—Regular Articles—

A Method for Detecting Injury of People's Health from Prescriptions at a Pharmacy

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A method is proposed to detect the abnormal situations of people's health in case of the unexpected outbreak of a disease by monitoring the daily variations in the prescriptions at a pharmacy. The abnormal situations are defined as the situations which are not included in the majority (99.9%) of the normal situations. An epidemic probably caused by infectious micro-organisms in a terrorist attack is taken as an example. The drugs for the typical symptoms are monitored: influenza anti-viral agent and common cold drug. This paper demonstrates that the border between the normal and abnormal situations corresponds to the detection limit which is a fundamental concept in analytical chemistry.

Key words——pharmacy; FUMI theory; terrorism; detection limit; spectral analysis

INTRODUCTION

It is probable that the health conditions of people are reflected by the daily variations in the sales at a pharmacy or drugstore of the area where they live. Quite recently, an attempt has been made to keep vigil over the people's health extensively on the basis of the information network among pharmacies and drugstores. This study is referred to as health vigilance.[1,2] In Japan, Infectious Diseases Surveillance Center and ML Influenza Ryukou Zensen Jouhou DB have already conducted the nationwide surveillance of influenza patients based on the information from hospitals and clinics. On the other hand, the feature of health vigilance is that the states of people's health can be grasped through not only doctor's diagnosis but also self-medication by people.

Along the line of health vigilance, the present paper proposes a method for detecting the injure of the health conditions of people. There can be a variety of national emergencies, e.g., biological and chemical terrorism, pandemic outbreak of an infectious disease, etc. For the sake of demonstration, this paper assumes the following story of biological terrorism. Of course, the method proposed here is applicable to the detection of other abnormal situations of people's health.

The subject taken here is: 1) Infectious micro-organisms are deliberately released in a terrorist attack at a site of Tokyo; 2) The effect of the biological weapon is not quick-acting, but slow-acting, and the incipient stage of the disease is not serious; 3) The citizens around the venue lose their health "slightly", go to hospitals or clinics and obtain drugs at pharmacies; 4) As a consequence, the amount of prescriptions at a nearby pharmacy increases "slightly".

The detection of the "slight" change in the amount of drug supply at the nearby pharmacy is the aim of this paper. The daily prescriptions for influenza and cold at a pharmacy are analyzed, since the symptoms caused by the biological weapon are similar to the influenza or cold.[3—8)]

The problem is how to make a decision between the abnormal and normal situations of the above scenario. It is impossible to take into account all the individual examples of the abnormal situations in case of bioterrorism. Then, we first define the normal situations and second, recognize the abnormal situations as the situations which are not included in the majority of the normal situations.

The Venn diagram of Fig. 1 illustrates 99.9% (majority) and 0.1% (minority) of the normal situations and the entire elements of the abnormal situations. The probability of detecting (erroneously) that the situation is not normal when it is normal is 0.1% (gray area). Of course, when it is normal, the probability of the right decision is 99.9%. However, if the situation is abnormal, the probability of the correct or erroneous judgment is not known, because the probability of the abnormal situations is not defined.

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The study of this paper proceeds as follows: 1) to express the normal situations numerically; 2) to estimate the probability distribution of the normal situations and to calculate the standard deviation (SD), σ, of the distribution; 3) to refer to the value of 3σ as a critical value; 4) to define the situation which has a value more than the critical value as abnormal; 5) to confirm the adequacy of the critical value, 3σ, by adapting it to the actual data of drug prescriptions at a pharmacy.

