

Intratympanic drug administration

A challenge for PK modelling

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Background

Intratympanic (IT) drug delivery (see **Table 1**) refers to drug administration in the middle ear beyond the tympanum with these main objectives:

- (i) maximize the delivery in the site of interest;
- (ii) minimize systemic exposure and side effects [2,3,4].

Pros	Cons
Drug diffusion into inner ear not limited by low cochlear blood flow and the blood-labyrinth barrier (BLB): - Higher bioavailability than with systemic administration - High intralabyrinthine concentrations - Low systemic side effects [1,2,3,5].	- High variability in perilymph drug levels after drug applications into the inner ear observed in animals [1]. - Challenging evaluation of pharmacokinetics (PK) due to difficulty in accessing the inner ear and its limited size [8,9].

Pharmacokinetics after IT administration

- Drug diffuses from the middle ear across the round window membrane (RWM), which is the only soft tissue structure located at the end of the scale tympani and separates the middle ear and the inner ear [6,7] (**Figure 1**).
- Factors such as the permeability of RWM to drugs, diffusion and clearance mechanisms affect perilymph drug levels responsible for the efficacy [1].

Aim of the present work

The development of a model to predict inner ear and systemic PK following IT administration would support dosing regimen selection and study design in both preclinical and clinical settings. Modelling approaches proposed in the literature were therefore reviewed.

Materials and Methods

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- Keywords:**
- intratympanic pharmacokinetic
 - intratympanic model
 - intratympanic administration
 - inner ear administration

Exclusion criteria: (i) no full text available; (ii) focus on administration routes other than IT; (iii) no relevant information on PK after IT administration and no modelling approach described.

Additional research: Relevant articles were also selected among the references of those found with the above criteria.

Current capabilities of the main tools for physiological based (PB) PK modelling (GastroPlus, PKSim, and Symcip [10,11,12]) were investigated.

Results

- A total of 39 papers were found; 10 were discarded because of exclusion criterion (i), 8 because of (ii), 7 because of (iii).
- Empirical compartmental models:** no examples were found for IT administration, neither in preclinical nor clinical setting.
- PB models:**
 - The computer simulation software FluidSim written in XoJo by Washington University (**Figure 2**) includes PB models of the mouse, guinea pig, and human ear [13,14]:
 - simulation of solute movements in fluid and tissue spaces of the cochlea and vestibular systems
 - elimination to systemic circulation [8,13,15,16,17]
 - applied in the preclinical setting to explore perilymph PK both after systemic and local administration [15,16,17,18]
 - applied in the clinical setting to compute inner ear drug concentrations after IT administration and associate them with hearing changes, and risk of hearing loss and deafness in Ménière’s disease and idiopathic sudden sensorineural hearing loss patients [19,20].
 - Mathematical equations to quantify the permeability coefficient through the RWM based on drugs’ physicochemical properties were obtained [21].
 - State-of-the-art of common PBPK tools (Gastroplus, Symcip, and PKSim) do not currently include a description of the ear and do not allow simulation of IT administration.

Conclusions

Literature search results highlighted a knowledge gap about PK after IT administration. The physiological structure of the ear is complex and extrapolation from animal to humans is not easy: animals like guinea pigs are used in preclinical studies, however anatomical differences with humans should be considered (see box on the right).

Furthermore, data collection in the inner ear is challenging both in animals and (especially) in humans [8,9], because of its invasiveness and of possible cerebrospinal fluid contamination.

Empirical approaches have not been attempted yet, however simple compartmental PK models and deconvolution techniques (to separate the intratympanic component of systemic absorption) might be coupled to describe drugs’ PK after IT administration and scale across species.

A **PB model** of the ear for different species is currently available, however well-defined criteria for parameters selection and integration of a whole-body description for systemic exposure prediction are still open challenges.

Table 1. Examples of drugs and therapeutic areas for IT administration [1,2].

Types of drugs	Therapeutic areas
- Glucocorticoids - Anesthetics - Antibiotics (aminoglycosides) - Neurotransmitters - Neurotransmitter antagonists - Monoclonal antibodies - Apoptosis inhibitors	- Sudden onset neurosensorial hearing loss - Ménière’s disease - Autoimmune ear diseases - Hearing loss due to sudden events of unknown etiology or secondary to immune reactions

Figure 1. Anatomy of the human ear (adapted from [22]).

