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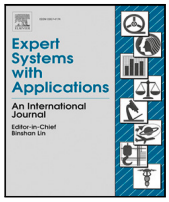

A prediction framework for pharmaceutical drug consumption using short time-series

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ABSTRACT

The increasing pharmaceutical expenditure in many countries has raised concerns regarding the sustainability of healthcare services. To address this issue, accurate forecasting of pharmaceutical demand is crucial for healthcare planning and policy development. This paper proposes a novel prediction framework that integrates different types of historical data and simulates a part of the generative process that produces pharmaceutical consumption, considering both exogenous and endogenous factors, such as per capita consumption trends and population dynamics. The output of the framework is a distribution of likely values, enabling the use not only of the central value for making a prediction but also of the explicitly stated uncertainty, which is crucial for decision-makers in such a critical and complex context. The reliability and consistency of the framework are ensured through backtesting and comparing the predicted results with actual data.

1. Introduction

Over the last few years, pharmaceutical expenditure have significantly increased in many countries (Rodwin, Fabre, & Ayoub, 2018). While some initiatives have been implemented to control pharmaceutical expenditure, various factors such as ageing populations, patient expectations, and the introduction of innovative and expensive drugs have increased the budget devoted to medications (Godman et al., 2018). Pharmaceutical needs and medication consumption forecasting play a key role in healthcare planning, especially in relation to economic analyses and decision-making processes (Azadeh, Saberi, & Jiryaei, 2012; Poyraz & Gürhanlı, 2020). Thus, the ability to forecast pharmaceutical demand could guarantee a supply of medicines aligned with patients' health needs (Pall, Gauthier, Auer, & Mowaswes, 2023). Consequently, forecasting pharmaceutical consumption could inform policy development (Rémuzat et al., 2013) allows a proper resource allocation by providing insights into future status, also highlighting demographic shifts and disease burdens (Pall et al., 2023), and assists all private and public stakeholders in the healthcare supply chain in taking more informed decisions, minimizing costs, reducing delivery lead-time, embracing environmental sustainability principles, and enhancing supply chain resilience (Abdolazimi, Salehi Esfandarani, Salehi, Shishebori, & Shakhsi-Niaei, 2023; Roman & Bertolotti, 2023).

In the last 40 years, the development of information technology has enabled the easy storage and retrieval of huge amounts of data, allowing predictive analytics, data-driven business intelligence, and artificial intelligence (AI)-based decision support systems to become widely diffused, also for supporting pharmaceutical forecasting (Pramanik et al., 2020), leading to higher efficiency of healthcare processes (Davenport & Kalakota, 2019), which is a crucial issue for policymakers (Nikolopoulos, Patrikakis, & Lin, 2004). The ease of making predictions in this domain in the contemporary era, in contrast to the period when computer science had not yet achieved widespread commercialization, should not be mistaken for a general ease in prediction-making. Predicting pharmaceutical needs is also necessary to address challenges derived from the sector's endogenous complexity, such as the variability of medication demand, regulatory problems, and co-operation issues among supply chain stakeholders (Albu, Precup, & Teban, 2021; Fildes & Goodwin, 2021). In the healthcare context, it is also important to underline the fact that the process of forecasting, considering both budgeting generation and medication use, is based on the historical consumption evaluation, an approach that undermines the sector complexity. Furthermore, exogenous elements, such as seasonality, epidemic diseases, the drugs' patents expiration, the new surgical procedures or innovative drugs introduction, could impact on the market share of competitive products, or on the marketing conditions, significantly affecting pharmaceutical demand forecasting by modifying historical consumption (Candan, Fatih Taskin, & Yazgan,

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2014). Finally, the approval process and associated timelines for new drugs entering the market have a high level of uncertainty, as well as technological constraints related to data collection make the available data not always robust or reliable (Merkuryeva, Valberga, & Smirnov, 2019).

This study proposes a novel prediction framework for identifying the future pharmaceutical consumption of a single active agent in a specific medication area. The underlying idea is to not only analyze the previous time-series, considering historical information as the basis of the analysis, but also to simulate the generative process that underlies the behavior of the system components, taking into consideration that pharmaceutical consumption arises from both exogenous and endogenous factors (Bilal & Oyedele, 2020; Hanh, Chen, & Van Hop, 2022; Zhang et al., 2021). Consequently, it is not feasible or realistic to provide a single value as a result, especially since the model is supposed to be used by healthcare decision-makers. The framework starts from historical data and provides a probability distribution for next-year consumption. This could help manufacturers adjust their production, thereby avoiding supply shortages and overproduction (Lin & Hatcher, 1989). Additionally, it could support stakeholders and healthcare professionals to order the correct amount of active agents and prevent stockouts and inefficiencies.

Although the proposed methodology is intrinsically simple, it is relevant compared to state-of-the-art methodologies for two reasons. First, it permits to perform predictions even with short time series, whereas the typical methodologies require a significant amount of data, and associates to each prediction an uncertainty. Second, owing to the sensitivity of the topic, it ensures the explainability of the results to policymakers. This method could be considered as a grey-box approach (Obermann & Waack, 2015), where data-driven forecasts are combined with an explicit representation of the functional dependencies between different parts of the system that are relevant to demand generation (Aielli et al., 2016), including population dynamics, pathology prevalence, and annual drug consumption per patient.

The reliability and consistency of the forecasting methodology were assessed with back testing, generating a prediction regarding a moment when data were available, and then comparing the actual data with the prediction, both in terms of absolute deviation and data likelihood. This back-test was performed on data taken from each of the 21 Italian regions for three relevant and different active agents.

The remainder of this paper is organized as follows. Section 2 presents the main work in this field. In Section 3, the methodology is presented, considering the difference between the proposed prediction technique and the data collection process. The results are presented in Section 4. Finally, Section 5 presents the main conclusions of this study and possible future developments and implications.

2. Related works

Several studies have highlighted the importance of accurate forecasting of medications' consumption and its impact on the healthcare industry (Ganapathy et al., 2022), also to correctly define the pharmaceutical expenditure. Precise prediction of medications' consumption allows the optimization of supply, ensuring that the right number of products and services are available to patients and medical staff when needed (Makenova, Tuleubayeva, Issayeva, & Daurenbekova, 2020; Yang, Lee, & Chang, 2023), and it helps avoiding underestimation and overestimation of purchase volumes at the same time (Ghousi, Mehrani, Momeni, & Anjomshoaa, 2012; Liang, 2022; Sakeena, Bennett, Carter, & McLachlan, 2019). Moreover, a correct foresight could enable healthcare providers and hospitals, who are trying to increase their cost effectiveness (Leal, Manetti, & Buchanan, 2018), to purchase the required drugs at advantageous prices, thereby avoiding more expensive out-of-tender purchases and taking advantages of economies of scale (Chen et al., 2022; Edussuriya et al., 2020).

Nevertheless, forecasting the pharmaceutical demand is a complex process due to the peculiar nature of the healthcare market, which can be impacted by regulatory changes, shifts in disease prevalence, and subjected to the introduction of new and innovative drugs. To address these challenges, various forecasting techniques have been employed, including regression analysis, time-series analysis, and machine learning techniques (Xie et al., 2022).

