Convection-enhanced delivery of therapeutics for brain disease, and its optimization

RAGHU RAGHAVAN, PH.D., MARTIN L. BRADY, PH.D., MARÍA INMACULADA RODRÍGUEZ-PONCE, PH.D., ANDREAS HARTLEP, PH.D., CHRISTOPH PEDAIN, PH.D., AND JOHN H. SAMPSON, M.D., PH.D.

Therataxis, LLC, Baltimore, Maryland; BrainLAB AG, Heimstetten, Germany; Division of Neurosurgery, Department of Surgery; and Department of Pathology, Duke University Medical Center, Durham, North Carolina

Convection-enhanced delivery (CED) is the continuous injection under positive pressure of a fluid containing a therapeutic agent. This technique was proposed and introduced by researchers from the US National Institutes of Health (NIH) by the early 1990s to deliver drugs that would otherwise not cross the blood–brain barrier into the parenchyma and that would be too large to diffuse effectively over the required distances. Despite the many years that have elapsed, this technique remains experimental because of both the absence of approved drugs for intraparenchymal delivery and the difficulty of guaranteed delivery to delineated regions of the brain. During the first decade after the NIH researchers founded this analytical model of drug distribution, the results of several computer simulations that had been conducted according to more realistic assumptions were also published, revealing encouraging results. In the late 1990s, one of the authors of the present paper proposed the development of a computer model that would predict the distribution specific to a particular patient (brain) based on obtainable data from radiological images. Several key developments in imaging technology and, in particular, the relationships between image-obtained quantities and other parameters that enter models of the CED process have been required to implement this model. Note that delivery devices need further development.

In the present paper we review key features of CED as well as modeling of the procedure and indulge in informed speculation on optimizing the direct delivery of therapeutic agents into brain tissue.

KEY WORDS • convection-enhanced delivery • brain • computer simulation • drug delivery system

Motivated in part by the profound difficulties associated with improving treatment for glioblastoma multiforme, many people have been exploring positive-pressure infusion as a means of delivering therapeutic agents into the brain. Pioneered by researchers at the NIH in the US, CED of an agent through the interstitial space provides a means of achieving therapeutic drug concentrations within the parenchymal tissues on a regional basis, without the limitations imposed on delivery by the BBB. In the prototypical version of such an approach, one or more catheters are implanted into the brain under image guidance, an infusion pump is connected to the catheter(s) to drive the flow, and the agent is then pumped directly into the target tissues, which dilate in response to the pressure field and allow permeation of the agent (Fig. 1).

A potential advantage of this method is the ability of the agent to reach cells that have invaded the peritumoral region and beyond, and thus making it arguably possible to offer hope of significantly reducing (if not halting) the spread of the disease. A number of clinical centers are now involved in instrumentation and imaging development, testing of experimental protocols, and clinical trials of the technique in humans in the hopes of bringing the procedure into routine clinical use (for example, see the review by Broaddus and colleagues). For large molecules having a 50,000-D or greater mass, the diffusive spread will often extend less than 1 mm in a day, and only as large as that if metabolic and other loss mechanisms do not flush it from the parenchyma. The flow of such a fluid co-injected with a drug can carry such molecules much farther, however, and in certain idealized scenarios can fill the intervening region with a full concentration of drug per unit of available volume. (Diffusive spread, of course, results in exponentially decreasing concentrations away from a source.) Nonetheless, the success of these attempts has to date been limited given the lack of appropriate planning, guidance, and infusion technologies. Currently, intraparenchymal...
We address the development of drugs requiring or significantly benefiting from direct intraparenchymal delivery.

Factors Affecting Drug Distribution by CED

In most procedures for intraparenchymal infusion or injection, the delivery device is stereotactically guided to its intracranial target through a bur hole. For slow infusion processes (in humans, typically \(< 0.3\) ml/hour), the catheter might be left indwelling for several days. Conventional MR imaging or CT scanning studies are typically used preoperatively to estimate the optimal insertion trajectory. However, the final details of the implantation procedure are usually specific to the design of the delivery device, the rate at which the infusion or injection is to occur, and the number of devices that must be inserted and/or passes that must be made to obtain adequate therapeutic coverage of the targeted volume. Infusion methodologies for both framed and frameless stereotaxy have been developed, with forms for the latter being optimized for use in the interventional MR imaging context.

Key features affecting the distribution of molecular solutions when pumped into brain parenchyma are summarized in Fig. 2. Once the pump parameters (flow rate and duration) have been set, the fluid flow in the poroelastic medium of the brain parenchyma acts as the primary carrier of large-molecule drugs. The interstitial pathways in the brain allow such convective transport independent of the molecule size, for a range of sizes. Of course, factors such as lipophilicity can affect the transport; for water-soluble proteins, however, convective transport dominates at least for short times. The flow of fluid in the brain is quite tortuous, and the distribution of drug molecules, even for convective transport, exhibits what is known as “hydrodynamic dispersion”—namely, a seemingly diffusive spread given the tortuosity of the paths, with apparent diffusivity being related to the speed of convective flow. Furthermore, various barriers including the pial surfaces of the cortex limit convective transport of the drug. Over longer time periods, diffusion (random movement of the molecules within the extracellular spaces of the interstitium), loss through the capillaries, and, of course, drug action (metabolism) determine the distribution patterns of the drug. These processes are represented in Fig. 3, which shows the results of a 90-minute infusion into a pig brain (Fig. 3b) followed by imaging 20 hours thereafter (Fig. 3c). These data were obtained from an experiment directed by Michael Moseley at Stanford University, Stanford, California, and funded by what was then Image-Guided Neurologics, Inc.