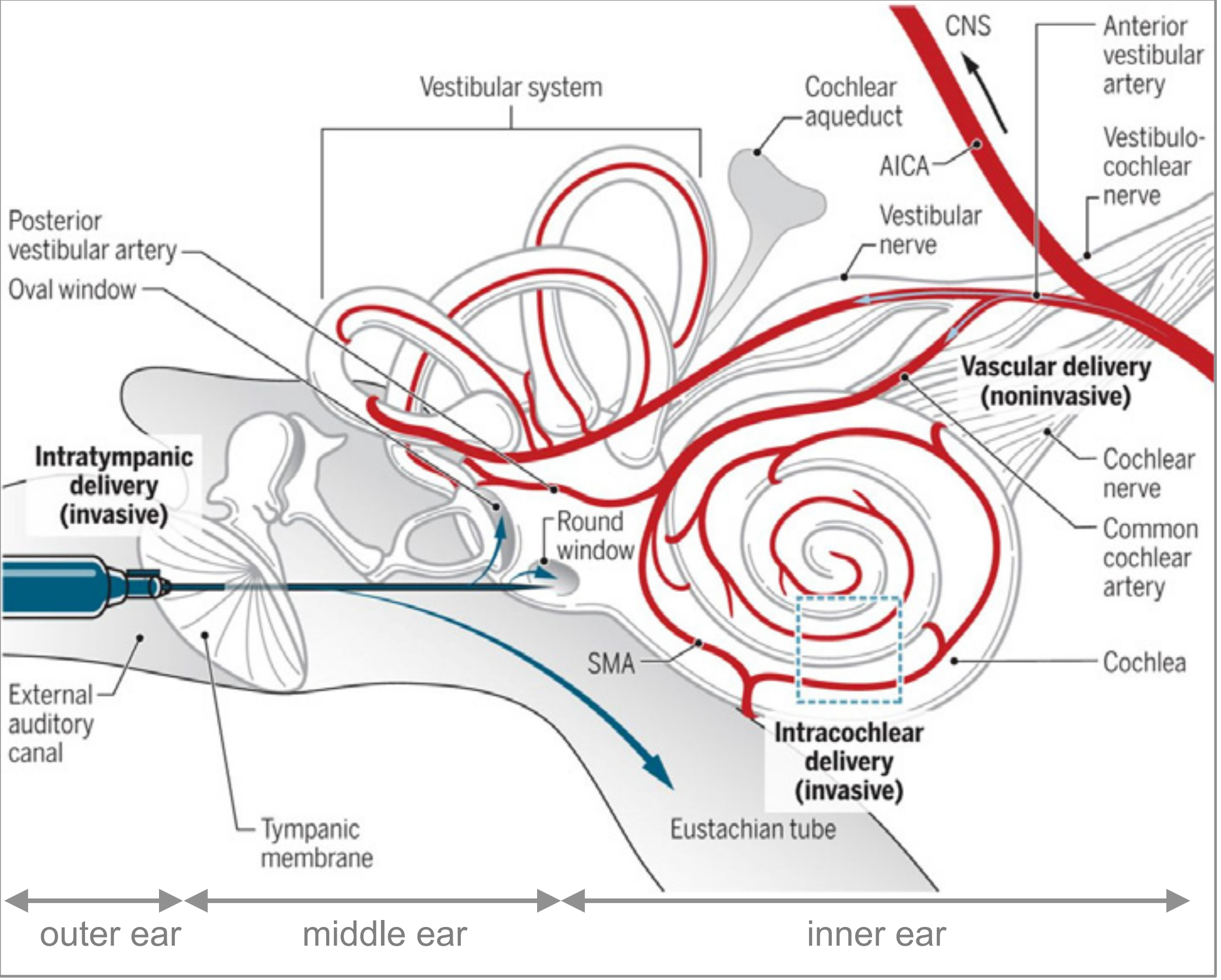
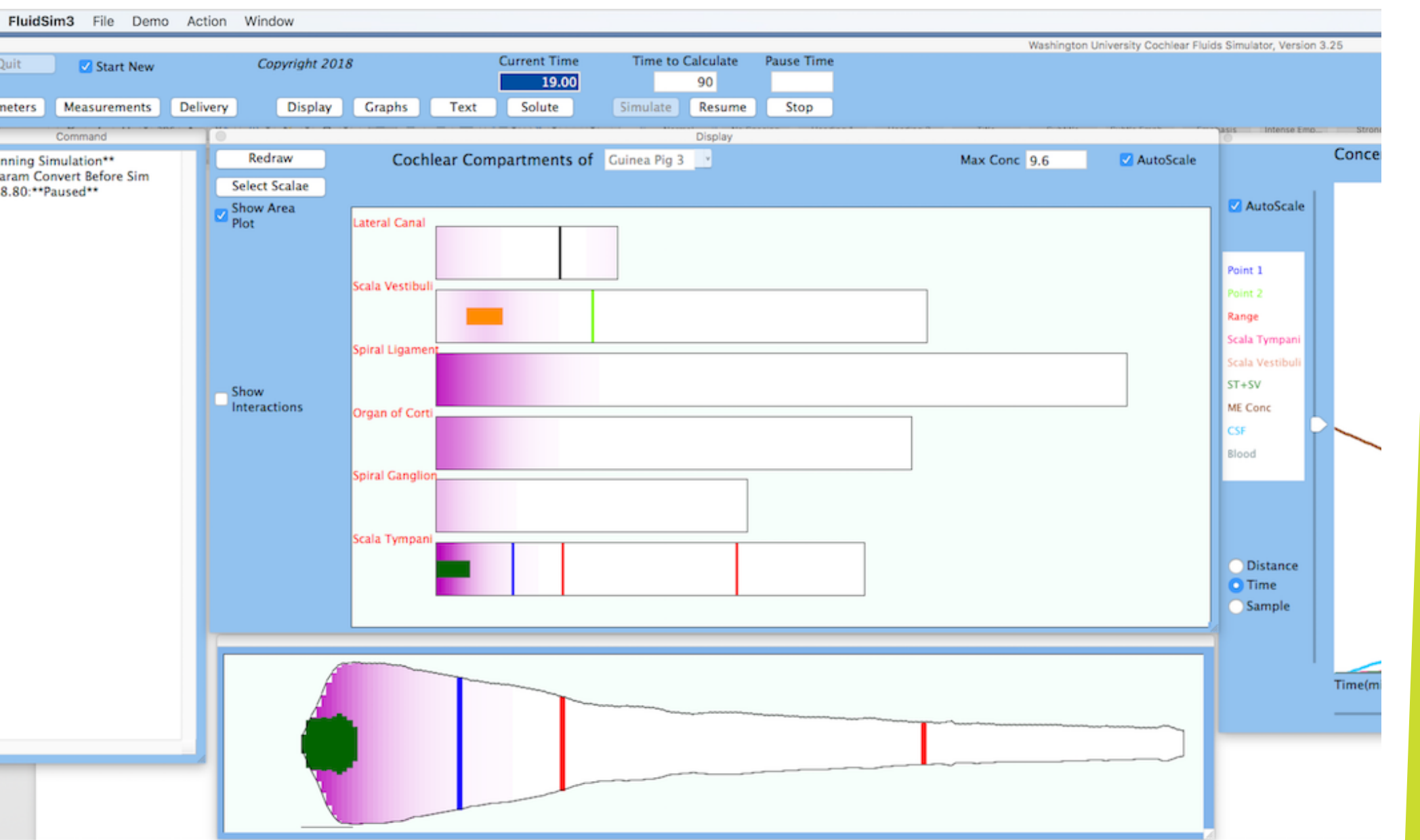


Figure 2. Screenshot of FluidSim (from [14]).



Examples of anatomical differences of human ear with respect to animal [1,2]

- Thicker and harder bony otic capsule (different permeability, also influenced by pathologies)
- Narrower cochlear aqueduct
- More variable cerebrospinal fluid pressure