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Inverse Numerical Simulation of Drug Movement in the Middle Ear and the Cochlea

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Abstract
The research proposed an inverse numerical simulation method to recognize the mechanisms of the drug movement from the middle ear to the cochlea and calibrate the associated parameters. A real 3D model was obtained from the CT image and the relative geometry and mesh were built by ICEM-CFD. The simulation was processes by ANSYS-CFX. A set of drug concentration measurement in the cochlea was used in calibrating the parameters. Two new mechanisms: a relaxation time of the absorption via the wall of the middle ear and a concentration threshold to start the permeation from the middle ear to the cochlea were also proposed in this research to complete the phenomena of drug movement. The results indicate a reasonable mechanism to expound the process of drug movement.
Keywords: inverse numerical simulation, drug movement

Introduction
In the field of treatment to inner ear disorders, local drug delivery is becoming wide useful method. The method uses some application systems such as the Microotoscope 'Model Tübingen', GYRUS Medical GmbH (former Explorent® /STUEMED®) to apply drug on the round window membrane (RWM) directly. Such systems guide a tube or pipe going through the ear and finally release the drug on the middle ear side of the RWM (RWM@ME). The drug passes into the inner ear via the mechanism of permeability. However, the disadvantage is it probably damages the wall of the ear and/or the RWM during guiding the tube or pipe. On the other hand, Drug injected into the middle ear is believed to diffuse within the middle ear, permeate through the RWM and then diffuses within the cochlea. In this study, a numerical simulation method was established to study the phenomenon of drug movement in the middle ear and the cochlea. Besides, the experiment measurement of concentration in the cochlea was also made to adjust the associated coefficients and verify the simulation results.

The drug movement within the middle ear, pass through the RWM, and movement within the cochlea were controlled by the physiological coefficients, such like the diffusion coefficient in the middle ear and the cochlea, the absorption coefficient of the middle ear wall and cochlea wall, the permeability and active concentration threshold of the RWM, the permeability between the compartments (i.e. scala tympani, ST; scala vestibuli, SV; cochlea endolymphatic space, EL, and spiral ligament, SL). Stefan et al. (2006) [1] studied the drug movement in the cochlea with a 3D model but simplified as a 1D numerical model. Furthermore, Stefan et al. (2006) [2] used a middle ear clearance to represent the physiological phenomenon in the middle ear without a real simulated domain.

Besides the simulation techniques, the drug concentration measurements in the middle ear and the cochlea are not easily to obtained. The past researched focused on the effect of treatment on the hearing aids. The real data of drug concentration appears the overall effect the mechanisms of drug movement dominate the transportation and/or diffusion of the drug in the middle and the cochlea, and also facilitate the knowing to the above-mentioned mechanisms.

In this research, a time series data set of average drug concentration in the ST and SV was measured. The measurement was used to clarify the mechanisms of drug movement and calibrate the associated parameters. Some mechanisms which are not seen in the previous research were proposed to complete and interpret the phenomena of drug movement.

Materials

Geometry and Mesh:

Fig. 1 shows a real 3D model of the middle ear. Fig.2 shows the direction of the drug injected and the gravity. Fig. 2 also shows the pathway to the round window in the middle ear. The pathway reveals the round window is not located at the bottom of the middle ear and the drug can not arrive at the round window directly by injection. Fig.3 shows the geometry and space relation of the cochlea and the round window. Fig. 4 shows the divisions in the cochlea. All the geometry and associated mesh were built from CT images and histological sections by our group [3]. The CAD model was established by ICEM-CFD.

