Factor Analysis of Drug Supply Time Series at Pharmacies

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The stochastic properties of the daily variations in drug sales at a community pharmacy in the season of 2004/2005 are studied by a factor analysis. The four factors which can closely be related to chronic diseases, common cold, influenza and allergies are extracted from the data of 31 drugs. For most of the drugs, the sales time series can approximately be represented by the four factors alone. Similar results are obtained from the same pharmacy in the 2003/2004 season and also from two other pharmacies. Interestingly, the classification of drugs according to the factor analysis corresponds to their medicinal actions.

Key words —— factor analysis, pharmacy, drug sale, prescription drug

INTRODUCTION

More attention has been paid to the sales of over-the-counter (OTC) pharmaceutical products and prescription drugs at drugstores and pharmacies ever since a study published in 1979 indicated that the monitoring of the sales of nonprescription cold remedies is a beneficial technique of influenza surveillance.[1)]

Syndromic surveillance is known as a method for early detecting outbreaks attributable to bioterrorism or other causes.[2)] The syndromic surveillance focuses on the patients' symptoms during the early phases of illness (*e.g.*, cough and fever). Actually used for analysis are the clinical data and alternative data. The latter includes school and work absenteeism, OTC drugs. Magruder observed that in the National Capital Area of U.S.A., some OTC influenza-remedy sales tended to occur approximately 3 days prior to the physician-patient encounters.[3)] He asserted that the monitoring of OTC sales may be used as an early warning about developing public health conditions. There can be found many publications concerning the evaluation of OTC pharmaceutical sales.[4–10)]

Quite recently, a new method was proposed for estimating the geographical route and speed of influenza propagation from prescription drug sales at distant pharmacies.[11)] The infection pattern in three seasons in and around Tokyo was investigated.[12)]

An analytical challenge in the above studies is to identify a signal indicating an outbreak of disease amid the ubiquitous background noise in the data. The border between the signal and noise is recognized as the detection limit which is a fundamental concept in the area of analytical chemistry.[13)] Originally, the detection limit is a statistical definition.[14–17)]

The time variation in drug sales is important in science as well as society. Mathematical knowledge on the sales will help calculate the detection limit and early grasp a warning of national emergencies such as bioterrorism and influenza pandemic. The times are right for the study of prescription drug sales with a traditional technique, factor analysis.

MATERIALS AND METHODS

The records of the daily variations in drug sales were offered by the following pharmacies located in prefectures near Tokyo: 32 drugs in 2003/2004 season and 31 drugs in 2004/2005 season at Kamome Yakkyoku (Kanagawa, Japan); 36 drugs at Kosumo Chouzai Yakkyoku (Saitama, Japan) in 2003/2004 season; 57 drugs at Kuoru Yakkyoku (Fukushima, Japan) in 2004/2005 season. The season means the period from November 1st to October 31st. The pharmacies are not located near emergency hospi-

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tals, but near general clinics. The pharmacies did not deal in urogenital and anal organ agents, epidermides, dental preparations, dialysis agents, radioactive drugs, *etc*. Non-therapeutic purpose agents and narcotics are not taken in this paper.

The original time series of drug sales have the hebdomadal frequency which looks like noise.[12] Actually, however, the frequency with a period of seven days originates from the life style of residents around the pharmacies. In this paper, the hebdomadal cycle is eliminated by the moving average method with a window of seven days to avoid erroneous results.

In order to describe the features of the multivariate variation of drug sales, the factor models are fitted to the square root transformed time series, which can approximately be regarded as multivariate normal data, because the square root transformation is typical variance stabilizing transformation for frequency data. In this analysis, the factors are drawn by using the maximum likelihood factor analysis with the promax rotation and the number of factors are determined by referring to the goodness of fit of the test statistics of multi-factors models. Finally, the factor scores are calculated by the Bartlett method. The factanal function in the free statistical software R 2.5.1 is used for these analyses. For the free software, R represents a language and environment for statistical computing and graphics similar to S (see http://cran.r-project.org/).

RESULTS AND DISCUSSION

Figure 1 shows typical examples, out of 31 drugs, of the daily variations in drug sales at a pharmacy. Norvasc® tablets 5 mg (Pfizer, Tokyo, Japan) is a drug for hypertension and its time series (Fig. 1A) is typical of chronic diseases. The drug is supplied constantly throughout the year, except the sale rapidly goes down on New Year's holidays, Golden Week holidays (early part of May) and summer holidays.

