

MODELING LONGITUDINAL MEASUREMENTS OF CLINICAL AND EPIDEMIOLOGICAL PARAMETERS USING JOINPOINT REGRESSION

Mihaela Moscalu^{1*}, Ionela-Lăcrămioara Șerban^{2*}, Norin Forna³, Mihaela Pundiche⁴,
Loredana Mitran⁵, Madalina-Elena Datcu¹, Dragomir Nicolae Șerban²,
Alin Constantin Pînzariu²

¹Department of Preventive Medicine and Interdisciplinarity, “Grigore T. Popa” University of Medicine and Pharmacy, 700115 Iasi, Romania

²Department of Morpho-Functional Sciences II, “Grigore T. Popa” University of Medicine and Pharmacy, 700115 Iasi, Romania

³Department of Orthopedics and Traumatology, “Grigore T. Popa” University of Medicine and Pharmacy, 700115 Iasi, Romania

⁴Department V, Faculty of Medicine, “Ovidius” University, 900470 Constanta, Romania

⁵ENT Department, Elias University Emergency Hospital, 011461 Bucuresti, Romania

* These authors contributed equally

Corresponding author: Norin Forna *e-mail*: norin.forna@umfiasi.ro

ABSTRACT

Aim of the study The rapid advancement of medical technologies and the growing volume of data generated in clinical practice and research have created a continuous demand for sophisticated statistical tools for analysis. Currently, longitudinal data and information regarding time-to-event outcomes (e.g., death, recurrence, remission) are ubiquitous in medical studies. In this context, analytical methods capable of detecting and interpreting temporal changes in clinical parameters have become essential. This article aims to provide a comprehensive synthesis of the applications of Joinpoint regression in medicine, with a particular focus on the modelling of longitudinal measurements. **Materials and methods** The Joinpoint regression model was employed in integration with joint longitudinal–time-to-event models, as well as with Bayesian extensions. **Results** Joinpoint regression was applied to detect significant changes in temporal data trends. In the medical field, this method provides valuable opportunities for analysing the evolution of clinical indicators and modelling time-dependent risks of events. The conducted study required the modelling of temporal changes, as time-related trends in medicine are not always linear or stable. Sudden shifts may occur due to the introduction of new treatments, public health interventions, or unknown biological mechanisms. Joinpoint regression accurately identified inflection points, offering a clearer perspective on the underlying processes. **Conclusions** The utility of this method is highlighted in supporting evidence-based decision-making in both clinical practice and research, while also emphasizing the methodological challenges and future directions for development. Joinpoint regression is emerging as an indispensable tool in the arsenal of modern medical statistics, playing a critical role in enhancing the understanding of disease dynamics and optimizing informed clinical decision-making.

Key words: joinpoint regression, Annual Percent Change (APC), modeling longitudinal

INTRODUCTION

In recent decades, data analysis in medicine has experienced remarkable expansion due to technological advancements in the collection and storage of clinical information. Longitudinal studies, national health databases, and disease registries now offer an ever-increasing volume of temporal data [1].

These data may reflect the evolution of a biological marker, a chronic disease, or a population-level phenomenon. In this context, statistical methods capable of capturing temporal dynamics are essential for generating meaningful insights.

In clinical and epidemiological settings, trends are not always linear or stable. The

introduction of a new treatment, a public health policy, a behavioural intervention, or the emergence of a pandemic can result in sudden changes in the trajectory of a given phenomenon. Identifying these inflection points known as “joinpoints” is crucial for understanding the causal impact of events or interventions, as well as for anticipating and adjusting therapeutic decisions. Joinpoint regression has emerged as a specialized tool to address this analytical need [2, 3].

The primary objective of this article is to systematically explore the utility of Joinpoint regression in medicine, with a focus on two major directions: modelling longitudinal measurements and analysing time-to-event data. Additionally, the theoretical foundations of the method are discussed, along with illustrative applications in epidemiology, oncology, and biomarker analysis. Joinpoint regression also encompasses several methodological extensions, including Bayesian Joinpoint regression and its integration into joint modelling frameworks.

MATERIALS AND METHODS

Joinpoint regression is a segmented modelling approach that assumes the relationship between the dependent variable and time consists of multiple linear sections connected at specific “joinpoints” or change points. These points indicate moments where the slope of the line shifts significantly, suggesting a change in trend. The Joinpoint model divides the time series into linear segments, each joined at these discontinuity points. Each segment is characterized by its own slope, and the differences between segments may reflect medically or

epidemiologically significant events.

