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New Method for Liquid-Medication Filling Systems

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***Abstract*— For the systems used to fill large numbers of containers with liquid medication, a permissible relative error is $\pm 1.0\%$. Here, a medication filling and estimating system was designed to improve cycle time. The nonlinear least squares (NLS) method was used with the proposed system, and the results succeeded in providing the medication fill ration meeting certain specifications and below the permissible relative error. The proposed method also realizes medication filling accuracy comparable to that achieved by the conventional method, but additionally made it possible to shorten the time needed to compute the weight value by approx 60%. Moreover, since a low-pass filter does not need to be used with the proposed method, the new method is not subject to the influence of a time delay.**

I. Introduction

Systems that can accurately process liquid drugs are needed. The high costs of many liquid medications necessitate very accurate filling of the drugs' containers, with little or no waste (e.g., when a container is over-filled with the medication). A permissible relative error in a filling process is $\pm 1.0\%$ of the medication fill ration.

There are generally two kinds of methods for measuring a medication fill ration. The first is the use of a flow instrument. Although flow instruments can measure a medication fill ration with a high degree of accuracy, the cost of a flow instrument may be prohibitive. The second method uses a weight scale. Although weight scales are more affordable, their vibration during the filling process requires a waiting period until the vibration stops after the medication fill ration is completed, making a longer cycle time.

A method that can shorten liquid medications' container-filling cycle time is necessary. One method that uses a weight scale removes vibration by passing an oscillatory waveform of the medication filling process through a low-pass filter. However, a time delay is caused by the use of a low-pass filter.

Studies of weight-measuring methods that use a vibrating body have been reported. Prabuwono developed a digital measurement system for measuring the weight of the product in a manufacturing process; this system uses a load cell as the sensor, with easy customization [1]. Ono described a simple estimation algorithm for mass and weight which can be applied to a wide range of dynamic weighing devices [2]. A de-noising method that is more effective than the Kalman filter for continuous glucose monitoring was developed by Facchinetti [3]. That method, when compared with the Kalman filter, showed reasonable efficacy; the amount of glucose was estimated in a continuous glucose monitoring time series. However, to guarantee a medication fill ration at a higher level, a medication fill method that improves the cycle time at low cost is needed.

In the present study, a system that estimates medication filling with a lower permissible relative error to improve the cycle times in medication filling processes is described. The medication fill ration was estimated by applying the nonlinear least squares (NLS) method.

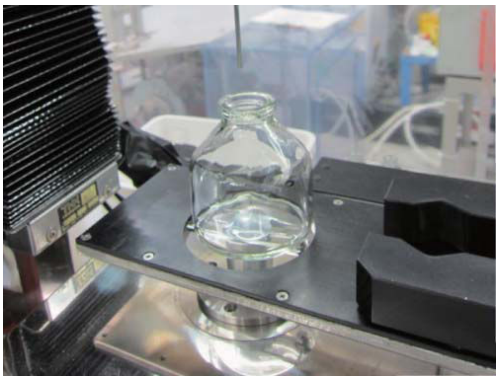

Fig. 1. Experimental device

II. Experimental device

The experimental device is shown in Fig. 1. With this device, the container weight is measured first. Then the weight-filler device (which is always filled with a fixed weight) is used by setting up the filling pressure. A vial is used for the container, the load cell is used as a weight scale. The load cell consists of a flexure element which changes in proportion to force, and a strain gauge is attached to the load cell. When an object is put on the load cell, the flexure element becomes deformed, and a very small voltage signal in proportion to the strain is outputted. This small signal is amplified, and it outputs as weight. Since the amount of displacement of the load cell is relatively small, it can be approximated with one degree of freedom of translational motion, and is expressed by the following equation when the measured object is loaded onto the load cell:

$$M\ddot{x}(t) + C\dot{x}(t) + Kx(t) = Mg, \tag{1}$$

where M, C and K are the weight of the measured object $[\mathrm{g}]$, the damping coefficient $[\mathrm{Ns/m}]$, and the spring rate $[\mathrm{N/m}]$, respectively, $x(t)$ is the displacement of the load cell $[\mathrm{m}]$, and g is the acceleration of gravity $[\mathrm{m/s^2}]$.