PL® granule (Shionogi & Co., Osaka, Japan) is a common cold drug and its supply has a peak over autumn and winter (Fig. 1B). Unlike Norvasc®, the time series for PL® granule lacks the conspicuous slowdown on the Golden Week holidays. This might imply that people, if infected with cold, have a trend to obtain the drug hastily.

Influenza rages from winter to early spring in Japan. The time series for the influenza anti-viral agent for adults (Tamiflu® capsules, Chugai Pharmaceutical, Tokyo, Japan) synchronizes with the disease activity (Fig. 1C).

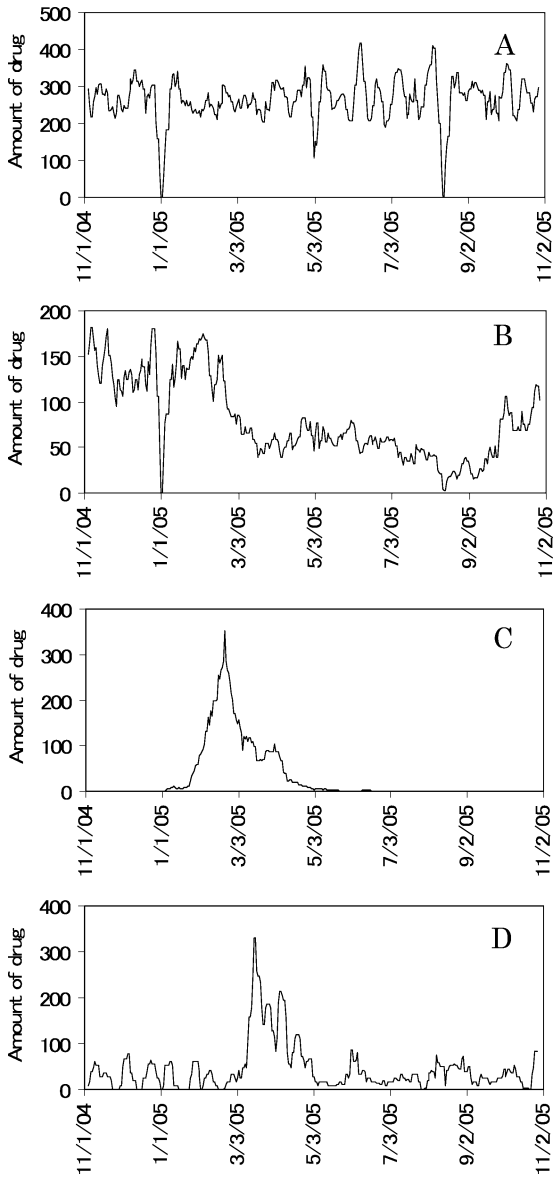

Fig. 1. Time Series of Drug Supply at a Pharmacy (Kamome Yakkyoku, Kanagawa) in 2004/2005 Season

A: Norvasc® tablets 5 mg, B: PL® granule, C: Tamiflu® capsules, D: Onon® capsules. Y axis denotes the number of tablets or capsules or weight.

An allergic agent, Onon® capsules (Ono Pharmaceutical, Osaka, Japan) is effective for the treatment of allergic rhinitis. This drug is prescribed for asthma constantly throughout the year and also for pollinosis. In Fig. 1D, the sales peak around March and April corresponds to the pollinosis and the other random fluctuation represents the asthma.

Table 1 lists the results of the factor analysis including the loadings and proportion variances of the factors and communality of the drug sales. In gen-

