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The complexity of pharmaceutical expenditures across U.S. states

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Understanding the complexity of pharmaceutical expenditures across U.S. states is critical for designing efficient healthcare policies and ensuring equitable drug access. This study applies network-based economic complexity methods to analyze state-level Medicaid drug spending, leveraging Medicaid State Drug Utilization Data (SDUD) from 2018 to 2024. Using Revealed Comparative Advantage (RCA) and the Method of Reflections, we quantify the sophistication of pharmaceutical consumption and identify structural inefficiencies in drug reimbursement policies. Our findings reveal substantial heterogeneity in pharmaceutical complexity across states, with highly diversified markets in states like California and Texas, while others, such as Wyoming and West Virginia, exhibit lower complexity due to restrictive formulary policies and healthcare infrastructure limitations. A 15% decline in network density over the study period suggests consolidation in reimbursement practices, influenced by regulatory interventions and cost-containment strategies. Additionally, Medicaid expansion states show a 20% increase in prescription utilization, particularly for antiviral and mental health medications. Null model comparisons highlight systematic deviations from expected expenditure patterns, with states like Arkansas and Nebraska showing lower-than-expected pharmaceutical embeddedness, whereas Massachusetts and California appear more integrated than network models predict. These findings suggest that state-specific policies, provider behavior, and market dynamics significantly shape pharmaceutical expenditures beyond structural network constraints, as well as they offer significant implications for policymakers and healthcare providers seeking to balance cost efficiency with equitable medication distribution.

The complexity of pharmaceutical expenditures across U.S. states presents a significant challenge for policymakers, healthcare providers, and economists. Prescription drug spending constitutes a major component of healthcare costs, with Medicaid playing a critical role in financing medications for low-income populations. However, pharmaceutical consumption and reimbursement patterns vary substantially across states, influenced by demographic factors, healthcare infrastructure, regulatory policies, and economic conditions. Understanding these variations is essential for designing policies that enhance drug accessibility, optimize Medicaid reimbursements, and ensure cost-effective pharmaceutical distribution and health conditions[1–19]. Medicaid is a joint federal and state program in the United States that provides health insurance coverage to low-income individuals, including families, children, pregnant women, seniors, and people with disabilities. While Medicare is a federally administered program primarily serving individuals aged 65 and older, Medicaid is jointly funded by the federal government and the states, with each state operating its own program within federal guidelines. This decentralized structure allows flexibility to tailor coverage but leads to considerable variation in eligibility, benefits, and drug reimbursement policies across US states.

Despite the growing body of research on healthcare systems as complex networks[20–25], the economic complexity of pharmaceutical expenditures remains underexplored. Understanding how drugs are allocated, marketed, and financially managed is essential, particularly in the face of possible future pandemics and healthcare emergencies. Prior research has explored strategies for optimizing drug distribution through community pharmacies to enhance accessibility and resilience in crisis situations[26]. Additionally, the impact of marketing interventions on the diffusion of new pharmaceutical products has been analyzed using trial-repeat diffusion models, providing insights into both longitudinal marketing effects and cross-sectional between-drug influences[27]. Moreover, historical patterns of pharmaceutical spending in key healthcare sectors, such as non-federal hospitals and clinics in the U.S., offer valuable predictive insights for future expenditure trends[28]. This study builds upon these concepts by examining drug expenditure and distribution dynamics, aiming to contribute to the discussion on efficient pharmaceutical policies and decision-making frameworks.

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Against this background, tools borrowed from social network theory and complex systems can constitute a basis for the analysis of such and many other related phenomena. Generally speaking, a network is a mathematical structure used to model pairwise relationships between entities, consisting of nodes (or vertices) and edges (or links) that connect them. When the elements belong to two different sets and connections occur only between, not within, those sets, the network is referred to as a bipartite network. Network-based frameworks, such as social network theory and complex systems, provide a powerful lens for analyzing diffusion, (economic) complexity, and system-wide interactions of many kinds[29–44]. Research on economic growth and development has highlighted the role of network structures in shaping economic outcomes[45–47]. By modeling trade data as a bipartite network connecting countries to the products they export, it is possible to quantify the complexity of an economy and its development potential through, e.g., the Method of Reflections[48]. This approach has been extended to analyze production patterns across different economic domains, revealing interdependencies between economic complexity, future income growth, and innovation potential[49]. Furthermore, the structure of the "product space" - a network of relatedness between goods - demonstrates that sophisticated products cluster in a densely connected core, whereas simpler products remain on the periphery, influencing economic diversification strategies[31]. Besides the Method of Reflections[31,48], another dominant approach has emerged in the literature, namely the Fitness-Complexity Method (FCM)[50,51]. While both methods analyze bipartite country-product networks, they differ significantly in methodology, interpretation, and predictive power. Mathematically, while the first approach employs an eigenvector decomposition of the country-product matrix, the FCM introduces non-linearity through an iterative fixed-point method that explicitly accounts for capability hierarchies.

Network-based methods have also been applied to other domains, such as health and healthcare[52–54].In pharmaceutical research, for example, the construction of a drug-disease network using machine-readable databases and natural language processing has enabled the identification of potential drug-disease interactions through link prediction methods, opening new possibilities for drug repurposing and medical innovation[55]. A relevant strand of the literature focuses on Medicaid and Medicaid's State Drug Utilization Data (SDUD) to study pharmaceutical utilization and expenditures across U.S. states. Several studies evaluate the effect of policies such as: the drug utilization review (DUR) letter intervention[56], finding that prescribers' behavior changed after the DUR letters were sent out, resulting in a reduction in the average marginal days of drug therapy and drug reimbursement per recipient; the 2014 Affordable Care Act (ACA) Medicaid expansions[57,58], finding that within the first 15 months of expansion, Medicaid-paid prescription utilization increased by 19 percent in expansion states relative to states that did not expand, as well as that the expansion benefited a population with unique needs, and that Medicaid expansion could be a valuable tool in addressing the opioid overdose epidemic; the addition of medical cannabis to their state Prescription Drug Monitoring Programs (PDMPs)[59], with results suggesting that providers may have bias against patients who use cannabis and deny them life-improving medications (like controlled ADHD medication or opioids) on the basis of medical cannabis use; the utilization of preferred pharmacy networks to reduce drug prices in recent prescription drug plans (PDPs)[60], highlighting that Medicare Part D plans with preferred pharmacy networks pay lower retail drug prices, while subsidized enrollees' insensitivity to preferred pharmacy cost-sharing discounts reduces these savings. Comparisons of drug utilization across countries have also been conducted[61], showing wide variations between countries, starting from differences in available drugs, package forms and dosages, as well as the impact of policies such as *Prescrire* on national public pharmaceutical expenditure and consumption[62] and studies related to the average cost of drug development to inform the design of drug-related policies[63].

The present work builds upon the aforementioned body of literature and approaches to provide a novel analysis of pharmaceutical expenditures in the U.S. In our study, we use a bipartite network to model the relationship between U.S. states and the pharmaceutical drugs reimbursed through Medicaid. Each edge in the network represents the expenditure of a specific state on a specific drug, linking states (one set of nodes) to drugs (the other set). Using SDUD, drug spending is examined through a bipartite network representation linking states and pharmaceuticals, capturing variations in specialization and expenditure patterns over time. This representation enables a structured analysis of how drug spending is distributed and specialized across states, capturing the complexity and diversity of Medicaid pharmaceutical consumption through the lens of network theory. The Revealed Comparative Advantage (RCA) framework is employed to assess whether specific states exhibit disproportionate spending on certain drugs, while the Method of Reflections refines measures of pharmaceutical sophistication, revealing differences in expenditure complexity (See Section "Methods")[48]. A network-based approach allows for the quantification of pharmaceutical embeddedness, identifying structural inefficiencies in Medicaid reimbursements and market fragmentation.

The findings reveal substantial heterogeneity in pharmaceutical complexity across U.S. states. States such as California and Texas exhibit diverse pharmaceutical portfolios aligned with national consumption trends, while states like Wyoming and West Virginia display lower complexity, potentially reflecting restrictive formulary policies and limited healthcare infrastructure. The analysis also highlights a 15% decline in network density between 2018 and 2024, suggesting a consolidation in drug reimbursement practices that may be driven by cost-containment strategies and regulatory interventions. Additionally, Medicaid policies appear to shape pharmaceutical spending significantly, with expansion states exhibiting a 20% increase in prescription utilization, particularly in antiviral and mental health medications. However, observed discrepancies between expected and actual pharmaceutical embeddedness indicate that factors beyond network structure, including state-specific policy interventions and provider behavior, play a critical role in shaping expenditure trends. By integrating economic complexity analysis with healthcare policy evaluation, the outlined data-driven framework sheds light on the state-level disparities in drug expenditures. The methodological approach contributes to the broader literature on network-based analyses of economic systems, while the empirical findings offer valuable insights for optimizing Medicaid and, possibly, other reimbursement frameworks, improving drug pricing strategies,

and addressing disparities in medication accessibility. The results can guide policymakers seeking to enhance pharmaceutical affordability and efficiency across U.S. states, highlighting the need for targeted interventions that balance cost containment with equitable access to essential medications.

Results

Preliminary analysis

We conduct a preliminary analysis of the data concerning the pharmaceutical expenditure across U.S. states. Figure 1 presents a choropleth map illustrating the total pharmaceutical expenditures across U.S. states over the period 2018-2024. We specifically focus on total expenditures for understanding the fiscal impact on state budgets and for identifying states with particularly large funding demands, regardless of population size. This perspective can be especially relevant for policy discussions around budget allocation and program sustainability. The color gradient, ranging from black to white, represents increasing levels of expenditure, with darker shades indicating lower spending and lighter shades signifying higher spending. The scale on the right quantifies expenditures is U.S. dollars. The distribution of expenditures highlights significant geographic variations. Beside California and North Carolina that emerge as the states with the highest expenditure, states with the larger pharmaceutical spending are concentrated in the Northeast, Southeast, and parts of the Midwest, where large healthcare demand contribute to elevated drug costs. Conversely, states in the central and western regions, including parts of the Great Plains and Mountain West, exhibit lower expenditures, likely reflecting differing healthcare utilization patterns. For the sake of visualization, Alaska and Hawaii are not included in the map; however, their expenditures are relatively low compared to other states. In Table 1 we presents the 2-digit U.S. State abbreviations along with the extended names, useful for figures readability.

Figure 2 illustrates the evolution of pharmaceutical expenditures across U.S. states over time and reveals a clear upward trend, with notable fluctuations corresponding to major healthcare and economic events. As depicted in the figure, total expenditures exhibit steady growth, with a significant surge beginning in 2020. This sharp increase likely reflects the heightened demand for pharmaceuticals during the COVID-19 pandemic, driven by increased medication prescriptions, emergency treatments, and shifts in healthcare utilization. The subsequent decline observed post-2023 may be attributed to the reduction of emergency-related spending, the expiration of pandemic-era financial support programs, and adjustments in insurance coverage and drug pricing policies.

