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A multiparametric analysis of molecular complexities vs. economic data towards the continuous pharmaceutical manufacturing (CPM) of antibiotics

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Abstract

Continuous pharmaceutical manufacturing (CPM) has a documented potential to reduce production costs, offering opportunities to simultaneously streamline product development and improve economics for the pharmaceutical industry. Selecting technically feasible and economically viable candidate active pharmaceutical ingredients (APIs) for CPM is imperative for this transition to succeed. The present paper outlines a statistical correlation analysis of structural complexity and trade statistics for antibiotics, towards establishing economically viable CPM candidates. Bertz molecular complexity indices (CIs) are compared with molecular weights and price, sales and revenue data to identify the strength of correlation among variables. Sales data show that penicillins and quinolones are the most economically promising antibiotic families, composing 60% of total antibiotic revenues in the period 2009-2011. Spearman's rank correlation coefficients confirm strong monotonic relationships between antibiotic Bertz CIs and trade parameters. To the best of our knowledge, this is the first study highlighting promising antibiotics towards systematising CPM pursuits.

Keywords: Continuous Pharmaceutical Manufacturing (CPM), statistics, antibiotics.

1. Introduction

The pharmaceutical industry faces increasing financial pressure due to globalised competition and rapidly increasing R&D expenditure: these pressing challenges can be alleviated by a judicious shift from the currently prevalent batch production to Continuous Pharmaceutical Manufacturing (CPM) (Anderson, 2012). Economic analyses are required for systematic evaluation to identify economically viable compounds for CPM. Antibacterial drugs, also known as antibiotics, have revolutionized modern medicine, and are an essential part of human life; however, their production is often expensive due to the elaborate processes required to obtain their complex molecular structures. Previous work has established that antibiotics have a particularly high economic potential for CPM, based on recent UK trade data for a vast dataset of currently marketed and regulated antibiotics (Nagy et al., 2016). While it is essential to ensure a robust continuous flow synthetic route is established for a candidate API prior to CPM implementation (Plutschack et al., 2017), identifying the economic viability of a new production paradigm for an API is equally important.

Statistical analysis of economic trade data for antibiotics can highlight promising candidates for CPM implementation, if a continuous route is established and scalable.

Molecular complexity indices (CIs) are important tools for predicting toxicological and physicochemical properties of chemical structures in drug design and pharmaceutical development (Li and Eastgate, 2015). This paper conducts statistical analyses between structural metrics and pharmaceutical trade data, to identify correlations between CIs and demand of various antibiotics, potentially highlighting promising API candidates for CPM implementation. We emphasise that such a statistical correlation analysis can be a very useful (not the sole) criterion for CPM opportunity identification, and must be used in tandem with pharmacokinetic, pharmacodynamic (PKPD) and clinical evidence.

2. Methodology and Analysis

2.1 Economic Data

Acquiring recent economic trade data is essential for conducting an accurate economic analysis of candidate antibiotics for CPM implementation. Sales and price data for the period 2009-2011 for 37 antibiotics from lists of the best performing antibiotics by sales (Vitaku, 2010; FDA, 2010; FDA, 2012) and those on the World Health Organisation (WHO) essential medicine lists (WHO, 2017) have been compiled. These antibiotics represent societally important products with high economic potential: the most recent economic data have been used, to ensure relevance to pharmaceutical industry trends.

2.2 Molecular Complexity

In this work, we quantify complexity via the Bertz CI, which is a weighted sum of numbers of different groups on organic molecules, including rings, non-aromatic unsaturated C-atoms, heteroatoms and chiral centres (Bertz, 1981). Bertz CI values for the full list of antibiotics considered are available in the literature (PubChem, 2017).

2.3 Statistical Correlations

A wide range of statistical correlation coefficients exist to determine the strength of different types of correlation between two sets of data. Spearman's rank correlation coefficients (r_S, Eq. 1) have been calculated to determine the strength of a monotonic relationship between two data sets. Here, d is the difference in rank of members of each dataset and n is the length of the dataset. The strength of correlation is quantified by the magnitude of the coefficient: r_S = 0.6–0.8 indicates a "strong" correlation and r_S > 0.80 shows a "very strong" indication of a monotonic relationship between two data sets.

$$r_s = 1 - \frac{6 \sum d^2}{n\,(n^2 - 1)} \tag{1}$$

3. Results and Discussion

3.1 Economic Data vs. Antibiotic Complexity Indices and Families

Fig. 1 shows Bertz CIs for the full set of antibiotics considered here; antibiotics are arranged in order of ascending MW. Bertz CI values generally increase with MW, reflecting the increasing number bond connections and variety of functional groups present in larger molecules. Economic data were compiled and compared for this set of antibiotics to establish promising antibiotics with high potential for CPM application.