Linear regression is a popular statistical technique used in drug demand forecasting to model the relationship between environmental variables and perform predictions trough extrapolation (Zhao & Tu, 2021). This method assumes that the relationship between variables is linear, which may not always true in the pharmaceutical industry (Tang, 2022). Time-series analysis is a powerful tool for predicting future trends (Wu, Wang, & Wu, 2022), particularly within the healthcare setting to define the better drugs' consumption prediction (Lenglet et al., 2022). By analyzing past data on drug consumption, such as search queries and sales figures over time, time-series analysis could help forecast future trend in medications' usage. A popular approach for time-series analysis of drug consumption prediction is the utilization of Vector Autoregressive (VAR) models (Lim, Kim, Park, & Kwon, 2021). VAR models enable the analysis of multiple time-series variables simultaneously (Reyes, de Souza, & de Oliveira, 2022), making them suitable for the complex nature of drug consumption prediction. Using VAR models, past data on drug consumption can be leveraged to make accurate predictions regarding future trends in drug usage (Shalini & Mohan, 2018). Moreover, time-series analysis tends to ignore the underlying process that generates the data, and can be sometimes misleading to use to predict future states of complex and non-trivial markets (Gustriansyah, Ermatita, & Rini, 2022)

In recent years, machine learning techniques have gained attention owing to their capability to handle elaborate nonlinear relationships between variables and generate more accurate forecasts (Božić & Stojanović, 2011). They play a crucial role in predicting drugs' consumption (Pall et al., 2023). Various techniques, including Decision Trees (Ghousi et al., 2012), Random Forest (Yani & Aamer, 2023), Naïve Bayes (Crosier, Borodovsky, Mateu-Gelabert, & Guarino, 2017), Support Vector Machines (SVM) (Battineni, Chintalapudi, & Amenta, 2019), and Gaussian process regression (GPR) (Li, Jiang, Pan, Li, & Xu, 2021), have been employed for predict medications' consumption and other variables necessary to take pharmaceutical-related decisions. These techniques have applications in drug discovery, personalized medicine, and clinical decision-making, empowered by the abundance of data (Karatas, Eriskin, Deveci, Pamucar, & Garg, 2022). In the healthcare context by analyzing extensive amounts of data on past pharmaceutical sales and patient demographics, machine-learning algorithms can accurately forecast future demand (Intarapak, Supapakorn, & Vuthipongse, 2022). Oppositely, GPR is gaining popularity when only few data are available, due to its effectiveness in handling small datasets and providing uncertainty estimations for predictions (Srinivas, Krause, Kakade, & Seeger, 2012).

These machine learning methods enable real-time monitoring and adjustment of forecasts based on variables, such as market trends, regulatory changes, and seasonal fluctuations (Pall et al., 2023; Poyraz & Gürhanlı, 2020; Rathipriya, Abdul Rahman, Dhamodharavadhani, Meero, & Yoganandan, 2023). Rathipriya et al. (2023) present a demand forecasting model for time-series pharmaceutical data, employing both shallow and deep neural network models, demonstrating that the last one has a better performance in that peculiar setting. Pall et al. (2023) presents the analysis of historical drug shortage data from 22 Canadian reports, to build machine learning models that can predict drug shortages with a 69% accuracy rate. Also, a recent study compared the performance of different prediction methodologies such as linear regression, Gaussian process estimation, SMOreg, Multilayer Perceptron, M5P, and Random Forest (Poyraz & Gürhanlı, 2020). Their results show that the two approaches outperform the others (where the

performance is measured with mean absolute percentage error - MAPE), namely Gaussian process estimation and linear regression.

Although machine learning algorithms have achieved remarkable success in various applications, one of the main concerns with these techniques is their black-box nature (Bhatt et al., 2020; Sachan, Almaghrabi, Yang, & Xu, 2021). This implies that it could be difficult or impossible to understand the path followed by these algorithms to reach their final decision (Ahn, Kim, Park, & Cho, 2020; McCoy, Brenna, Chen, Vold, & Das, 2022), particularly in cases where the models are highly complex. This lack of transparency poses significant challenges in ensuring accountability and trustworthiness, especially in sensitive domains (Kolyshkina & Simoff, 2021), such as healthcare (Vellido, 2020). As a result, there is an increasing interest in developing explainable machine learning techniques that could provide insights into the underlying decision-making process of these models (Bhatt et al., 2020).

Explainable forecast could be achieved by "white-box" models that make prediction simulation the underlying generative processes, such as random walk. Random walk is a mathematical technique used to model systems that presents a random behavior (Freitas & Junior, 2023). It can be applied to forecast future status of a system of which there is at least an observable variable, assuming that past values contain most of the information required to forecast future behaviors (Sitte & Sitte, 2002). It has various application in healthcare sector (Jain, Rao, Jain, & Hu, 2023). For medications' consumption, random walks could be used by analyzing historical patterns and variability, projecting them forward, but at the best of authors' knowledge they were never used for such a purpose. However, the success rate of random walk techniques in forecasting could be improved by combining them with replication techniques to increase the likelihood of obtaining relevant information (Buturac, 2021). Replicating the simulation of a time series by a random walk and studying its final distribution means applying a methodology called "Monte Carlo" simulation (Bertolotti & Roman, 2022; Khan & Sheikh, 2023; Zhao, Ma, Li, & Zhang, 2023). Monte Carlo is a technique that uses repeated random sampling to obtain numerical solutions (Yeganeh, Chukhrova, Johannssen, & Fotuhi, 2023), with a wide variety of applications (Lawal & Teh, 2023), including healthcare related applications (Pereira, Ferreira, Figueira, & Marques, 2021). Published evidence presents the implementation of a one-way Monte Carlo simulation to forecast the medications consumption by modeling the behavior of individual consumers and predicting overall demand based on simulated outcomes, considering factors such as demographics, marketing efforts, and changes in drug policy (Kosmidis & Dassios, 2019).

3. Materials and methods

The methodology section is divided into four parts. In the first one the prediction framework is described. Then, the validation process employed is presented. Later, the implementation is depicted. Finally, the limitations of the study are explained.

3.1. Prediction methodology

The temporal length of pharmaceutical consumption datasets is often limited, presenting significant challenges for the application of advanced forecasting algorithms such as N-BEATS (Oreshkin, Carpov, Chapados, & Bengio, 2019), N-HiTS (Challu et al., 2023), PatchTST (Nie, Nguyen, Sinthong, & Kalagnanam, 2022), and Smoothed-CNN (Wibawa et al., 2022), which necessitate extensive historical data to fine-tune their predictive capacities. This scarcity of longitudinal data exacerbates the difficulty inherent in producing reliable forecasts from sparse datasets. To mitigate this, we propose a methodological shift towards the synthesis of time-series data through partial emulation of the generative mechanisms that govern the observed phenomena. This simulation-driven approach facilitates the extension of data sequences, thereby augmenting the available information set for model training and validation (Bertolotti, Locoro, & Mari, 2020). While the methodology is delineated within the context of drug consumption patterns, it bears relevance for a broad spectrum of time-series forecasting scenarios.