This paper formulates the above separation between the abnormal and normal situations as the detection limit which is a fundamental concept well-known in analytical chemistry. Several theories to predict the detection limit have been proposed since more than three decades ago in the fields of instrumental analysis.[9–16] This paper applies a theory called FUMI theory (Function of Mutual Information)[15,16] to the actual data of a pharmacy. Only a few relevant publications with terrorism as a keyword could be found.[17]

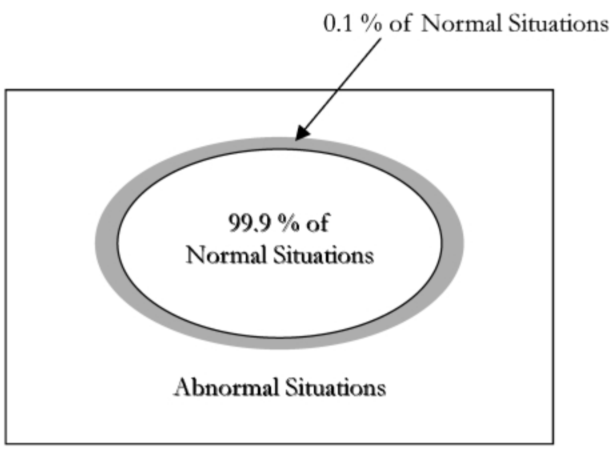

Fig. 1. Venn Diagram of the Normal and Abnormal Situations

The majority of the normal situations is illustrated as 99.9%. The minority (0.1%) of the normal situations is drawn as gray zone.

METHODS

1. Information on Prescriptions The information about drug prescriptions was collected from pharmacies in Tokyo: Tanashi Honcho Pharmacy, 4–25–5 Tanashi, Nishi-Tokyo, Tokyo. The pharmacy is located near an emergency hospital, open throughout the year and the data of weekends were available.

2. Numerical Expression of Normal Situations Figure 2 shows an example of the time series of drug prescriptions at a pharmacy. In general, the histogram of the daily amount of drug sale will not correspond to a distribution treated in statistics (as an example, *see* Fig. 3(A)). Therefore, we need a new expression of quantity which is easy to handle in a stochastic way. This paper takes the weekly amount of drug sale relative to a zero level.

The zero level is defined as the average of the prescription amounts over seven days. The amounts over later seven days are summed relatively to the zero level. This sum, called the change in amount, can be positive or negative.

The change in amount, observed at Tanashi Honcho Pharmacy in 2004, can be regarded as the numeri-

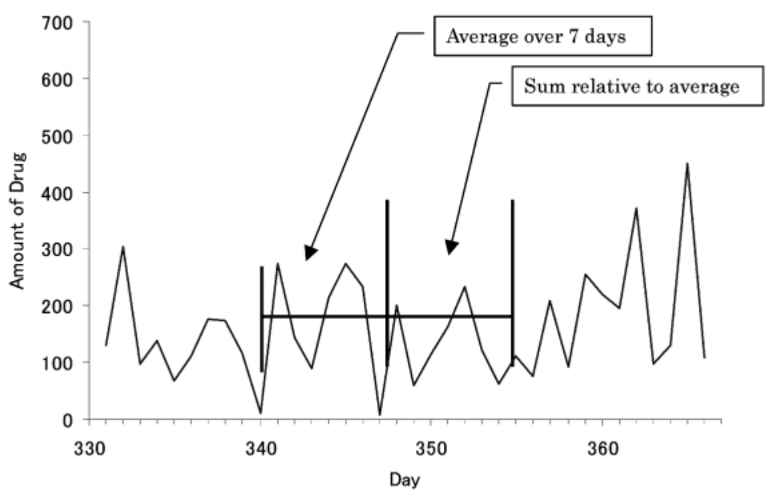

Fig. 2. Definition of Change in Amount

''Average over 7 days'' denotes the zero level of the change in amount. The amount of drug prescribed over another 7 days is summed relatively to the zero level. The relative amount is called change in amount. The zigzag line is the time variation for a common cold drug (PL®, Fig. 4(A)).