Table 1. Loadings of Drug Supply Time Series at a Pharmacy in 2004/2005 Season

Drug	Standard Commodity Classification	Communality	Factor (Proportion Variance)						
			1 (0.19)	2 (0.15)	3 (0.090)	4 (0.053)	5 (0.044)	6 (0.033)	7 (0.028)
Loxonin® tablets	Antipyretics and analgesics, anti-inflammatory agents	0.69	0.48*				0.55		0.11
Brufen® tablets	Antipyretics and analgesics, anti-inflammatory agents	0.80		0.12	0.60*	−0.14		0.13	0.50*
PL® granule	Common cold drugs	0.89	−0.22	1.00**			0.15	−0.12	
PA® tablets	Common cold drugs	0.61		0.65*	−0.29	−0.12		0.14	
Myonal® tablets	Antispasmodics	0.31	0.48*			−0.16		−0.31	0.10
Ternelin® tablets	Antispasmodics	0.34	0.41*		−0.24	0.27	0.12		0.23
Merislon® tablets	Vertigo agents	0.44	0.54*	0.21	−0.17			−0.11	
Cephadol® tablets	Vertigo agents	0.28			0.12	−0.42	0.12		
Blopress® tablets	Antihypertensives	0.80	0.88**		0.12				
Norvasc® tablets	Vasodilators	0.90	0.92**					0.19	
Lipitor® tablets	Hyperlipidemia agents	0.84	0.91**						
Mevalotin® tablets	Hyperlipidemia agents	0.51	0.59**				0.14		−0.21
Mucodyne® tablets	Expectorants	0.90	0.24	0.70**	0.19				
Medicon® tablets	Antitussives	0.90		0.79**	0.40				
Gaster® tablets	Peptic ulcer agents	0.68	0.66*					0.17	
Mucosta® tablets	Peptic ulcer agents	0.75	0.77**	−0.13			0.23	0.17	
Thyradin-S® tablets	Thyroid and parathyroid hormone preparations	0.21	0.32	0.16		−0.21	−0.10		−0.23
Mercazole® tablets	Thyroid and parathyroid hormone preparations	0.34		0.24	−0.10		−0.22	0.40	0.13
Methycobal® tablets	Vitamin B preparations	0.36	0.55*						
Dasen® tablets	Enzyme preparations	0.95		0.85**	0.17				0.18
Arimidex® tablets	Antineoplastics (Miscellaneous)	0.13	0.19	−0.35	0.12	−0.19	−0.11		0.14
Allelock® tablets	Allergic agents (Miscellaneous)	0.93		0.13	0.24	0.78**	0.62*		−0.11
Onon® capsules	Allergic agents (Miscellaneous)	0.52	0.17	−0.18		0.72**	0.11	−0.15	
TSUMURA Kamishoyosan Extract Granules for Ethical Use	Traditional Chinese medicines	0.18	0.45*	−0.20		0.14	−0.19		
TSUMURA Hangekobokuto Extract Granules for Ethical Use	Traditional Chinese medicines	0.42	0.32	−0.25				0.55*	−0.17
Flomox® tablets	Antibiotics (Acting mainly on gram-positive and gram-negative bacteria)	0.79		0.58*			0.23	−0.12	0.47*
Clarith® tablets	Antibiotics (Acting mainly on gram-positive bacteria and mycoplasma)	0.40	0.13			−0.16	0.19	0.50	0.12
Cravit® tablets	Synthetic antibacterials	0.74	0.36	0.70*			−0.17		−0.15
Tamiflu® capsules	Antivirals	1.00			0.95**	0.15			
Tamiflu® dry syrup	Antivirals	0.97			0.97**				
Lamisil® tablets	Chemotherapeutics (Miscellaneous)	0.30		0.15			0.54*		0.11

The loadings are presented as *greater than 0.4 and less than or equal to 0.7, and **greater than 0.7.

eral, a loading approximately suggests the correlation coefficient between a factor and the time series of a drug. If a loading of a drug sales time series is greater than 0.7, at least about 50% (= 0.7^2) of the time variation can be explained by the corresponding factor. In Table 1, 94% (= 0.97^2) of the sales of Tamiflu® dry syrup can be explained by the third factor.

The greater the proportion variance of a factor, the larger part of all the time series the factor can describe approximately. Therefore, the factors are called as the 1st factor, 2nd factor, *etc*. in the descending order of the values of the proportion variance (see Table 1). The communality is the degree of how successfully a sales time series can be described by the set of all the factors. The value of the communality means the degree of usefulness of the factor analysis. In case of Arimidex® tablets (Astra Zeneca, Osaka, Japan), it is so small (= 0.13) that its time series is mostly independent of any combination of the seven factors.

Figure 2 illustrates the time variation plots of the four factors listed in Table 1. The factors of Fig. 2 are similar in shape to the plots of Fig. 1. This can be interpreted in terms of large loadings. The sales of Norvasc® of Fig. 1A can be described by the first factor with 85% (= 0.92^2) approximation. For PL®, the approximation degree is almost 100% (= 1.00^2). For Tamiflu® tablets, it is 90% (= 0.95^2). For Onon® capsules, it is 52% (= 0.72^2).

Because of the small values of the loadings (< 0.4), the factor analysis is not suitable for the following time series: Cephadol® tablets (NIPPON SHINYAKU, Kyoto, Japan), Thyradin-S® tablets (ASKA Pharmaceutical, Tokyo, Japan), Mercazole® tablets (Chugai Pharmaceutical), Arimidex® tablets, Clarith® tablets (Taisho Pharmaceutical, Tokyo, Japan). In other words, the sales pattern of 26 drugs out of 31 can be explained by appropriate combinations of the seven factors with the loadings more than 0.4. In the same manner, the major 4 factors (see Fig. 2) can describe the pattern of 25 drugs satisfactorily.