Before the fundamental mechanisms of transport and metabolic action take place, however, several issues must be overcome or avoided: tissue damage on catheter insertion, ever-present air bubbles that, if not properly addressed, can provide unpredictable paths for subsequent fluid flow, and so forth. We have attempted to list such factors in Table 1 and describe them in more detail in the text.

Tissue Damage and Reflux

One important phenomenon during infusion is back-
flow of the infused agent along the catheter’s insertion track, which can happen for one of two reasons. First, and most obvious, backflow can occur if the catheter has mechanically disrupted the tissue enough to allow a void to form around its outer wall. In such cases, the infused agent simply refluxes through that gap with relatively little pressure-driven flow into the target tissues. It seems obvious, and the point has been confirmed in at least one carefully performed study,¹¹ that soft catheters are less likely to cause mechanical disruption. In particular, surgeons routinely see brain shifts during craniotomies, requiring them mentally to adjust the image guidance system for proper catheter positioning during postoperative infusions. Reported data confirm that soft catheters can move with the brain shift and cause less disruption and breaking of seals, thereby preventing this form of backflow. The more intrinsic reason for backflow is described next.

**Transient and Steady-State Characteristics: Intrinsic Backflow**

Even when no void has formed during catheter insertion or when the tissue has sealed against the outer wall, a second type of backflow can occur. During this intrinsic backflow, pressure associated with the infusion process pushes against the tissues and causes them to separate minutely from the catheter, until the shear forces in the tissue balance the pressure field and the retrograde axial flow stops (Fig. 4). To our knowledge, intrinsic backflow was first described by Morrison and colleagues.²⁶

The predictions or theories of backflow have been based on steady-state considerations and depend on the assumption that the backflow is fully developed before the fluid has spread significantly into tissue. The basic mathematics of poroelasticity reveals that the pressure is diffusive and thus does not reach a constant value in a finite amount of time. Therefore, the experimental conditions in which backflow predictions can be validated are particular, requiring relatively small-diameter catheters and strong resistance to spread in the tissue or tissue easily deformed by fluid pressure or both. An initial detailed experimental study has been conducted and its data reveal many interesting effects of pressure disequilibrium that make the accurate quantitative prediction of backflow difficult (ZJ Chen, et al., unpublished data).

Nevertheless, certain facts remain: backflow can occur, allows fluid to flow back along the catheter track for several centimeters for a catheter having an outer diameter of 1 mm, and must be taken into account. Such backflow can lead to spreading of the agent into regions of the brain.

**Fig. 2.** Diagram depicting a possible subdivision of the problem involved in CED. The distribution can be inferred from knowledge about influx, transport, and efflux parameters.

**Fig. 3.** a: Sketch illustrating an infusion catheter in tissue (not to scale). Orange elongated cells represent white matter tracts. The fluid infused from the catheter forms a small annulus around the outside of the catheter, the backflow. This cylinder is the source of the subsequent infusion, which preferentially follows the white matter tracts. b: A T₁-weighted MR image demonstrating the infusion of Gd-DTPA into a pig brain. The infusion pattern has an irregular shape, preferentially following the white matter tracts. The image was acquired at the end of the infusion. c: A T₁-weighted MR image obtained 1 day after the infusion was finished, depicting the effects from the same infusion shown in panel b. The Gd-DTPA has diffused to distances far beyond the original volume shown in panel b.
where it is not intended and, possibly, in a diminution of the dose otherwise needed within the target tissues. (The same principle, of course, holds for reflux during catheter withdrawal.) The problem could be particularly acute in cortical infusions, when backflow of the agent along the insertion track and into the subarachnoid space might occur, with subsequent widespread distribution of the agent by the circulating CSF. A model of the mechanics of the backflow process indicates that the backflow distance (for a fixed rate of fluid delivery through the catheter) varies as the four-fifths power of the outer radius of the catheter. Thus, other things being equal, the use of a thin catheter is advantageous, as proven by other researchers, and the difficulty in placing a very thin catheter due to its floppiness can be overcome by having a “step design” in which the thinner catheter protrudes for a short length beyond a more rigid and wider cannula. The thinness will prevent backflow beyond the protruding length for sufficiently small infusion rates. Current clinical trials, however, involve the catheters with outer diameters of 1 mm (the infusion catheter in the step design was 168 μm). In testing the model compared with observations of infusions, predicted backflow distances on the order of 20 mm were indeed found to occur. As a result of these studies, some navigation systems come with guidelines, recommended by us, for catheter placement for infusions in humans to avoid backflow into cavities that would compromise the infusion. We quote from those offered by BrainLAB AG (catheter package insert)

1. Depth Line, which displays a cylinder along the catheter trajectory representing a recommended zone within which the catheter should not cross any pial surfaces. This line must be computed dynamically based on at least flow rate and catheter size. Further the depth line should show a sphere around the catheter tip representing a recommended distance to fluid filled cavities.

