Model of Distribution of Anticancer Agents Transplanted into the Brain Tissue Using the Random Walk Method

J POLÁK[1], P. KVASNIČKA[2], D. CHORVÁT[2], and Z. KÁLLAY[1]

1 *Institute of Preventive and Clinical Medicine, Limbová 14, 833 01 Bratislava, Czecho-Slovakia*
2 *Department of Biophysics, Faculty of Mathematics and Physics, Comenius University, Mlynská dolina, 842 15 Bratislava, Czecho-Slovakia*

Abstract. A Monte-Carlo approach to analysis of dispersion in the tissue of a locally administered drug is presented. The distribution of a drug in the tissue is simulated as a distribution of randomly walking particles. The approach is demonstrated on a simple situation for which both experimental results and an analytical solution are known. The approach can be used in situations, where common numeric methods are difficult to use, especially for analyses of drug transport in an inhomogeneous space, and problems with complex boundary conditions, e.g. in analyses of dispersion of anticancer agents locally applied into tumours.

Key words: Cisplatin — Monte-Carlo simulation — Drug transport — Modelling — Intratumour chemotherapy

Introduction

Chemotherapy of central nervous system tumours is made difficult by the presence of a blood-brain barrier that prevents most anticancer drugs from leaving capillaries and entering the interstitial space of the brain tissue. Two methods of anticancer drug administration were developed to overcome this problem, namely chemoembolization and localized therapy. By chemoembolization, the drug is targeted to tissue sites through selective arterial catheterization using microcapsules with controlled release of anticancer agents (Nishino et al. 1986; Sakatoku et al. 1984). With the other method, either a capsule with controlled release of an anticancer agent is implanted directly into the cancerous tissue (Yoshida et al. 1985, 1989; Yamashita et al. 1986;) or the drug is delivered to the cancerous tissue by infusion via a microcannula (Dakhil et al. 1981; Kroin and Penn 1982; Penn et al. 1983). The approach presented herein allows to predict the distribution of anticancer agents in the tissue and to determine the region of the tissue reached by the drug. Various methods and arrangements of drug administrations as well

as boundary effects and space variations of drug transport constants due to tissue inhomogeneity can be taken into account in a straightforward manner.

Model description

To make arguments simpler, let us start with a Cauchy problem for a one-dimensional diffusion equation

$$\frac{\partial c(x,t)}{\partial t} = D\frac{\partial^2 c(x,t)}{\partial x^2} \tag{1}$$

with the initial condition

$$c(x,0) = c_0(x)$$

and the boundary condition

$$c(x,t) \to 0 \quad \text{as } x \to \infty, \text{ all } t$$

This problem can, of course, be easily solved. We will, however, consider the following method of finding the concentration profile $c(x,t)$ for some $t > 0$. Equation (1) may be interpreted as a Fokker-Planck equation (FPE) describing evolution of (non-normalized) probability distribution $c(x,t)$ of a position $x(t)$ of a particle, undergoing Brownian motion on a line, with initial position $x(0)$ distributed according to probability density $c_0(x)$ at $t = 0$. Generating a large number (say, N) of particles, starting their Brownian random walks at positions, distributed according to probability density $c_0(x)$, one can estimate $c(x,t)$ considering number of particles, found in some neighbourhood of x at time t, i. e., a histogram of particle positions at time t gives some approximation of the concentration profile $c(x,t)$. The Khintchine limit theorem (Feller 1950) states that, under fairly general conditions regarding the random walk, the (appropriately normalized) distribution of particles at time t approaches $c(x,t)$ as N increases to infinity.

This is the basic idea underlying Monte-Carlo imitations of transport processes (Uffink 1990). The procedure consists of:

1. Rewriting and interpreting the corresponding transport equation as a Fokker-Planck equation, and constructing random walks with probability distribution obeying (to a desired degree of accuracy) the FPE and the corresponding initial and boundary conditions.

2. Generating a large number of realizations of the random walks and constructing histograms of particle states in the times of interest.