The drugs examined here can be classified by the major factors with the loadings greater than or equal to 0.7. The first factor represents the drugs for chronic diseases such as antihypertensive (Blopress® tablets, Takeda Pharmaceutical, Osaka, Japan), vasodilator (Norvasc® tablets), hyperlipidemia agent (Lipitor® tablets, Astellas Pharma, Tokyo, Japan) and peptic ulcer agent (Mucosta® tablets, Otsuka Pharmaceutical, Tokyo, Japan).

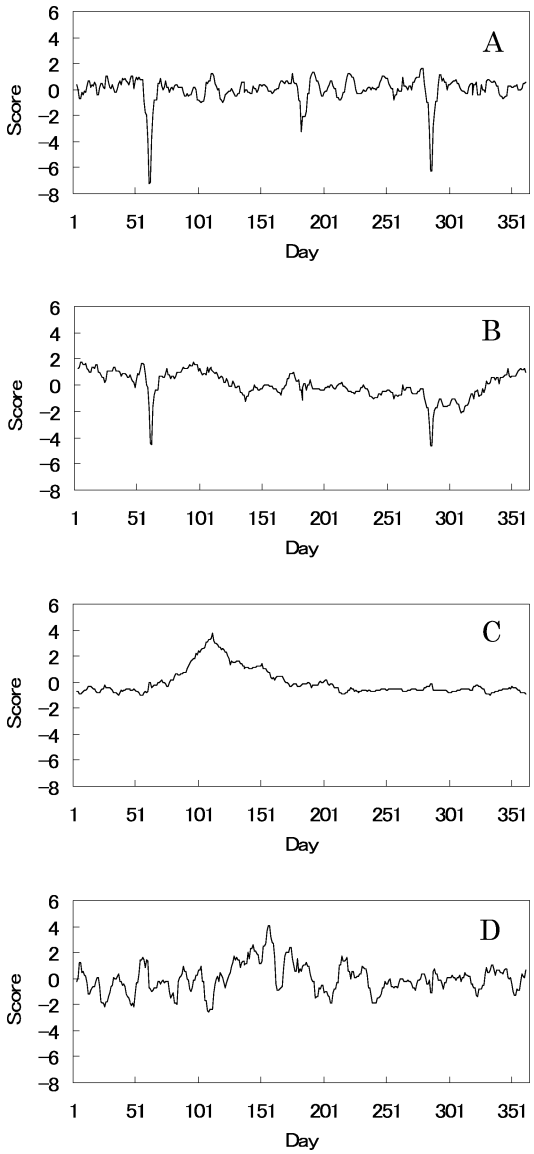

Fig. 2. Time Series Plots of the Four Factor Scores of the Data of Fig. 1

A (communality): 1st factor (0.19), B: 2nd factor (0.15), C: 3rd factor (0.090), D: 4th factor (0.053).

Patients of common cold are treated with a variety of drugs, some of which can be described by the second factor. Included are a common cold drug (PL® granule), expectorant (Mucodyne® tablets, Kyorin Pharmaceutical, Tokyo, Japan) and antitussive (Medicon®, Shionogi & Co.). An enzyme preparation (Dasen® tablets, Takeda Pharmaceutical) has an expectorant effect and is also used to relax this typical symptom of cold.

The third factor is specific only to influenza anti-viral agents (Tamiflu® capsules and Tamiflu® dry syrup) of chemotherapeutics. Allergic agents [Allelock® tablets, Kyowa Hakko Kogyo (Tokyo,

Japan), Onon® capsules] which are prescribed for seasonal diseases such as pollinosis are represented by the fourth factor.

In a previous study,[18] drug sales were divided into three groups according to the strength (strong, weak and none) of auto-correlation of their time series. The first factor of this study corresponds, though not exactly, to the group of no auto-correlation. The third factor for influenza can be characterized by the strong auto-correlation. The second and fourth factors have weak auto-correlation.

The factor analysis was also applied in the same manner to the time series of drug sales in another season at the pharmacy (2003/2004 at Kamome Yakkyoku) and at other pharmacies (Kosumo Chouzai Yakkyoku and Kuoru Yakkyoku). The four factors, mentioned above, relating to chronic diseases, common cold, influenza and allergies were also obtained by the factor analyses, though in some cases combined or separated. It is interesting that the results of the factor analysis can closely be connected with the target-oriented classification of drugs (standard commodity classification in Table 1).

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