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Two-dimensional Axisymmetric Model for the Sensitivity Analysis of a Chronic Drug Infusion into the Brain

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***Abstract*—A 64-run, 2-level partial factorial experimental analysis was conducted on a 2D axisymmetric finite-element model of the convection-enhanced drug delivery to the parenchyma of the brain. The purpose of this ANOVA analysis was to determine the relative importance of eight factors and their interaction in the volume of distribution for the drug. The analysis revealed that the infusion flowrate and concentration, the overall half-life of the drug and the *in vivo* effective concentration played an overwhelmingly dominant role in the drug distribution. The results of this analysis will guide the design of an appropriate drug delivery device by focusing research resources on the determined factors of most importance.**

I. Introduction

THE technique of convection-enhanced delivery (CED) of drugs to the brain has opened up a whole new world of possible pharmaceutical therapies that would not have been considered previously. CED effectively circumvents the blood-brain barrier (BBB), allowing large molecules specifically designed for treating the disease state to be administered directly into the parenchyma of the brain [1]. The effective combination of a drug and a delivery vehicle could provide a viable treatment for debilitating neurological diseases such as Alzheimer's, Parkinson's, and Huntington's disease.

Delivering drugs in this fashion is not without its challenges, however. Although minimized as much as possible, the placement of a catheter directly into the parenchyma of the brain is inherently invasive and requires precise placement. Once the catheter is in place, the delivery of the drug to the anatomy of interest is competing with the body's response to clear the drug. As such, the volume of distribution V_d, or the volume in the brain where the drug has a meaningful effect, is largely determined by the rate at which the drug is being delivered versus the rate at which the drug is being "destroyed" or taken out of the extracellular space by cellular uptake, metabolism and interstitial fluid (ISF) bulk flow.

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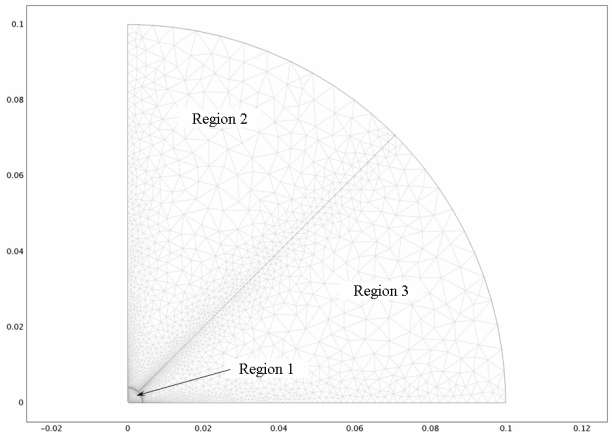


Fig. 1. 2-dimensional axisymmetric model used to solve for the drug concentration distribution. The diameter of region 1 is 8 mm. A small infusion sphere of 0.5 mm in diameter is placed at the center of region 1. The mesh consists of 8382 triangle elements. The axis of symmetry is the vertical line and the plane of symmetry is the bottom horizontal line. The units of the axes are in meters.

A variety of factors go into the design of a drug and its delivery system, all of which have a varying degree of effect on the resultant V_d. When designing a product and a drug, it is desirable to have an understanding of the relative importance that each design factor has on the final desired outcome. With the importance of each factor known, it is possible to focus research and development resources in understanding these factors. The method by which we determined the most important factors in designing a drug-delivery system was to perform an ANOVA sensitivity analysis on a simplified 2D finite-element model (FEM) of the brain. This knowledge will be very important in focusing our design energies on characterizing these important factors. With this knowledge in hand, our capability in designing an effective drug/delivery combination system will be greatly improved.

II. Methods

A. Finite-Element Model

Comsol Multiphysics (Comsol AB, Stockholm, Sweden) was used to construct the 2D FEM used in the ANOVA sensitivity analysis. The model is axisymmetric and consists of three distinct, isotropic regions surrounding a small infusion point of 0.25 mm (Fig. 1). Brain matter approximates rigid porous media, where the cells compose

the "solid" portion of the media, and the extracellular space surrounding the cells compose the pores. Consequently, the porosity of the brain tissue is defined as

$$\phi = V_f / V_t , \quad (1)$$

where ϕ is the porosity, V_f is the volume of the interstitial fluid, and V_t is the total volume of the brain.