Figure 3 reports the distribution of drug expenditures, which follows a power-law pattern with a cumulative exponent of approximately $\gamma = 2.72$. This indicates a highly skewed allocation of spending, where a small number of drug categories account for the majority of expenditures, while most transactions involve relatively low amounts. This structure may reflect systemic factors in pharmaceutical markets, including the dominance of high-cost prescription drugs, variations in healthcare policies across states, and differences in population sizes.

In fact, U.S. pharmaceutical expenditures are mainly driven by high-cost biologics, chronic disease therapies, and antiviral treatments, as shown in Fig. 4. The main spending categories include immunomodulators for autoimmune diseases such as Humira and Enbrel, and antiviral therapies for HIV and hepatitis C, such as Biktarvy and Epclusa. Diabetes medications, including insulin analogues and GLP-1 receptor agonists, also

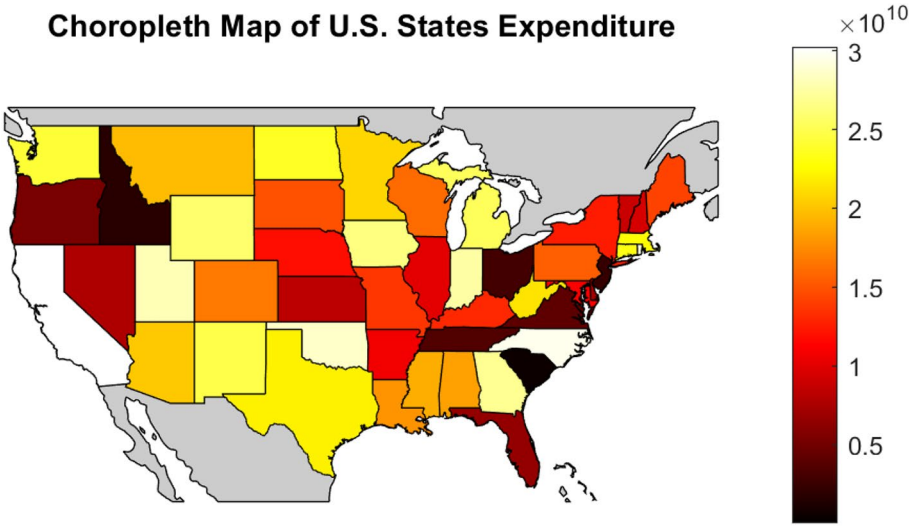

Fig. 1. Geographic distribution of pharmaceutical expenditures across U.S. states. The choropleth map illustrates total state-level pharmaceutical expenditures during the period 2018-2024, with darker shades representing lower spending and lighter shades indicating higher expenditures. California, the state with the highest spending, is depicted in white. States in the Northeast, Southeast, and parts of the Midwest exhibit relatively high expenditures, while lower spending is observed in central and western states. Alaska and Hawaii are excluded for visualization purposes but have relatively low expenditures. The scale on the right represents expenditures in U.S. dollars.

AB	State	AB	State	AB	State
AL	Alabama	AK	Alaska	AZ	Arizona
AR	Arkansas	CA	California	CO	Colorado
CT	Connecticut	DE	Delaware	FL	Florida
GA	Georgia	HI	Hawaii	ID	Idaho
IL	Illinois	IN	Indiana	IA	Iowa
KS	Kansas	KY	Kentucky	LA	Louisiana
ME	Maine	MD	Maryland	MA	Massachusetts
MI	Michigan	MN	Minnesota	MS	Mississippi
MO	Missouri	MT	Montana	NE	Nebraska
NV	Nevada	NH	New Hampshire	NJ	New Jersey
NM	New Mexico	NY	New York	NC	North Carolina
ND	North Dakota	OH	Ohio	OK	Oklahoma
OR	Oregon	PA	Pennsylvania	RI	Rhode Island
SC	South Carolina	SD	South Dakota	TN	Tennessee
TX	Texas	UT	Utah	VT	Vermont
VA	Virginia	WA	Washington	WV	West Virginia
WI	Wisconsin	WY	Wyoming		

Table 1. U.S. State abbreviations and extended names.

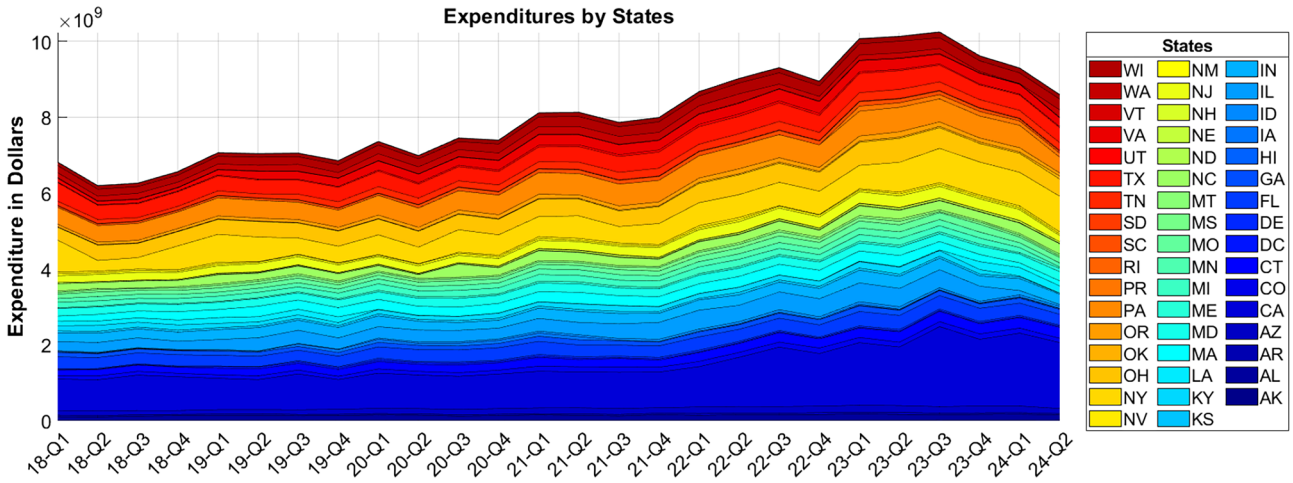

Fig. 2. Quarterly pharmaceutical expenditures across U.S. states (2018–2024). The stacked area plot illustrates the quarterly pharmaceutical expenditures of each U.S. state, with the total area representing aggregate national spending, where the color-coded gradient differentiates between states according to the legend. The overall trend shows a steady increase in spending over time, with a notable surge around 2020 due to the COVID-19 pandemic.

rank high. Respiratory treatments for asthma and COPD, such as Trikafta and ProAir, are costly. Neurological and psychiatric medications, including antipsychotics and opioid addiction treatments, further contribute to spending. The levels of expenditures related to these categories highlight persistent healthcare challenges and the need for policy monitoring and interventions to manage costs while ensuring access to essential medications.

Analysis of the state-drug networks

In what follows, we present the results of the network-based economic complexity method employed to model the dynamics of the state-drug networks (see "Methods" Section). A key metric in this analysis is the total amount reimbursed by Medicaid and non-Medicaid entities for a given drug within a state, serving as a robust measure of drug adoption and expenditure. We represent the total reimbursement as a bipartite network X_{sd}, where each entry denotes the total amount reimbursed by Medicaid and non-Medicaid entities to pharmacies for drug d in state s. We repeat this process for each quarter of the period ranging from 2018-Q1 to 2024-Q2, obtaining a total of 26 adjacency matrices. The network density remains relatively stable over time, with a mean value of $10.49\% \pm 0.49\%$. However, the average expenditure per drug and per U.S. state shows an increasing trend over the observation period. Specifically, the average node strength for U.S. states increases from approximately 140

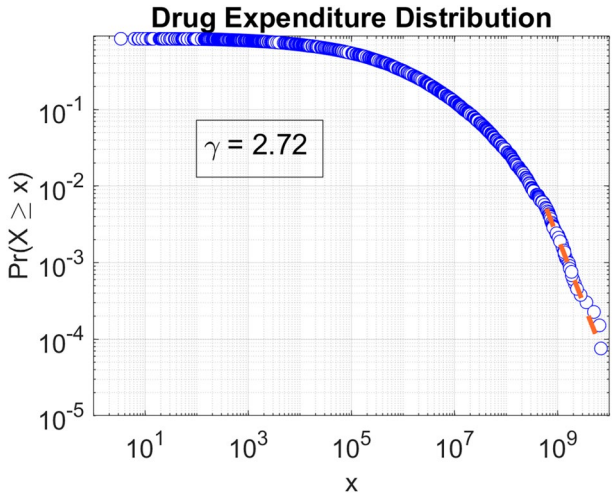

Fig. 3. Cumulative distribution of drug expenditures. The figure shows the cumulative distribution of drug expenditures, which follows a power-law behavior with an estimated exponent of $\gamma = 2.72$. This indicates a heavy-tailed distribution, where a small number of instances account for a disproportionately large share of total expenditure.

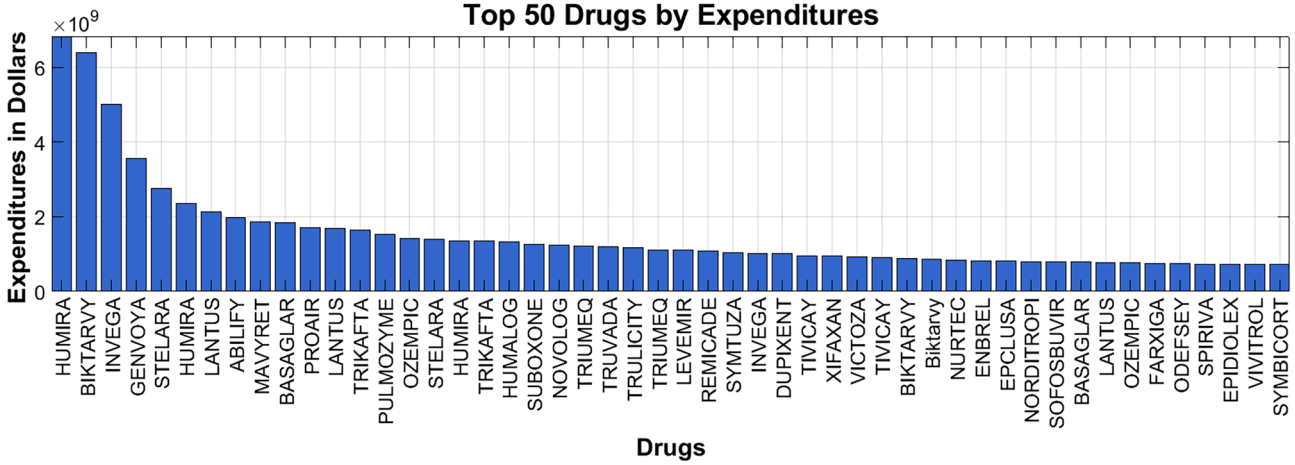

Fig. 4. Bar-plot of the top 50 drugs by expenditure in the U.S. from 2018 to 2024. The bar chart provides a detailed view of total spending on the most costly medications, with expenditures mainly driven by high-cost biologics, chronic disease therapies, and antiviral treatments.

million in 2018 to 165 million in 2024, with a peak of 200 million in 2023. Similarly, the average strength per drug rises from approximately 75, 000 to 100, 000 over the same period.