The framework delineates a quintuple-step methodology to model the consumption of active pharmaceutical agents, as illustrated in Figure ***1***. Initially, it involves the simulation of population dynamics to account for demographic shifts over time. Following this, we simulate the prevalence of a proxy pathology to understand disease patterns that precipitate drug consumption. Subsequently, we forecast the cohort of future patients, incorporating epidemiological trends and healthcare access variables. The fourth step entails simulating the annual consumption of active agents per patient, segmented by region, reflecting variations in treatment protocols and healthcare practices. The final step aggregates these simulations to compute the overall consumption of active agents per Region.

The foundational hypothesis posits that the consumption of active pharmaceutical ingredients is multifactorial. Hence, an integrative analysis that independently assesses each determinant is essential for achieving robust predictive accuracy. To this end, we leverage a composite of predictive models—a technique that has garnered substantial validation within the domain of time-series forecasting (Khashei & Bijari, 2010). Prior to the implementation of this multi-step framework, data preprocessing is paramount to refine the inputs for the model, as characterized by the black box schematic referenced in Fig. 2. The preprocessing process consists in the conversion of the number of boxes, which was the unit of measure present in the data, into units of active ingredients was necessary to accurately observe drug consumption. This was made possible by the detailed records of the specific number of boxes distributed to each region by product code and year, along with the corresponding amount of active ingredient per product code.

The constructed framework endeavors to mitigate reliance on a single short time-series, but it maintains a data-driven analytic foundation. Specifically, this framework is contingent upon three distinct data: demographically-oriented data capturing population dynamics, epidemiological data delineating the prevalence of the targeted pathology for the active agent under scrutiny, and pharmaco-utilization data detailing annual consumption metrics per patient. To ensure methodological coherence and analytical precision, it is imperative that data corresponding to each active agent under examination possess uniform geographical and temporal resolution.

Even if it can be modeled in more sophisticated ways (Patrascu, Stancu, & Pop, 2014), for the purpose of this analysis the simulation of the population dynamics was developed using a simple one-equation stock-flow model:

$$p_t = p_{t-1} \times g \tag{1}$$

where p_t is the population level at time t and g a fixed growth (or decrease, when $g < 1$) rate that takes into account birth and death rates, immigration and emigration rates, as well as regional variations in population dynamics. More precisely, since the simulation is employed at the regional level, each population change is accounted in a specified territorial area, without considering the heterogeneity of demographic dynamics throughout different parts of the country (Von Bertalanffy, 1973). A stock-flow model is an adequate tool for simulating population dynamics because it can consider together multiple factors that affect the size and distribution of a population (Sterman, 2001).

The second element of the framework is the prevalence of the pathology, which is typical a critical element of disease forecasting models (Johansson, Reich, Hota, Brownstein, & Santillana, 2016; Kakarla et al., 2023), especially with short time series and no knowledge of the underlying generative phenomena (Mbonyinshuti, Nkurunziza, Niyobuhungiro, & Kayitare, 2021). Within this context, the framework is constructed upon two cardinal assumptions. Initially, it

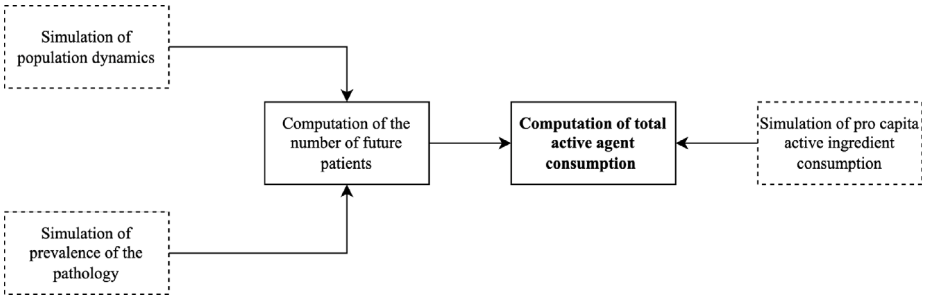

Fig. 1. Process of prediction generation of the proposed framework.

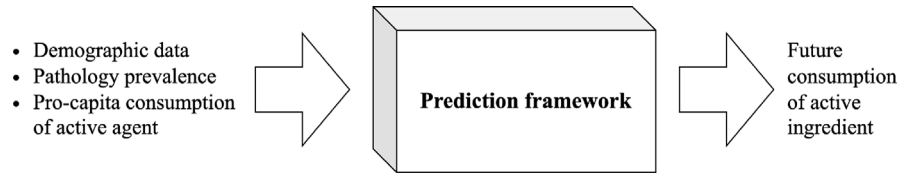

Fig. 2. Black box representation of the input data and output data of the proposed framework.

posits the existence of a linear trend, denoted as α_p, in the pathology's prevalence, with a linear regression model being employed to eschew potential overfitting, due to the limited number of data points. Secondly, it assumes that annual variations in prevalence adhere to a normal distribution, implying that these changes are symmetrically distributed concerning the mean and remain within a bounded range from this central tendency. So, from the time series of prevalence, μ_p and σ_p can then be determined. Under these two assumptions, for each time step a random value i_t can be generated as it follows.

$$i_t \sim \mathcal{N}(\mu_p + \alpha_p \times t, \sigma_p) \tag{2}$$

As delineated in Fig. 1, the estimation of the patient population within the model is quantified as the product of the population size and the prevalence rate of the corresponding proxy pathology. This multiplication yields the simulated number of individuals likely to manifest the condition within the given demographic. Mathematically, it is formalized as

$$pt(t) = pop(t) \times prev(t), \forall t \tag{3}$$

The forecasting model pivots on the simulation of prospective annual per capita consumption of active pharmaceutical agents. Thus, a prerequisite condition for deploying this framework is the availability of comprehensive data pertaining to such consumption metrics. Without this foundational dataset, the application of the forecast model is untenable.

The forecast methodology is tripartite, encompassing three sequential stages of implementation. Initially, the time series is splitted into two sub-series: the first encompassing the entire sample, designated as the A data, and the second comprising the terminal N data points, referred to as the B data.

In the second phase, both subsets of the time series are subjected to linear regression analyses to ascertain the respective trends, denoted as α_A and α_B. Acknowledging that the linear approximation of complex phenomena represents a simplification, this approach was nevertheless selected for its clarity and interpretability. Also, it intentionally eschews the presumption of non-linearity within the underlying generative process, thereby mitigating the risk of over-fitting. The concordance between predicted and observed values was also rigorously evaluated using the Root Mean Squared Error (RMSE), providing a statistical measure of predictive accuracy.

Furthermore, the variability inherent in both models was quantified by calculating the standard deviations σ_A and σ_B of the respective series.