The chronic, steady-state distribution of the drug concentration through the extracellular space of the brain is described by the diffusion-convection equation

$$\nabla \cdot \left(\frac{\vec{u}}{\phi} c - D \nabla c \right) = -\frac{0.693}{t_{1/2}} c , \quad (2)$$

where $\vec{u}$ is the volume average velocity, c is the extracellular concentration, and D is the diffusion coefficient. The half-life, $t_{1/2}$, accounts for all of the half-lives associated with metabolism, interstitial bulk flow clearance and cellular uptake. The analysis considered does not take into account any second-order or non-linear effects typically seen with actively mediated cellular uptake and metabolism.

The momentum in the model is accounted for using Darcy's law

$$\vec{u} = -\frac{K}{\mu} \nabla p , \quad (3)$$

where K is the hydraulic permeability of the brain tissue, and μ is the viscosity of the infusate. As the entire domain is considered to be incompressible, the continuity equation becomes:

$$\nabla \cdot \vec{u} = 0 . \quad (4)$$

The boundary conditions for the model were specified as follows. The concentration at the infusion sphere boundary was set at the concentration of the infusate. The drug transport across the outer circular boundary was assumed to be dominated by the convective flux,

$$\nabla c \cdot \vec{n} = 0 \quad (5)$$

where $\vec{n}$ is the unit normal vector at the boundary. The infusion sphere is set to a constant velocity of

$$u_{r=r_o} = U_{\text{infusion}} \vec{n} = \left(Q_{\text{infusion}} / 4\pi r_o^2 \right) \vec{n} \quad (6)$$

where Q_{infusion} is the infusion flowrate, and r_o^2 is the radius of the infusion sphere. U_{infusion} is the magnitude of the velocity at each point on the boundary. The large outlet curved boundary was set to a pressure of p=0.

TABLE I

VARIABLES CONSIDERED FOR ANOVA SENSITIVITY ANALYSIS

Variable	Units	Description	High Value	Low Value
A	nm^2	Permeability of region 1 (K_1)	1000	10
B	nm^2	Permeability of region 2 (K_2)	1000	10
C	nm^2	Permeability of region 3 (K_3)	1000	10
D	m^2/s	Diffusion Coefficient (D)	10^{-10}	10^{-11}
E	hour	Half Life ($t_{1/2}$)	24	2
F	µl/min	Infusion Flowrate (Q_{infusion})	2	0.1
G	mg/ml	Infusion Concentration	100	30
H	mg/ml	Effective Concentration	20	2

The viscosity, μ, of the infusate was taken to be 1×10^{-3} Pa-s. The resultant output, V_d, was determined in units of ml.

B. Experimental Setup

The sensitivity analysis was composed of a 64-run, 2-level partial factorial analysis of eight factors. The variables and their high and low levels are shown in Table I. All values were chosen to represent a large experimental space, with most of the variables ranging over at least one order of magnitude. To approximate anisotropic hydraulic conditions, the regions were all given a separate permeability. This type of experiment assumes that only main effects or two-way interactions are significant in the outcome. Three-way interactions or greater are considered to be negligible. The experimental setup and subsequent analyses were performed in the Design Expert software by Stat-Ease, Inc. (Minneapolis, MN).

The drugs considered for administration into the parenchyma are by definition too large to cross the BBB. Molecules of this size are unlikely to have a diffusion coefficient larger than 1×10^{-10} m^2/s. Fenstermacher and Kaye [2] estimate that for a relatively small molecule, sucrose, the diffusion coefficient is approximately 3.0×10^{-10} m^2/s. For a larger, therapeutic substance such as β-nerve growth factor (NGF - 26,500 Da), Thorne and Frey [3] state that the diffusion coefficient ranges between 1×10^{-11} and 8×10^{-11} m^2/s. For a large protein, such as albumin (66,000 Da), the diffusion in grey matter has been measured to be 1.34×10^{-11} m^2/s [4]. A range of 10^{-11} to 10^{-10} provides an estimate of the minimum and maximum of all possible diffusion coefficients for large molecules.