A “joinpoint” refers to a point on the temporal axis at which the trend of a dependent variable undergoes a statistically significant change. In the context of regression analysis, this corresponds to a shift in the slope of the linear relationship [4, 5, 6].

Formally, Joinpoint regression is a piecewise linear model, expressed as:

$$y_i = \beta_0 + \beta_1 x_1 + \sum_{k=1}^K \delta_k (x_i - \tau_k)_+ + \epsilon_i$$

where:

τ_i denotes the joinpoints (change points);

$(x_i - \tau_k)_+ = \max(0, x_i - \tau_k)$ represents the positive part function used to define the segmented linear structure;

δ_k indicates the change in slope after each joinpoint;

each slope coefficient (β) reflects the rate of increase or decrease within a specific time interval;

ϵ is the random error term.

A clinical interpretation may, for example, correspond to the rate of change in disease incidence over time.

Statistical analysis

Crude rate trends were analysed using the Joinpoint Regression Program (version 5.4.0 – April 16, 2025; National Cancer Institute, Bethesda, USA). This software enabled the identification of joinpoint models and the estimation of Annual Percent Change (APC) values, which quantify the magnitude and direction of trend shifts within each segment. Statistical significance of observed changes in trend was evaluated using the Monte Carlo permutation method, which tests whether the apparent inflection points in crude rate trajectories represent statistically meaningful deviations.

RESULTS AND DISCUSSIONS

In epidemiology, the monitoring and analysis of incidence and mortality constitute a fundamental pillar in assessing population health. Joinpoint regression is widely used to

detect significant shifts in these trends, whether as a result of public health interventions, changes in risk behaviors, or modifications in screening policies [7, 8].

The classical joinpoint regression model is

typically represented as a segmented function. Numerous studies conducted within the SEER (Surveillance, Epidemiology, and End Results) programs have employed joinpoint regression to evaluate trends in breast, colorectal, and prostate cancer. For instance, trend analyses in colorectal cancer identified two inflection points: the first associated with the introduction of colonoscopy screening, and the second with advancements in therapeutic treatments [9, 10]. Estimating the location of change points is a complex task that involves iterative and adaptive methods. Algorithms such as Grid Search combined with permutation testing (in the frequentist framework), or Markov Chain Monte Carlo (MCMC) methods (in the Bayesian framework), are employed to estimate both the number and the optimal position of inflection points [11]. Bayesian Joinpoint regression can be applied to model mortality associated with

various diseases, enabling robust estimations and the integration of uncertainty regarding the number of change points [12]. In selecting the optimal number of change points, complexity-penalization criteria were employed, including the Bayesian Information Criterion (BIC), the Akaike Information Criterion (AIC), and the Bayes Factor in the Bayesian context. These criteria help prevent overfitting and support the robustness of the estimations [13, 14].

An analysis of mortality rates due to cardiovascular diseases, diabetes, and respiratory conditions clearly demonstrated the importance and relevance of evaluation using the joinpoint regression model (Table 1 and 2, Fig. 1). The processed data were obtained from the website of the Romanian National Institute of Statistics, specifically from the TEMPO online platform.

Table 1. Mortality rate due to cardiovascular diseases, diabetes and respiratory diseases

Year of diagnosis (2008-2023)*	Crude Rate*	Count*	Population*	Standard Error	Modelled Population	Joinpoint Location
2008	9.8	2022	20635460	0.22	9.67	
2009	10.1	2064	20440290	0.22	10.02	
2010	10.9	2212	20294683	0.23	10.38	
2011	9.9	2000	20199059	0.22	10.75	
2012	11.4	2291	20095996	0.24	11.13	
2013	11.1	2222	20020074	0.24	11.53	
2014	11.3	2255	19953089	0.24	11.95	
2015	12.7	2524	19875542	0.25	12.37	
2016	13.6	2687	19760585	0.26	12.81	
2017	13.1	2573	19643949	0.26	13.27	
2018	14.2	2774	19533481	0.27	13.75	Joinpoint 1
2019	14.8	2875	19425873	0.28	16.31	
2020	20.5	3968	19354339	0.33	19.36	
2021	22.7	4365	19229519	0.34	22.98	Joinpoint 2
2022	18.5	3523	19043098	0.31	18.55	
2023	15	2858	19054548	0.28	14.98	

*<http://statistici.insse.ro:8077/tempo-online/#/pages/tables/insse-table>

Table 2. Trend's magnitude (APC) of mortality rate (for each segment).