2. Distance Line, which displays a sphere of 2 cm diameter around the catheter tip representing the recommended minimal distance between catheters. The outer circle gives the Distance Line and the inner circle in combination with the cylinder along the trajectory the Depth Line.

Refer to Fig. 5 for additional information.

An example of the need for such guidelines is represented in Fig. 6, which illustrates the leakage of infused agent into the subarachnoid space via backflow up the catheter during an actual infusion. A 0.85-mm-diameter catheter was inserted through a bur hole into an in vivo pig brain to a depth of 14 mm from the cortical surface. A Gd-DTPA and water solution (1:200) was infused at 5 μl/min. A three-dimensional fast spoiled gradient–recalled acquisition MR image (TR 7.8 msec, TE 3.2 msec, matrix 256 × 256, field of view 20 cm, slice thickness 1 mm, number of slices 60, number of excitations 2, and flip angle 15°) was obtained to analyze dispersion of the Gd marker. Images obtained after 32 minutes of infusion showed evidence that the infused agent had mostly leaked into the subarachnoid space, distributing widely along the contours of the cortex, whereas little distribution into the white matter had occurred. These data were obtained from

---

**TABLE 1**

**Phenomena relevant to CED and their determining parameters**

<table>
<thead>
<tr>
<th>Phenomenon</th>
<th>Determining Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>tissue damage on catheter</td>
<td>obviated by catheter design &amp; insertion procedure</td>
</tr>
<tr>
<td>insertion</td>
<td></td>
</tr>
<tr>
<td>air bubbles</td>
<td>obviated by stylet &amp; catheter design &amp; insertion protocol</td>
</tr>
<tr>
<td>backflow along catheter walls</td>
<td>poroelastic parameters near catheter: elastic moduli, extracellular volume, &amp; hydraulic conductivity of tissue</td>
</tr>
<tr>
<td>fluid flow in extracellular brain tissue</td>
<td>hydraulic conductivity of tissue &amp; induced variation of excess pressure</td>
</tr>
<tr>
<td>efflux rate of water from brain tissue</td>
<td>capillary hydraulic conductivity</td>
</tr>
<tr>
<td>drug transport</td>
<td>diffusion tensor of drug &amp; convective velocity</td>
</tr>
<tr>
<td>drug efflux from tissue</td>
<td>capillary molecular permeability–surface area product</td>
</tr>
<tr>
<td>drug metabolism, binding, &amp; other effects</td>
<td>reaction rates</td>
</tr>
</tbody>
</table>

---

**Fig. 4.** a: Schematic depicting two infusion catheters in inhomogeneous tissue (not to scale). The backflow distances, represented by the dark blue cylinders around the catheter tips, vary depending on the hydraulic conductivity of the adjacent tissue. The backflow length is extended in areas of low conductivity. b: An overlaid T₂-weighted MR image demonstrating backflow distances (green areas) simulated for two different catheter trajectories (yellow lines). The simulated backflow distances vary significantly within a patient, depending on the chosen trajectory.
an experiment conducted by Michael Bronskill at the University of Toronto and funded by BrainLAB AG.

**Air Bubbles**

Dissolved air and air bubbles are important factors affecting the reproducibility and predictability of drug delivery. Significant air bubbles, although not directly a health hazard, determine the flow along unpredictable paths and are best avoided. Current best practice (which of course includes prefilling the catheter) in intraparenchymal delivery does seem to indicate that air bubbles do not affect delivery; nevertheless, predictability may perhaps be further improved by optimal designs for removing air bubbles (Brady M, Pedain C: US patent submission 20040215143, 2004).

**White Matter Edema**

So far, we have focused on situations in which the backflow or flow into fluid-filled cavities would almost totally compromise infusion. There is, however, another factor that very significantly affects infusions and must be considered: the increased fluid permeability offered by the white matter tracts, which dramatically increases in edematous brain tissue. In fact, just infusing fluid into white matter produces changes that appear very similar to the edema often seen with brain cancers. When infusing into white matter that is not already marked by edema, edema appears around the catheter (Fig. 7).

As can be seen in this figure, relatively little edema appears near the site of tumor recurrence, which lay below the resection cavity before infusion. After 44 hours of infusion, extensive and intense edema surrounds the catheter. The extent of the edema appears to match the extent of the infused fluid closely, according to the infiltration pattern of the Gd and SPECT markers. The level of infusion-related edema for a 4.5-μL/minute infusion is often greater than that observed in tumor-induced vasogenic edema. On T₁-weighted images, the signal levels near the infusion site reach levels very near those of fluid-filled cavities and ventricles. The infused agent itself may have a higher signal than that for CSF, so it is difficult to make a
quantitative assessment from the \( T_2 \)-weighted signals as to whether the infusion-induced edema has a water fraction different from that of the average vasogenic edema. Either form of edema increases the fraction of extracellular space, thereby dramatically increasing fluid conductivity along the edematous pathways. This phenomenon can have a number of repercussions, but the one that concerns us here is the fact that the flow of the infused agent can become enslaved to this effect.