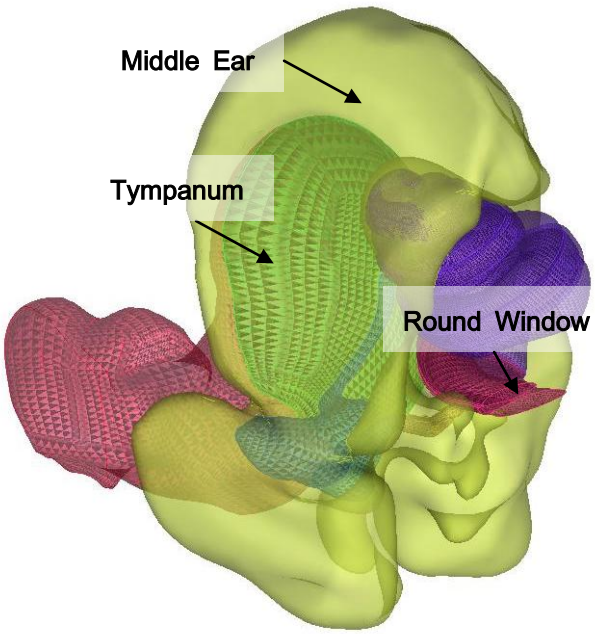

Fig.1 The geometry and space relation of the middle ear and the round window

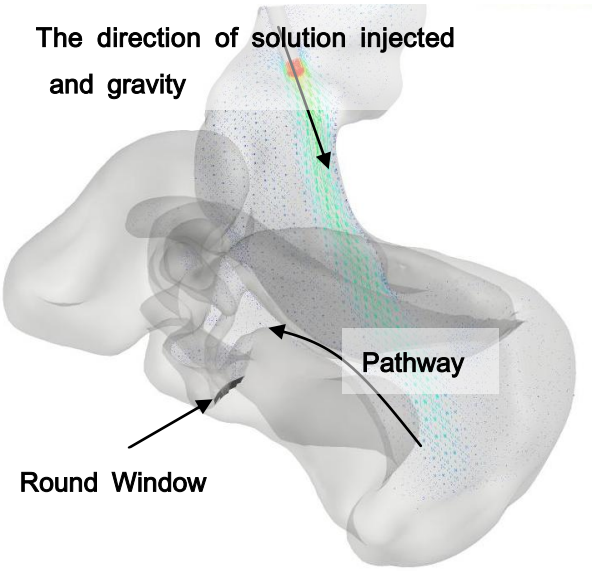

Fig.2 A view described the direction of solution injected and gravity and the location of the round window

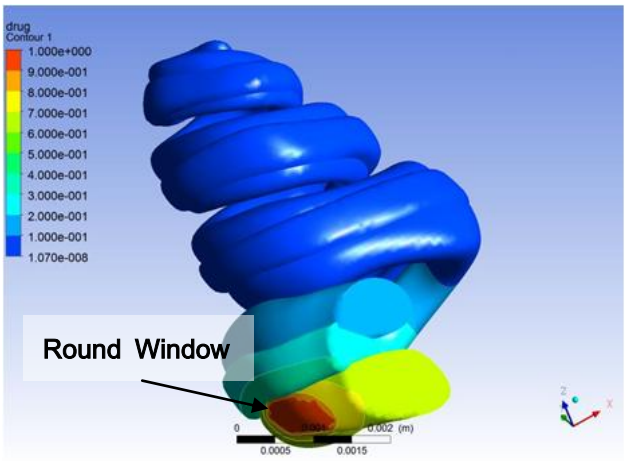

Fig. 3 The geometry and space relation of the cochlea and the round window

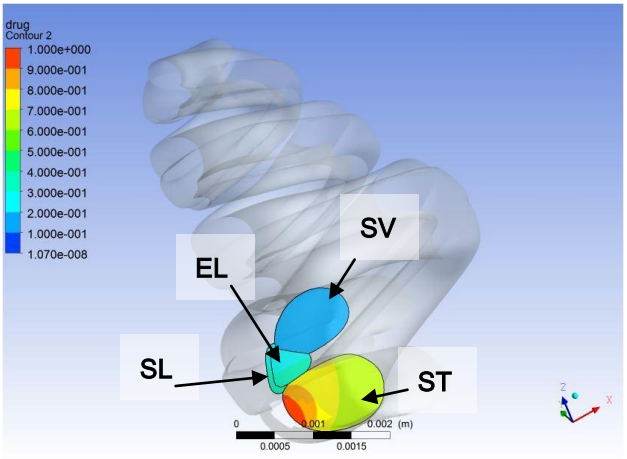

Fig. 4 The space relation of SL, EL, SV and ST in the cochlea

Concentration Measurement:

The drug (density 32.5 kg/m^3) was dissolved in normal saline and the solution was injected into the middle ear with a constant flow rate of 3.33x10^{-10} m^3/s which is equaled to velocity of 2.65x10^{-3} m/s. The inject time was lasted 32 minutes. A time series of the average concentration of ST and SV was measurement as shown in Fig. 5.