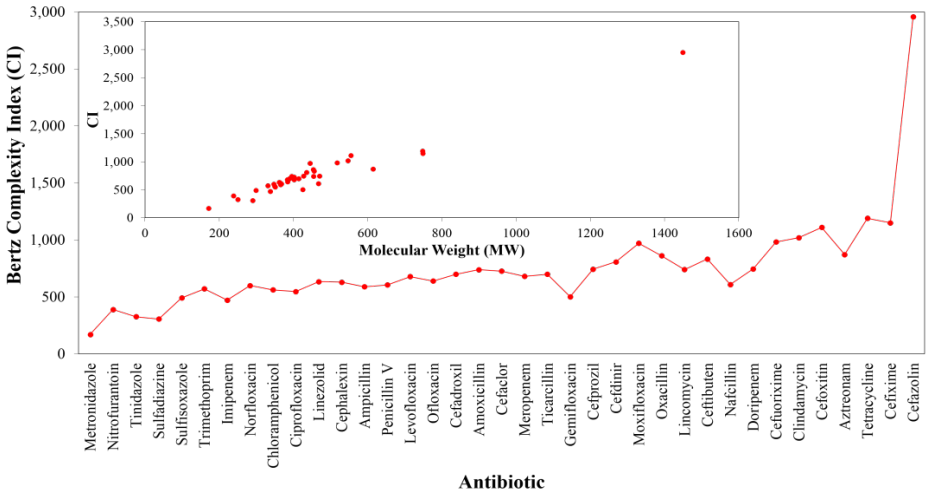

Figure 1: Bertz complexity index (CI) as a function of antibiotic molecular weight.

Fig. 2 shows compiled sales and price data for the total list of antibiotics. Antibiotics are arranged in order of ascending average sales (by mass) over the period of 2009-2011. From the set of antibiotics considered, amoxicillin has significantly higher sales over other antibiotics. Amoxicillin is a broad-spectrum antibiotic with various applications, and thus its wide utility makes it particularly important in modern society (Kaur et al., 2011). Cephalexin, ciprofloxacin, piperacillin and penicillin V are the subsequent best-performing antibiotics in terms of sales. Comparison of the economic performance of different antibiotic families can give an indication of antibiotics with CPM potential. Prices for different antibiotics vary significantly, thus annual revenues from different antibiotics allow an alternative economic comparison of promising antibiotic families.

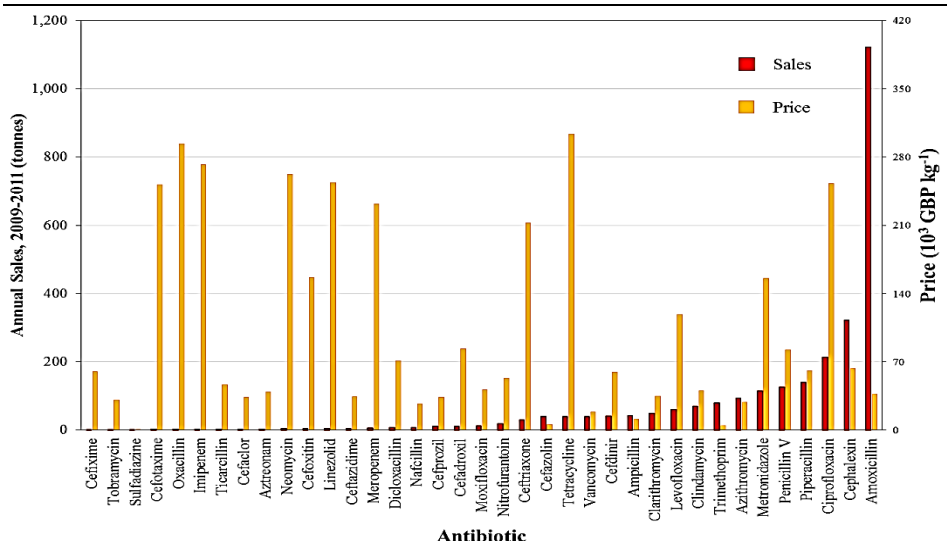

Figure 2: Average antibiotic annual sales (2009-2011) and unit prices (mass bases).