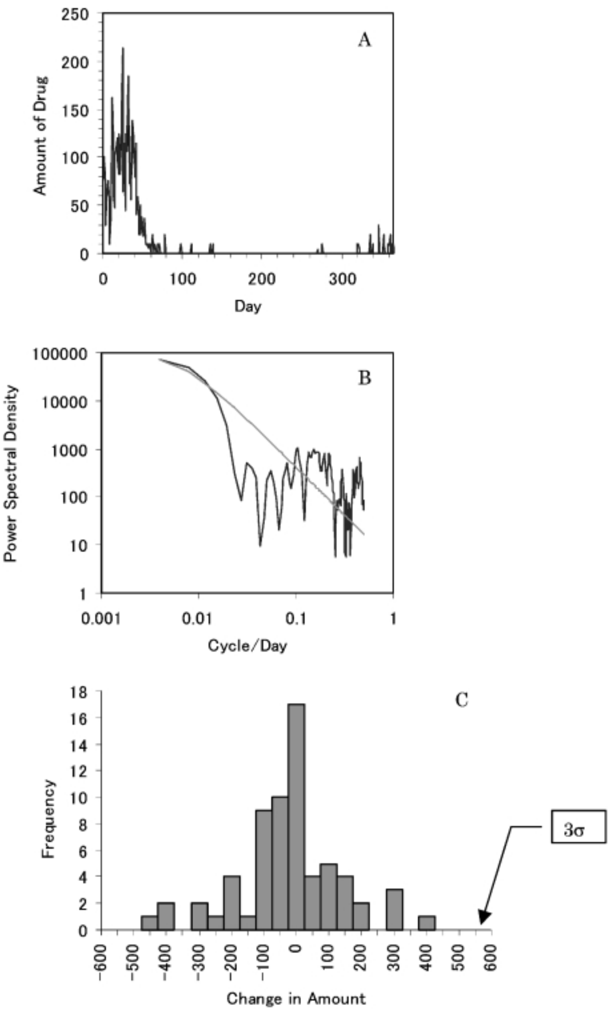

Fig. 3. Time Series (A), Its Power Spectral Density (B) and Histogram of the Changes in Amount (C) for an Influenza Anti-viral Agent (Tamiflu Capsule 75®)

(A): the data range from January 1st to December 31st in 2004 (366 days). (B): observed power spectral density (zigzag line) of the data from January 1st to September 12th (256 days); theoretical power spectral density (smooth line). (C): the data from January 8th to March 6th (66 days) are used. The Y scale denotes the number of capsules. The noise parameters: $\tilde{w}=0$, $\tilde{m}=12.7$, $\rho=0.959$. The critical value $(3\sigma)=583$.