Though it may not seem a good idea to solve equation (1) in this manner, this approach proved to be very efficient in problems with complex boundary conditions, where common numeric methods for solving partial differential equations are difficult to use. Moreover, in some cases it is possible to construct a random walk

imitation, though the transport equation and/or the initial or boundary conditions are difficult to formulate.

The general transport equation, describing drug dispersion in the brain tissue, can be written as follows (Morrison and Dedrick 1986):

$$\frac{\partial c(\boldsymbol{x},t)}{\partial t} = D\Delta c(\boldsymbol{x},t) - \boldsymbol{v}\nabla c(\boldsymbol{x}t) - pA(c(\boldsymbol{x}t) - C_B) - S. \tag{2}$$

Here, $c(\boldsymbol{x},t)$ is the concentration of free drug, averaged over microscopic inhomogenities of the tissue (cells). The first and second terms on the right side correspond to diffusion and convection, D is the diffusion coefficient of the drug, equal to the product of the extracellular fraction and tortuosity-corrected extracellular diffusion constant, and v is convective flow velocity. The third term describes elimination of the drug by capillaries; p is the capillary permeability, and A is the capillary area per unit tissue volume. C_B is the concentration of the free drug in the plasma. Finally, S is a reaction term describing reaction of the drug with macromolecules. In case there is no substantial depletion of protein binding sites for the drug, S may be expected to depend linearly on $c(\boldsymbol{x},t)$.

Following Morrison and Dedrick (1986), we adopt several additional assumptions concerning the coefficients in eq.(2): (i) There is no convective flow, i.e., $v = 0$ throughout; (ii) Resorption of the drug from plasma can be neglected, i.e., $C_B = 0$; (iii) S depends linearly on $c(\boldsymbol{x},t)$: $S = k \cdot c(\boldsymbol{x},t)$. Under these assumptions, eq.(2) becomes

$$\frac{\partial c(\boldsymbol{x},t)}{\partial t} = D\Delta c(\boldsymbol{x},t) - (k + pA)c(\boldsymbol{x},t) \tag{3}$$

In practice, it is possible to measure the total amount of drug contained in macroscopic sections of the volume of interest. Therefore, another equation is needed, describing the kinetics of the bound drug concentration field $b(\boldsymbol{x},t)$. In our case, such an equation would read

$$\frac{\partial b(\boldsymbol{x},t)}{\partial t} = kc(\boldsymbol{x},t) - k'b(\boldsymbol{x},t) \tag{4}$$

simply stating that the bound drug is produced by binding of the free drug and disappears due to protein turnover.

We will now define rules for random walks, corresponding to eqs. (3) and (4). These rules can be derived from a finite-difference approximation of eqs. (3),(4). The resulting random walks take place on a three-dimensional lattice, i.e. random walks with fixed displacement per step u (however, with random direction, as will be shown below), and fixed time interval per step τ.

Such walks can easily be implemented on a computer, because they can be simulated using only uniformly distributed random numbers, and lattice structure of the available space allows for simple implementation of boundary conditions.

The error of discretization can be made as small as desired by choosing sufficiently small parameters u and τ The random walks are defined by the following rules

(i) Each particle can adopt one of three states
- Free state (F) at some position (x,y,z), in which it is allowed to diffuse,
- Bound state (B) at some position (x,y,z), corresponding to an immobilized (bound) particle,
- Lost state (L) corresponding to a particle, which was resorbed into a capillary net,

(ii) A particle in the free state may
- Move to an adjacent position

$$x' = x + u^* r_1$$
$$y' = y + u^* r_2$$
$$z' = z + u^* r_3$$

with probability p_{FF}, r_1, r_2, r_3 are random numbers, which adopt the values $+1$ and -1 with equal probabilities (Fig 1),
- Change its state to bound (B) at (x, y, z) with probability p_{FB},
- Change its state to lost (L) with probability p_{FL},