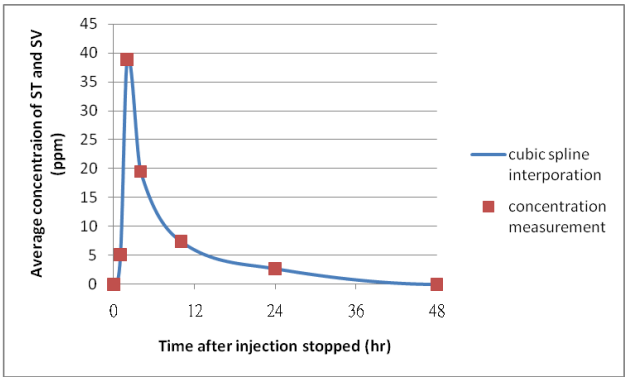

Fig. 5 The measurement and cubic spline interporation of average concentration of ST and SV

Simulation Methods

The Mechanisms:

Intuitively, the drug movement in the middle ear and the cochlea is dominated by the several mechanisms. After the drug injected into the middle ear, the drug moves within the middle ear by the **momentum** from the initial injecting velocity and the particle **diffusive phenomenon**. Some particles or spray could touch the wall of the middle ear and permeate through the wall. **Permeability** is used to describe the phenomenon. Besides the permeating part, some particles or spray touched the wall may condense together and form as a larger particle. Finally the larger particle could deposit at the concave and may form a small pond. This part of drug may not really arrive at the RWM and the physical phenomenon is difficult to simulate. We proposed a **relaxation time** concept to interpret the totally effect. The relaxation time is a representative which describes the effect causes the drug decrease.

Some other particles or spray can move toward the RWM by convection and diffusion effects and permeate through the RWM. Based on the physical phenomenon of a membrane, it is believed there is a **concentration threshold** to control the material pass through the membrane. The concentration threshold provides an initiate mechanism to start the permeate effect [4]. Also, the RWM has a coefficient called as **permeability** which controls the material pass through the membrane, too.

After the drug permeates through the RWM and goes into the cochlea, the particle is diffused in the lymph within the cochlea. Fig. 4 shows there are four chambers, SL, EL, ST and SV within the cochlea so the drug can permeate through the interfaces between each two. The each interface has a **permeability** to control the material pass through and the each chamber has its own **diffusive coefficient** to control the movement within the each chamber.

Coefficient and Parameter List:

Table 1 lists the coefficients used in this research and some of them (marked with a *) need to be calibrated.

Table 1

Permeability(mm/s)	
SV-SL	1.10E-03
ST-SL	5.00E-04
SV-EL	6.00E-04
ST-EL	4.00E-04
SL-EL	5.00E-04
*RWM	About 2.00E-08
Wall@Middle Ear	1.00E+00
END@Cochlea	1.00E+00
Diffusion Coefficient(mm^2/s)	
Middle Ear	7.84E-04
Cochlea	7.84E-04
*Concentration Threshold of RWM	unknown
*Relaxation Time	unknown

Stefan et al. (2006) [2] suggested a permeability of the RWM; however, these researches lacked measurements to verify the coefficient. Under the consideration of the importance of the RWM, we treat the permeability as an adjustable parameter and calibrate it with the measurement concentration.

Simulation Methods and Results:

The numerical simulation was done by ANSYS-CFX. According to the above discussion, the dug movements within the middle ear and within the cochlea were simulated separately. In the middle ear, the drug movement was simulated by a convection-diffusion equation [5]. Refer to Fig.6, the figure shows the setup of boundary conditions in the middle ear. Besides the governing equation and the boundary condition, we proposed a conceptual relaxation time to interpret the phenomena which are difficult to simulate. The relaxation time control the initial time to activate the permeable effect on the wall. By adjusting the relaxation time, we can control the time of peak concentration appeared at the middle ear side of the RWM (RWM@ME) and compared with the concentration measurement. The calibration method will describe in detail in following section.

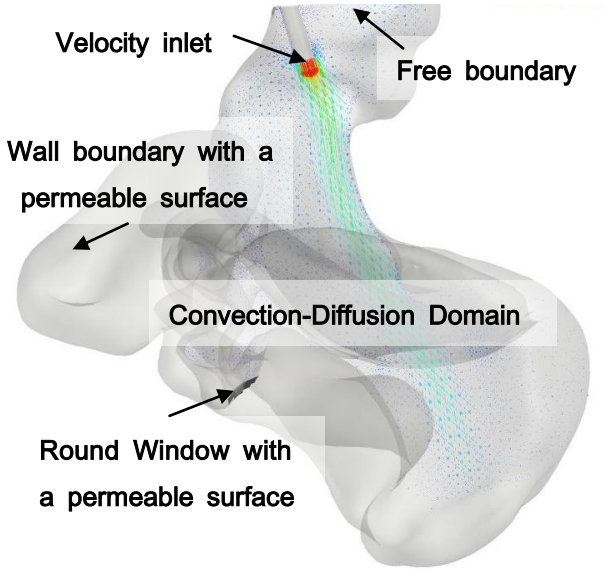

Fig. 6 The setup of boundary conditions in the simulated domain of the middle ear