**Target Heterogeneity**

In describing the strong effects of edema, which are largely confined to white matter on distribution of the infused agent, we have implicitly remarked on the inhomogeneity of the brain tissue, although it is induced by the infusion. Even in its initial state, however, resistance to fluid flow in brain tissue is both anisotropic (dependent on the direction of the flow) and heterogeneous (dependent on location within the brain). These two aspects are illustrated in Fig. 8, which involved both imaging and mathematical developments. For the moment, the figures may be taken as direct representations of the degree of inhomogeneity variations with location in tissue of the hydraulic conductivity. Because the hydraulic conductivity is really a symmetric tensor, it is represented by a symmetric matrix, which has principal values (or eigenvalues) and principal axes. So, heterogeneity means that these principal values are different in different parts of the brain. In other words, the ease of fluid flow is direction-dependent and flow does not occur only in the direction of the pressure gradient. The brightness of the image is a direct map of these quantities so that the brightness in Fig. 8a traces the estimated hydraulic conductivity tensor, whereas that in Fig. 8b measures the anisotropy of this tensor.

**Active Tumors and BBB Disruption**

Active tumors present a variety of additional barriers to drug delivery (following extensive pioneering work by Rakesh Jain and his collaborators).\(^{12-17}\) high interstitial tumor pressure, decreased vascular surface area with a markedly more heterogeneous distribution of blood vessels than in normal cells, increased intracapillary distances, and peritumoral edema. Most of these factors originate in the context of a disrupted BBB. The elevated IFP within a tumor enhances the rate of drug efflux. Increased IFP also restricts the movement of fluid and macromolecules into the high interstitial pressure regions, as revealed by experimental data showing radially outward convection emanating from the tumor. This counteractive convection hinders the penetration of interstitially delivered therapeutic agents into the tumor. Groothuis, et al.\(^9,10\) have demonstrated that intratumoral drug concentrations in rodents were extremely variable even after CED. In fact, in these studies, CED failed to deliver any drug to active tumors. Thus, elevated IFP is a significant parameter that must be accounted for in explaining the uneven spatial distribution of therapeutic agents delivered via CED. Although directly administered molecules will have much higher initial concentrations near the tissue injection site, their rapid clearance and variable distribution in the tumor further complicate the development of an effective drug treatment strategy for highly malignant tumors. We believe that all the data necessary to derive patient-specific estimates of these parameters can be obtained from diffusion tensor and dynamic contrast-enhanced imaging in individual patients, as we will discuss later.

Figure 9 features a schematic of the problem and MR images visualizing the inefficacy of direct agent delivery into a tumor. Focusing on the MR images in Fig. 9, which were obtained from Dr. Fred Lang at the MD Anderson Cancer Center in Houston, Texas, we see in panel b a standard perfusion image obtained after the intravenous injection of a contrast agent (Gd-DTPA). The presence of this marker in the tissue signifies disruption and opening of the BBB and is clearly apparent in the figure. Absent other reasons for BBB disruption, this perfusion pattern is taken to be indicative of an active tumor (which in this case was implanted in a dog). After sufficient time for this Gd bolus to have washed out (as confirmed on imaging), the contrast agent was administered intraparenchymally via a catheter, which can be seen in outline in Fig. 9c. The catheter was inserted directly into the tumor. Interestingly, infusion was clearly confined to one side of the tumor and failed to penetrate the other half. A convincing explanation for this result is detailed above; that is, the high intratumoral pressures forced the infused agent to one side.

In summary, delivering therapeutic agents directly into
brain parenchyma will revolutionize the treatment of neurological disease provided that the process becomes ever more simple, safe, and effective, with continually decreasing invasiveness across the BBB while remaining in targeted brain regions. Ideally, such a procedure would have the simplicity of an injection but allow targeted and localized access to brain tissue. (These features translate immediately to delivery into other solid tissues, such as hepatomas.) Many people, including us, have shown that the brain is not a structure with static constitutive properties for infusions, as illustrated previously. So, for example, infusion of fluids into the brain must allow for changes in the hydraulic resistance of the brain in response to the infusion itself. To reliably account for all factors in planning therapy for an individual, it would be ideal to have a patient-specific computational model that works. Mathematical and physical modeling of brain physiology sets up general equations for the distribution of variously delivered material. The structure of the equations and their solutions clarifies the requirements for in vivo data that are required to predict this distribution and for optimal design of supporting devices and delivery methods. We will resume our discussion of the model construction and imaging design needed after a detour through the topic of device technology.

**Delivery Devices: Catheters**

We interrupt the conceptual discussion of factors affecting agent distribution to discuss some aspects of the delivery devices, specifically, catheters used for CED. (Pumps for acute and chronic infusions remain issues, but that is not the subject of this paper, in part because we have insufficient evidence for or against certain points of view.) Early on, catheters used for intraparenchymal delivery were multiport catheters originally devised for ventricular shunts, for example, for hydrocephalus. An example of one of the delivery devices used to date is the catheter used in the Phase II clinical trial of HN-66000, a diphtheria toxin conjugate developed at the NIH. Two catheters (PS Medical CSF cardiac/peritoneal catheter; Medtronic, Goleta, CA) with a 2.1-mm outer diameter and 1.2-mm inner diameter were stereotactically inserted so that the distal ends were spaced approximately 1 cm apart. We will not discuss other details of these studies (such as the flow rates, and so forth) given that our focus in this section is the catheters.