The third stage involves the construction of a random-walk generative model tailored to the consumption patterns of individual active agents, with the purpose of simulating the subsequent state of the system, i.e., the projected future usage. Within this model, the projected value for the forthcoming time step is predicted upon the previously determined trends α_A and α_B, modulated by the variability σ_A and σ_B, and further refined by the discrepancy between the observed data and the linear model as quantified by $RMSE_A$ and $RMSE_B$. Equation 4 formalizes the underlying mechanics of the random walk's progression, while Equation 5 and Equation 6 delineates the stochastic generation mechanism, inherent to each individual step within the model.

$$c_t = c_{t-1} + \beta\varepsilon_{A,t} + (1-\beta)\varepsilon_{B,t} \tag{4}$$

$$\varepsilon_{t,A} \sim \mathcal{N}(\alpha_A, \sigma\gamma) \tag{5}$$

$$\varepsilon_{t,B} \sim \mathcal{N}(\alpha_B, \sigma\gamma) \tag{6}$$

At time t, c_t denotes the per capita consumption of active agents, with β encapsulating the relative weight of recent data in contrast to the complete historical dataset. The random perturbations, analogous to those observed in the prevalence of proxy pathology, follow a normal distribution—characterized by symmetry and a pronounced clustering around the mean within a narrow band demarcated by a few standard deviations. The parameter γ serves a recursive adjustment function, calibrating the synthetic time series such that its corresponding linear model yields a Root Mean Squared Error $RMSE$ congruent with that of the original dataset. The recalibration of γ ensures that the generated series replicates the original data's variability, where the adjusted $RMSE$ is formalized as $RMSE*$, defined as

$$RMSE* = \beta RMSE_A + (1-\beta)RMSE_B \tag{7}$$

Ultimately, to extrapolate the future regional consumption of active agents, the model computes the product of the projected annual consumption per patient and the simulated future patient counts. This multiplication aggregates individual consumption forecasts to a regional scale, thereby yielding an estimation of total active agents usage within the defined geographic domain.

Inherent to each stage of the proposed forecasting framework is an element of stochastic variation, a consequence of the inevitable divergence between model representations and the multifaceted nature of real-world dynamics. The intrinsic error of the models, stemming from this divergence, is encapsulated within the stochastic parameters

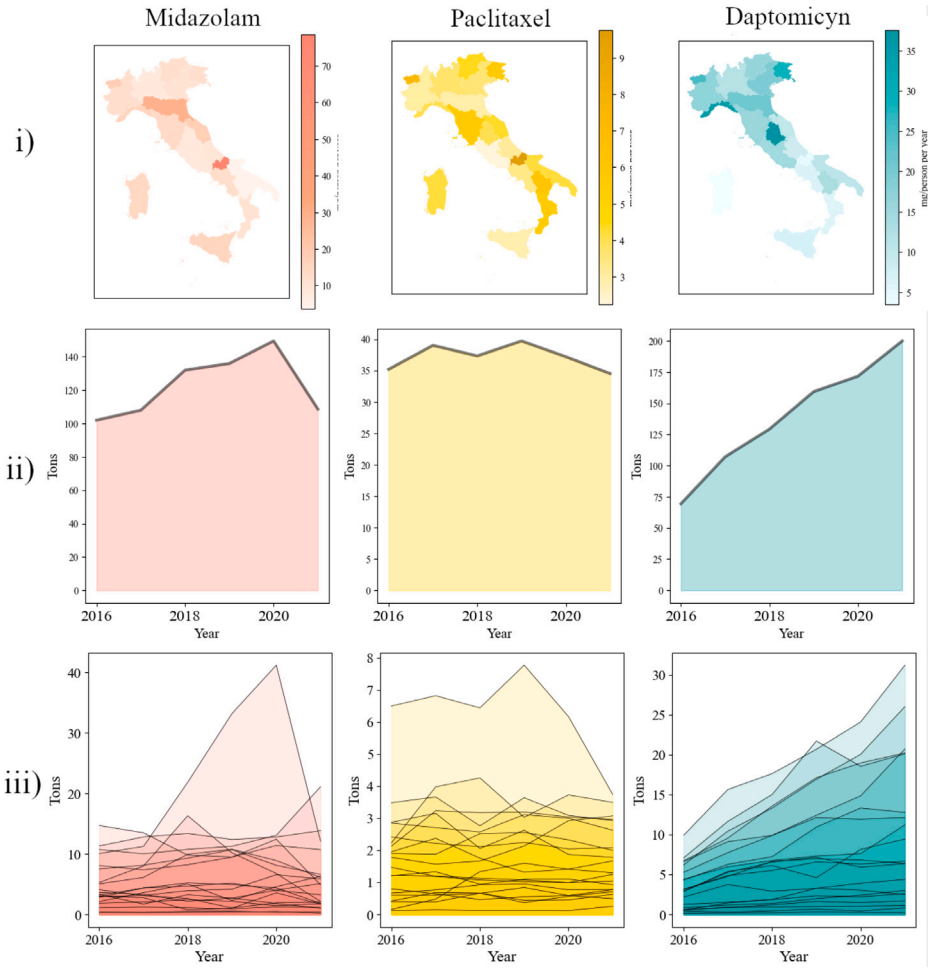

Fig. 3. The validation process is elucidated through graphical illustrations of the employed datasets, collated at a regional granularity to capture the heterogeneity in per capita consumption of the designated active agent across diverse geographical areas, as delineated in subfigure (i). Subfigure (ii) consolidates these data to present a comprehensive time series of total consumption at the national scale. Subfigure (iii) disaggregates this information, delineating the total consumption of the active agent within each individual region, thus providing a granular view of regional consumption patterns. These visual representations serve to contextualize the variability and trends pertinent to the study's scope.

of the generative models employed at each step, as described above. Consequently, every iteration of the framework yields a potential future trajectory; these are inherently imbued with a degree of unreliability due to their genesis from stochastic processes akin to random walks, even if realistic.

The aggregation of multiple iterations, each producing unique outcomes, facilitates the generation of a multitude of potential points in the forecasted future space. Implementing the framework iteratively, an ample number of times – akin to a Monte Carlo simulation – allows for the construction of a frequency distribution derived from the collective outcomes. The use of Monte Carlo simulations within healthcare has been affirmed as a potent tool to underpin clinical decisions and the efficient allocation of resources, a testament to its utility and strategic importance (Briggs et al., 2013; Johnson et al., 2023).

Such a distribution offers a panoramic view of the probable scenarios rather than a monolithic forecast, elucidating the expected values and the associated variance of future demand for active agents within specified regions. Analyzing the statistical properties of this frequency distribution yields insights into the central tendencies and dispersion of forecasted values, thereby enhancing the robustness and reliability of the predictions.

3.2. Validation process

This section describes the approaches used for testing the validity of the results related to the implementation of the suggested methodological approach. The purpose of the validation process was to determine whether the predictions identified by our framework were sufficiently accurate to be relevant for policy makers and practitioners. Additionally, we aimed to assess whether our framework constitutes a significant improvement on the state-of-the-art and is therefore suitable for publication on a scientific venue (see Fig. 3). The test was performed on the Italian scenario, and for guarantee the robustness of the results, it was performed for three active ingredients midazolam, paclitaxel, and daptomycin (see see Fig. 3 for more detail regarding the trends and the geographical distributions of consumption). Midazolam, a benzodiazepine, is commonly used as a sedative, hypnotic, and anxiolytic agent before medical procedures such as surgery or diagnostic tests (SEDATION, 2009). Paclitaxel is a chemotherapeutic medication widely used in the treatment of various cancer types, including ovarian, breast, and lung cancer (Cantu et al., 2002), while Daptomycin is an antibiotic frequently used to combat infections caused by gram-positive bacteria such as Staphylococcus aureus and Enterococcus faecalis (Biziotis, Plessa, Peppas, & Falagas, 2010). The chosen unit of spatial resolution for the analysis was the regional level, thereby necessitating the replication of the analytical process across each unique active agent-region permutation. Consequently, the assessment was iteratively conducted 63 times, corresponding to the total number of active agent-region combinations under investigation.