The steps for the filling process are as follows.:

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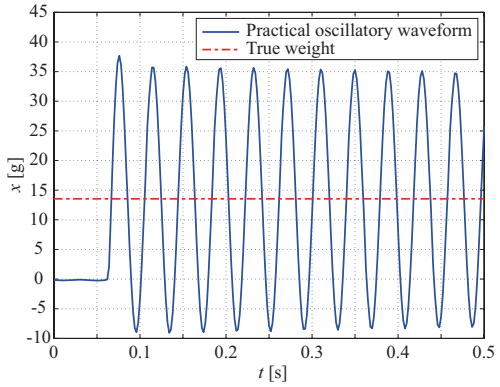

Fig. 2. Practical oscillatory waveform of the load cell

A1 The vial is held with the arm, which carries the vial to just above the load cell.
A2 The vial is disengaged and free-falls to the load cell.
A3 The load cell vibrates, and the oscillatory waveform of the weight is outputted.
A4 The vial weight is estimated from the oscillatory waveform.
A5 As soon as the vial weight is estimated, the timer filling is started.
A6 Total weight is estimated from the oscillatory waveform after the timer filling is completed.
A7 The medication fill ration is obtained by subtracting the vial weight from the total weight.

The oscillatory waveform of the load cell when the vial has the nominal weight 13.5 [g] is loaded, as shown in Fig. 2. As illustrated in the figure, since the oscillatory waveform of the practical load cell vibrates, it is difficult to calculate the weight value. Consequently, an accurate method of measuring weight is necessary.

III. Estimated Medication Fill Ration Method

Here, a method is proposed that provides medication filling accuracy equivalent to that obtained by the conventional method, and shortens the waiting period. Since the practical oscillatory waveform of the load cell is expressed by (1), (1) is expressed by the following equation by isolating the oscillatory waveform $x(t)$:

$$x(t) = \mathrm{e}^{-\varepsilon t}(A\sin\omega t + B\cos\omega t) + M, \tag{2}$$

where A and B are the gain [g], ω is the angular frequency [rad/s], ε is the damping coefficient [s^{-1}], and M is the weight [g]. These variable numbers are called parameters. To estimate the weight, (2) is fitted to the practical oscillatory waveform of the load cell using the NLS method. Since the angular frequency ω is important when using the NLS method, the method for calculating the angular frequency ω is described below in Section III-A. In the present study, it is important to be fitted to the practical oscillatory waveform of the load cell with sufficient accuracy, and calculate M. Even when nominal vial content is the same, the weight may differ within a permissible dimension tolerance.

Thus before filling a liquid medication, it is necessary to estimate the vial weight. In this study, the total weight (i.e., the sum of the vial weight and the medication fill ration) was estimated after the filling of the liquid medication, and the method of calculating the medication fill ration by subtracting the vial weight from the total weight was adopted.

First, the weight value is outputted at every sampling time (Δt = 0.002 [s]) with various types of converters by deforming the strain gauge of the load cell.

Next, the storage time T_i (in which the time spent using the oscillatory waveform of the load cell) is stored; this is expressed by the following equation:

$$T_i = i\Delta t, \quad i = j - N + 1, j - N + 2, ..., j, \tag{3}$$

where j is the count number of the present time, and N is the number of data. Regarding the number of data N, it is desirable to use the power of two in order to perform discrete fast Fourier transform (FFT) calculations later [4][5]. Hence, let the number of data N be 64 (= 0.128 [s]), and data storage waits until the 64 data inputted from the load cell system are stored. After the 64 data are stored, the data can be kept constant by storing the new weight value and removing the oldest weight value.

Since the oscillatory waveform produced after the vial is loaded onto the load cell is essential, the vial detection method is next to be described. The frequency analysis is conducted on the number of data N of the oscillatory waveform of the load cell by FFT. The white noise is contained in the oscillatory waveform of the load cell on the experimental device. If the power spectrum function $P_1(f)$ after FFT is calculated, the white noise is the same intensity in all of the frequency domains, as shown in Fig. 3(a). After the vial is loaded onto the load cell, the oscillatory waveform of a certain frequency is detected, and the power spectrum function $P_1(f)$ with a certain intensity can be detected and it can be determined whether the vial was loaded onto the load cell, as shown in Fig. 3(b). Accordingly, the frequency is repeatedly calculated until the power spectrum function $P_1(f)$ becomes $\max(P_1(f)) > 5.0$, and the frequency of the intensity determines the vial detection.

Next, the parameter ω (angular frequency) is calculated, and the vial weight and the total weight are estimated by the NLS method. Finally, the medication fill ration is calculated by deducting the vial weight from the total weight.