The ranges in the permeability are not meant to be an exact value of the resistance to flow, rather, the ratio of the hydraulic conductivities are critical in determining the anisotropic flow distribution in the tissue. When attempting to correlate the results of a radio-labeled albumin injected in a rat spinal cord to a 3-D FEM of the distribution, Sarntinoranont, *et al.* [5] found that the ratio of grey matter to white matter was required to be 100:1 for the model to be accurate. With this ratio, their distribution model results

matched very closely to the experimentally observed distribution. Consequently, the largest ratio of values expected to be seen in the brain is the ratio of grey matter permeability (10 nm^2) and white matter permeability (1000 nm^2).

The ranges chosen for the half-life are based on the clearance of inert tracers in the interstitial fluid of the brain. Cserr, *et al.* [6], predict that the rate of clearance of radio-labeled tracers from the brain of a rat results in a drug half-life of 6 to 16 hours. The low half-life value of two hours accounts for the addition of metabolism and cellular uptake. The half-life value of 24 hours takes into account that uptake and metabolism are negligibly slow and that human ISF clearance may be slower than in the rat.

Lastly, the infusion and effective concentration and the infusion flowrates are the type of values that we have observed as part of our practice of delivering into the parenchyma of the brain. The ranges shown here are an estimation of what might be administered and observed clinically, but they are likely to be highly drug specific. The effective concentration, especially, is a gross estimate. Highly potent drugs may have a value much lower, and relatively inert drugs may have a higher value.

For each experiment, the output was the volume of distribution and was calculated for regions 1 and 3 shown in Fig. 1. Regions 1 and 3 were the approximate "anatomy" of interest and were used to account for anisotropic distribution effects. The volume of distribution was calculated to be total volume of tissue where the extracellular concentration of the drug is greater than the effective concentration, *H*.

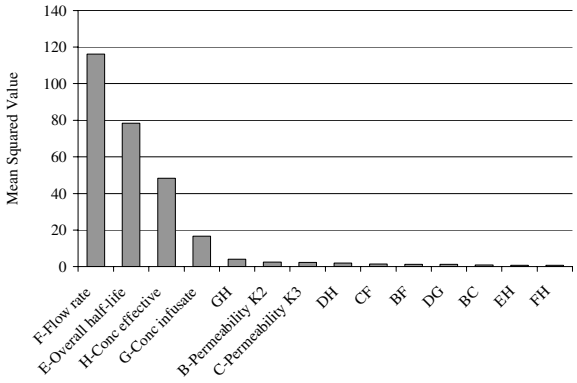
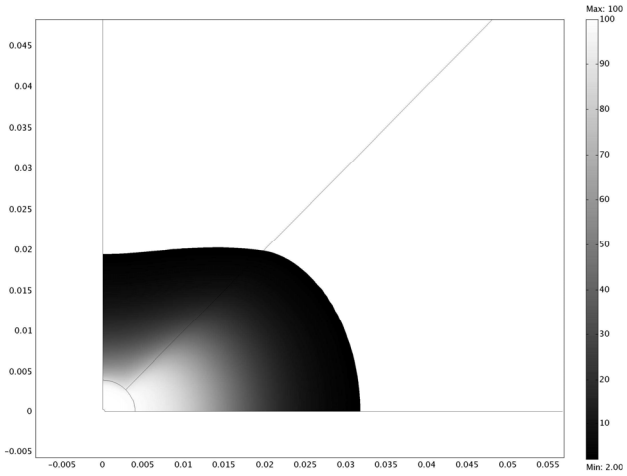


Fig. 2. The mean squared value for each of the significant experimental variables of the regression fit, in order of effect. The effect of diffusion only is insignificant and is not in the chart.

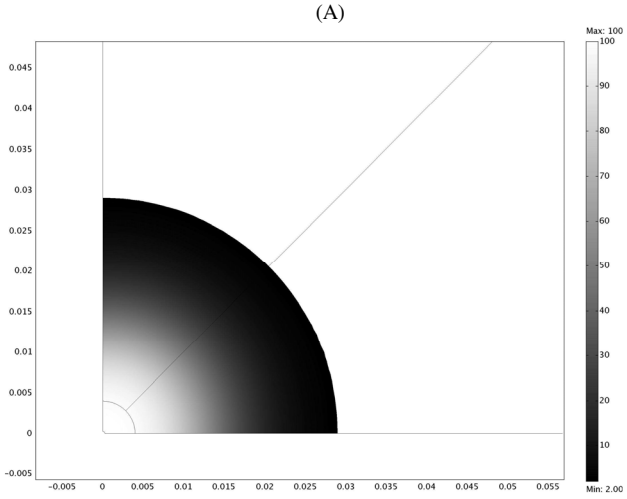
III. Results

The 64 experiments were conducted using the ranges shown in Table I, and the resultant volumes of distribution for each varied by nearly four orders of magnitude. This large variation in the output V_d required that a log transform be performed on the data to provide a high R-squared for the regression. A half-normal probability plot was used to pick the significant variables for the regression analysis. The resultant curve-fit to these significant variables was determined to be (in coded units)

