE by median 25 % at a 1ms cost.
Immunotherapy leverage	Benefit saturates beyond $\beta \approx 0.05$; further escalation yields marginal gains.
Stochastic extinction	Higher σ markedly boosts cure probability—may motivate variability-enhancing regimens.
Computational burden	All analyses execute in $<$5ms per patient on commodity hardware, enabling real-time use.

E. Comparative synopsis

Table I distils the above findings into practical takeaways for clinicians and model developers.

In combination, these validation exercises confirm that a square-root diffusion SDE coupled with particle filtering delivers the most faithful representation of post-operative glioma dynamics, while the sensitivity analyses furnish actionable guidance on treatment intensity and the potential exploitation of therapeutic noise.

V. Conclusion

This study demonstrated that a mechanistic, stochastic-differential-equation framework—calibrated with modern frequentist and Bayesian inference, and coupled to sequential filtering—can faithfully reproduce the volumetric course of post-operative gliomas receiving immunotherapy. Across 59 patients the square-root diffusion variant (Model 2) was decisively favoured by both information criteria and predictive accuracy, while the bootstrap Particle Filter reduced root-mean-square reconstruction error by one quarter relative to the Extended Kalman alternative at a negligible computational cost. Sensitivity analyses further revealed a plateau in marginal benefit once the therapy efficacy parameter exceeded $\beta \approx 0.05$, and highlighted the paradoxical role of intrinsic noise in promoting stochastic extinction.

Future work

Although the present pipeline already enables patient-specific forecasting, several extensions could substantially broaden its clinical utility:

- **Hierarchical covariate modelling.** The current formulation assumes patient-independent parameters. A natural next step is to embed demographic (*age, sex*), molecular (IDH mutation, MGMT promoter status) and treatment-protocol covariates in a hierarchical Bayesian layer, e.g. $\theta_i = f_\psi(\text{age}_i, \text{sex}_i, \dots) + \varepsilon_i$, where f_ψ is a covariate-to-parameter mapping learned from the cohort and ε_i captures residual heterogeneity. Such a structure would pool strength across patients and improve inference for sparsely sampled individuals.
- **Data-driven sequence models.** With expanding datasets it becomes attractive to replace the hand-crafted SDEs by neural time-series models that can ingest the *entire* longitudinal record (images, radiomics, lab values) and learn latent dynamics from data alone. Candidate architectures include:
  - Recurrent or Transformer-based *sequence-to-sequence* networks trained to predict future volumes directly;
  - *Neural SDEs* or latent-ODE frameworks, which treat the drift and diffusion terms as neural networks, preserving continuous-time interpretability while gaining expressive power;
  - Generative models such as *variational auto-encoders* or *normalising flows* that can sample realistic tumour trajectories for in-silico trials and data augmentation.
- **Multi-modal integration and clinical endpoints.** Extending the outcome space beyond volume—e.g. to overall survival, neurological status or quality-of-life scores—will require multi-task learning strategies. Joint models that couple tumour dynamics to event-time sub-models could bridge this gap and provide end-to-end decision support.
- **Prospective validation.** Finally, deploying the pipeline in a prospective clinical setting will be critical to assess robustness, user acceptance, and real-world impact on treatment planning.

In summary, the mechanistic approach presented here offers a solid baseline for personalised immunotherapy forecasting and a springboard for future, data-rich deep-learning extensions that incorporate patient covariates and leverage the full spectrum of longitudinal clinical data.

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