Using this data, the Revealed Comparative Advantage (RCA) framework identifies whether the state's spending on a particular drug is disproportionately high relative to the overall market share of the drug. This metric helps highlight regional pharmaceutical specialization and consumption trends.

Figure 5 illustrates the evolution of the density of the state-drug network as a function of different RCA thresholds over the period 2018-2024. Network density, defined as the fraction of observed state-drug connections relative to all possible connections, decreases as the RCA threshold increases. This behavior reflects the fact that fewer state-drug pairs meet higher RCA criteria, as stricter thresholds filter out less significant relationships. Color gradients distinguish between different time periods, with earlier quarters (2018–2020) shown in blue tones and later quarters (2021–2024) in yellow tones. Notably, the density of the networks in the earlier quarters is consistently higher across all RCA thresholds compared to the later quarters. This suggests that the number of strong state-drug connections has declined over time, potentially due to shifts in Medicaid reimbursement policies, changing pharmaceutical demand, or evolving market structures. The presence of a dashed vertical line around RCA = 1 marks the threshold at which a state is considered to have a revealed comparative advantage (RCA > 1). This threshold is commonly used, as it indicates that a country acquires a particular drug at a level higher than the average. Beyond this point, the density decline becomes more pronounced, emphasizing that most state-drug connections occur in lower RCA ranges.

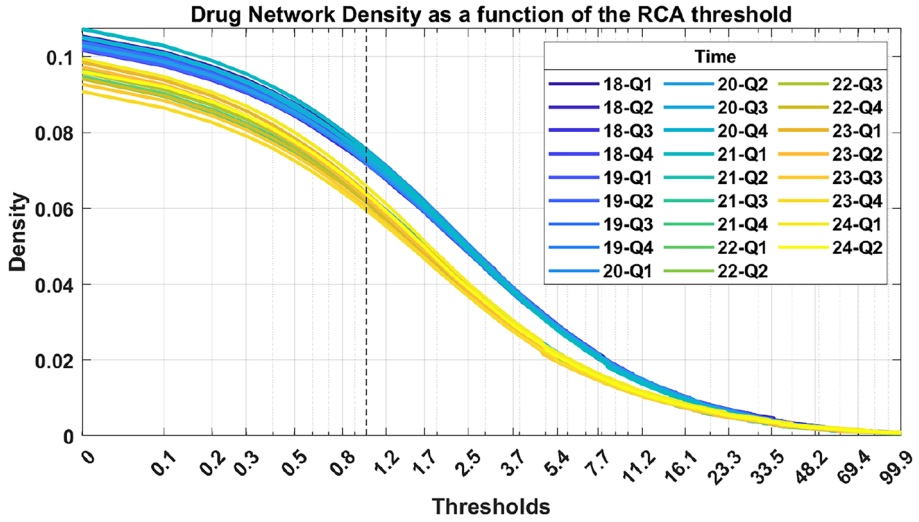

Fig. 5. Drug network density as a function of the RCA threshold from 2018 to 2024. The network density represents the proportion of observed state-drug connections relative to all possible connections, and decreases as the RCA threshold increases. Blue tones correspond to earlier quarters (2018-2020), while yellow tones represent later quarters (2021-2024). The shift in color gradient highlights a decrease in network density over time, suggesting evolving pharmaceutical spending patterns. The dashed vertical line at RCA = 1 indicates the threshold beyond which a state is considered to have a revealed comparative advantage in a given drug.

Definition	Name	Description and interpretation
$k_{s,0}$	Pharmaceutical breadth	Measures the pharmaceutical diversification of a state
$k_{d,0}$	Drug dispersion	Captures how widely a drug is used across the states
$k_{s,1}$	Pharmaceutical embeddedness	Indicates whether a state consumes commonly used or more specialized drugs
$k_{d,1}$	Drug embeddedness score	Indicates whether a drug is consumed by broadly or narrowly diversified states

Table 2. State-drug complexity metrics obtained through the Method of Reflections.

To examine the complexity of the U.S. state-drug expenditure network, for each time point, we introduce an adjacency matrix M_{sd}. Each entry M_{sd} is set equal to 1 if state s has a revealed comparative advantage in drug d, which occurs when $\mathrm{RCA}_{sd} \geq 1$. Conversely, if $\mathrm{RCA}_{sd} < 1$, then M_{sd} is equal to 0, indicating that the state does not demonstrate a significant specialization in that drug. Across all quarterly snapshots, the binary bipartite network exhibits stable structural properties. The average network density is $11\% \pm 0.35\%$, indicating a sparse yet consistently connected structure. The average degree for drugs is 5.65 ± 0.18, while for U.S. states it is substantially higher at 238.24 ± 48.00, reflecting the broad distribution of drug purchases across states.

The Method of Reflections, applied to the state-drug network expenditure, iteratively refines the economic complexity of states and drugs by leveraging the structure of the bipartite network M_{sd}, capturing the diversification of state pharmaceutical spending and the ubiquity of drug consumption. The first level of the Method of Reflections **(Level-0)** provides fundamental statistics about the structure of the bipartite state-drug network. The first measure, which we define as *Pharmaceutical Breadth*, captures the number of distinct drugs for which a state has a revealed comparative advantage. Formally, this is given by $k_{s,0} = \sum_d M_{sd}$, which quantifies the extent of pharmaceutical diversification within a state. The second fundamental measure at the first level is *Drug Dispersion*, which counts the number of states that have a revealed comparative advantage in a given drug. This is defined as $k_{d,0} = \sum_s M_{sd}$, and provides insight into how widespread the use of a drug is across states. At the second level of reflection (Level-1), the complexity of state-level pharmaceutical consumption and drug ubiquity is further refined. The measure *Pharmaceutical Embeddedness* characterizes a state's reliance on widely or narrowly distributed drugs and is calculated as $k_{s,1} = \frac{1}{k_{s,0}} \sum_d M_{sd} k_{d,0}$.. This value represents the average dispersion of the drugs consumed by a state, indicating whether a state predominantly consumes common or specialized drugs. Conversely, the measure *Drug Embeddedness Score* evaluates the average pharmaceutical breadth of states that primarily consume a given drug, and is given by $k_{d,1} = \frac{1}{k_{d,0}} \sum_s M_{sd} k_{s,0}$. This measure helps to identify drugs that are predominantly utilized in states with extensive pharmaceutical diversity versus those that are concentrated in less diversified pharmaceutical landscapes. Table 2 provides an intuition on the network measures used for the analysis.

Figure 6 presents the survival distributions for the four key pharmaceutical network metrics derived from the first two levels of the Method of Reflections applied to the state-drug expenditure network. Across all

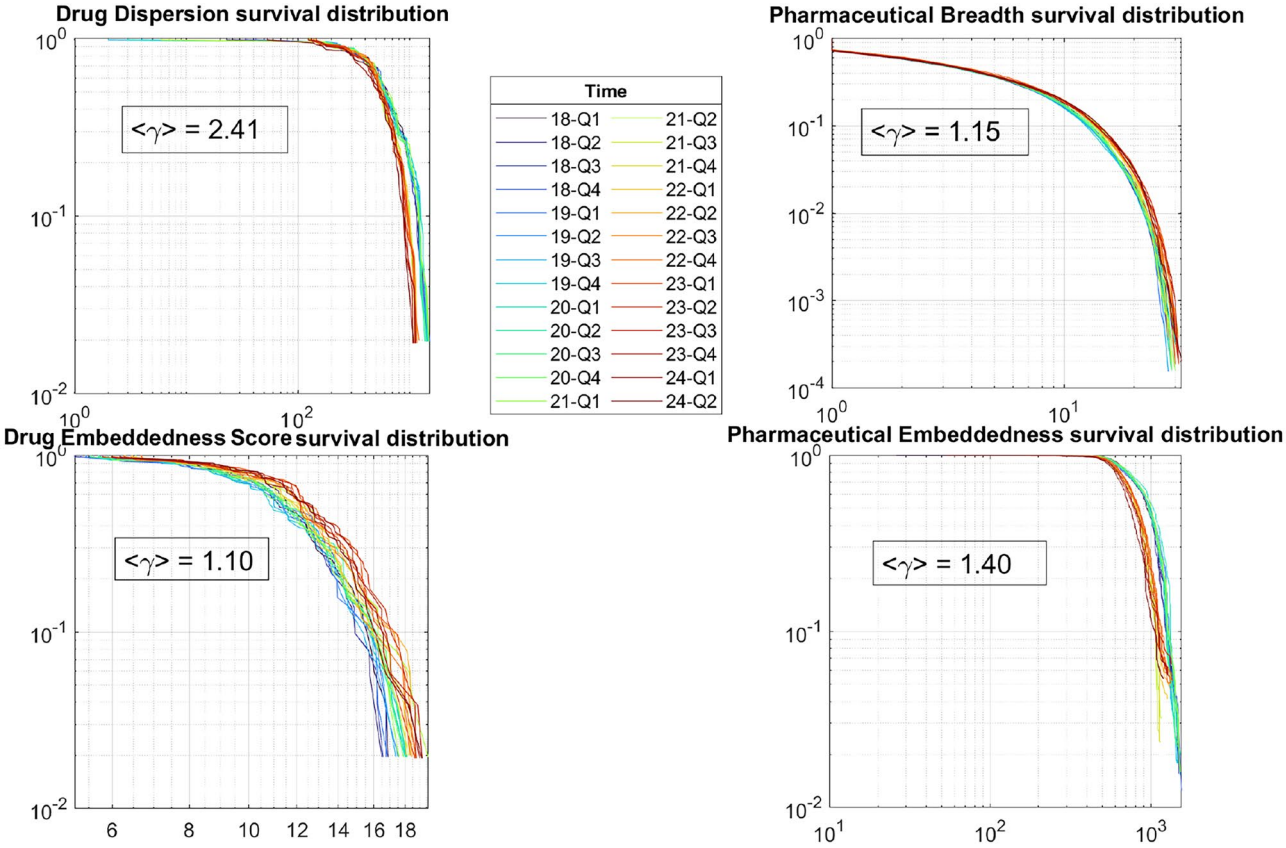

Fig. 6. Survival distributions of four key pharmaceutical network metrics derived from the first two levels of the Method of Reflections applied to the state-drug expenditure network. The Drug Dispersion (top left) quantifies the extent to which drugs are reimbursed across states, while the Pharmaceutical Breadth (top right) measures the diversity of drugs in which states exhibit significant spending specialization. The Drug Embeddedness Score (bottom left) captures how distinct a drug's demand is across states, and the Pharmaceutical Embeddedness (bottom right) reflects the extent to which a state's pharmaceutical portfolio aligns with the broader drug market structure. Each plot reports the survival distribution of the respective measure over time, with earlier quarters (2018-2020) in blue tones and later quarters (2021-2024) in red and orange. The average power-law exponent for each distribution is reported in the inset of each box, highlighting the underlying scaling behavior of each metric.