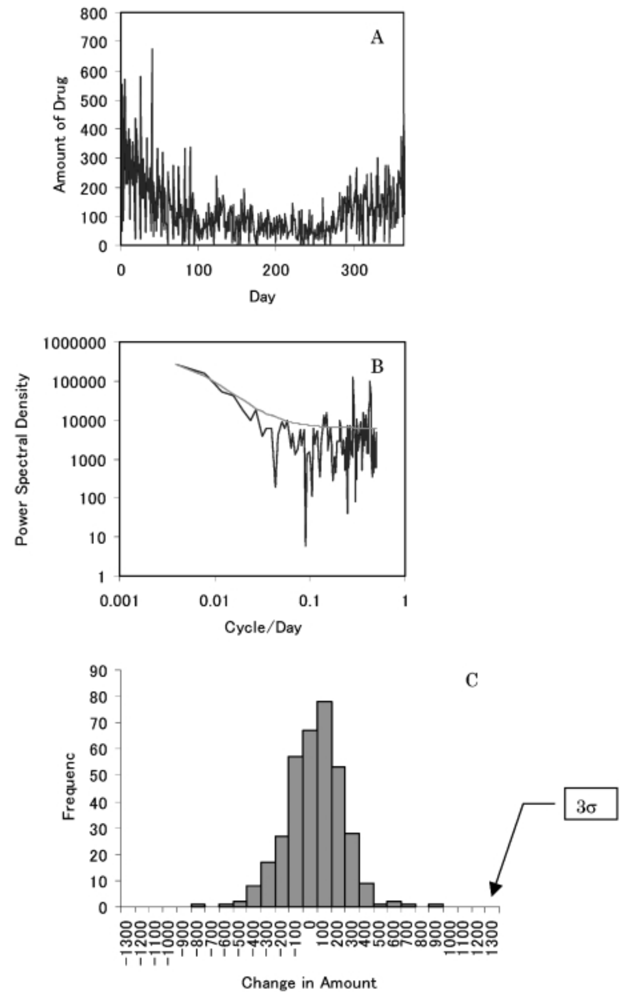

Fig. 4. Time Series (A), Its Power Spectral Density (B) and Histogram of the Changes in Amount (C) for a Common Cold Drug (PL®)

(A and B): the same as in Fig. 3 (C): the data from January 8th to December 25th (353 days) are used. The noise parameters: $\tilde{w}=79.0$, $\tilde{m}=20.3$, $\rho=0.969$. The critical value $(3\sigma)=1299$. PL has two formulations, but the total amount (gram) of granule prescribed is plotted on the Y scale.

cal expression of the normal situations (*see* Figs. 3 and 4).

3. Estimation of the SD of Changes in Amount In the FUMI theory,[15,16] a time series (here, daily variation) is Fourier-transformed into the power spectrum, to which the model power spectrum is least-squared-fitted. The parametrization by the model fitting can provide the SD of the changes in amount. All the calculations of the FUMI theory was carried out by a commercial software (MAY2000, Yazawa). The operation of drift elimination in MAY2000 was cancelled.

RESULTS

Figure 3 (A) shows the time series of the prescriptions of an influenza anti-viral agent (Tamiflu Capsule 75®, Chugai Pharmaceutical) at the pharmacy in 2004 (366 days, leap year). The Y scale denotes the number of capsules. Figure 3 (B) shows the power spectral density (zigzag line) of the time series and simplex least-squares fitting of the theoretical line (smooth line) to the power density. The power spectral density is downward to the right, indicating strong auto-correlation which looks like a 1/f fluctuation. The simplex fitting is carried out in the normal scale of Y axis, but the presentation is made in the log-log scale. Therefore, the actual deviation of the fitted line from the real data around 0.05 cycle/day is not so large as it appears in the log-log scale. There is no problem with the goodness of fit.

Figure 3 (C) shows the histogram of the changes in amount which are observed in the time series of Fig. 3 (A). Sixty-six data during the limited infection period participate in the histogram.

The critical value ($3\sigma=583$) is indicated in Fig. 3 (C). The parametrization by the simplex fitting provides the noise parameters, which in turn are used for the estimation of σ (=SD of changes in amount). The noise parameters include the SD, $\tilde{w}$, of the white noise, SD, $\tilde{m}$, of the Markov process and correlation coefficient, ρ, of the Markov process (for the observed values, *see* the figure legend). The calculation of σ has been described already.[15,16)]

By definition, one observation (change in amount), out of a thousand observations, will fall above the critical value, if the distribution of the changes in amount is normal. In Fig. 3 (C), nothing is observed above the critical value and the estimation of σ can be considered satisfactory. We can recognize that in our usual life (normal situations), an abnormal situation is impossible or difficult to observe. However, if it happens, the present method will be able to detect it.

Figure 4 (A) shows the time series of the prescriptions of a common cold drug (PL®, Shionogi & Co., Ltd.) at the pharmacy. The Y scale denotes the total amount (gram) prescribed there. The patients concentrate in the winter season, but do not so extremely as in the case of influenza (*see* Fig. 3 (A)). The power spectral density of the time series (Fig. 4 (B)) is downward to the right, but indicates weaker auto-correlation than that for influenza (Fig. 3 (B)). The difference between the power spectral densities for the prescriptions of infectious and non-infectious diseases has already been examined.[18)]

The histogram of the changes in amount for the common cold drug (Fig. 4 (A)) is shown in Fig. 4 (C). By the same parametrization and calculation as in Fig. 3, we can obtain the critical value ($3\sigma=1299$) (Fig. 4 (C)) and can spot no observation above the critical value out of 353 entries.