(iii) A particle in the bound state may change its state to lost (L) with probability p_{BL},

(iv) A particle in the lost state will remain lost forever

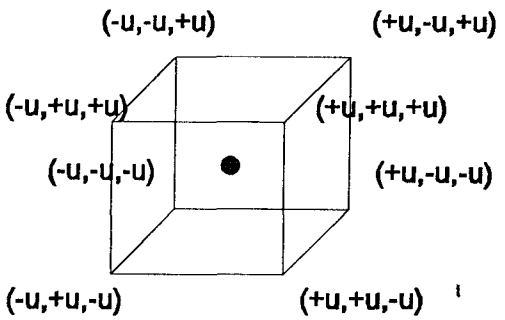

Figure 1. Eight possible step displacements of a particle A particle located at the centre of the cube (grey circle) can in one step move to one of the eight vertices of the cube, u is the lattice constant

Given lattice constant u and the kinetic parameters D, p A, k, k', the time per step τ and the transition probabilities can be expressed as follows Taking into account the relation between the diffusion coefficient D and the variance of the one-step probability distribution σ^2 (cf Fig 1)

$$D = \frac{\sigma^2}{6\tau,} \qquad \sigma^2 = 3u^2 \tag{5}$$

it is possible to express τ in terms of D and u;

$$p_{FF} = 1 - p_{FB} - p_{FL}, \quad p_{FB} = k\tau, \quad p_{FL} = pA\tau, \quad p_{BL} = k'\tau \tag{6}$$

To make the definition complete, one has to specify where the random walks would start and how would they behave on the boundaries. This requires specification of the appropriate initial and boundary conditions for eqs. (3),(4), and these in turn depend on the way of administration of the drug to the tissue.

We have used the data of Kroin and Penn (1982) to verify the random walk model. In their experiment, a 0.32 mm cannula was stereotactically placed in the centre of the cerebellum of a normal rat and then cisplatin was infused into the brain at a concentration of 1000 $ng \cdot \mu l^{-1}$ by means of an Alzet osmotic minipump at a rate of 0.9 $\mu l \cdot h^{-1}$. After 160 hours, the cerebellum was removed and cut into sagittal sections approximately 1mm thick. The average total platinum concentration per section was determined by atomic absorbtion spectrophotometry.

The corresponding initial and boundary conditions for random walks are as follows: Particles are created in free state at the tip of the cannula at moments uniformly distributed over infusion time (initial); diffusing particles are forbidden to enter the region occupied by the cannula (boundary).

Table 1. Parameters relative to the experiment of Kroin and Penn (1982).

Parameter	Definition	Value
q [$\mu mol \cdot s^{-1}$]	Mass infusion rate	8.3×10^{-7}
q_v [$ml \cdot s^{-1}$]	Volume infusion rate	2.5×10^{-7}
t [s]	Time of infusion	5.76×10^{5}
r [cm]	Cannula radius	0.032

A computer program written in C language was developed for drug distribution simulation. The input data used as starting parameters for simulation are listed in Tab. 1 and Tab. 2. We have chosen the lattice constant u equal to 0.1 mm. The following additional input parameters were calculated: step time τ, effective mass of platinum per particle m, and the transition probabilities p_{FF}, p_{FB}, p_{FL} and p_{BL}. The calculated values of the input parameters for the model are in Tab. 3. Twenty-three thousand random trajectories were generated according to the rules described above, and particles with the x coordinate between $(k \times 0.1 - 0.05)$mm and $(k \times 0.1 + 0.05)$mm were counted to give mass of cisplatin in the k-th section.