Variables	Segment	The edges of the segment		APC	APC		Test Statistic (t)	p-value
		Lower Endpoint	Upper Endpoint		Lower 95%CI	Upper 95%CI		
Year	Slope 1	2008	2018	3.6*	2.3	4.8	6.7	0.000
	Slope 2	2018	2021	18.7*	4.2	35.2	3.0	0.000
	Slope 2	2021	2023	-19.3*	-29.4	-7.7	-3.7	0.000
	Full Range	2008	2023	3.0*	0.1	5.8	2.1	0.000

(*) Marked effects are significant at $p < 0.05$

CI – Confidence interval

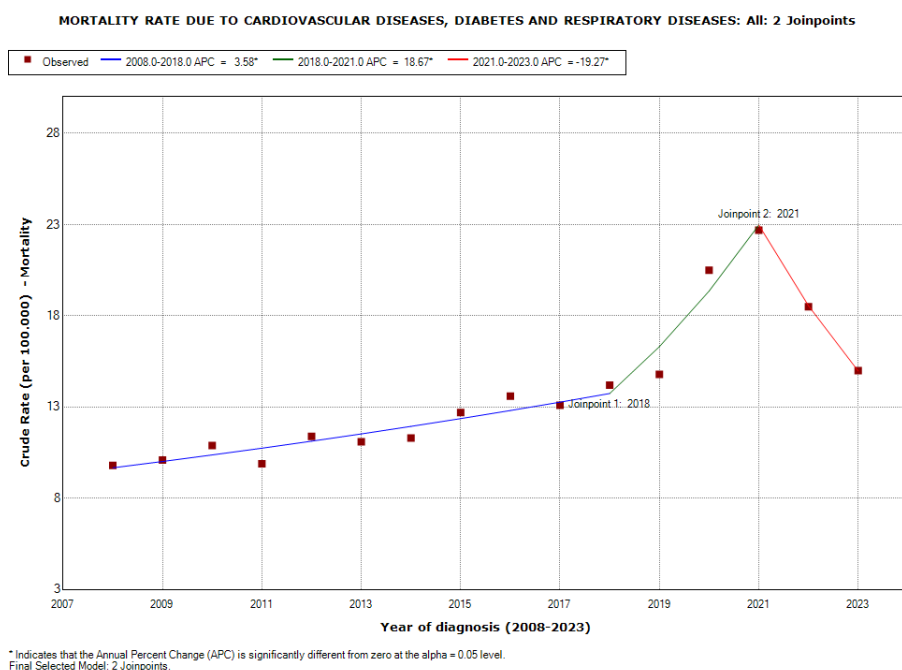


Figure 1. Scatter plot of Mortality rate due to cardiovascular diseases, diabetes and respiratory diseases from 2008-2023

The 2008–2018 segment indicates a moderate yet statistically significant increase in mortality rates, with an Annual Percent Change (APC) of 3.6% (95% CI: 2.3%–4.8%, $p < 0.05$), suggesting a progressive deterioration in mortality due to cardiovascular diseases, diabetes, and respiratory illnesses. Additionally, the 2018–2021 segment is characterized by a sharp rise in mortality, with an APC of 18.7% (95% CI: 4.2%–35.2%, $p < 0.05$), potentially reflecting acute stressors on the healthcare system. In contrast, the 2021–2023 segment reveals a significant decline in mortality, with an APC

of –19.3% (95% CI: –29.4% to –7.7%, $p < 0.05$), indicating a recovery or a beneficial effect of medical interventions and healthcare system stabilization. Over the entire period from 2008 to 2023, the overall trend remained upward, with a mean APC of 3.0% (95% CI: 0.1%–5.8%, $p < 0.05$), confirming a statistically significant long-term increase in mortality despite short-term fluctuations (Table 1 and 2, Fig. 1). These results highlight not only the capability of joinpoint regression to detect clinically and epidemiologically relevant inflection points, but also the necessity of contextualizing these shifts in

light of the social, political, and healthcare-related events that have contributed to their emergence. Joinpoint regression has a broad and complex range of applications, particularly in identifying critical time points in disease progression. In clinical studies, certain diseases may follow a slow and gradual course, yet may exhibit sudden shifts or trend reversals due to factors such as therapeutic interventions, the onset of complications, or underlying biological mechanisms.