DISCUSSION

The practical method for the early detection of the injury of people's health has been proposed in the present paper. It is interesting that the method in analytical chemistry (FUMI theory) is applicable to the problems about the national defense and the detection limit is available for the detection of the abnormal situations in a society. The variant terminologies of the detection limit in different disciplines of science are listed in Table 1.

The absolute values of the drug sales (Figs. 3 (A) and 4 (A)) will provide the meaningful quantity for pharmacists and managers. However, the SD of the absolute values cannot be an indicator for the judgment of the normal and abnormal situations. In this paper, the change in amount (a numerical expression of situation) is defined such that its SD and detection limit serve our purpose.

The change in amount is made up of the zero window (seven days to be averaged) and relative sum (*see* Fig. 2). The seven days are selected to eliminate the possible adverse effect of the hebdomadal cycle on the data processing. The cycle of a week, due to the life style of people, appears in the power spectral density as a strong intensity of 0.14 cycle/day (=1/7) (Fig. 4 (B)).[18)]

As far as the early detection of the abnormal situations are concerned, the monitoring day can be fixed at the last day of the 14 days including the zero level setting and relative summation. Some modification of the setup of the change in amount is inevitable to improve the performance of the detection method.

The SD, σ, of the changes in amount could have been directly estimated from the elements of the histograms of Figs. 3 (C) and 4 (C), since the sample sizes of the histograms are enough for the estimation. They are 66 and 353, respectively, for Figs. 3 (C) and 4 (C). The reason why the FUMI theory is necessary for the estimation of σ is discussed below.

Table 1. Terminology in Different Fields

	Analytical chemistry	Analytical chemistry	Instrumental analysis	ISO, JIS	Situation
Below the limit	Not detected	Not detected	Baseline, noise	In the basic state	Normal
Above the limit	Detected	Detected	Peak, signal	Not in the basic state	Abnormal

The data for the first change in amount range from January 1st to 14th (7 for the zero window and 7 for the amount), the data for the second change in amount range from January 2nd to 15th and so forth. Therefore, the values of the changes in amount are not independent of each other and the correct estimate of the population SD cannot be obtained in the usual statistical way from this set of the non-independent values.

If the periods of the changes in amount are completely separate, the statistical method will give a right answer. However, only four samples can be afforded from the histogram of Fig. 3 (C) (note that 66÷14). The chi-squares distribution tells that the scattering (95% confidence intervals) of the SD estimates from four samples ranges about ±75% of the true value and then the estimates themselves are not reliable in case that $n=4$. Furthermore, the strong auto-correlation of the time series of the influenza drug requires more separation of the periods of the changes in amount to guarantee their statistical independency. This additional separation reduces the affordable number of samples (<4).

The statistical estimates for 3σ in Figs. 3 (C) and 4 (C) are 494 ($n=66$) and 609 ($n=353$), respectively, whereas the values estimated by the FUMI theory are 583 and 1299, respectively. A great difference can be recognized for the latter. In principle, the FUMI theory is preferred to the traditional method based on replications, since the FUMI theory is created so that it can circumvent the above problem of independency.

The amount of drug supplied at a pharmacy (capsules or gram) is plotted in the present paper, instead of the number of patients. The former will offer slightly more detailed information, e.g., if a patient take a two-fold amount of drug at one time. However, the problem of preferability remains open.

The series of papers in health vigilance has demonstrated the typical usage of the information that the pharmacies have in possession.[1,2] Besides the pharmaceutical sciences, the health vigilance will be connected with a variety of matters in social science.

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