The difficulty with CED is in obtaining predictable and adequate flows from all of the catheter’s ports; frequently, fluid flows from the most proximal port. This factor can make it difficult to control the flow from a linear sequence of ports placed along the catheter axis, unless the pressure field inside the catheter is hydrostatic, which is unlikely given that most flow impedance occurs in the tissues themselves and that there is typically a small but non-negligible gap between the outer wall of the catheter and the parenchymal tissues, serving as a sink for the pressure field. An example of this phenomenon is shown in Fig. 10: the distribution of dye from an eight-port ventricular catheter inserted into gel reveals that flow occurs only from the proximal ports. The fundamental cause for this phenomenon is not yet known, although we can speculate about more than one factor that might create a pressure gap across a port that must be breached; once a port is

---

**Fig. 9.** a: Schematic demonstrating the pressure differential between the extratumoral and the intratumoral interstitial pressures. b: Contrast-enhanced $T_1$-weighted MR image showing a tumor in a dog brain. A catheter was placed through the tumor with the tip approximately 1 cm beyond the tumor mass, inside adjacent tissue. c: A $T_1$-weighted MR image showing the same slice as that featured in panel b, with Gd-DTPA infused through the catheter. The image reveals that the fluid does not suffuse the tumor mass but rather distributes around one side of the catheter and the border of the tumor.

**Fig. 10.** Digital camera shot depicting infusion of blue dye from an eight-port ventricular catheter inserted into an agarose gel preparation. Flow originated only from the most proximal port, rendering the remaining ports useless for drug delivery.
breached, all flow will occur through that port, leaving the pressure gaps at other ports still intact. Bubbles, viscosity differences, and other phenomena can account for this. A well-designed study to isolate the cause would be very valuable scientifically but has not, to our knowledge, been conducted.

Figure 10 shows an infusion of bromophenol blue dye through an eight-port ventricular catheter placed in gel. The dye infuses through the most proximal ports only, with no distribution through almost any of the other ports. The pressure decreases mostly across the most proximal port only, even in the case of an essentially hydrostatic pressure field inside the catheter. The same phenomenon has been observed during clinical infusions (JH Sampson, et al., unpublished data).

Motivated by these deficiencies, we tested several different designs to evaluate the volumes of distribution and pressure profiles. The studied devices are shown in Fig. 11. The in vitro test procedures and other details, including results and images of the infusions, were published in the report by Bauman and colleagues.1 The physical characteristics of the catheters are listed in Table 2, including the configuration of the portholes and component materials. (Parenthetically, we may remark that the great advantages of this type of in vitro study include the relative speed with which the exploratory infusions can be performed and the very low cost of doing such experiments; for example, the agarose gel costs only pennies per sample, in contrast to the vivarium expenses that can accumulate in in vivo testing. Although in vivo testing of medical devices like these is an unavoidable necessity before ultimately using them in clinical trials in humans, a substantial fraction of the expenses can nevertheless be avoided by following the gel-based approach.)

Representative data demonstrating the volumes of distribution and pressure profiles for each catheter are shown in Figs. 12 (Catheter 1) and 13 (Catheter 2). The dye infused into the 0.6% gel was bromophenol blue (molecular weight 690), the flow rate was 5 μl/minute, and the pressure was measured in millimeters of Hg. Photos were obtained 10 and 40 minutes after the start of the infusion; the run was ended at 40 minutes.

A clear result of these studies was the lack of predictability or uniformity of flow from multiport catheters. Thus, the original ventricular and similar multiport catheters are no longer used for intraparenchymal delivery. Of course, there are several possible solutions to the problem with multiport catheters. One solution, originally performed by students at The Johns Hopkins University, is to significantly increase resistance within the catheter by introducing porous material. This high resistance removes the sensitivity of the flow to small variations in individual pressure drops across the ports and allows all ports to permit fluid flow. Another solution to this problem is to have several separate lumens within one catheter body, with each lumen feeding its own porthole. This ensures that there will be adequate flow from each porthole and, in fact, allows for separate adjustment of each flow rate and/or the simultaneous infusion of different agents into the targeted tissues.2 A logical extension of any of these strategies is

![Fig. 11. Photograph depicting the different types of catheters tested in the gel experiments. Scale on the left side of the image is 1 mm.](image)

<table>
<thead>
<tr>
<th>Catheter No.</th>
<th>Outer Diameter (mm)</th>
<th>Inner Diameter (mm)</th>
<th>Material</th>
<th>Port Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.95</td>
<td>0.75</td>
<td>rigid polyamide</td>
<td>single, end</td>
</tr>
<tr>
<td>B</td>
<td>2.5</td>
<td>1.25</td>
<td>flexible silicone</td>
<td>single, end</td>
</tr>
<tr>
<td>C</td>
<td>2.5</td>
<td>1.25</td>
<td>flexible silicone</td>
<td>single, laser-cut end</td>
</tr>
<tr>
<td>D</td>
<td>2.25</td>
<td>1.0</td>
<td>flexible silicone</td>
<td>four, radial slits</td>
</tr>
<tr>
<td>E</td>
<td>1.75</td>
<td>0.75</td>
<td>clear silicone</td>
<td>3 radial lines of 10 laser-cut holes</td>
</tr>
<tr>
<td>F</td>
<td>2.0</td>
<td>1.0</td>
<td>barium-impregnated silicone</td>
<td>single, end</td>
</tr>
<tr>
<td>G</td>
<td>2.25</td>
<td>0.75</td>
<td>silicone</td>
<td>fishmouth</td>
</tr>
</tbody>
</table>

TABLE 2
Characteristics of catheters evaluated in vitro
that of introducing a catheter with controllable portholes. Indeed, specialized injection cannulas with multiple side ports and coaxial lumens have been used in trials of cell delivery in humans; the cannula has been withdrawn from the brain in time sequences that allow surrounding tissue to hold the implant in place, thus circumventing the reflux problem.