A. Calculating the angular frequency

When the nonlinear function (2) is approximated to enumeration of measured value, the NLS method determine the parameters of the function by calculating repeatedly so that the nonlinear function may serve as a good approximation to the measured value. There are both linear parameters and nonlinear parameters among those discussed here; A, B and M are linear parameters, and ω and ε are nonlinear parameters in (2). Depending on the number of nonlinear parameters used in the NLS method, the repeat count increases and the processing time increases. Moreover, if the nonlinear

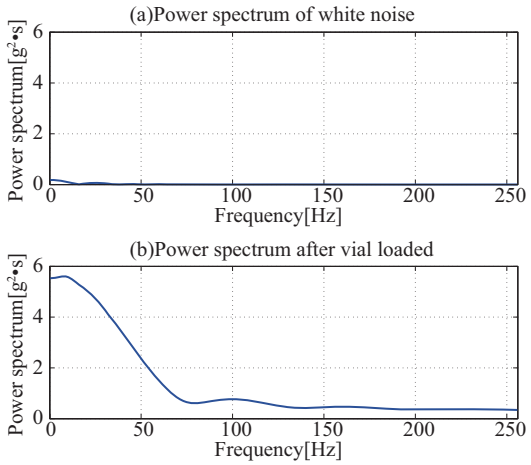

Fig. 3. Power spectrum function $P_1(f)$ of white noise and after the vial is loaded, by performing FFT

parameter is not set to an initial value that is near the true value, it is diffused without fitting to the nonlinear function. Generally, since there is a great change in the value of the angular frequency ω with each change in the present time, it is necessary to calculate the angular frequency ω in sequence. Then, the angular frequency ω is calculated by a frequency analysis using FFT. If the angular frequency ω is set the initial value as the value near the true value, the repeat count until the practical oscillatory waveform of the load cell fits the nonlinear function decreases. The flow which estimates the frequency from the power spectrum function $P_2(f)$ after FFT is summarized as follows.

By using the window function correctly, the spectral resolving power as the result of the frequency domain improves. The window function is used for the pretreatment to the time dimension of the measured value. In this study, we employed the widely used the Hanning window. The Hanning window has a characteristic in which the side lobe falls sharply, and it is very effective at discriminating the angle frequency component. The Hanning window $H_{\mathrm{w}}(n)$ is expressed by the following equation:

$$H_{\mathrm{w}}(n) = \begin{cases} 0.5 - 0.5\cos(\frac{2\pi n}{N-1}), & \text{if } n = 0, 1, ..., N-1 \\ 0, & \text{otherwise,} \end{cases} \quad (4)$$

where N consists of the number of data.

After applying the Hanning window the edge effect can be minimized, and it is easy to determine the frequency. However, it is known that the frequency of the oscillatory waveform of the load cell used by only adopting the Hanning window is not very accurate. And so, the peak of the power spectrum function after FFT is interpolated, and the calculation accuracy of the frequency is improved.

As shown in Fig. 4, the estimation method by the quadratic interpolation of the peak of the power spectrum function is performed. Sufficient accuracy is acquired in addition to the merit of simplicity and processing efficiency with this method [6]. Now, let the angular frequency be $\hat{\omega}$ after the quadratic interpolation.

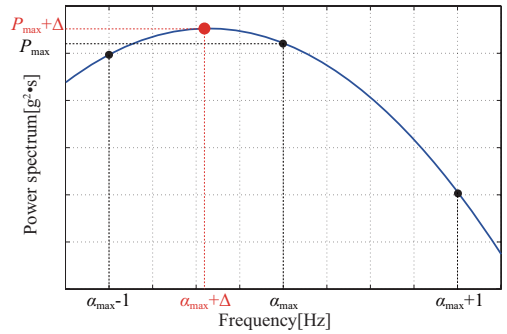

Fig. 4. Frequency $(\alpha_{\max} + \Delta)$ by quadratic interpolation using $\alpha_{\max}$ and the two neighborhood of $\alpha_{\max}$

TABLE I

COMPARISON OF THE ANGULAR FREQUENCY ω USING THE TRUE VALUE 160.6875 [rad/s]

Parameter \ Quadratic interpolation	Not adopt	Adopt
Angular frequency ω, $\hat{\omega}$ [rad/s]	159.5340	160.7060
Relative error %	0.7179	0.0115

As shown in Fig. 4, α is the discrete frequency. The peak of the interpolation function $(P_{\max} + \Delta)$ is detected, and this peak value is used to calculate the angular frequency $\hat{\omega}$ in the time sequence. The equation of the angular frequency ω is expressed as $\omega = 2\pi\alpha$ in the time series.