$$\begin{aligned}\ln(V_d) = &-0.35 - 0.20B + 0.19C - 0.034D + \\ &1.11E + 1.35F + 0.51G - 0.87H + 0.12BC \\ &- 0.15BF + 0.15CF + 0.14DG - 0.18DH \\ &- 0.11EH + 0.10FH + 0.25GH\end{aligned} \quad . \quad (7)$$



(A)



(B)

Fig. 3. Example results of drug distribution. The volume of distribution shown is for an effective concentration of greater than 2 mg/ml. All other variables are set to their high values, except in (A) the permeability *B* of region 2 is set to its low value.

The adjusted R-square value of this regression curve-fit was 0.9803, and every variable had $p < 0.005$, with the exception of diffusion *D* ($p = 0.3677$). The mean-squared value for the regression is shown in Fig. 2, in order of effect. Fig. 3 shows two examples of the volume of distribution for two experimental runs.

IV. Discussion

The ANOVA analysis evaluating the importance of all the factors in a convection-enhanced drug distribution seems to weigh heavily toward the pharmacokinetic and pharmacological aspects of the problem. The four major factors can be divided into two major constituents: the dose rate delivered (flowrate x concentration) and the body's response to the drug. The other main effects, permeability and diffusion, have little to no bearing on the final distribution volume. Indeed, a rather surprising result is that, under theses constraints, the diffusion effect is so low that it is statistically insignificant.

The CED technique was developed to extend the volume of distribution of a drug in the parenchyma farther than would be realized by diffusion alone. The analysis reveals that the convective flux is much greater than the diffusive flux and plays the dominant role in the distribution. In the regions where the Peclet number is low and the diffusive flux is dominant, the rate of drug "destruction" due to half-life prevents any further distribution, and the steady-state volume is achieved. Thus, the distribution is the balance of the introduction of drug flow by convection and the destruction of the drug by the half-life.

The second most important factor, half-life, is an estimation of all the many processes that are taking the drug out of the extracellular space. For actively mediated drug transport across the cellular membrane, a simple first-order approximation is insufficient to describe accurately the rate at which the drug is removed due to uptake. Sarntinoranont, *et al.* uses a sophisticated method of accounting for all the rate constants that are present in the uptake of a NK_1 neurotoxin causing cell death [7, 8]. In their analysis, they account for the rate constants related to receptor association and disassociation, internalization, transfer from endosome to cytosol, cytosolic sorting rate, and endosomal recycling. Varying these parameters did show a marked change in the region of cytotoxicity. In order to be able to analyze the effect of these rate constants, it is necessary to have a reasonable understanding of the mechanism of action for the drug. In many cases, this mechanism of action is not well understood, if at all. It may only be possible to measure the overall half life, however approximately, to determine the rate of removal from the extracellular space. Consequently, a drug whose pharmacodynamics are well understood makes an excellent candidate for numerical analysis.

The most difficult factor to interpret is the effective concentration. The effective concentration *in vivo* rarely has correspondence to the concentration observed in *in vitro* experiments. For an *in vitro* experiment, transfection agents are used to elicit a pharmacological effect. These transfection agents are not used *in vivo*, so the mechanism of action is quite different. Determining the effective concentration *in vivo* is a difficult task, but it is this value that ultimately controls the volume of distribution.

V. Conclusion

The sensitivity analysis presented herein is the first step in understanding what is required in a high-quality drug delivery device. Each factor encompasses a large technical challenge. With this analysis, it is possible to prioritize the resources used to research these aspects of the design problem. Once the form of the design becomes more apparent, a more complex set of experiments and numerical analyses becomes possible. Using a sensitivity analysis enables the complete design of both the drug and the delivery device. The effective combination of drug and device will allow therapies to be brought to market that would not have been considered due to the pharmacological challenge of delivering a drug past the BBB.

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