The selection of this particular triad of active pharmaceutical ingredients (APIs) was rigorously based on a constellation of critical factors. Primarily, these agents are deeply entrenched in clinical practice, offering a broad spectrum of therapeutic applications. Moreover,

their consumption trends have exhibited a remarkable consistency, an attribute largely owing to their current generic status following the expiration of their patents. This strategic choice was further underpinned by comprehensive consultations with an interdisciplinary panel of healthcare professionals, encompassing both clinicians and pharmacists, thereby ensuring an all-encompassing perspective in their selection. These experts, who are eminent within the national healthcare milieu and possess over ten years of practical experience in the pertinent therapeutic domains, provided insights into the usage patterns of the medications in question. These discussions substantiated the assertion that no imminent introduction of novel pharmacological innovations is expected to disrupt the consumption trajectories of these agents in the near future. Documentation of these interviews, encapsulating the expertise of the panel, is available for review, contingent upon justified academic or research requisitions.

The necessary data were collected from different sources. The demographic and the epidemiological data were collected from ISTAT (the Italian Institute of Statistics), while the pharmaceutical data were provided by AIFA (the Italian Pharmaceutical Agency). The demographic data include projections of population change made for different geographical areas, so that a tailor-made projection could be made for each region. The data consist of the expected annual population change, indexed per year. The epidemiological data provide the prevalence in the population of the pathologies associated with each active substance, also indexed per year. Finally, the prevalence was expressed as a proportion of the total population and divided by each active substance. The pharmaceutical dataset records the number of boxes for each specific product code and the active agent contained therein, and therefore covers the consumption each of the three active agents in Italy. All the data were available for each year of the analysis. Details on the datasets utilized are also documented in the supplementary material accompanying this paper. Furthermore, to promote transparency and enable reproducibility, the datasets underpinning the analysis are accessible subject to reasonable academic requests.

In forecast methodology validation, a multitude of methodologies exists to assess the fidelity of predictive models. In the investigation, we leveraged a dual back-testing approach, wherein back-testing is defined as the retrospective application of a predictive model or strategy to historical datasets to appraise its predictive prowess and operational efficacy (Olorunnimbe & Viktor, 2023). For the purpose of this evaluation, the available time series data were partitioned into two distinct subsets: a training set, encompassing the temporal interval from 2016 to 2020, and a test set, constituting the data from the year 2021 (a short time series of 6 points).

To commence the validation, we juxtaposed the actual data from the test set, pertaining to the year 2021, against the predictions proffered by the model for the same year. The congruence of the forecast was quantitatively determined by tallying instances wherein the observed consumption values ($data_{2021}$) fell within the bounds of one standard deviation (σ) from the mean (μ) of the predicted distribution. Specifically, this criterion was satisfied for cases where $\mu - \sigma < data_{2021} < \mu + \sigma$. This approach allowed for a statistical assessment of the model's precision in capturing the central tendency and dispersion of actual consumption metrics.

Subsequently, for each scenario, we evaluated the probability of the observed data materializing, conditional on the outcomes forecasted by the model. This estimation was premised on the probability distribution derived from the simulation outputs, which were presumed to approximate a normal distribution. Under this assumption, the likelihood function was constructed to quantify the plausibility of the actual data points given the specified parameters of the model's predictive distribution.

3.3. Implementation

The implementation was carried out using Python version 3.9.1, supplemented by several specialized libraries to enhance functionality. Specifically, the Pandas 1.5 library was utilized to read and store the data efficiently. For the generation of random numbers and general numerical simulation tasks, the Numpy 1.24.0 library was employed. Lastly, the Matplotlib 3.7.0 library provided the necessary tools for visualizing the results.

The framework was implemented using a Jupyter Notebook within the Visual Studio Code environment. Employing a Jupyter Notebook enabled us to write and test each function individually, as well as the aggregate functions of every phase, in a step-by-step manner. This methodology facilitated the validation of intermediary results, both during development, enhancing ability to troubleshoot throughout the process, and final outcomes generation.

As the code was implemented on a Jupyter notebook, which breaks the whole process down into sub-processes, and tested step-by-step, it was deemed unnecessary to implement complex error handling procedures or exception management.

As the entire simulation process can be completed within a few minutes, the methodology does not require the use of particularly powerful computing resources. A commercially available personal computer is sufficient to run the simulation within a reasonable timeframe. As a result, the methodology is scalable and can accommodate a significantly larger number of regions without requiring more advanced hardware. This scalability ensures that the simulation remains accessible and feasible as the scope of the study expands. As such, the approach could provide a cost-effective solution for large-scale data analysis in diverse geographical contexts.

Similarly, the rapid execution of the code meant that there was no need to focus on algorithmic improvements or performance optimization. The initial efficiency of the code negated the need for such improvements.

3.4. Settings

A Jupyter Notebook was used to set up the validation environment to perform the actions depicted at the end of Section 3.2, which compared two datasets: one containing real data and the other consisting of generated samples from each region. This setup allowed for back-testing by comparing the results against data from the last year of the dataset. All experiments and validation processes were conducted on a MacBook with an Apple M2 Pro processor.

To increase the effectiveness of the validation methodology, the forecasting algorithm was repeated 100,000 times for each drug-region dyad, ensuring a robust statistical framework from which to derive significant results. The high number of iterations underpins the reliability of the data generated and strengthens the integrity of the inferential conclusions. It is important to note that the intention of these simulations was to illustrate the viability of the proposed methodological framework, rather than to optimize empirical congruence; therefore, a fixed value of the only parameter $\beta = 0.25$ was adopted, giving a higher weight (75%) to the most recent biennial data in the forecasting process. Future research may seek to fine-tune the β parameter to improve forecast accuracy under different circumstances.

3.5. Methodology limitations

The methodology delineated herein, while innovative, is not without its limitations, which merit explicit acknowledgment given the high sensitivity of the application domain to the public welfare. The public good is contingent upon the reliability and accuracy of such forecasting techniques, underscoring the importance of a thorough understanding of the method's constraints within the healthcare decision-making milieu. Consequently, a circumspect interpretation of the outcomes is

advised, emphasizing the cautious application of this methodology in policy development and resources allocation.

Firstly, the proposed framework operates under the simplifying assumption of homogeneity within the population, positing that each individual bears an identical susceptibility to the proxy pathology. This assumption is a recognized abstraction, as epidemiological evidence unequivocally demonstrates that the incidence of a particular pathology is not uniform but rather varies with age demographics. Nevertheless, the lack of granular, age-stratified data generally precludes the integration of this heterogeneity into the analysis, and reduce its application range.

Secondly, the framework posits that the dynamics of the selected proxy pathology are representative of all conditions amenable to treatment with the given active agent, albeit with an acknowledged degree of uncertainty. The robustness of this proxy was further corroborated through validation by an expert panel of clinicians, who, via semi-structured interviews, concurred with the assumption that the pharmaceutical market is not anticipating the introduction of novel active principles that could potentially compete with the agent in question.