distributions, the earlier quarters (2018-2020) are shown in blue tones, while later quarters (2021-2024) are depicted in red and orange. Differences over time suggest a shift in the pharmaceutical expenditure landscape, potentially driven by changes in drug availability, policy interventions, or market trends. The Drug Dispersion (top left) measures how widely a drug is reimbursed across states. The survival distribution exhibits a heavy tail with an average power-law exponent of 2.41, indicating that while most drugs are reimbursed in a limited number of states, a few are widely distributed. The Pharmaceutical Breadth (top right) captures the number of drugs in which states exhibit significant spending specialization. The survival distribution follows a power law with an exponent of 1.15, suggesting that while most states specialize in a small set of drugs, some exhibit broader pharmaceutical spending patterns. The Drug Embeddedness Score (bottom left) measures the average pharmaceutical breadth of states that primarily consume a given drug. A power-law exponent of 1.10 suggests that most drugs are concentrated in states with low pharmaceutical diversification, but a few are embedded in states with broad pharmaceutical portfolios. The Pharmaceutical Embeddedness (bottom right) measures the extent to which a state's pharmaceutical portfolio aligns with the broader drug market structure. The survival distribution follows a power law with an exponent of 1.40, indicating a hierarchical structure where most states have a moderate level of pharmaceutical integration, but some are highly embedded in the network.

Figure 7 illustrates the number of times that states and drugs enter the top 15 rankings based on the two levels of the Method of Reflections applied to pharmaceutical expenditures. The top-left panel presents the Pharmaceutical Breadth measure, which captures the diversity of a state's pharmaceutical spending. States such as California, Alabama, and Wisconsin appear frequently in the top rankings, indicating a wide range of pharmaceutical expenditures. This suggests that these states have diverse healthcare needs, large populations, or highly complex pharmaceutical markets. The top-right panel shows the Pharmaceutical Embeddedness measure, which identifies states whose pharmaceutical spending patterns align with national consumption trends. States such as Arkansas, North Dakota, and Alaska exhibit the highest rankings, suggesting that their

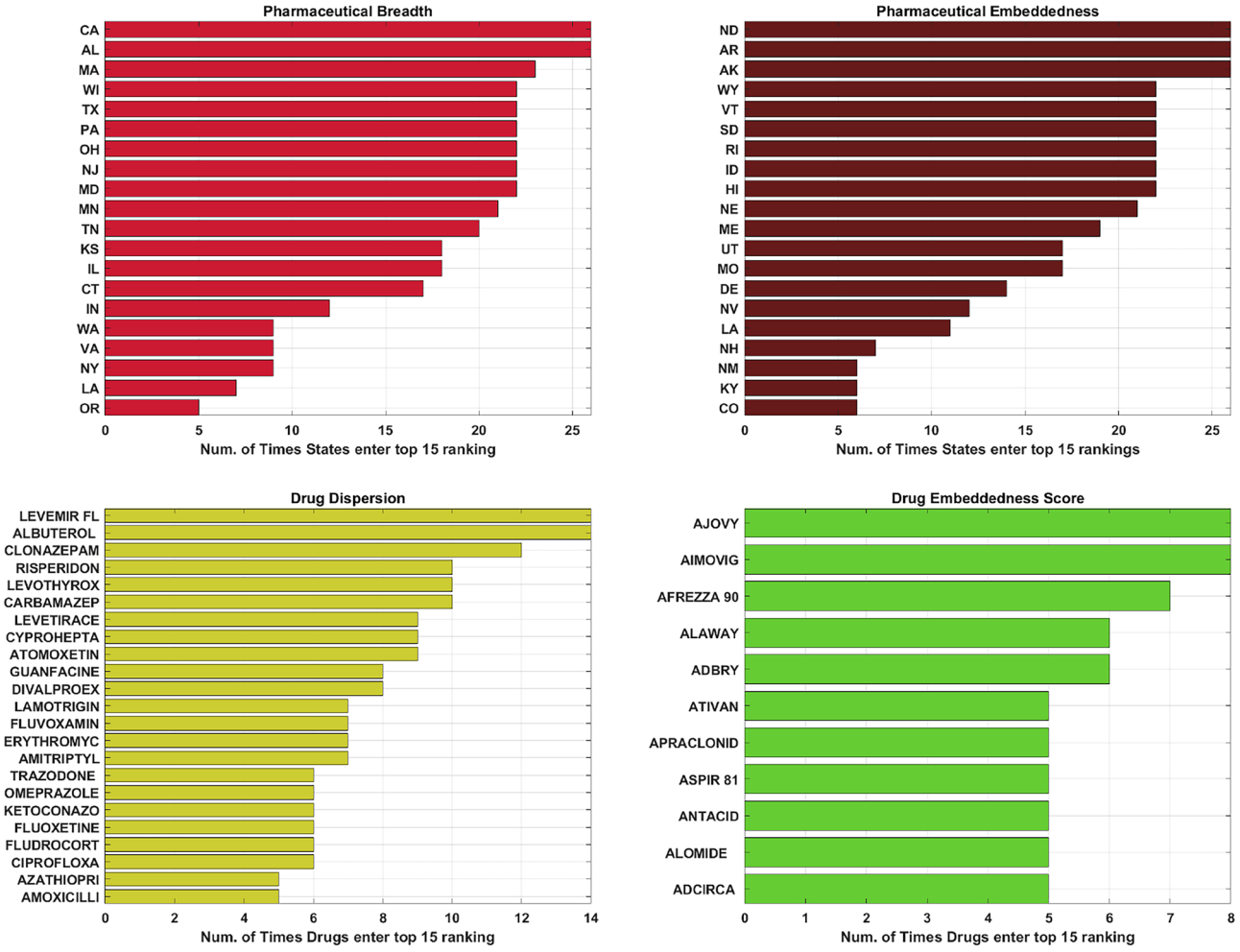

Fig. 7. Frequency of states and drugs entering the top-15 rankings based on the first two levels of the Method of Reflections applied to pharmaceutical expenditures. The top-left panel (Pharmaceutical Breadth) measures the diversity of a state's pharmaceutical spending, with higher values indicating broader expenditures across different drugs. The top-right panel (Pharmaceutical Embeddedness) captures how well a state's pharmaceutical expenditures align with national consumption patterns. The bottom-left panel (Drug Dispersion) identifies drugs that are widely reimbursed across multiple states, reflecting their centrality in pharmaceutical demand. The bottom-right panel (Drug Embeddedness Score) measures whether a drug is predominantly consumed in states with broad or narrow pharmaceutical portfolios, indicating whether its usage is concentrated in highly diversified versus less diversified state markets.

pharmaceutical purchases reflect the overall structure of drug expenditures in the U.S.. These states, rather than demonstrating unique patterns, appear to be well-integrated into the broader pharmaceutical market. The bottom-left panel examines Drug Dispersion, highlighting the number of times individual drugs enter the top 15 rankings based on their widespread use across states. Drugs such as Albuterol, Levemir, and Clonazepam exhibit high rankings, suggesting that they are commonly reimbursed across multiple states. These drugs are widely prescribed for respiratory conditions, diabetes management, and neurological disorders, respectively, indicating their centrality in pharmaceutical demand. The bottom-right panel presents the Drug Embeddedness Score, which identifies drugs that are predominantly consumed in states with broad or narrow pharmaceutical portfolios. Medications such as AJOVY, AIMOVIG, and AFREZZA rank among the most embedded in highly diversified states, implying that they are more commonly reimbursed in states with broad pharmaceutical markets rather than being concentrated in just a few locations. This pattern may be influenced by state-level healthcare policies, population health characteristics, or differences in insurance coverage. Indeed, recent reviews of state Medicaid formularies and clinical policies confirm that innovative migraine therapies like AJOVY, AIMOVIG, and AFREZZA are widely reimbursed in states with diversified pharmaceutical portfolios. These facts suggest that state-level healthcare policies, alongside differences in population health and insurance coverage, are key factors in ensuring these medications are broadly embedded in the market rather than being concentrated in just a few locations[64].

The changes observed in the regression coefficients (see "Methods" Section) reported in Fig. 8 suggest structural shifts in the underlying pharmaceutical network over time. At the drug level (top panel), the initially

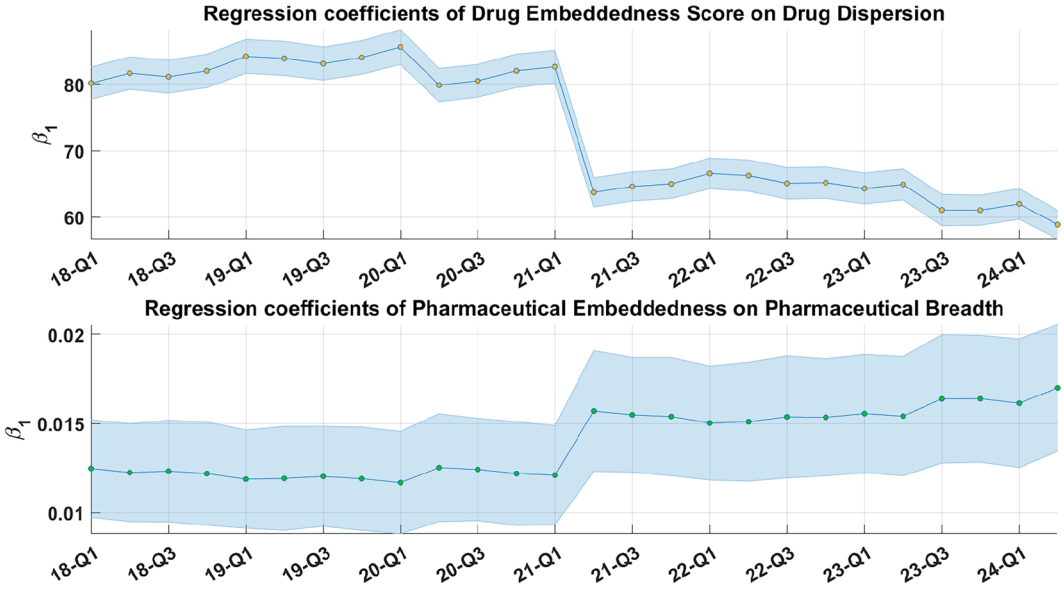

Fig. 8. Time series of the regression coefficients linking level-1 measures to level-0 metrics for both drugs and states. The top panel shows the regression coefficients β_1 of drug embeddedness scores on drug dispersion, showing an initial period of stability followed by a sharp decline in 2020-Q2, suggesting a structural shift in drug distribution patterns. The bottom panel presents the regression coefficients of pharmaceutical embeddedness on pharmaceutical breadth, illustrating a relatively stable relationship until 2020, after which the coefficients increase, indicating a growing influence of embeddedness on the diversity of reimbursed drugs. The shaded regions represent confidence intervals.