However, the simplest solution is to use catheters with a single end port. Catheters currently used for infusion are substantially larger than the very thin cannulas, which have been characterized as optimal in the rodent brain. Nevertheless, the larger scale of the human brain and the time allowance after placement of infusion catheters is expected to allow some backflow along the catheter tract while maintaining good distribution of the infused agent.

In addition to all of these possibilities, there is another broad class of alternatives that focuses on the active control of the infused agent once it has been pumped from the catheter(s). We shall not discuss this topic further here. Finally, we should mention that there are several device designs that are available or in various stages of development that aim to minimize backflow.

Modeling

In *Factors Affecting Drug Distribution by CED*, we described several of the important determinants of the flow of an infused agent continuously injected into the brain. The equations that describe such flow in the idealized situation of a small spherical source and isotropic, homogeneous tissue have been analyzed by Morrison and colleagues. In Table 3, we display the parameters that are computed from the imaging data, whereas Table 4 shows the validation studies for intermediate variables in the computation itself, which are not directly derived from image processing. In the present paper, we first briefly review the methodology of the mathematical model and then proceed to the principal imaging methods we currently use and the parameters we expect to obtain from these methods. Numerical solutions of the mathematical model have been developed, and one of us (R.R.) has proposed patient-specific numerical solutions for eventual clinical use, which require, of course, patient-specific parameters to obtain the solutions. A more detailed discussion of how these parameters are obtained follows.

Flow Equations

We have been using equations that describe the movement of large (usually hydrophilic) molecules in solution; these equations are essentially the same as those featured in the NIH study. These equations allow us to compute the pressure distribution in a rigid porous medium; and through the Darcy Law, the interstitial fluid velocity. The

**Fig. 12.** a: Digital camera shot depicting the volume of distribution for Catheter 1 at 10 minutes into the infusion. b: Digital camera shot depicting the volume of distribution for Catheter 1, 40 minutes into the infusion. c: Graph of a pressure profile over time (pressure scale in mm Hg), showing a regular, slightly ellipsoid distribution, which is achieved due to the short backflow distance in conjunction with maintaining the structural integrity of the surrounding gel. The gel trial does not reveal issues that would limit the usability of the catheter for CED.

**Fig. 13.** a: Digital camera shot depicting the volume of distribution for Catheter 2, 10 minutes into the infusion. b: Digital camera shot revealing the volume of distribution for Catheter 2 at 40 minutes into the infusion. c: Graph depicting a pressure profile over time (pressure scale in mm Hg), revealing a long backflow distance and a helical disruption of the gel structure, both indicating the limited suitability of this catheter for use in CED.
equation for the time-dependent concentration of molecules can also be solved numerically under general boundary conditions. The boundary conditions specify the concentration at the source of the infusion for the entire duration of the infusion as well as an initial condition (usually 0) at the start of the computation time. Such problems are called “initial boundary value problems.” The point is that the equations for both pressure and concentration have the form of a law of conservation (particles or fluid) together with a proportionality of the fluid or particle current to a force derived from a potential (pressure and concentration gradient). The result is, in either case, a parabolic or elliptical partial differential equation with diffusive rather than wave behavior. Note, however, that with nonlinearities in the coefficients, this conclusion does not, in general, hold true.

Software Development

To provide useful solutions for these equations that can be implemented on neurosurgical workstations, tissue parameters of sufficient accuracy and precision must be extracted from diffusion tensor MR images. The simulation produces patient-specific maps of tissue hydraulic conductivity and diffusivity (both are tensor fields), as described later. The application then simulates convection-enhanced infusions in rigid media. Tissue pressure and infusate concentration over time are estimated. A screenshot from commercially available software (iPlan! flow application, version 2.0; iplan networks, Buenos Aires, Argentina) is shown in Fig. 14.

The simulation output can be visually and quantitatively compared with experimental results. Studies with pigs are underway at Virginia Commonwealth University Health System (Richmond, VA) to test these simulations.

We now turn to the imaging methods used in obtaining the parameters.

Diffusion Tensor Imaging

Diffusion tensor MR imaging with suitable postprocessing reveals the self-diffusion tensor coefficients of water in brain tissue, according to well-known techniques. After suitable filtering and correction for motion and distortion, average diffusion coefficients are computed for at least six independent gradient directions. A linear system of equations is then solved using these average diffusion coefficient values to obtain the six coefficients of the water self-diffusion tensor at each sample point. Furthermore, cross-property relations between diffusion and other transport processes can be used to estimate seemingly unrelated parameters from the diffusion tensor coefficients. This method has been used recently to estimate the electrical conductivity tensor. One key to utilizing diffusion tensor data is an ability to extract the extracellular diffusion tensor, by which we mean essentially (thought experiment) zeroing out the contribution of any intracellular water and any exchange (that is, the loss of extracellular water to the intracellular compartment). We have developed an imaging technique to accomplish this task (unpublished data). Roughly speaking, building on the relatively complete model of the MR imaging signal under diffusion-weighted protocols, we choose different magnetic field gradient strengths so that the variation in the signals at different gradients is bieponential to an excellent approximation, and the exchange contribution to the signal is negligible. We then obtain just the extracellular component by comparing normalized signals at two such gradient strengths. For this process to work, the diffusion times must be relatively short. We have developed this technique to obtain the hydraulic conductivity tensor, which is key to any simulation involving convective transport. We currently estimate three sets of parameters from diffusion tensor imaging data.