Thirdly, the temporal scope of the model is intentionally circumscribed to the projection of the ensuing year's data. Given the path-dependent nature of the underlying generative model, skeptics might argue that the prediction of the immediate future constitutes a modest endeavor rather than a significant breakthrough. However, it is important to recognize that this model still represents a substantive progression within the field, predicated on its ability to derive forecasts from a minimal data set. This characteristic is of paramount significance not only to private entities but also to public stakeholders, especially those involved in public procurement and resource allocation, for whom accurate short-term predictions are essential for informed decision-making.

Fourth, the model presupposes that the stochastic fluctuations inherent in the random walk are governed by a normal distribution. Critics might contend that distributions emergent from socio-economic or epidemic processes could exhibit heavier tails or more pronounced kurtosis, leading to a greater incidence of extreme values. However, this concern is somewhat mitigated by the observation that the off-patent generic drugs market dynamics typically do not experience acute month-to-month oscillations, as evidenced by the absence of such extremes also in the 2020 dataset. Consequently, the normality assumption was deemed to be a reasonable approximation for the purpose of this model, although openness to alternative distributions that may better capture the data characteristics is maintained. It may be postulated that these model assumptions could impinge upon forecast precision. Nonetheless, the crux of the matter is not the absolute elimination of error – akin to the philosophical understanding that a map is a simplified representation of the terrain, not the terrain itself – but rather the explicit articulation of underlying premises and the implementation of rigorous, reliable error quantification methods. Such measures are indispensable to unequivocally ascertain, with all other conditions being equal, the dependability of the forecast outcomes.

4. Results of methodology testing

Fig. 4 presents the validation results of the predictive model, delineating the forecasts $P_{i,j}$, where i represents a specific region and j denotes a particular active ingredient, across three sampled regions.[1] Each panel within the figure illustrates four distinct elements: the historical data encompassing active agents' consumption from 2016 to 2020, the recorded consumption for the prediction year 2021, denoted as $c_{i,j}$, the mean value of the model's forecasted consumption for 2021, symbolized as $E[P_{i,j}]$, and the bounds of prediction uncertainty, defined by the interval $[E[P_{i,j}] - SD[P_{i,j}], E[P_{i,j}] + SD[P_{i,j}]]$. The extent of the predictive uncertainty range is directly influenced by the variance observed in the historical consumption data, reflecting the random walk simulation ability, to replicate similar variability patterns in its projections. Moreover, the overall variability within the model encompasses oscillations attributable to other framework components, including population dynamics and epidemiological trends.

In evaluating each prediction within the model, we categorize them based on two dimensions: correctness and uncertainty. Correctness is quantified by determining the percentile of the actual historical data within the predicted distribution $P_{i,j}$. A prediction is deemed more accurate if the actual value is proximal to the median of the predicted values. Conversely, predictions where the historical value's percentile approaches either 0 or 1 are considered less precise. In the framework, a prediction is classified as correct if it falls within the range above the 5th percentile and below the 95th percentile, thereby situating it within the central 90% of the predicted value distribution. Fig. 5 illustrates this correctness distribution, mapping the actual data points against their corresponding percentiles in the predictive distribution.

On the other end, the uncertainty of each prediction is given by

$$u[P_{i,j}] = \frac{SD[P_{i,j}]}{E[P_{i,j}]} \tag{8}$$

which is the ratio between a measure of variability compare to the expected value. In the context of this study, due to the lack of established benchmarks in existing literature, we adopted a provisional threshold of 20% to delineate the boundary of uncertainty in the predictions. This arbitrary but pragmatically chosen figure serves as a critical point of reference in this analysis. As depicted in Fig. 6, we have illustrated both the overall distribution of uncertainty across data set and the specific placement of this 20% threshold, thereby providing a visual and analytical framework for interpreting the extent and implications of predictive uncertainty in the results.

This leads to four classes of results: corrected prediction with low uncertainty, corrected prediction with high uncertainty, incorrect prediction with low uncertainty, and incorrect prediction with high uncertainty. See For a comprehensive understanding of these classifications, Fig. 7 provides a graphical representation, and Table 1 an overview of the numerosity of each occurrence.

Table 1
Number of occurrences of the results for each of the 60 couples region i and active agents j.

	Below 5% percentile	Correct	Above 95% percentile
High uncertainty	6	23	0
Low uncertainty	3	27	1

In the study, we observed that 83.33% of predictions were classified as correct according to predefined criteria, highlighting a significant accuracy rate. However, it is noteworthy that approximately 48.33% of these predictions were associated with high uncertainty, indicating a potential reduction in the reliability of these results. A particularly critical aspect of these findings pertains to the four instances where predictions were incorrect despite being associated with low uncertainty. Detailed analysis revealed two primary factors contributing to this phenomenon. Firstly, two of these instances occurred in Regions with low populations, which implies an highly variable drug consumption patterns that rendered them inherently unpredictable. Secondly, the remaining two instances were both linked to a single Region, which, as corroborated by domain experts and independent data, experienced substantial fluctuations in active agent purchase and consumption between 2020 and 2021 due to the COVID-19 pandemic. Excluding these specific cases, the analysis did not identify any other instances of low uncertainty paired with incorrect predictions, underscoring the general reliability of the framework. In the preceding section, we acknowledged certain limitations of the approach. However, we advocate for its use,

[1] Detailed results are available in the supplementary material. For confidentiality, Regions are anonymized; full data are accessible upon legitimate request.

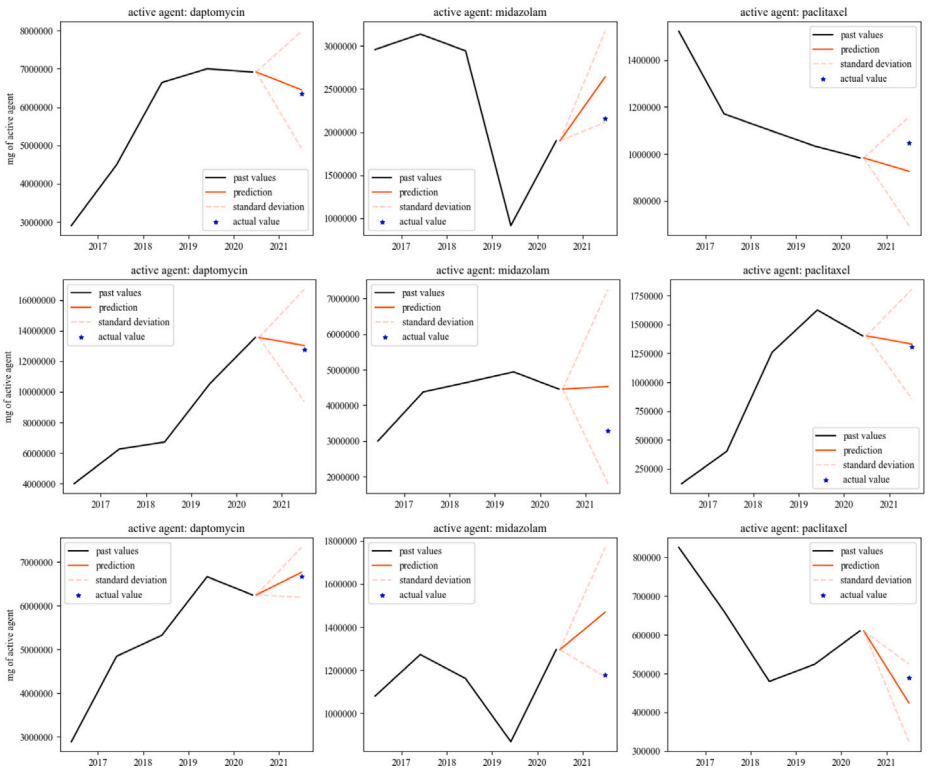

Fig. 4. The results of the back-testing procedure, conducted for three different active pharmaceutical ingredients, considering the 21 Italian Regions (in the figure, represented three of them) are visually encapsulated in a series of graphs. In these graphical representations, the forecasted expected values are indicated by a peach continuous line, symbolizing the central momentum of the distribution, forecasting the predictive model. Accompanying this, the variability inherent in the predictions, represented as the standard deviation, is illustrated by a peach dotted line. These are juxtaposed against the empirical data points, denoted by black stars.