high and stable regression coefficients indicate that drugs predominantly consumed in highly diversified states were also more widely dispersed across states. This suggests a well-connected and relatively stable pharmaceutical network where drugs embedded in broad pharmaceutical markets were also widely reimbursed. However, the sharp decline in 2021-Q1 suggests a disruption in this relationship, likely driven by external factors such as supply chain disruptions or shifts in prescribing patterns. This could reflect the impact of the COVID-19 pandemic, which altered drug demand and distribution channels. After 2021, stabilization at a lower coefficient level suggests that the link between the embeddedness of a drug and its dispersion weakened. This could indicate a shift toward a more concentrated pharmaceutical landscape, where highly embedded drugs were no longer as widely reimbursed across states as before. Possible explanations include decreased diversification in drug reimbursement, regulatory changes, or the emergence of new key pharmaceuticals that reshaped spending patterns. At the state level (bottom panel), the relatively low and stable regression coefficients until 2020 indicate that pharmaceutical breadth (the number of distinct drugs reimbursed in a state) had a weak but consistent effect on pharmaceutical embeddedness. This suggests that until 2020, the extent of a state's drug reimbursement diversification had only a limited impact on how closely its pharmaceutical spending aligned with national trends. The increase in coefficients post-2020 suggests that pharmaceutical breadth became a stronger determinant of pharmaceutical embeddedness, meaning that states with a more diverse range of reimbursed drugs increasingly exhibited pharmaceutical spending patterns that reflected national consumption trends.

Figure 9 examines the evolving relationship between Pharmaceutical Breadth (Lev-0, i.e. the number of distinct drugs reimbursed in a state) and Pharmaceutical Embeddedness (Lev-1, i.e. the alignment of a state's pharmaceutical spending with national consumption patterns) over time. Understanding this relationship is crucial to assess how states diversify or consolidate their drug reimbursements and whether they increasingly conform to national pharmaceutical consumption trends. This has important implications for healthcare policy, cost management, and access to medications at the state level. The scatter plots display data for the top nine states in terms of Pharmaceutical Breadth, with each point representing a quarterly observation. Colors indicate different time periods, blue shades correspond to earlier years (closer to 2018), while yellow and red represent more recent periods (up to 2024). A general trend emerges across states: over time, observations tend to shift from high Pharmaceutical Breadth (Lev-0) and low Pharmaceutical Embeddedness (Lev-1) to low Pharmaceutical Breadth and high embeddedness. This suggests that states are reducing the diversity of their reimbursed drugs while increasing their alignment with national consumption patterns. This shift is particularly noticeable in states like PA, TX, and AL, where earlier observations (blue) are concentrated in the lower-right region, indicating high breadth and low embeddedness. In contrast, more recent observations (red) are found in the upper-left region, corresponding to a lower breadth but a higher embeddedness. This suggests a progressive consolidation of drug reimbursement practices, possibly due to cost-containment strategies, regulatory changes, or changes in prescription behaviour. As a matter of fact, evidence highlights that states are implementing cost-containment strategies, such as narrowing formularies and enhancing utilization controls, to manage these expenses[65]. Additionally, the adoption of standardized prior authorization and step therapy protocols has been

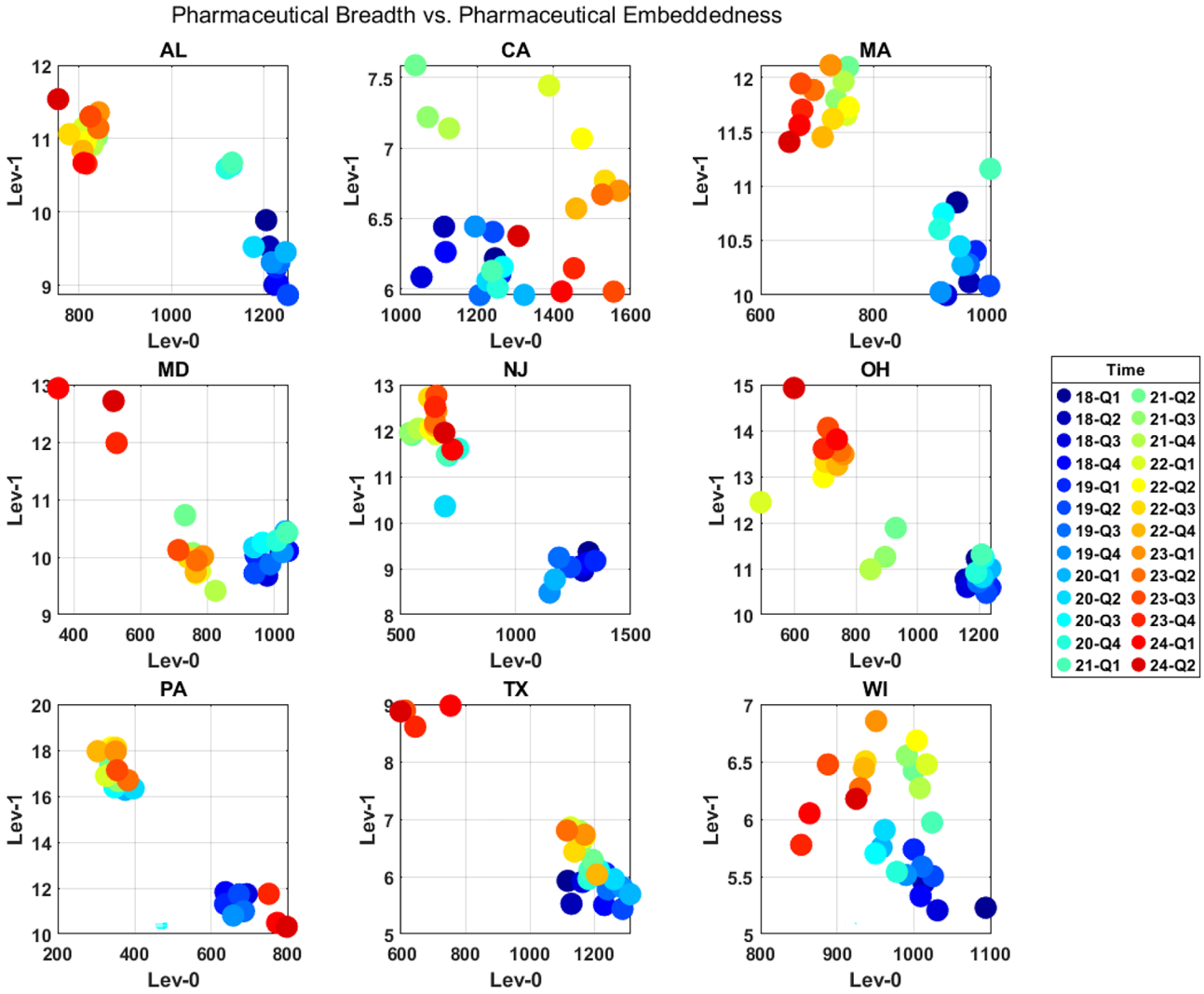

Fig. 9. Evolution of the relationship between pharmaceutical breadth (Lev-1, i.e. the number of distinct drugs reimbursed in a state) and pharmaceutical embeddedness (Lev-0, i.e. the alignment of a state's pharmaceutical spending with national consumption patterns) for the top nine states (reported in the title of each panel) in terms of pharmaceutical breadth. Each circle represents a quarterly observation, with blue colors for earlier years (2018) and red for more recent years (2024). Over time, most states exhibit a shift from high pharmaceutical breadth and low embeddedness (bottom-right) to lower breadth and higher embeddedness (top-left).

shown to reduce drug spending in the short term, although the long-term effects on overall healthcare costs and patient outcomes remain mixed[66].

Figure 10 examines the relationship between Drug Dispersion (Lev-0), which quantifies the number of US states that reimburse a drug, and the Drug Embeddedness Score (Lev-1), which captures the extent to which the reimbursement pattern of a drug aligns with national spending trends. The analysis focuses on the nine most widely reimbursed drugs, tracking their evolution from the first quarter of 2018 (18-Q1) to the second quarter of 2024 (24-Q2). Each scatter plot represents a different drug, with each circle corresponding to a quarterly observation, colored according to time (dark blue for early periods, progressing through lighter shades to red for more recent periods). The general pattern observed varies across drugs, but follows a recurring dynamic. For some drugs, such as Atomoxetine and Levothyroxine, there is a visible downward shift in Lev-1, indicating a lower alignment with national trends. In contrast, drugs such as Risperidone and Clonazepam show more dispersed trajectories, with fluctuations in both dimensions rather than a clear directional shift. Albuterol and Levemir exhibit a more clustered structure, where reimbursement patterns remain relatively stable, but slight decreases in Lev-1 over time suggest a marginal contraction in state coverage. This evolution could reflect multiple factors, including changes in state-level policies, shifts in drug formularies, market dynamics such as generic competition, and broader cost-containment strategies. The divergence in trends between drugs highlights the complexity of pharmaceutical reimbursement, where some drugs remain widely reimbursed while others experience gradual reductions in coverage. These measures suggest a trend towards reduced pharmaceutical