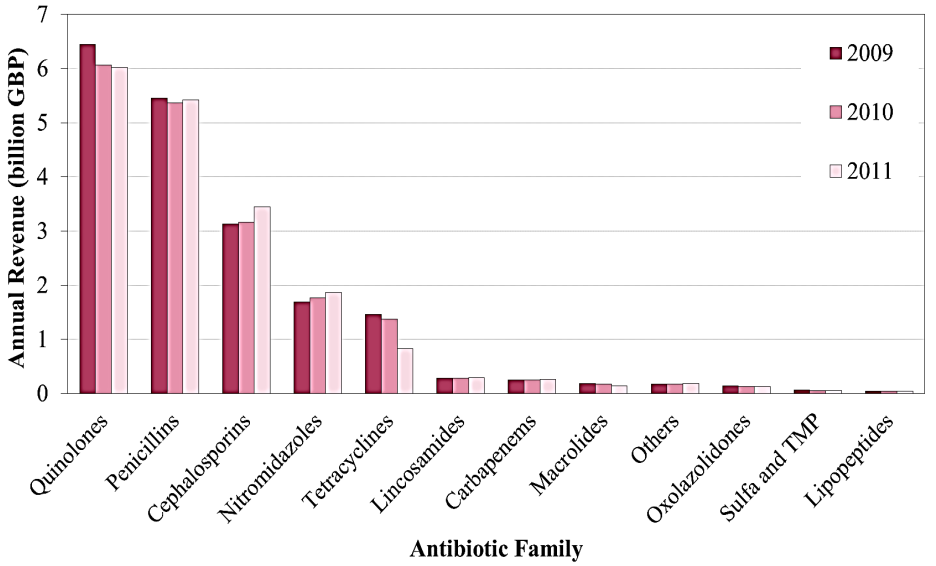

Figure 3: Annual revenues of different antibiotic families (2009-2011).

Fig. 3 compares annual revenues of the highest performing antibiotic families over the years for which sales and price data are available (2009-2011). Quinolones and penicillins dominate the pharmaceutical industry for antibiotics, contributing 60% of the total antibiotic revenue and are thus of high commercial importance. Fluctuation is recognised in all families of antibiotics present, but most notably for quinolones (a reduction of 0.38 billion GBP is clear in 2009-2010). Nevertheless, these families of antibiotics are consistently high performers, presenting strong economic incentives.

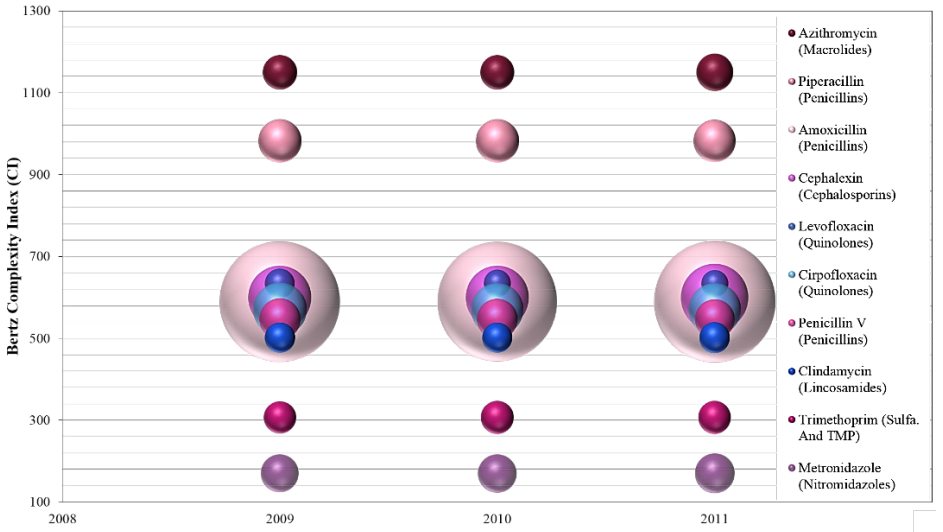

Figure 4: Bertz complexity index (CI) for the top 10 antibiotics by annual sales.

Over the period 2009-2011, revenues for quinolones, tetracyclines and macrolides decrease annually, while revenues for cephalosporins and nitromidazoles increase. Despite these changes, the overall market revenue remains relatively consistent between 2009-2011 (average = ± 3%), indicating a consistently high market for antibiotics. Economic stability of revenues is a key factor in new product R&D (Teoh et al., 2015), as is ensuring a technically feasible continuous flow synthesis (CPM) route for the API.