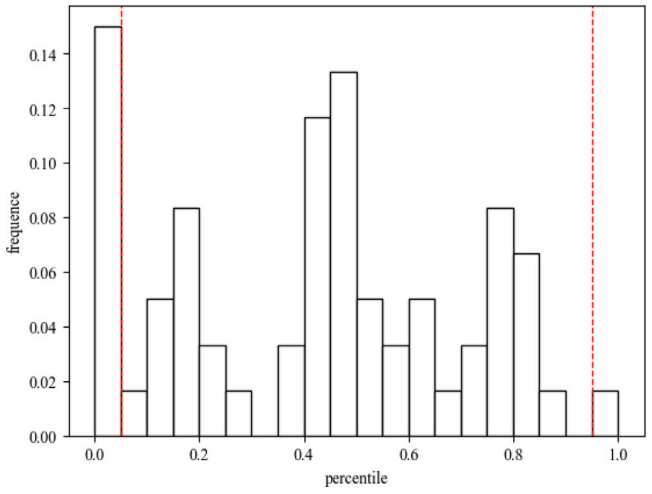

Fig. 5. Distribution of frequency of correctness for each of the 63 couples region i and active agents j.

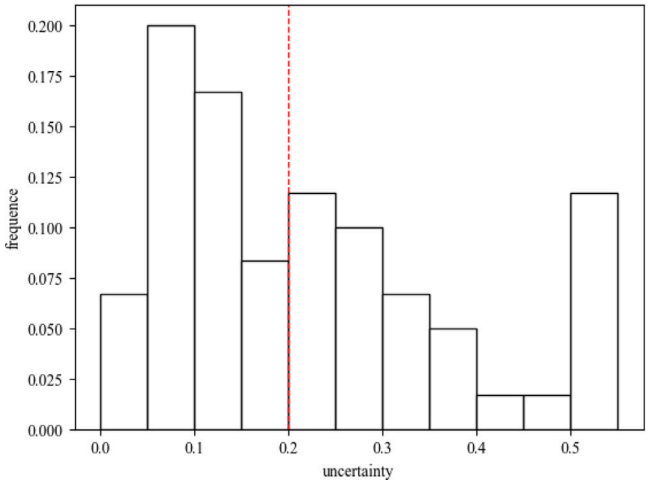

Fig. 6. Distribution of frequency of uncertainty for each of the 60 couples region i and active agents j.

particularly because it effectively incorporates uncertainty measures, enabling us to make predictions and assess their robustness. This finding is crucial, as it confirms that cases of low uncertainty coupled with incorrect predictions are exceptionally rare and typically arise under conditions that are challenging for any data-driven model with limited data points to accurately predict.

In the analysis, the decision to utilize the measure of correctness was primarily driven by its ability to accommodate the probabilistic nature inherent in predictive modeling. This measure effectively captures the likelihood of predictions aligning with observed outcomes, thereby providing a nuanced understanding of predictive accuracy. However, to further enhance the robustness of the analytical framework, we also considered the Mean Percentage Error (MPE) and the Root Mean Square Error ($RMSE$) as additional metrics. These metrics offer a concrete measure of prediction accuracy by quantifying the deviation between the historical consumption data of the active agent, denoted as $c_{i,j}$, and the average predicted results, $P_{i,j}$, calculated respectively as the percentage error $PE[P_{i,j}] = \frac{(E[P_{i,j}]-c_{i,j})}{E[P_{i,j}]}$ that generate the $MPE = \frac{\sum_{i=1}^{n}\sum_{j=1}^{m} PE[P_{i,j}]}{nm}$, and $RMSE = \sqrt{\frac{\sum_{i=1}^{n}\sum_{j=1}^{m}(E[P_{i,j}]-c_{i,j})^2}{nm}}$, where n is the

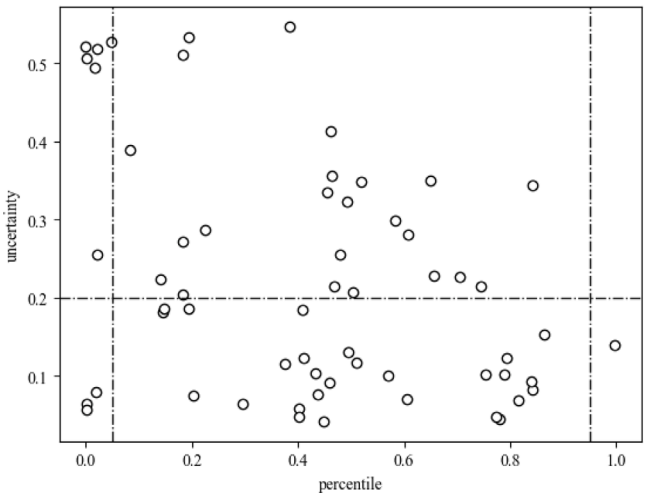

Fig. 7. Joint distribution of correctness and uncertainty for each of the 60 couples region i and active agents j, together with the relative threshold.

number of regions i and m the number of active agents j. These metrics provide a grounded and quantifiable assessment of the prediction accuracy, factoring in both the magnitude and direction of errors. Fig. 8 delineates the frequency distribution of each percentage error $PE[P_{i,j}]$ that compose the MPE and each squared error $SE[P_{i,j}]$ that compose the $RMSE$ across different Regions and active agents, offering a visual representation of the variability and accuracy of the prediction.

The overall results of the MPE associated with each prediction is interesting. Approximately 3 out of 4 predictions have a $PE[P_{i,j}]$ between -0.2 and 0.2, indicating that the central tendency of the predictive distribution closely aligns with the actual outcomes. However deviations do occur, with notable instances where the $PE[P_{i,j}]$ exceeds 0.5. Notably, all such instances are linked to predictions involving Midazolam, an active ingredient extensively used in COVID-19 treatments. This effect is likely attributable to the variable progression of the pandemic between 2020 and 2021, which could naturally lead to significant discrepancies in consumption patterns. Nevertheless, given an average uncertainty for all the results $u[P_{i,j}] = 0.22$, it is observable that $u[P_{i,j}|(PE[P_{i,j}] > 0.5) \wedge (PE[P_{i,j}] < -0.5)] = 0.46$. This elevation in uncertainty for these specific predictions indicates that the model inherently accounts for the increased likelihood of error under these circumstances, thereby reflecting the adaptability and responsiveness of the predictive framework to variable conditions. Finally, the computation of the Root Mean Squared Error yields a value of $RMSE = 6162322.96$ mg, which is 0.043% of the mean actual consumption $E[c_{i,j}] = \frac{\sum_{i=1}^{n}\sum_{j=1}^{m} c_{i,j}}{nm}$. As in the previous instances, the result suggests that even in absolute terms, the performance of the prediction framework was satisfactory. Fig. 8 also shows how this result was obtained due to a single high value.