Next, to verify the calculation accuracy of the quadratic interpolation, the angular frequency ω (that did not adopt the quadratic interpolation and adopted the quadratic interpolation) are compared using the sample of the load cell waveform. The angular frequency ω of the sample waveform is 160.6875 [rad/s], and let this be the true value. The comparison result is listed in Table I. As listed in the table, although the angular frequency ω that did not adopt the quadratic interpolation is 159.5340 [rad/s] and the relative error is 0.7179%, the angular frequency $\hat{\omega}$ that adopted the quadratic interpolation is 160.7060 [rad/s], and it turns out that the relative error is decreasing by approx 0.7% to 0.0115%. The relative error is the difference between the true value and the estimated value. The method of calculating the angular frequency $\hat{\omega}$ by the quadratic interpolation was adopted in this study.

B. NLS method

The NLS method is the method of minimizing the objective function (which is the nonlinear function). The parameters of (2) are changed, and curve fitting is performed in such a way as to accord with the oscillatory waveform of the load cell [7]. The objective function $J(\boldsymbol{X}_k)$ is expressed by the following equation:

$$J(\boldsymbol{X}_k) = \sum_{i=j-N+1}^{j} r(\boldsymbol{X}_k, T_i)^2, \quad (5)$$

where $r(\boldsymbol{X}_k, T_i)$ is the residual error, and k is the repeat count in the NLS method. Parameter $\boldsymbol{X_k}$ is expressed by the following equation:

$$\boldsymbol{X_k} = \left(\ A_k, B_k, \hat{\omega}_k, \varepsilon_k, M_k \ \right)^{\mathrm{T}}. \quad (6)$$

The algorithm for the concrete NLS method is as follows.:

B1 $W_j = 0, N = 64$.

B2 The angular frequency $\hat{\omega}_0$ of the oscillatory waveform of the load cell $x(T_i)$ is calculated by FFT and determines $\boldsymbol{X}_0$.

B3 $k = 0$.

B4 $r(\boldsymbol{X}_k, T_i) = \hat{X}(T_i) - x(\boldsymbol{X}_k, T_i)$.

B5 $\Delta\boldsymbol{X}_k = \boldsymbol{H}_k^{-1}\boldsymbol{V}_k$.

B6 $\boldsymbol{X_{k+1}} = \boldsymbol{X}_k + \Delta\boldsymbol{X}_k$.

B7 If $\omega_k < 2\hat{\omega}_k$, $0 < \omega_k$ and $k \leq k_{\max}$, then go to B8, otherwise $j = j + 1$, and go to B2.

B8 If $\max(\Delta\boldsymbol{X}_k) \leq Er_1$, then go to B9, otherwise $k = k + 1$, and go to B4.

B9 $W_j = M_k$.

B10 If $W_j - W_{j-1} \leq Er_2$, the estimation is completed, otherwise $j = j + 1$, and go to B2.

where M_j is the estimated weight [g], $\hat{X}(T_i)$ is the oscillatory waveform of the load cell, and Er_1 and Er_2 are scalar constants, respectively ($Er_1 > 0$, $Er_2 > 0$). $k_{\max}$ is 100. The matrix $\boldsymbol{H_k}$ and the vector $\boldsymbol{V_k}$ are expressed by the following equations:

$$\boldsymbol{H_k} = \begin{pmatrix} \sum \frac{\partial r}{\partial A}\frac{\partial r}{\partial A} & \sum \frac{\partial r}{\partial A}\frac{\partial r}{\partial B} & \sum \frac{\partial r}{\partial A}\frac{\partial r}{\partial \hat{\omega}} & \sum \frac{\partial r}{\partial A}\frac{\partial r}{\partial \varepsilon} & \sum \frac{\partial r}{\partial A}\frac{\partial r}{\partial M} \\ \sum \frac{\partial r}{\partial B}\frac{\partial r}{\partial A} & \sum \frac{\partial r}{\partial B}\frac{\partial r}{\partial B} & \sum \frac{\partial r}{\partial B}\frac{\partial r}{\partial \hat{\omega}} & \sum \frac{\partial r}{\partial B}\frac{\partial r}{\partial \varepsilon} & \sum \frac{\partial r}{\partial B}\frac{\partial r}{\partial M} \\ \sum \frac{\partial r}{\partial \hat{\omega}}\frac{\partial r}{\partial A} & \sum \frac{\partial r}{\partial \hat{\omega}}\frac{\partial r}{\partial B} & \sum \frac{\partial r}{\partial \hat{\omega}}\frac{\partial r}{\partial \hat{\omega}} & \sum \frac{\partial r}{\partial \hat{\omega}}\frac{\partial r}{\partial \varepsilon} & \sum \frac{\partial r}{\partial \hat{\omega}}\frac{\partial r}{\partial M} \\ \sum \frac{\partial r}{\partial \varepsilon}\frac{\partial r}{\partial A} & \sum \frac{\partial r}{\partial \varepsilon}\frac{\partial r}{\partial B} & \sum \frac{\partial r}{\partial \varepsilon}\frac{\partial r}{\partial \hat{\omega}} & \sum \frac{\partial r}{\partial \varepsilon}\frac{\partial r}{\partial \varepsilon} & \sum \frac{\partial r}{\partial \varepsilon}\frac{\partial r}{\partial M} \\ \sum \frac{\partial r}{\partial M}\frac{\partial r}{\partial A} & \sum \frac{\partial r}{\partial M}\frac{\partial r}{\partial B} & \sum \frac{\partial r}{\partial M}\frac{\partial r}{\partial \hat{\omega}} & \sum \frac{\partial r}{\partial M}\frac{\partial r}{\partial \varepsilon} & \sum \frac{\partial r}{\partial M}\frac{\partial r}{\partial M} \end{pmatrix} \tag{7}$$