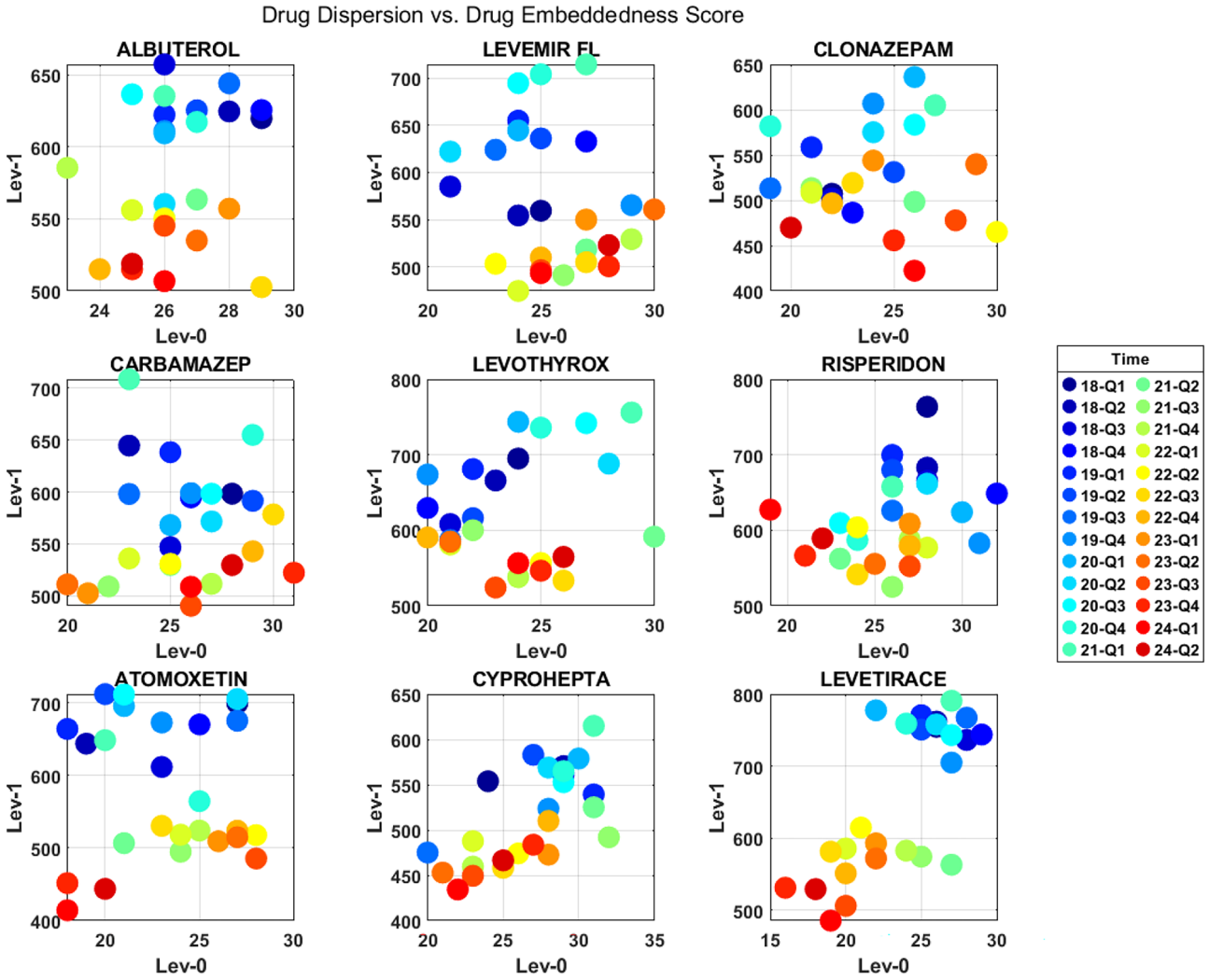

Fig. 10. Evolution of Drug Dispersion (Lev-0) versus Drug Embeddedness Score (Lev-1) for the top nine most widely reimbursed drugs (reported in the title of each panel) across U.S. states from 2018 to 2024. Each point represents a quarterly observation, with colors indicating time (blue for earlier years, red for recent). The general trend shows that while some drugs have a clear contraction in reimbursement coverage (decreasing Lev-1), others exhibit more dispersed or stable patterns.

diversity and increased alignment with national consumption patterns, particularly in states like Pennsylvania, Texas, and Alabama[67].

Quantitative relationship between level-0 and level-1 measures

The modeling and understanding of the structure of the state-drug network is crucial to assess the complexity of pharmaceutical access and spending across U.S. states. The Hidalgo-Hausmann framework[48], originally developed for economic complexity analysis, provides a structured way to quantify the interdependencies between states and drugs by assigning them complexity-based measures. In our framework, Level-0 measures represent the Pharmaceutical Breadth of states and the Drugs Dispersion, capturing how central they are within the network in terms of reimbursement patterns. Level-1 then builds upon this by refining the positioning of states and drugs based on their connections to each other. A key question in this analysis is whether the simpler, first-order network structure (Lev-0) contains enough information to explain the more refined complexity measure (Lev-1) for both drugs and states. If Level-0 alone is highly predictive of Level-1, it suggests that pharmaceutical reimbursement patterns are largely shaped by a state's overall drug portfolio or a drug's overall presence in state spending. However, if there are substantial deviations, it may indicate the influence of additional factors, such as state-specific regulations, formularies, or economic conditions, that are not immediately apparent from the first-order structure of the network. To assess the role of Level-0 in determining Level-1, we construct 1000 null models that simulate alternative versions of the state-drug network while preserving key structural constraints[68–71]. By comparing the observed Level-1 values to those generated under the null model through the z-score, we can determine whether the empirical relationship between such measures is stronger than expected at random.

Figure 11 presents the absolute z-score of discrepancies between the observed and expected pharmaceutical embeddedness across U.S. states, distinguishing between under-estimated (top panel) and over-estimated (bottom panel) cases. The top ten states in each category are highlighted, providing insight into which states exhibit the most significant deviations from the null model. The color gradient within each bar represents different quarters, allowing for an assessment of the temporal evolution of these discrepancies. The states classified as under-estimated, including Arkansas, Idaho, Nebraska, South Dakota, Utah, and West Virginia, display a lower pharmaceutical embeddedness than what the null model predicts. This suggests that these states possess less complex and interconnected pharmaceutical market than expected based on simpler network measures (Level-0). In addition, certain rural states may have specific pharmaceutical programs that reduce access despite relatively high total spending. Moreover, regional market structures, including the presence of major pharmaceutical distributors or state-led negotiations with insurers, may also play a role[72]. The time-based color gradient reveals a gradual increase in the absolute z-score over time in states such as South Dakota and West Virginia, suggesting that their pharmaceutical markets have become progressively less embedded beyond what would be predicted by a simple degree-based measure. Conversely, the states classified

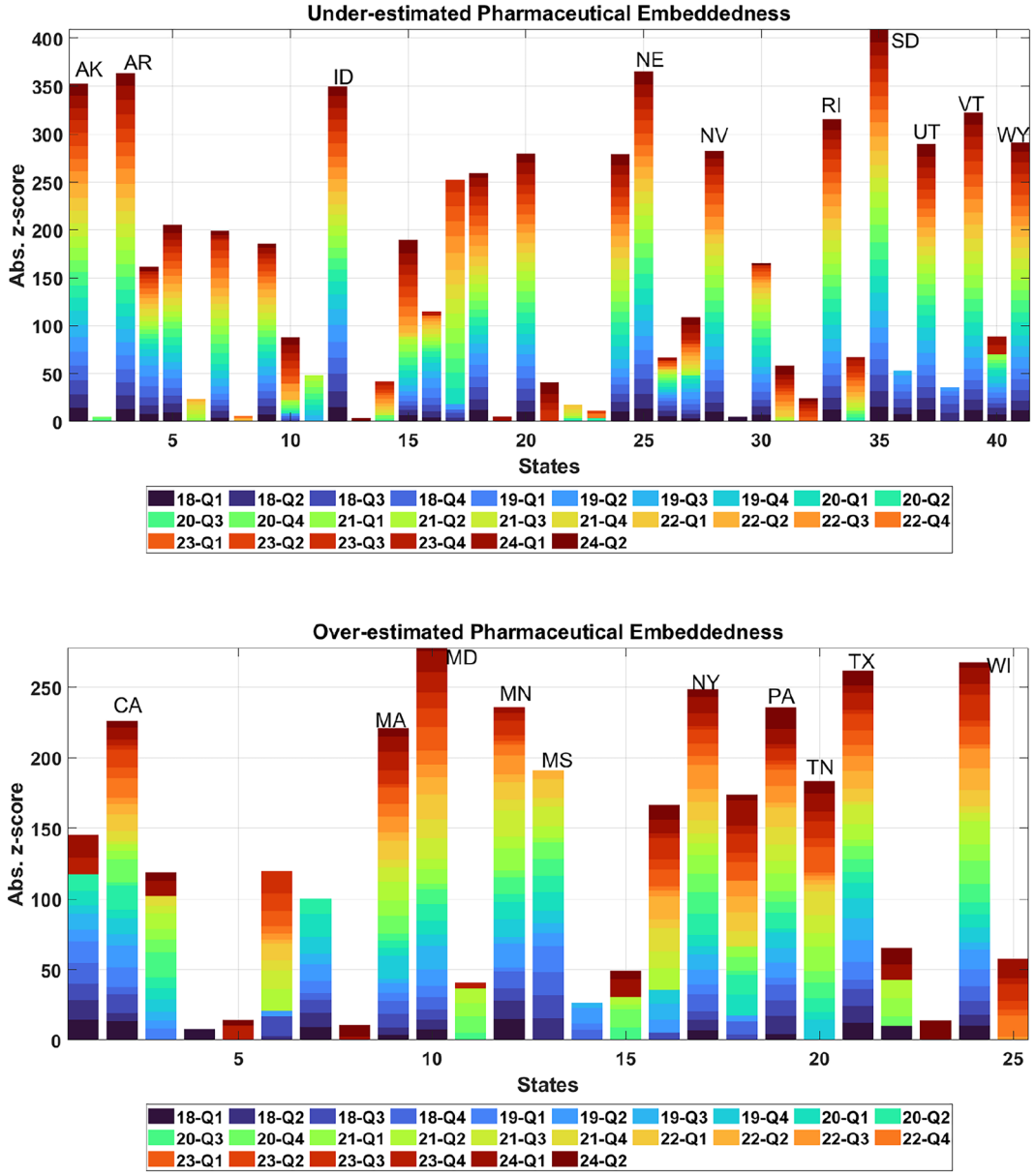

Fig. 11. Absolute z-scores of pharmaceutical embeddedness discrepancies across U.S. states. The top panel shows states where embeddedness is under-estimated by the null model, meaning they exhibit lower-than-expected pharmaceutical integration. The bottom panel displays states where embeddedness is over-estimated, indicating higher-than-expected integration given their pharmaceutical expenditure and distribution. The color gradient within each bar represents different time stamps, illustrating the temporal evolution of these discrepancies. Highlighted state labels indicate the ten most extreme cases in each category.