Fig. 4 shows sales volumes (bubble radius) of the top 10 antibiotics by sales and their Bertz CIs over the period 2009-2011. Amoxicillin and cephalexin contribute the highest sales volumes and thus strong market opportunities for UK production are evident. Amoxicillin, piperacillin and penicillin V belong to the penicillin family and ciprofloxacin and levofloxacin belong to the quinolone family, those that dominate the pharmaceutical industry (Fig. 3). Size variation for bubbles of each antibiotic is minimal over the period considered (2009-2011), indicating little variation in sales volumes; thus, each antibiotic listed is a consistently high marketing drug. All antibiotics shown in Fig. 4 are strong performers based on structure-trade correlation, thus potentially promising CPM implementation candidates, if continuous synthesis routes are available.

3.2 Statistical Correlation of Complexity Index with Economic Data

Spearman's rank correlation coefficients between different datasets are shown in Table 1. A "very strong" correlation ($r_S > 0.8$) exists between Bertz CI and MW due to the increasing size and complexity of molecules with increasing number and diversity of functional groups and bond types present as MW increases. as expected from the results presented in Fig. 1. "Strong" correlations ($0.6 < r_S < 0.8$) exist between sales and price data and molecular complexity. Fig. 5 shows average antibiotic sales (2009-2011) and prices versus Bertz CIs associated with the correlation Spearman's rank coefficients presented in Table 1. The strength of correlation between economic data and molecular complexity is directly related to the high performance of the antibiotics considered in the data set; correlations are made between the most recent economic data available.

Table 1: Spearman's rank correlation coefficient between paired data sets.

	$\log_{10}$(Bertz CI)	**$\log_{10}$(Average Sales, 2009-2011)**	**$\log_{10}$(Price)**
MW	0.976	0.621	0.687
Bertz CI	n/a	0.634	0.718

3.3 Discussion

The present work has established penicillins and quinolones as economically promising candidates for CPM, based on previous work highlighting antibiotics as a promising class of APIs for CPM implementation (Nagy et al., 2016). Statistical analyses indicate strong monotonic relationships between Bertz CIs and economic data for the set of antibiotics considered here, which can be further validated with a wider data set where available. Addressing technical challenges in switching from batch to continuous manufacturing routes for candidate APIs is equally important to highlighting economic potential of antibiotics (Bana et al., 2017); these efforts must be conducted in tandem to establish the strongest candidate APIs for CPM implementation (Teoh et al., 2015) to facilitate the rapid transition of manufacturing paradigm in the pharmaceutical industry.

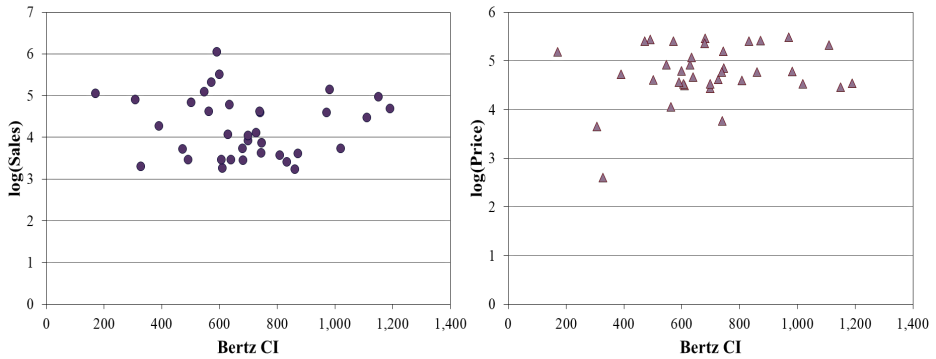

Figure 5: Antibiotic average sales (2009-2011) and prices vs. Bertz complexity index.

4. Conclusions

The statistical analysis of economic data indicates that penicillins and quinolones dominate the antibiotic market in terms of annual sales volumes and revenue, emerging as the most promising candidates for CPM. Amoxicillin contributes the most significant portion of total revenue (2009-2011) for the antibiotics considered here, followed by cephalexin and ciprofloxacin. Bertz CIs of a wide variety of antibiotics have been compiled and analysed vs. relevant economic data. Statistical analysis highlights a strong correlation between molecular complexity (MW, Bertz CI) with sales and price. The need for systematic evaluation of more trade data over a longer horizon is clear, as is the high incentive for selecting penicillins and quinolones as viable CPM candidates.

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