Table 2. Kinetic constants for cisplatin dispersion in the brain tissue (Morrison and Dedrick 1986)

Parameter	Definition	Value
k [min^{-1}]	Binding rate	$(5 \pm 2.3) \times 10^{-3}$
k' [min^{-1}]	Turnover rate	$(1.4 \pm 1.1) \times 10^{-6}$
p [$cm \cdot s^{-1}$]	Capillary permeability	$(9.0 \pm 4.4) \times 10^{-7}$
A [cm^{-1}]	Capillary area per unit volume of brain	240
D [$cm^2 \cdot s^{-1}$]	Diffusion coefficient of cisplatin in the tissue	1.9×10^{-6}

Table 3. Parameters of numeric simulation

Parameter	Definition	Value
τ [s]	Time interval for one step	25
m [ng]	Mass of Pt per particle	4.07
u [mm]	Lattice constant	0.1
z_{FB}	Binding probability per step	2.08×10^{-3}
p_{BL}	Turnover probability per step	5.83×10^{-6}
p_{FL}	Resorption probability per step	5.41×10^{-3}

Results

The simulated distribution of platinum, averaged over 0.1 mm sections, can be seen in Fig. 2. The distribution shows an approximately exponential decrease with distance. This picture also allows to grasp the quality of the simulation results: variances of the distribution curve values are proportional to numbers of particles found in the corresponding sections.

In Fig. 3 we present a comparison of our results to those of Kroin and Penn (1982). In this Figure, the simulated distribution is recalculated to obtain information comparable to that presented by Kroin and Penn (1982). Namely, we have assembled data points to represent amounts of platinum in 1 mm sections, and used masses of the sections (published by Morrison and Dedrick 1986) to correct our data for variations in thickness of the sections analyzed for platinum by Kroin and Penn (1982).

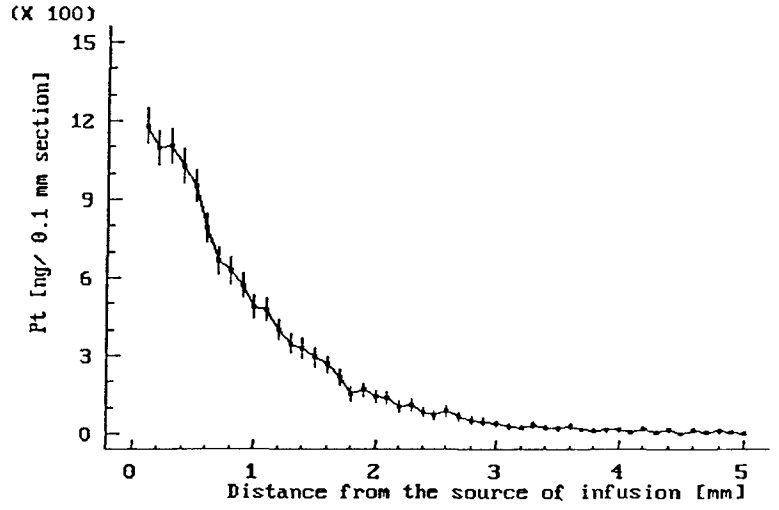

Figure 2. Simulated concentration profile of cisplatin after a 160 hour infusion to the rat brain tissue. Twenty-three thousand trajectories were generated in the course of simulation. The curve represents amounts of platinum found in 0.1 mm thick sagittal sections of the brain as a function of distance from the cannula.