Tissue Hydraulic Conductivity, K. The essential idea used in inferring the tissue hydraulic conductivity, K, is that the anisotropies of the diffusion tensor give us geometric information about the medium, which we can then use in inferring the hydraulic conductivity. More precisely, one can develop a formalism for an expansion of transport functions in terms of point probability functions, which in turn contain all the geometric information about the media. This expansion can be used for the diffusion tensor of water, which is known from MR imaging data, and the probability functions inferred in a least-squares sense at the very least. These estimated probabilities can then be plugged into the expansion of the hydraulic conductivity, which can then be calculated. The basic technique was reported by Tuch and associates, and we have extended the calculation to several levels of approximation of the cluster expansion beyond the least-squares one. Furthermore, there are several other expressions for transport coefficients, which may be utilized to derive bounds on such cross property values (for example, inferring hydraulic conductivity, K, from diffusivity, D), and we are exploring these.

Pore Fraction ϕ. As a byproduct of the work involved in obtaining the extracellular diffusion tensor, we can also estimate the extracellular volume, or pore, fraction ϕ in conjunction with standard MR imaging (M Brady, et al., unpublished data). The essential idea again involves choosing the imaging parameters so that a two-component model, with little exchange, suffices. If we assume that the sig-
nal from the intracellular (slow) compartment comes from water that remains in that compartment during the diffusion time, the intracellular water fraction due to the loss of some of the water across the membrane will be underestimated. Furthermore, the apparent intracellular water fraction is expected to decrease as diffusion time increases, as more intracellular water will cross the membrane. This reduction in the intracellular water fraction can be described by an equation, which can be used as a correction term to improve the estimate of the extracellular water fraction.

The extracellular water fraction does not directly provide an accurate estimate of the extracellular volume, or pore, fraction \( \varphi \), because water is not uniformly distributed throughout the volume. This is particularly true within the white matter, where myelin takes up a significant fraction of the volume but does not contribute much to the MR imaging signal. Assuming that the extracellular fluid contains a density of water similar to that of CSF, the pore fraction \( \varphi \) can be estimated by scaling the water fraction by the normalized fraction of water per unit volume, \( \rho \). We obtain this variable from a normalized proton density image. A region known to be nearly 100% water (the ventricles) is selected to normalize this proton density image, so that the CSF has \( \rho \) of 1. Multiplying the extracellular water fraction by \( \rho \) then gives the desired pore fraction \( \varphi \).

**Diffusion Tensor for Drug Molecules, \( D_M \).** The diffusion tensor for drug molecules, \( D_M \), diffusing within the extracellular fluid can be inferred in exactly the same manner as \( K \). Specifically, the diffusion tensor for a large and approximately spherical molecule can initially be approximated as a scaled extracellular diffusion tensor for the water molecule. Of course, we must know the intrinsic value of the diffusion coefficient of the molecule in an infinite medium from other sources, but these are generally available. If we do not have ready access to that information, we scale this value according to the size of the molecule. Future developments can include enhancing the theory-based scaling to allow for the shape of the molecule or its interactions with the local environment or both (M Brady, et al., unpublished data).

It is well known that the diffusion tensor field can also be used to identify fiber pathways, and in fact this application is now available commercially from BrainLAB, which has licensed the Mori method for commercial use.\(^{25}\) We will further develop this method to identify directions for axonal transport.

**Dynamic Contrast-Enhanced Imaging**

Dynamic contrast-enhanced imaging provides quantitative means of obtaining several physical parameters important in tissues with BBB disruption by following changes in signal intensity from tracer molecules injected into the bloodstream. This imaging modality follows the movement of tracer concentrations from the blood vessels into tissue—and back into the vessels, if the measurements are performed long enough—the signal located principally in regions of BBB disruption. In particular, the permeability-surface area product of the capillaries, local blood flow, and blood volume can be estimated with image postprocessing using various models of tracer transport. These data are essential for simulations of transport near tumor tissue. The permeability-surface area product, however, is

![Fig. 14. Screenshot of the iPlan! flow application (version 2) showing the planned trajectories for five catheters and the results of simulated infusion from these positions.](image-url)
specific to the tracer molecule used. By varying the size of the tracer element, one can develop methods for estimating the permeability of larger molecules. This factor will lead to the assumption, for example, that albumin, suitably attached with a marker such as Gd,\(^{31}\) will behave in its movement across the BBB in essentially the same way as a similarly sized therapeutic molecule, for example, interleukin-13 (both are hydrophilic and have molecular weights close to one another; approximately 60,000 D). It has been discovered, through microdialysis measurements, that Gd-enhanced regions in brains with active tumor coincide with regions of quick ingress and egress of systemically delivered drugs. Tying Gd to the drug, or a similarly sized, molecule will allow us in a predictable way to compute residence time and other quantities of interest—for systemically administered drugs as well. However, such topics are beyond the scope of the present paper.