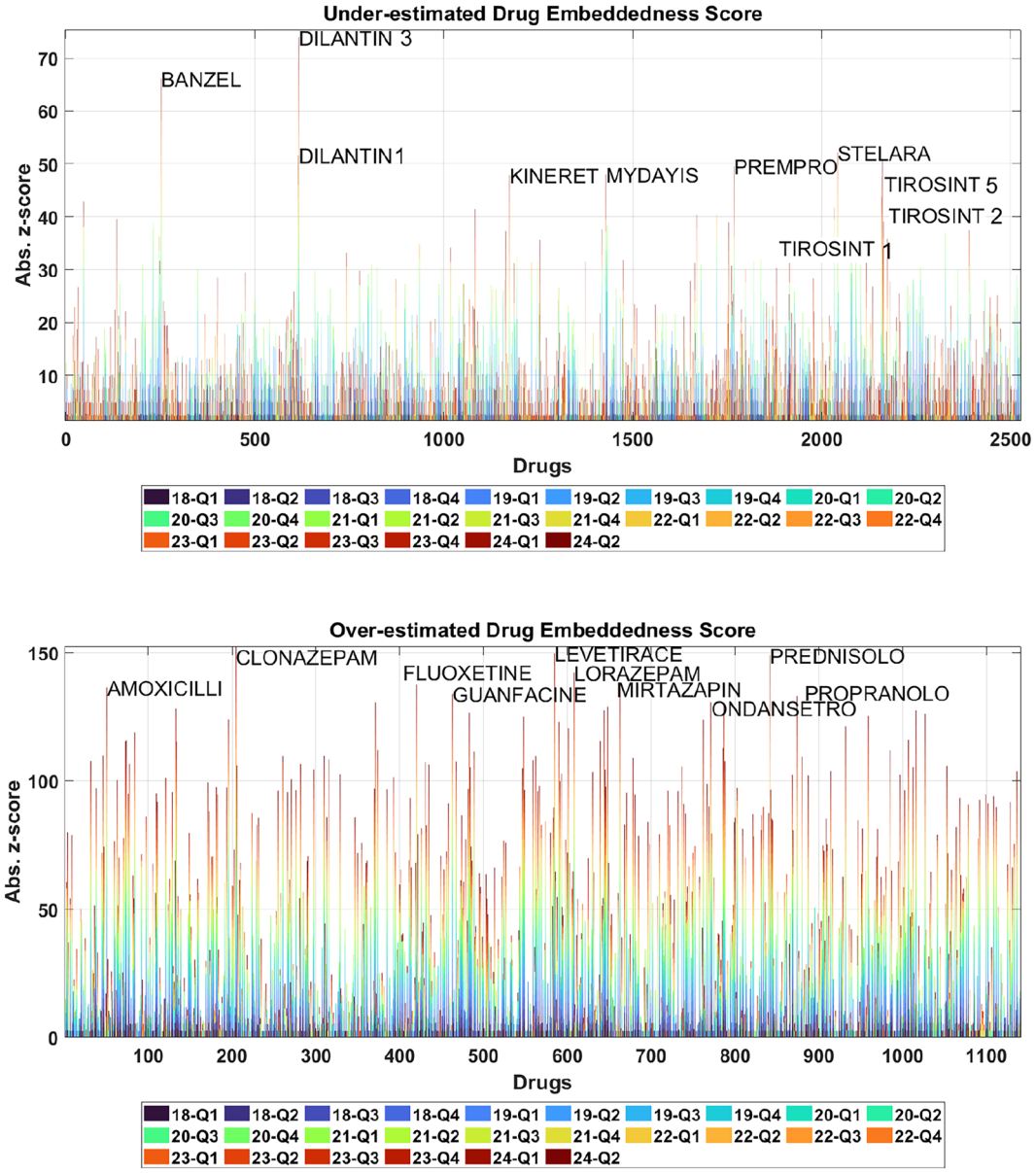

Fig. 12. Absolute z-scores of drug embeddedness discrepancies in the pharmaceutical network. The upper panel displays drugs for which the observed embeddedness is statistically lower than predicted by the null model (under-estimated), indicating weaker integration than expected given their network position. The lower panel highlights drugs whose embeddedness is statistically higher than predicted (over-estimated). The color gradient in the bars represents different time stamps, illustrating the persistence of these discrepancies over time.

as over-estimated, including California, Massachusetts, Maryland, Pennsylvania, and Texas, exhibit higher pharmaceutical embeddedness than the null model suggests. This finding implies that these states have a more integrated pharmaceutical market than anticipated by the Level-0 measure. Several explanations may explain this discrepancy. In states such as Massachusetts and California, which serve as hubs for pharmaceutical research and biotechnology, spending may be directed toward broad pharmaceutical accessibility. The role of managed care and formulary restrictions is also relevant, particularly in states such as Pennsylvania and Texas, where high managed-care penetration may favor pharmaceutical adoption, several factors may contribute to this pattern[73]. The temporal evolution indicates persistent deviations in states like Texas and Massachusetts, suggesting that their pharmaceutical markets have become consistently more embedded than expected based on network degree alone. The results suggest that factors beyond simple network connectivity, such as regulatory policies, healthcare programs, and market specialization, significantly influence pharmaceutical embeddedness across states.

Figure 12 presents the absolute Z-scores for under- and over-estimated drug embeddedness in the pharmaceutical network. The upper panel highlights drugs that are under-estimated by the null model, meaning that their real embeddedness is lower than expected based on simpler network measures (Level-0). This suggests

that these drugs, despite their predicted centrality, exhibit weaker integration into the pharmaceutical network. Drugs such as Dilantin, Banzel, and Stelara may have niche markets or specific prescription constraints that prevent them from achieving the level of connectivity predicted by the null model. For instance, Dilantin (an antiepileptic drug) is an older medication, and its use may be gradually declining in favor of newer alternatives, reducing its network integration. Similarly, Stelara, a biologic for autoimmune diseases, is highly specialized and may be limited to select healthcare providers, restricting its pharmaceutical connectivity despite its clinical importance. The presence of Prempro (a hormone replacement therapy) in this category further underscores the impact of shifting medical guidelines and prescription habits on network structure. The time-based color gradient indicates that these discrepancies have persisted over time, suggesting structural constraints rather than temporary fluctuations. The lower panel displays drugs classified as over-estimated, meaning their real embeddedness is statistically higher than what the null model predicts. This implies that these drugs are more interconnected in the pharmaceutical network than would be expected from simple degree-based measures alone. Drugs such as Amoxicillin, Clonazepam, Fluoxetine, and Ondansetron exhibit a high degree of co-prescription and widespread distribution, leading to greater-than-expected embeddedness. Amoxicillin, as a first-line antibiotic, is prescribed across a vast range of conditions, ensuring a strong network presence. Similarly, Fluoxetine (an SSRI antidepressant) and Clonazepam (a benzodiazepine) are commonly co-prescribed in mental health treatments, reinforcing their pharmaceutical integration. The inclusion of Ondansetron, an anti-nausea medication frequently used in chemotherapy and post-surgical care, highlights how clinical co-utilization strengthens a drug's network positioning. The over-estimation associated to these drugs suggests that network embeddedness is not solely dictated by market size, but also by prescription patterns, therapeutic versatility, and the extent of co-prescription dynamics. The persistence of these deviations over time, as shown by the color gradient, indicates that these drugs have maintained their strong embeddedness, reinforcing their structural importance in the pharmaceutical market.

Discussion

The network-based analysis of pharmaceutical expenditures across U.S. states gives novel insights to analyze the complexity of drug spending, state-level specialization, and systemic inefficiencies. The network framework makes use of the Revealed Comparative Advantage (RCA) and the Method of Reflections, yielding insights on when certain states exhibit disproportionate expenditures on specific drugs, thereby revealing structural imbalances in pharmaceutical accessibility, pricing, and policy effectiveness.

A key finding of this study is the significant variation in pharmaceutical complexity across states. The results indicate that states with high pharmaceutical complexity, such as California, New York, and Texas, tend to have a more diverse portfolio of reimbursed drugs, aligning closely with national consumption patterns. In contrast, states with low complexity, such as Wyoming, South Dakota, and West Virginia, demonstrate a narrower range of expenditures, which may reflect limited healthcare infrastructure, restrictive formulary policies, or economic constraints that affect drug accessibility. This suggests that pharmaceutical expenditures are not solely driven by population size, but also by policy frameworks and healthcare market structures that shape state-level drug reimbursement patterns.

The application of the Method of Reflections reveals systemic patterns in pharmaceutical spending that go beyond simple cost analysis. Our results show that between 2018 and 2024, there has been a 15% decrease in network density, indicating that fewer drugs are meeting high RCA thresholds over time. This decline is particularly evident in states like Pennsylvania and North Carolina, where budget constraints and formulary adjustments have likely reduced the number of drugs with significant spending specialization. The finding that the complexity of a state's pharmaceutical portfolio is increasingly aligning with national trends over time suggests a consolidation in drug reimbursement practices. This may be driven by regulatory changes, market forces, or cost-containment measures that encourage states to standardize their pharmaceutical expenditures. However, this shift also raises concerns about the potential loss of flexibility in addressing state-specific healthcare needs, particularly for populations with unique medical requirements.

The role of Medicaid policies in shaping these spending patterns is particularly important. Our analysis finds that states experienced roughly a 20% increase in prescription utilization, with significant increases in antiviral medications and mental health drugs. This reinforces the need for ongoing assessment of Medicaid reimbursement frameworks to ensure that cost efficiencies do not come at the expense of medication access. For instance, the reduction in network density over time suggests that some drugs may be falling out of favor, potentially due to policy-driven cost-cutting measures or formulary exclusions. This underscores the need for balanced policy approaches that both manage costs and preserve access to essential treatments.

Furthermore, the observed discrepancies between actual and expected pharmaceutical embeddedness highlight the influence of factors beyond network structure alone. The presence of states with over- or under-estimated embeddedness suggests that local market conditions, state-specific healthcare regulations, and providers behavior play crucial roles in shaping pharmaceutical expenditures. For example, Arkansas, Idaho, and Nebraska exhibit lower-than-expected embeddedness, indicating that their pharmaceutical markets are less integrated than predicted by network models. Conversely, states such as California and Massachusetts show significantly higher embeddedness, suggesting stronger integration into the national pharmaceutical market, possibly due to their roles as innovation hubs in biotechnology and healthcare services.

