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WHEN MATHEMATICAL MODELLING MEETS CLINICAL REALITY: CHALLENGES REVEALED BY LONGITUDINAL ONCOLOGY DATA

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ABSTRACT

Longitudinal clinical data promise a more complete description of disease evolution and treatment response than static baseline characteristics and have therefore become an attractive target for mathematical modelling. Two broad philosophies naturally emerge: employing general statistical methodology capable of handling repeated measurements, or constructing specialised models that explicitly describe the underlying biological process. Regardless of the chosen approach, the ultimate objective remains the same — to support medical decisions by producing information that is robust, interpretable, and actionable for an individual patient. However, the clinical reality often challenges assumptions of existing modelling frameworks.

This perspective emerged while working on two oncology studies conducted at the Maria Skłodowska-Curie National Research Institute of Oncology Gliwice Branch. Despite addressing very different clinical questions, they converged on the same methodological dilemmas. The first study investigated longitudinal complete blood count (CBC)-derived inflammatory biomarkers in advanced non-small cell lung cancer, asking whether post-baseline laboratory trajectories improve prognostic assessment during immunotherapy. The second examined therapeutic monitoring of mitotane concentrations in adrenocortical carcinoma, an ultra-rare malignancy, evaluating whether achieving therapeutic drug levels translates into improved clinical outcomes. Although one biomarker primarily observed the disease while the other actively influenced treatment, both projects gradually revealed remarkably similar modelling challenges.

The first obstacle, particularly relevant for the mechanistic approach, proved to be the process itself. For inflammatory, and more generally, CBC-related biomarkers, the biological mechanisms underlying longitudinal changes are too numerous and interconnected to model explicitly. Mitotane concentrations initially appear to offer a simpler pharmacokinetic problem, yet in practice their trajectories reflect not only drug metabolism but also physician-guided dose modifications,

treatment tolerance, patient adherence, and other incompletely recorded clinical factors, such as the drug accumulation in adipose tissue, itself a dynamic component.

A second challenge concerns the definition of clinically meaningful outcomes. The processes of genuine interest — tumour progression, treatment efficacy or biological response — are rarely observed directly or continuously. They must instead be approximated by surrogate endpoints such as progression-free, recurrence-free, or overall survival. Choosing an endpoint therefore becomes part of the modelling process rather than a purely clinical decision. In the mitotane study, for example, analysing recurrence only during the treatment period proved more informative than considering the entire disease course, as post-recurrence or post-discontinuation management introduced additional sources of heterogeneity unrelated to the original clinical question. Additionally, time-to-event analyses are defined not only by the endpoint but also by the choice of time zero. As longitudinal biomarker measurements frequently occur after this point, immortal time bias becomes a common pitfall.

The third challenge arose from the observations themselves. Neither study generated regularly sampled longitudinal trajectories. Laboratory measurements were obtained according to routine clinical practice rather than a predefined schedule, patients differed in follow-up duration, and clinically important events frequently altered the observation process itself. These characteristics naturally reflect retrospectively collected real-world clinical data, where biomarker measurements follow the realities of everyday oncology care rather than the regular schedules of prospective study protocols. These limitations were particularly evident in the mitotane cohort. Although concentration measurements were available approximately monthly (denser than in most published studies) they still contained substantial gaps and irregular sampling intervals. Moreover, the extreme rarity of adrenocortical carcinoma — approximately 30–80 new cases nationally each year — combined with the evolving landscape of diagnostics, imaging and treatment guidelines, makes cohort construction a delicate balance between maximizing sample size and preserving cohort comparability. Consequently, methodological choices begin long before model fitting, as inclusion criteria and cohort definition become parts of the analytical strategy rather than merely preparatory steps.

Instead of converging on a single analytical solution, these observations encouraged an iterative process in which the problem was repeatedly reformulated and examined from several methodological perspectives. Landmark analyses with trajectory summaries, time-dependent models, clinically motivated endpoint redefinition, and carefully selected analysis populations each captured different aspects of the same process. These seemingly competing approaches may prove complementary, provided that their interpretation remains anchored in the clinical question they were designed to answer. Looking at the same longitudinal data through several well-understood methodological lenses may ultimately provide more meaningful clinical insight than searching for a universally optimal model.

Rather than presenting these case studies as methodological success stories, this contribution uses them as examples of recurring challenges encountered when mathematical modelling meets routine clinical practice. The aim is to encourage dialogue between clinicians, biostatisticians and mathematicians on how future methods can better accommodate the realities of longitudinal clinical data. Ultimately, meaningful clinical translation depends not on choosing between clinical intuition and mathematical rigour, but on allowing each to shape the other.