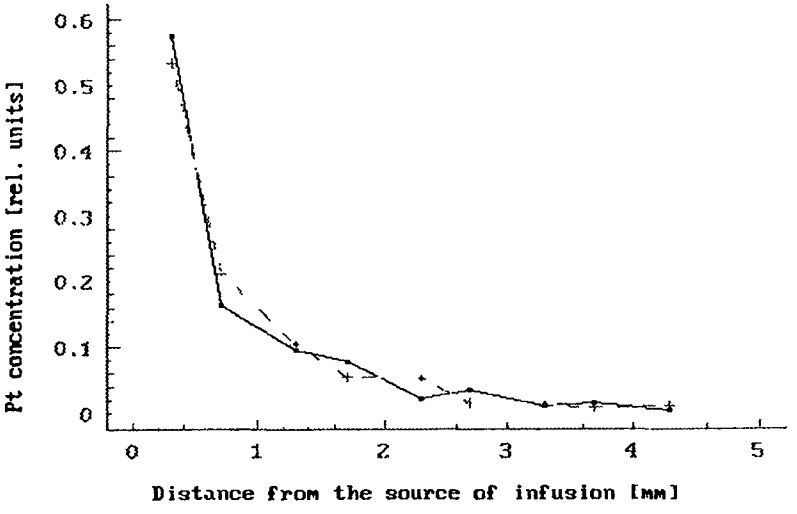

Figure 3. Comparison of the experimental curve (Kroin and Penn 1982, solid line) with our random walk simulation (dashed line). The data presented in Fig. 2 were assembled in order to reproduce values over sections, analyzed for platinum by Kroin and Penn (1982)

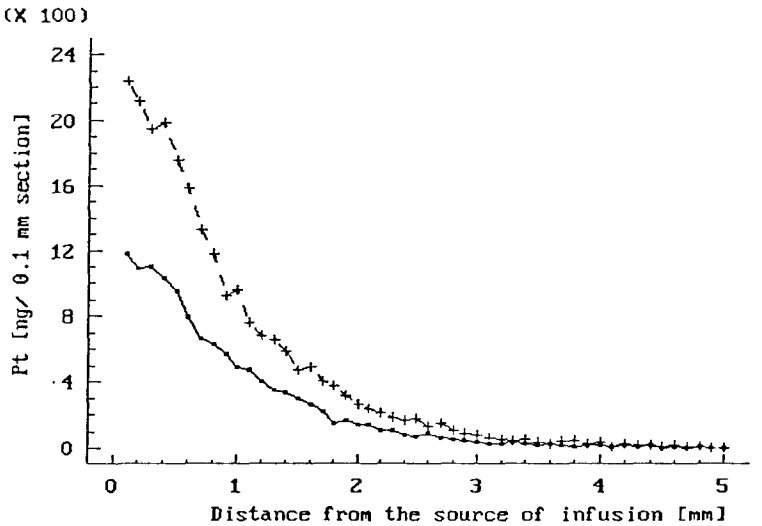

Figure 4. Simulated concentration profiles of platinum in the brain tissue after 160 (solid line) and 320 (crosses) hour infusion time. Twenty-three thousand trajectories were generated in the course of simulation. The curve represents amounts of platinum, found in 0.1 mm thick sagittal sections of the brain as a function of distance from the cannula.

In Fig. 4, concentration profiles taken after 160 and 320 hours infusion time are compared. The only difference between the two profiles is that, after a 320 hour infusion, the concentrations of Pt are approximately twice those taken after 160 hours. Otherwise, the concentration profile remains the same.

Discussion

We have used the data of Kroin and Penn (1982) to test the Monte-Carlo approach to investigation of dispersion in the tissue of a locally dosed drug. The situation under consideration is quite simple, and indeed, Morrison and Dedrick (1986) have presented a closed-form analytical solution to the transport equation for this case Thus, the data used herein are an extremely useful material for the testing of any method of modelling drug transport in tissues. In our simulations, a more complicated case was considered compared to the treatment of Morrison and Dedrick (1986): we have explicitly accounted for the presence of the cannula, represented by a semi-infinite rod-like region where the particles were forbidden to enter. However, our results proved the approximation: there was practically no difference between our results and those of Morrison and Dedrick (1986).

As can be seen from the results presented above, a good agreement was obtained between experimental and simulated data. A relatively simple manner, in which Monte-Carlo algorithms can be constructed for complex situations, where one not only cannot hope to find an analytical solution to the transport equation, but where it is difficult to implement common algorithms for solution of partial differential equations, seems to outweigh its cost in terms of computation time.

We stress that no assumption was made about a similarity in movement of our fictive particles and the molecules of the drug. In fact, (1) no such assumption is necessary for our method to work well in case the transport equation describes the drug dispersion with sufficient accuracy; (2) various random walks can be used to simulate the same form of distribution.