Detection of Inflection Points in Biomarker Trajectories

Joinpoint regression is particularly valuable in identifying time points at which the trajectory of a biomarker undergoes a significant change in trend. For instance, in a longitudinal study tracking the evolution of glycated haemoglobin (HbA1c) levels in patients with type 2 diabetes, a change point may be observed following the initiation of treatment with a novel antidiabetic agent. The application of Joinpoint regression enables precise delineation of such phases, providing critical insights for treatment personalization and for assessing the effectiveness of the intervention [15].

Comparison with Linear Mixed Models

Linear mixed models (LMMs) are widely used in the analysis of longitudinal data, offering flexibility in modelling both fixed and random effects. However, in the presence of abrupt changes in trend, LMMs may prove inadequate without the explicit incorporation of change points. Joinpoint regression provides an alternative or a complementary approach by identifying such shifts without relying on rigid assumptions regarding the variance structure. As such, the two methods can be used synergistically: LMMs offer a global perspective on variability, while joinpoint regression pinpoints the temporal locations where interpretive adjustments are warranted [16].

Modeling Time-to-Event Data Using

Joinpoint Regression

Time-to-event analysis such as time to death, recurrence, complication, or remission represents a fundamental component of medical research. Survival models, particularly the Cox proportional hazards model, are widely employed to estimate the hazard function, which reflects the instantaneous event rate over time. However, these models typically assume that risk evolves according to a continuous or log-linear function. Joinpoint regression provides a valuable alternative by allowing the hazard function to be modelled as a segmented structure, thereby highlighting distinct periods with significantly different risk profiles [16, 17]. Joint modelling of longitudinal data and time-to-event outcomes has been developed to address the need for simultaneously incorporating information on the temporal evolution of a biomarker and the risk of an associated event. This approach offers the advantage of linking the latent processes underlying disease progression with the timing of event occurrence, thereby reducing estimation errors and maximizing the utility of available information [18].

The standard framework consists of two components: a longitudinal submodel (e.g., a linear mixed model describing glycaemic evolution) and a survival submodel (e.g., a Cox model) that conditions the hazard function on the predicted value of the biomarker at a given time point [19]. The integration of joinpoint regression into these models enables more refined detection of trend changes in the biomarker trajectory, with a direct impact on risk estimation [20, 21].

Incorporating change points into the longitudinal model enables the identification of distinct phases in the evolution of a biomarker or clinical state. These points may serve as early predictors of disease progression and can be included as latent variables within the risk estimation model for event occurrence.

Joint modelling with joinpoint allows for the capture of such nonlinear and time-varying effects, enhancing the accuracy and interpretability of dynamic risk assessments.

An emerging direction is the application of joinpoint regression in the analysis of multi-omic data (including genomic, transcriptomic, proteomic datasets, etc.) and in the real-time monitoring of patients via wearable devices or mobile health applications. The automated detection of significant changes in a patient's biological profile may enable proactive medical interventions, paving the way toward personalized and predictive medicine. In such

CONCLUSIONS

Joinpoint regression has proven to be a vital tool for the analysis of temporal medical data, enabling the identification of significant changes in the evolution of clinical and epidemiological parameters. Through its ability to delineate inflection points, the method facilitates a deeper understanding of treatment effects, public health policies, and population-level risk behaviours.

The application of joinpoint regression

contexts, joinpoint regression can serve as an anomaly detection module for continuous clinical data streams.

To fully harness the potential of joinpoint regression, future research should explore methods for its automatic integration into real-time clinical data pipelines, the development of hybrid models incorporating neural networks, and the expansion of its applications in omics and continuous monitoring environments. Furthermore, standardization of implementation and validation procedures across diverse clinical settings is essential to ensure robustness and reproducibility.

in medical research provides a more refined approach to longitudinal analysis, with direct implications for the planning of therapeutic strategies and public health interventions. Its use in clinical trials, biomarker monitoring, and joint modelling opens new avenues for advancing data-driven personalized medicine. Moreover, its applicability to complex survey designs and its potential integration with modern machine learning techniques suggest substantial opportunities for interdisciplinary development.

CONFLICT OF INTEREST AND FUNDING

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