Fig. 7 shows the simulated concentration on RWM@ME with a different relaxation time. From the results, it is obvious the relaxation time controls the time of the peak appears. For example, the green line (1hr) represents the permeate mechanism of the wall of the middle ear is activated at the time after stopping injecting the drug. A flat concentration variation after the peak and the descended rib implies there may be a concentration threshold to suppress the permeable effect through the RWM. The associated parameter will be calibrated later.

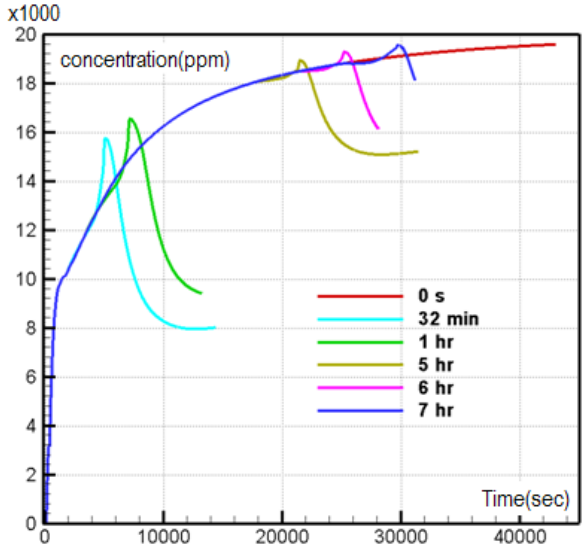

Fig.7 The simulated concentration on (RWM@ME) with a different relaxation time

In the cochlea, it is believed that the drug movement is only dominated by the diffusion equation [5] due to the presence of lymph. Fig.7 shows the setup of boundary conditions in the cochlea. The most important is the boundary condition at the cochlea side of the RWM (RWM@cochlea). The time series of the concentration on RWM@cochlea is input information to perform the simulation; however, it is not easy to know the distribution. We use the method called the unit hydrograph (UH) method to overcome the difficult and seek for a proper input series which can obtain a simulation result similar to the concentration method.

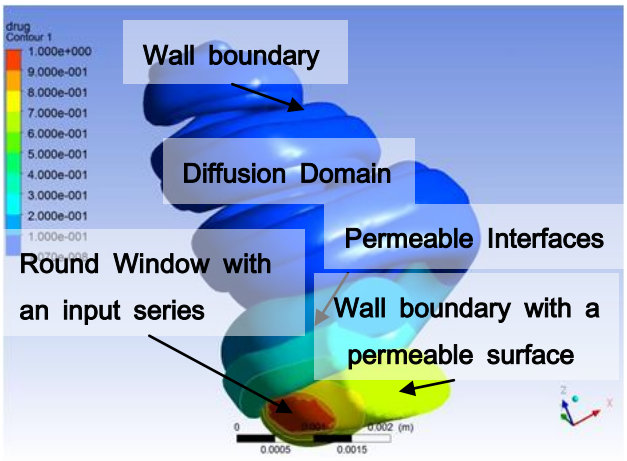

Fig. 7 The setup of boundary conditions in the simulated domain of the cochlea

Unit Hydrograph (UH) Method:

Unit hydrograph theory was proposed by Sherman (1932) [6]. At first, the method is used to derive the relationship between the input (rainfall) and the response (runoff) of a watershed. The concept of the UH method is the system character between the input and the response is linear and can be cumulate. “Linear” means a doubled input will lead a doubled response which is suite for the diffusion equation. The usage of UH in this research is described as following step: (1).Give a unit concentration (1 ppm) in a unit time (1 min) as the input and perform the simulation, (2). Take the simulated result as a unit system response to a unit input; the unit system response is called as unit hydrograph, (3). Use the convolution integral method with the unit hydrograph and the concentration measurement to obtain the real input series, and (4). Use the real input series and perform the simulation again. With a proper regressive and adjusting technique, the simulated result in step (4). should be similar to the concentration measurement.