and

$$\boldsymbol{V_k} = \left(\sum r\frac{\partial r}{\partial A}, \sum r\frac{\partial r}{\partial B}, \sum r\frac{\partial r}{\partial \hat{\omega}}, \sum r\frac{\partial r}{\partial \varepsilon}, \sum r\frac{\partial r}{\partial M} \right)^{\mathrm{T}}. \tag{8}$$

The medication fill ration is calculated by the above algorithm. In these equations, the summation ranges of all $\sum$ are $i = j - N + 1, ..., j$. Similarly, r, A, B, $\hat{\omega}$, ε and M are short for $r(\boldsymbol{X}_k, T_i)$, $A_k(T_i)$, $B_k(T_i)$, $\hat{\omega}_k(T_i)$, $\varepsilon_k(T_i)$ and $M_k(T_i)$, respectively.

IV. Experiment

The oscillatory waveform of the load cell is acquired in real time, and the oscillatory waveform of the load cell is analyzed by batch processing. We use real time as the system that processes the input data from the device in consecutive segments, and we define "batch processing" as the system that collects fixed data and performs batch processing in a lump. Here we describe how we verified whether the proposed method is more effective regarding the medication fill ration and the estimated time compared to the conventional method. The conventional method uses the weight value after a pass through an analog low-pass filter and the use of a simple moving average, and the estimation of the vial weight or total weight required 0.75 [s]. We used an electronic balance that measures to the ten-thousandth place to determine the vial weight and the medication fill ration, and let this be the true value. Moreover, four kinds of vials were prepared, and the medication fill rations were 5.0 [g] by timer filling.

TABLE II

Experimental results using the proposed method

Category \ Experiment	1	2	3	4
Vial weight [g]	13.5607	13.5578	13.5536	13.5649
Estimated vial weight [g]	13.3956	13.3791	13.3563	13.3538
Estimated total weight [g]	18.3390	18.3197	18.2962	18.2833
Medication fill ration [g]	4.9434	4.9406	4.9399	4.9295
True value of medication fill ration [g]	4.9415	4.9348	4.9312	4.9237
Relative error %	-0.0385	-0.1175	-0.1764	-0.1158

The oscillatory waveform of the load cell is outputted every sampling time 0.002 [s], the number of data N is 64 and the scalar constants Er_1 and Er_2 are 1.0×10^{-5} and 1.0×10^{-4}, respectively. Four trials of experimental data are listed in Table II. In four experiments, the permissible relative error was less than $\pm1.0\%$, and all experiments fulfilled the specifications. Regarding the estimated time, since the present time passed approx 0.100 [s] after the vial is loaded, it is possible to estimate the vial weight in approx 0.230 [s]. Similarly, since the present time passed approx 0.140 [s] after the filling valve is closed, it is possible to estimate the total weight in approx 0.270 [s]. Consequently, while the proposed method realizes medication filling accuracy comparable to that achieved by the conventional method, our method makes it possible to shorten the time for computing the weight value approx 60%, and since the cycle time is significantly improved, the proposed method show reasonable efficacy.

V. Conclusion

We proposed a method for estimating the medication fill ration using the oscillatory waveform of the load cell. We used the method, which prevents diverging parameters by FFT, when changing parameters and performing curve fitting to nonlinear functions. The proposed method realizes medication filling accuracy comparable to that achieved with the conventional method, but made it possible to shorten the time to compute the weight value by approx 60%. In addition, since a low-pass filter is not used with the proposed method, the new method is not subject to the influence of a time delay. Further research is necessary to build a algorithm that can calculate at high speed.

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