5. Threats to validity

Based on the limitations of the methodology outlined in Section 3.5, this section discusses potential threats to the validity of the results. This discussion aims both to provide a better understanding of the possible fields of application and the scenarios where the framework might need adjustments or caution in interpretation.

The main threat to validity is the availability and quality of data. The results indicate that the model can make accurate predictions with short time-series. However, it does not address how to handle empty records in the data, which could have a significant impact, especially given the short length of the time-series. For the same reason, even sophisticated imputation mechanisms may not be effective. Furthermore, if the data was not collected correctly from the outset, the framework will not detect this problem (although it may return results with higher uncertainty). As per the GIGO (Garbage In, Garbage Out) principle, it will generate invalid results. Also, as more precise data become available, the framework could be refined to include variations in susceptibility among different demographics.

Secondly, the methodology applies only in cases where the meta-properties of the system that generated the data remain constant during the duration of the time-series and the prediction horizon. For instance, the framework takes into account the eventuality that the population increases or decreases during a given period, or that the incidence of the pathology varies. However, if a structural change occurs, the results will no longer be valid. This may occur, for instance, when there is a notable disruption in the population size or makeup caused by external factors like a natural disaster or war, or a technological advancement that changes the market composition and introduces new drugs or procedures for treating the same condition.

Thirdly, it is worth noting that the time scale of the data may affect the validity of the results. The framework is suited for short time-series and incorporates changes at the population level, such as variations in the number of inhabitants and the incidence of a pathology. It is recommended to observe these values with a sufficiently high temporal granularity to minimize noise and to capture semantically meaningful variations. Variations in the population of a region over ten consecutive days, weeks, or even months may not reveal significant or informative changes. The same issue could arise if the time granularity of the data is too coarse.

The proposed framework is not generally flexible and has not been designed for use in different fields or for long time-series. However, it may still be applicable in other contexts, particularly if the underlying structure is isomorphic, such as the growth of a product's market share. Nonetheless, the validity of the framework in different scenarios cannot be guaranteed without specific testing.

6. Conclusions

In this study, it is presented a novel predictive framework designed to forecast the future consumption of active pharmaceutical ingredients across various Regions. This approach integrates consumption data, demographic statistics, and disease prevalence information, employing random walk simulations to generate future values. The simulations incorporate components derived from stochastic processes, the parameters of which are informed by two distinct linear models from the training dataset. A key advancement of this methodology over existing techniques lies in its ability to yield reliable predictions even with a limited dataset. Additionally, it provides a quantified measure of uncertainty for each prediction, clearly delineating the degree of confidence that can be attributed to these forecasts. To validate the efficacy of this method, we conducted extensive simulations across multiple Italian regions, focusing on three different active agents, back-testing the framework results with the historical data, getting an accuracy of 83.33%. Notably, the model proved to be reliable even when tested against data from 2021, a year marked by unprecedented disruptions in the pharmaceutical industry due to the COVID-19 pandemic (Guerin, Singh-Phulgenda, & Strub-Wourgaft, 2020). This adaptability underscores the potential of the framework to support pharmaceutical expenditure planning and management.

In Italy's unified public procurement procedures, precisely identifying the country's short- to medium-term pharmaceutical needs has become increasingly important, for both economic, as well as planning and control reasons. The intricacy results from the engagement of several parties, as well as the absence of a well-defined objective to be achieved by all the stakeholders, which poses a difficult synergy between demand, consumption and economic amounts, oscillating between central and ministerial logic, and local adaptations and requirements.

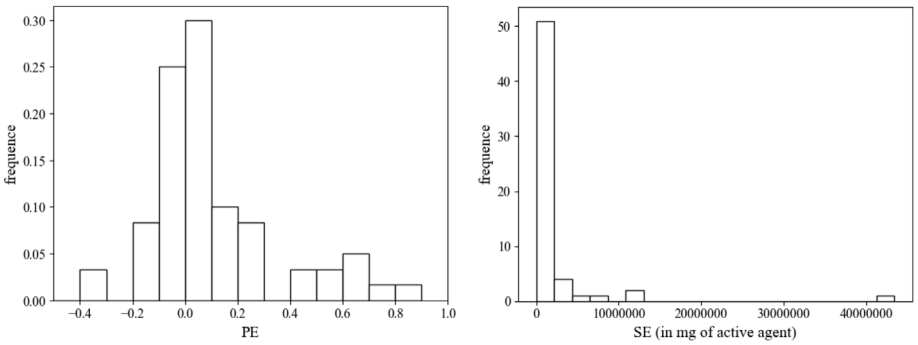

Fig. 8. Distribution of frequency of $PE[P_{i,j}]$, constituting the MPE, (left) and $SE[P_{i,j}]$ constituting the $RMSE$ (right) for each of the 60 couples region i and active agents j.

Moreover, the Italian Public Administration's procurement function has historically been focused more on respecting norms than on system performance measurement and management, with a final impact on internal production processes and caused problems concerning supply quality. Precise quantitative and qualitative requirements assessment is emphasized in the present legislation, factor of relevance to pave the way for an efficient budgeting, particularly for innovative drugs and the fluctuating expenses that go along with them.

One of the most important factors in assessing pharmaceutical demands is the payback mechanism, which is how pharmaceutical companies reimburse themselves for excess spending on direct purchases. For instance, in 2018 there were 2.245,3 million euros in excess spending, and pharmaceutical companies paid back 1.1074,1 million euros.

This case emphasizes the need for the National and Regional Healthcare Services in Italy to give healthcare providers targeted advice, potentially using predictive algorithms for every drug class.

Future expansions of this research are planned to include the use of regional consumption data from 2022, which are currently unavailable, alongside an exploration of additional active agents, to further confirm the goodness of the methodology. This expansion and updating is expected to provide a broader and more robust validation of the predictive model. Further, there exists a potential for the development of an agent-based simulation model, which would delve into understanding the behavioral dynamics driving the overall patterns of pharmaceutical consumption and supply. Such a model could reveal key insights into the micro-level interactions that cumulatively influence market trends. Additionally, integrating expert knowledge and perceptions into the predictive framework is proposed as a means to potentially enhance its accuracy, as underscored by extant literature on the topic (Constantinou, Fenton, & Neil, 2016). This integration could provide a more nuanced understanding of the healthcare industry. Lastly, incorporating demographic characteristics of geographical areas, such as population size, may also be beneficial. This could serve not only to refine the predictions but also to adjust the associated levels of uncertainty, thereby tailoring the model more closely to the realities of different regions.

CRediT authorship contribution statement

Francesco Bertolotti: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Fabrizio Schettini:** Conceptualization, Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration. **Lucrezia Ferrario:** Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Daniele Bellavia:** Validation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Emanuela Foglia:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used GPT-4 in order to perform a grammar and language readability check. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.eswa.2024.124265.

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