Fig. 8 shows the UH (unit system response) of a unit input in a unit time. Because the concentration measurement we have is the time series of the average concentration of ST and SV (shown in Fig. 5), the UH is calculated from averaged data of the concentration in SV and ST.

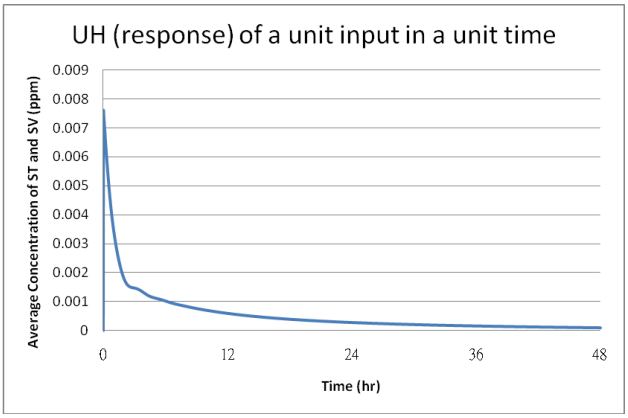

Fig.8 The UH of a unit input in a unit time

Fig. 9 shows the input concentration series on RWM@cochlea which is derived by the convolution integral with the concentration measurement and the UH series. The figure shows there is little concentration after the descended rib.

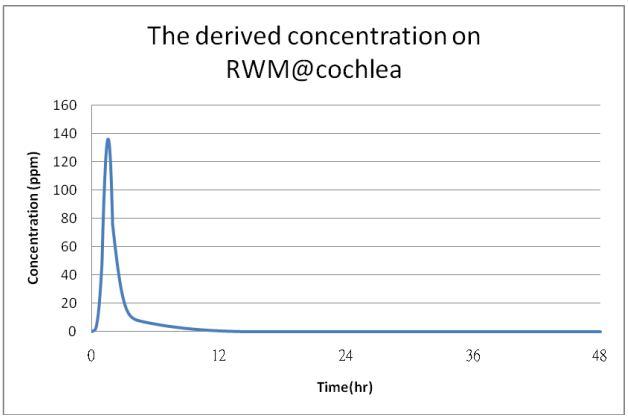

Fig.9 The derived concentration on RWM@cochlea

Fig. 10 shows the simulated result which uses the data shown in Fig. 9 as an input. The good comparison between the simulated result and the measurement implies the UH method is a good technique to perform an inverse simulation to obtain the input series data.

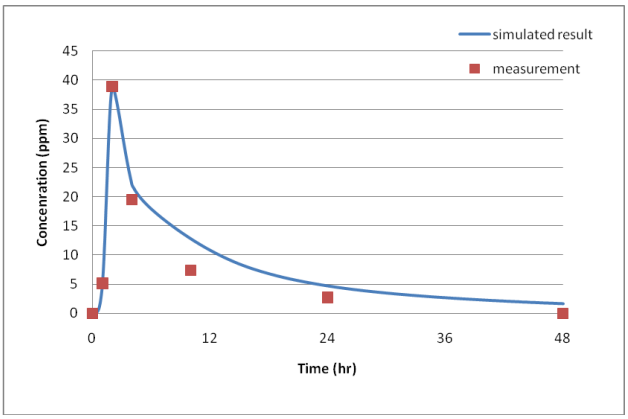

Fig.10 The comparison of the simulated result and the concentration measurement

The above discussion illustrates a direct simulation method of the concentration in the middle ear and an inverse simulation method of the concentration in the cochlea. We have the concentration series on RWM@ME controlled by the relaxation time and a concentration series on the RWM@cochlea. In the following section, the method of calibration and the method to link the two concentration series will be described.

Calibration Methods and Results

The Procedure of Calibration:

After arriving at RWM@ME, the drug permeates through the RWM and goes into the cochlea. Hence, the mechanism of drug permeation through the RWM and the associated parameters need to be clarified and calibrated. Refer to Fig. 11, the figure schematically shows the phenomenon around the RWM and indicates the mechanism we propose in this research.

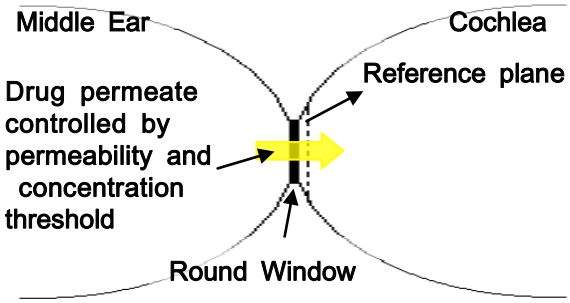

Fig.11 The schematically drawing of the phenomenon around the RWM

Fig. 12 illustrates the mechanisms around the RWM in detail.