In summary, we have attempted to describe how one can obtain patient-specific parameters so that a mathematical model of drug transport via CED can be plugged into software and used by surgeons to plan infusions to obtain the desired distributions.

### Tracking Infused Agents

The final analysis of any infusion model of course lies in the distribution of the particle in question, whether it involves a large-molecule protein therapy, a viral carrier of gene therapy, a cell, or some other particulate. To validate such a model, one must ideally be able to measure an agent’s concentration in tissue.\(^{22}\) Leaving aside immunohistochemical analyses, which involve the killing of animals, we briefly discuss in vivo measurements of concentrations of molecules and other particles, which may be suitable in human studies.

There is a great advantage in the use of in vivo imaging of drug distributions in humans because it opens the door to active feedback control of delivery in real time. The imaging techniques currently available to track fluid distribution provide indirect rather than direct information. Very recently, reports have been published on the suitability of T\(_2\)-weighted MR images to track agent distribution based on the drug effects on tissue.\(^{23}\) Other authors have also reported on the enhancement of the T\(_2\) signal as a consequence of fluid administration via CED (J Sampson, et al., unpublished data). Experiments with nonhuman primates in which Gd-chelate was coinfected with the drug to monitor its distribution have also been performed.\(^{25}\) A number of analyses have been conducted under the direction of one of the authors of the present paper (J.H.S.), who has tracked surrogate tracers using SPECT studies in which radioactive iodine-123 conjugated with albumin has been utilized (unpublished data).

Perhaps new markers for MR imaging can be developed; given the existing knowledge, however, we believe that there is an urgent need for experimentation with the well-known Gd-chelates, which make excellent markers. (We omit mention of magnetodendrimers simply to limit our discussion. These magnetic tags are not likely to be useful for molecular agents but rather for cells, and there are considerable difficulties in quantitative measurements of concentrations using these agents.) These chelates can be easily bound or conjugated to various proteins, including therapeutic proteins, and should therefore offer, at least in animal experimentation, direct visualization of a proposed drug. There are several obstacles to overcome before this method becomes practical. First, toxicity studies must be performed given that there are few data on the toxicity of these Gd compounds when they are deposited and reside in brain parenchyma. Nonetheless, it is encouraging that no toxicity has been displayed within cell cultures; that is, chelates remain stable, so that one can hope to observe the same effects in vivo. Second, Gd is a marker that works by its effects on surrounding water molecules, and hence is required in relatively large concentrations to be visible. Thus, for expensive drugs, it may be a problem to conjugate enough drug molecules for tracking the infused agent. One may need milligrams of a conjugated drug for Gd imaging, whereas the drug may only be available in microgram doses. In such cases, one might have to revert to surrogate tracers, as mentioned earlier.

At the moment, we do not have a definitive solution for monitoring drug distribution since each method has some well-known limitations. For example, in the case of SPECT, low resolution and variability in the threshold selection, especially when handling pathological brains, limits accurate tracking of drug distribution and homogeneity. Monitoring based on a T\(_2\) signal is particularly inefficient when extensive edema or other reasons for T\(_2\) signal enhancement are dominant. Positron emission tomography remains expensive and is still rarely used; in clinical settings, it barely improves on the spatial resolution of SPECT imaging (almost a centimeter in any case). The use of Gd-chelate appears to be a very appropriate surrogate marker for tracking fluid distribution, but the safety of intrastitial Gd-chelate for clinical use in human brains must still be guaranteed. A coregistration of T\(_1\)-weighted MR imaging with the results obtained both by tracking the distribution of an infused drug (both during and after treatment) as well as BBB permeability maps obtained using dynamic contrast-enhanced imaging will play an important role in discerning the appropriate explanation for T\(_1\) signal variability.

### Optimizing Delivery

We have touched on several factors that affect the disposition of an agent infused under positive pressure into the brain parenchyma. Factors that are essentially both unpredictable and manmade, such as tissue coring, introduction of air bubbles, and so forth, are best avoided by using good technology. The individuality of the brain, we believe, is validated by good simulations. We have discussed the hopes we entertain and every step with which such a simulation and its overall validation may be tackled.

### Conclusions

In the recitation of the details of the factors affecting CED, we may have lost sight of the fact that a systems approach is required; it is essential to develop devices and simulations together. We hope that, in time, those in drug development take note of all of these advances, and that the multitude of drugs abandoned by pharmaceutical companies because of the difficulty of delivering them into brain parenchyma may be reclaimed, and success in
improving therapeutic outcomes realized for brain cancer and other such devastating diseases.

Disclosure

Drs. Pedain, Rodríguez-Ponce, and Hartlep are employed by BrainLAB AG, which has a direct financial interest in the results of the authors’ research. The research reported on in this paper has been supported in part by BrainLAB AG, which has a direct financial interest in the results. The other authors have no financial interest in the outcomes beyond the support provided by BrainLAB, as mentioned.

References


Manuscript received February 1, 2006. Accepted in final form March 16, 2006. This work has been supported in part by NIH Grant No. R44-NS043105–03 (R.R. and M.L.B.). Address reprint requests to: Raghu Raghavan, Ph.D., Therataxis, LLC, 600 Wyndhurst Avenue, Suite 305, Baltimore, Maryland 21210-2415. email: raghu@therataxis.com.