

## STUDENT VERSION

### Inner Ear Drug Delivery for Treating Hearing Loss

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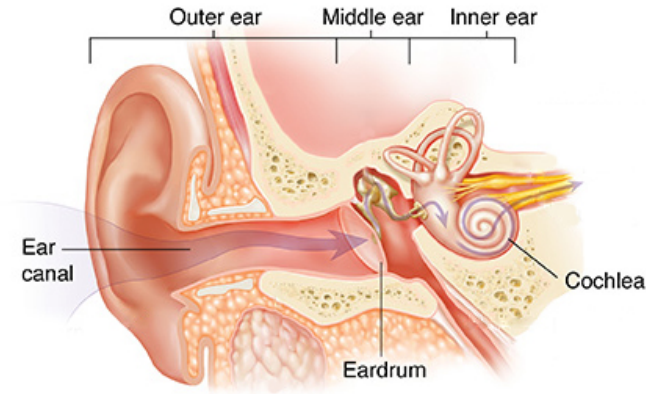
**Abstract:** Hearing loss is difficult to treat due to the inner ear location and structure. Drawing from this challenging case, this scenario guides students to transform a treatment protocol into a mathematical model. Students engage in pre-clinical studies to examine local drug delivery to the cochlea. The delivery system is modeled as a liquid mixing problem. Students formulate the differential equation, and solve the equation using separation of variables or integrating factor. They compute the amount and concentration of drug in the cochlea over time, and help design safe and effective devices. Through observation and interpretation of solutions in a real-life scenario, students enhance their understanding and application of a differential equation model.

#### SCENARIO DESCRIPTION

Over 5% of the world's population – or 466 million people – has disabling hearing losses [4]. The World Health Organization estimates that by 2050 over 900 million people – or one in every ten people – will have a disabling hearing loss.

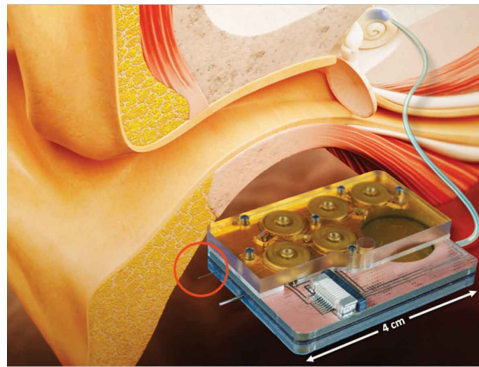
The inner ear is surrounded by dense temporal bone and protected by the blood-cochlea barrier, as illustrated in Figure 1. The cochlea, with the shape of a snail, is the part of the inner ear involved in hearing. It is lined by sensory hair cells and is filled with fluid (about 0.2 milliliters, or 200 microliters). The cochlea is a particularly challenging target for drug therapy in treating hearing loss. Oral medications and injections are typically blocked by the blood-cochlea barrier, and thus ineffective in reaching or precisely dosing drugs to the cochlea.

As an alternative to systemic administration, local drug delivery methods have emerged. Intra-cochlear delivery releases drugs directly to the inner ear in order to establish regeneration of the sensory hair cells and auditory nerve inside the cochlea. This enables precise targeting of drug concentrations within the therapeutic window for extended delivery. Reciprocating perfusion systems based on microfluidic technologies are showing promise for direct intracochlear delivery in order to



**Figure 1.** Human ear anatomy (adapted from [1]).

restore hearing [3]. A prototype of such system is shown in Figure 2. The implantable device is connected via a small tube to the cochlea. A battery-powered micropump pulses precise quantities of drug from a small reservoir into the cochlea in a “push-pull” mode, i.e. infusing and withdrawing cochlea fluid in a cyclic manner nearly simultaneously so that the fluid volume inside the cochlea stays constant.



**Figure 2.** Delivery chip component of an intracochlear drug delivery device comprising microfluidic drug storage and flow control [2].

In order to avoid damage to hearing structures, limitations on the maximum rate at which fluid can be pumped into the cochlea place stringent requirements on the system. It is challenging to design reliable systems that are capable of maintaining control over drug concentrations for long-term drug release. To address the difficulties in drug delivery and achieve safety and efficiency, **we need your help to establish effective models for pre-clinical studies.**

## 1. Think

Based on previous background information, let's see if you can come up with an appropriate differential equation model for this system.

(Hint 1: "The micropump is infusing and withdrawing inner ear fluids in a cyclic manner nearly simultaneously so that the fluid volume inside the cochlea stays constant.")

(Hint 2: Think about liquid mixing in the cochlea with the same flow rate in and out.)

## 2. Scenario

A patient is implanted with a reciprocating perfusion device to treat hearing loss. Suppose that the drug reservoir is primed with a drug solution at a concentration of  $1.2 \mu\text{g}/\mu\text{L}$  (microgram per microliter).  $1 \mu\text{L}$  of the drug solution is infused to the patient's cochlea every 30 minutes. Simultaneously the solution is withdrawn from the cochlea at the same rate. The fluid volume inside the cochlea stays at  $200 \mu\text{L}$ . Assume that the drug is delivered at a steady rate for simplicity. How much drug will be in the cochlea after a week? After two weeks? What is the concentration of the drug in the cochlea?

- Sketch a schematic liquid-mixing diagram for this model. Label the given numbers on your diagram.
- Before setting up the differential equation, define your variables clearly including units.
- What is the rate in? What is the rate out? Include the units.
- Set up an initial value problem for your model.
- Solve the differential equation and find out the amount and concentration of drug in the cochlea over time.
- Find out the amount and concentration of drug in the cochlea after a week, and after two weeks. What do you observe? Explain.
- Plot the amount and concentration of drug in the cochlea over time. What do you observe? Explain.

## 3. Design

You are in charge of designing a device for long-term drug release at a reduced delivery rate, so that after 60 days the cochlea would reach 90% of the concentration of drug solution, i.e.  $1.08 \mu\text{g}/\mu\text{L}$ . The other conditions remain the same as before. What should the delivery rate be set at?

## REFERENCES

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