The problem considered reads as follows: Given kinetic constants and the method of administration, find the drug concentration profiles at some set of times after administration. In practice, however, one is generally faced with an inverse problem, namely: Given a set of (as a rule, low resolution) concentration profiles, find the kinetic constants. If there is not a closed formula to fit the data, such a problem may be rather difficult to solve, or, at least, its solution may be rather time consuming. In these situations, the Monte-Carlo method is also applicable, but its use requires a lot of computation time.

There is one important point which should be drawn out of the present results, as demonstrated in Fig. 4: As long as saturation effects can be neglected, the shape of the drug concentration profile is determined by the kinetic constants, characterizing the transport of the drug (diffusion coefficients, binding constants etc.), rather than by the amount of the drug administered. A substantial increase of the affected volume can only be achieved by using drugs with different values of constants D, k_D, k', and p (for example, methotrexate $D = 1.2 \times 10^{-6}$ cm^2/s (Collins and Dedrick 1983)) that characterize the drug. We find this important from the point of view of evaluation of various methods of local administration of anticancer agents.

The approach presented herein is applicable for various shapes of microcapsules and for drugs with various values of kinetic constants. It also allows to simulate drug dispersion in inhomogeneous space. If the transport equation with its initial and boundary conditions is given, the rules for random walks can be derived in a straightforward manner from a finite difference approximation of the transport equation. The Monte- Carlo approach described here may be an efficient tool for the prediction of therapeutic effects of anticancer agents administered locally into the tissue.

References

Collins J.M., Dedrick R.L. (1983): Distributed model for drug delivery to CSF and brain tissue . Amer. J. Physiol. **245**, R303—R310

Dakhil S , Ensminger W , Kindt G , Niederhuber J , Chandler W , Greenberg H , Wheeler R (1981) Implanted system for intraventricular drug infusion in central nervous system tumours Cancer Treat Rep **65,** 401—411

Feller W (1950) An Introduction to Probability Theory and its Applications Vol I , Wiley, New York

Kroin J S , Penn R D (1982) Intracerebral chemotherapy chronic microinfusion of cisplatin Neurosurgery **10,** 349—354

Morrison P F, Dedrick R L (1986) Transport of cisplatin in rat brain following microin fusion An analysis J Pharm Sci **75/2,** 120—128

Nishino K , Nakazawa S , Mori T , Sugita K , Abe T , Suzuki T , Kinoshita A , Osano M (1986) Cytotoxic activity of monoclonal antibody (KOR-N34)-liposome-adrimycin conjugates to cultured lymphoid cell lines J Jpn Soc Cancer Ther **21,** 773—779

Penn R D , Kroin J S , Harris J E , Chiu K M , Braun D P (1983) Chronic intratumoral chemotherapy of a rat tumour with cisplatin and fluorouracil Appl Neurophysiol **46,** 240—244

Sakatoku M , Hirano M , Asano M , Iwa T , Kondo T , Arakawa M (1984) Study on 5-FU polylactic acid microcapsules Jpn J Artif Organs **13,** 1180—1183

Uffink G J M (1990) Analysis of Dispersion by the Random Walk Method, Delft

Yamashita R Sakatoku M , Hirano M , Iwa T (1986) Development of controlled release anticancer preparation 5 FU polylactic acid compound Jpn J Artif Organs **15,** 218—221

Yoshida M , Asano M , Kaetsu I , Imai K , Mashimo T , Yuasa H , Yamanaka H , Suzuki K , Nakamura M , Takasaki T , Hanyu F , Kubo O (1985) Necrosis of tissues caused with controlled release anticancer agent polymer composites in needle form Jpn J Artif Organs **14,** 830—833

Yoshida M , Asano M , Morita Y , Kaetsu I , Imai K , Mashimo T , Yuasa H , Yamanaka H , Kawaharada U , Suzuki K (1989) In vivo release of cisplatin from a needle type copolymer formulation implanted in rat kidney Biomaterials **10,** 16—22

Final version accepted August 20, 1992