The identification of regional specializations in drug consumption has critical policy implications. For example, the study finds that opioid-related medications and mental health treatments are disproportionately reimbursed in states such as Kentucky and West Virginia, while diabetes treatments, including insulin analogs, dominate expenditures in Mississippi and Alabama. Similarly, biologic and high-cost specialty drugs, such as Humira and Enbrel, account for a large share of spending in California and Massachusetts. These variations suggest that certain states may be experiencing either a greater burden of specific diseases or inefficiencies

in drug procurement and pricing. Understanding these trends can help policymakers design targeted interventions to promote cost-effective drug utilization, negotiate better pricing agreements, and enhance Medicaid reimbursement strategies to reduce unnecessary expenditures. Finally, the insights from this study are also valuable for pharmaceutical companies and healthcare providers. Understanding the complexity and specialization of drug spending at the state level can help optimize market entry strategies, inform pricing policies, and enhance supply chain efficiency. For example, pharmaceutical firms can use these findings to better align drug distribution with regional demand, ensuring that essential medications reach the populations that need them most. The regional disparities in drug spending and utilization revealed in this study call for state-specific policy adjustments. States with high burdens of chronic conditions, such as opioid use or diabetes, may require enhanced Medicaid formulary flexibility to ensure access to critical therapies. Meanwhile, the concentration of high-cost biologics in innovation hubs suggests opportunities for value-based pricing agreements. To address inefficiencies, policymakers should prioritize strategies that improve pharmaceutical market integration in low-embeddedness states while leveraging procurement reforms in high-spending regions. These targeted approaches can help balance cost containment with equitable access to essential treatments.

Methods

Data

The primary dataset employed in this study is Medicaid's State Drug Utilization Data (SDUD), which provides a comprehensive and granular record of drug expenditures across U.S. states (Data is publicly available at: https://www.medicaid.gov/medicaid/prescription-drugs/state-drug-utilization-data/index.html). This dataset is particularly valuable due to its broad coverage and alignment with public healthcare systems, making it a useful source for analyzing state-level drug adoption patterns. Given that Medicaid plays a central role in financing prescription drugs, especially for low-income populations, this dataset allows for an in-depth exploration of state-specific pharmaceutical consumption and reimbursement structures. The SDUD dataset includes detailed transaction-level information, including National Drug Codes (NDCs), units reimbursed, and the total amount reimbursed for each drug at a state level. The dataset spans multiple years, enabling both cross-sectional and longitudinal analyses of prescription drug expenditures. This richness allows for evaluating trends over time, identifying shifts in pharmaceutical policies, and assessing the impact of pricing regulations or new drug introductions.

To ensure data quality and relevance, a series of pre-processing steps are undertaken to remove extraneous or irrelevant entries. One of the primary steps was the exclusion of records where the state label is *XX*, which represents non-state-specific or aggregated data. These entries do not correspond to an individual U.S. state and thus do not contribute to the analysis of state-level economic complexity in drug expenditures. Additionally, entries where the *Units Reimbursed* field is recorded as zero were removed. These instances represent transactions that fall below a meaningful reimbursement threshold, which could introduce noise into the dataset. By filtering out such entries, the analysis remains focused on significant pharmaceutical transactions, ensuring that the derived complexity measures reflect substantive spending patterns rather than administrative anomalies.

The primary variable of interest in this study is the *total amount reimbursed by both Medicaid and non-Medicaid entities* to pharmacies for a given drug within a specified period. This total expenditure figure represents the full amount paid before any Medicaid rebates are applied. It includes both federal and state contributions, as well as dispensing fees associated with drug distribution.

Formally, the total reimbursement for a drug is given as:

$$X_{sd} = \left(\text{Federal Reimbursement}_{sd} + \text{State Reimbursement}_{sd}\right).$$

Mathematically, this network is represented by a weighted bipartite adjacency matrix X_{sd}, where each entry denotes the total amount reimbursed by Medicaid and non-Medicaid entities to pharmacies for drug *d* in state *s*. The reimbursement value includes both federal and state contributions, and accounts for dispensing fees but is not adjusted for Medicaid rebates. This aggregate value provides a measure of drug adoption and expenditure at the state level, serving as a building block to construct the Revealed Comparative Advantage (RCA) metric.

Revealed comparative advantage (RCA)

One way to empirically estimate whether a U.S. state significantly spends on a particular drug is to calculate the RCA. The RCA is a measure designed to determine whether a state's share of spending on a given drug is disproportionately large relative to the drug's overall market share. This allows for the identification of states that have a specialized demand for specific drugs, providing insights into regional pharmaceutical consumption patterns, healthcare needs, and policy implications.

Mathematically, the RCA of state *s* in drug *d* is defined as:

$$\text{RCA}_{sd} = \frac{S_{sd}}{T_d}, \tag{1}$$

where the term S_{sd} represents the proportion of total expenditure on drug *d* accounted for by state *s*. This proportion is computed as:

$$S_{sd} = \frac{X_{sd}}{\sum_d X_{sd}}, \tag{2}$$

where X_{sd} is the total expenditure of state *s* on drug *d*. The term T_d represents the overall market share of drug *d*, given by:

$$T_d = \frac{\sum_s X_{sd}}{\sum_{s,d} X_{sd}}, \tag{3}$$

which quantifies the importance of drug *d* in the entire market.

A state is said to have a revealed comparative advantage in a drug if its RCA value is equal to or greater than one. That is, if $\mathrm{RCA}_{sd} \geq 1$, it implies that the relative spending of the state *s* on the drug *d* is higher than the average across all states, indicating a distinctive demand pattern. This methodology allows for the identification of drugs that are particularly relevant to specific states, revealing regional differences in pharmaceutical expenditure. Such insights are valuable for policy makers, public health officials, and pharmaceutical companies, as they can inform decisions related to drug pricing, distribution, and healthcare access.

Method of reflections

To analyze the complexity of the state-drug expenditure network, we define an adjacency matrix M_{sd}, where each entry $M_{sd} = 1$ if state *s* has a revealed comparative advantage in drug *d*, meaning that $\mathrm{RCA}_{sd} \geq 1$. Otherwise, $M_{sd} = 0$, indicating that the state does not exhibit a strong specialization in that drug. This bipartite network representation allows for the application of the Method of Reflections, an iterative algorithm that refines the measures of state diversification and drug ubiquity.

The Method of Reflections operates iteratively as follows. First, the initial level of diversification for each state, denoted $k_{s,0}$, is computed as the total number of drugs for which the state *s* exhibits RCA. Similarly, the initial ubiquity of each drug, denoted $k_{d,0}$, is given by the number of states that exhibit RCA in that drug *d*:

$$k_{s,0} = \sum_d M_{sd}, \tag{4}$$

$$k_{d,0} = \sum_s M_{sd}. \tag{5}$$

Subsequent iterations incorporate information from the network structure to refine these measures. The next step in the iterative process is to compute the average ubiquity of the drugs consumed by each state and the average diversification of the states that consume each drug:

$$k_{s,n+1} = \frac{1}{k_{s,0}} \sum_d M_{sd} k_{d,n}, \tag{6}$$

$$k_{d,n+1} = \frac{1}{k_{d,0}} \sum_s M_{sd} k_{s,n}. \tag{7}$$

These equations update the values iteratively, capturing more information at each step. The recursive nature of this algorithm enables the differentiation of states based not only on the number of drugs they purchase, but also on the complexity of the drugs they acquire. A state that purchases drugs which are primarily acquired by highly diversified states will rank higher in complexity. Similarly, drugs that are predominantly consumed by highly complex states are considered less ubiquitous and more sophisticated.

The Method of Reflections thus provides a means of ranking states by their pharmaceutical complexity, identifying those that have more advanced healthcare consumption patterns. It also enables the classification of drugs based on their distribution across states, allowing researchers to distinguish between commonly used pharmaceuticals and those that are more specialized or restricted to advanced healthcare systems. By iterating over these equations, the Method of Reflections generates higher-order measures that can be used to create a hierarchy of states based on their pharmaceutical sophistication and to classify drugs based on their exclusivity.

Degree-preserving null model

To assess the statistical significance of the observed network structure, null models are constructed by randomizing the connections while preserving the total number of drugs associated with each state, and the total number of states associated with each drug. The approach follows an edge rewiring process that maintains the bipartite nature of the network and the original diversification and ubiquity values.

The procedure begins by randomly selecting two existing connections, (s_1, d_1) and (s_2, d_2), such that $M_{s_1 d_1} = 1$ and $M_{s_2 d_2} = 1$. A swap is then proposed, replacing these edges with (s_1, d_2) and (s_2, d_1), ensuring that $M_{s_1 d_2} = 0$ and $M_{s_2 d_1} = 0$ before the swap. This reassignment preserves the total number of connections for both states and drugs. The new connections are accepted only if they do not introduce duplicated links, thereby maintaining the original diversification and ubiquity distributions. If a swap violates these constraints, it is discarded, and a new set of edges is selected for rewiring. This rewiring process is repeated for a large number of iterations to generate an ensemble of randomized networks. These randomized networks serve as a benchmark for evaluating the observed network, enabling the identification of non-trivial structural patterns that deviate from randomness. By comparing the empirical network with the ensemble of null models, it is possible to assess whether the pharmaceutical complexity observed in the original data arises from underlying economic and

healthcare dynamics or is simply a consequence of degree distribution constraints. The comparison via z-scores allows us to assess whether Level-1 metrics, i.e. Pharmaceutical Embeddedness and Drug Embeddedness, are driven solely by local connectivity (Level-0), or if they reflect more complex structural interdependencies. Alternatively, entropy-maximizing approaches, such as the Bipartite Configuration Model [71], offer a principled statistical framework for constructing null models by maximizing the ensemble entropy subject to constraints on node degrees. Unlike the edge-rewiring procedure, which generates randomized networks through a sequential stochastic process, entropy-based methods define a probability distribution over all possible bipartite graphs that satisfy the imposed constraints on diversification and ubiquity. This allows for the analytical derivation of expected values and variances for network metrics under the null hypothesis, enabling more precise statistical testing. While our current analysis relies on a microcanonical approach, preserving degree sequences exactly through rewiring, we acknowledge the robustness and theoretical appeal of these canonical ensemble methods. Incorporating entropy-maximizing null models in future work could serve as a valuable robustness check, providing additional insights into whether the observed patterns stem purely from local constraints or reflect higher-order structural organization.

Relationship between Level-0 and Level-1 network measures

To quantify the relationship between Level-0 and Level-1 network measures, specifically between Drug Dispersion and Drug Embeddedness Score (at the drug level), and between Pharmaceutical Breadth and Pharmaceutical Embeddedness (at the state level), we employ a simple linear regression model of the form:

$$Y_{i,t} = \alpha + \beta X_{i,t} + \varepsilon_{i,t}$$

where $Y_{i,t}$ denotes the Level-1 metric (either drug or pharmaceutical embeddedness score) for entity i(a drug or a state) at time t, $X_{i,t}$ is the corresponding Level-0 metric (drug dispersion or pharmaceutical breadth), α is the intercept, β is the regression coefficient capturing the linear association between the two levels, and $\varepsilon_{i,t}$ is the error term. This model is estimated separately for each quarter in the dataset, allowing us to track how the strength and direction of the relationship evolve over time.

Data availability

Data is publicly available at: (https://www.medicaid.gov/medicaid/prescription-drugs/state-drug-utilization-data/index.html).

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Declarations

Competing interests
The authors declare no competing interests.

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