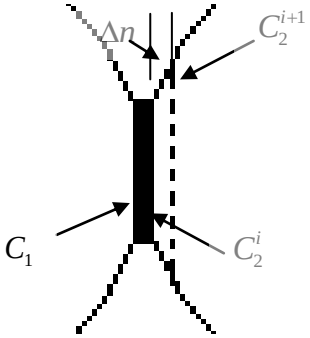

Fig.12 The detail drawing of the mechanism around the RWM

The permeate effect can be illustrated as the following equation:

$$D\frac{\partial C}{\partial n} = -\beta\left[\left(C_1 - C_T\right) - C_2\right] \qquad (1)$$

In equation (1), D is the diffusivity in the cochlea [L^2/T], $\partial C/\partial n$ is the gradient normal to the RWM [1/L], β is the permeability of the RWM [L/T], C_1 is

the average concentration on the RWM@ME [-], C_T is the concentration threshold to activate the permeable effect [-], and C_2 is the average concentration on the RWM@cochlea [-]. The equation means the drug permeate through the RWM from the middle ear to the cochlea is equaled to the drug diffusion in the cochlea. The amount permeated through is controlled by the concentration difference on the both side of the RWM, the diffusion coefficient, permeability of the RWM and the concentration threshold.

By proper derivation, equation (1) can be rewrite as follows

$$C_1 = \frac{D}{\beta \Delta n}\left(C_2^i - C_2^{i+1}\right) + C_2^i + C_T \qquad (2)$$

Refer to Fig.12 and equation (2), Δn is the distance between the surface at RWM@cochlea and the reference plane [L], C_2^i is the average concentration on the RWM@cochlea [-], C_2^{i+1} and is the average concentration on the reference plane [-]. The equation means a simple differential method is introduced to calculate the equation; however, there are two parameters, β and C_T need to be calibrated. Beside β and C_T, Table 2 shows there is another parameter, relaxation time, needed to be calibrated.

Fig.13 shows the simulated results of calibration where the relaxation time is 0.5 hr, the permeability β is 3.2×10^{-8} mm/s, and the concentration threshold C_T is 8900 ppb. The curves of concentration are drawn from about time=0.5hr because the part of injection was not considered in the calibration.

Based on the mechanisms we proposed, when the concentration at the RWM@ME is below the concentration threshold, the permeable effect is disabled. It means the calculated concentration below the 8900 does not have a significant meaning. The the peak time and peak value of the curves are fit well, the span of the curves are also similar. Therefore, it is believed the proposed mechanisms and the calibrated parameter can present the phenomena of the drug movement.

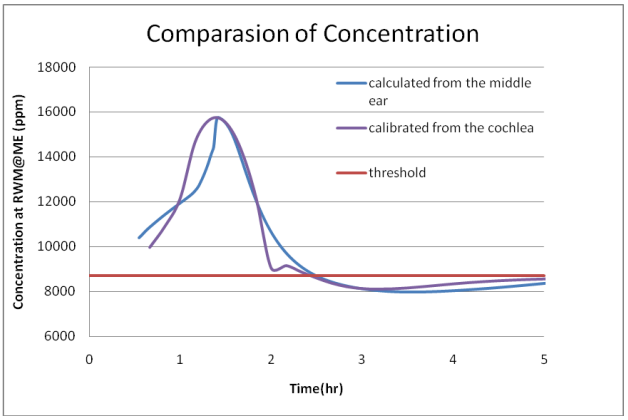

Fig.13 The results of calibration

Conclusion

An inverse simulating method was proposed in this research. The method consists of three major parts.

First, the drug movement in the middle ear was simulated by the convection diffusion equation with a relaxation time directly. The different relaxation times result the different peak time of the concentration arriving at the RWM@ME. The peak value of the concentration is somewhat different, too.

Second, the UH method and the diffusion equation are applied in the cochlea. By the UH method, a proper boundary concentration on RWM@cochlea which results in a well-fitting concentration can be obtained.

Finally, the linked mechanism between the middle ear and the cochlea is established by the RWM. The adjustable permeability and concentration threshold provide the flexibility to match the peak times and peak values of the concentration on RWM@ME and RWM@cochlea.

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