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ABSTRACT

A PHARMACOKINETIC MODEL OF THE LIVER

by
Samirbhai Rameshbhai Patel

The liver is the major organ where chemical breakdown of organic and inorganic compounds takes place. A pharmacokinetic heterogeneous model was developed for the local anesthetic and antiarrhythmic drug lidocaine. It was assumed that transport and elimination of lidocaine and its metabolites are linear with concentration. Simulations were done using VisSim software on a 486 based personal computer to obtain concentration profiles for hepatic clearance and for step input of the drug and its metabolites. It was found that the rate of uptake and rate of breakdown were 0.48 min^{-1} and 0.49 min^{-1} respectively for lidocaine. The results are consistent with published data. Similar simulations were done for the lidocaine metabolites MEGX and 3-OHLID.

The same heterogeneous model was used with appropriate changes to include cellular inactivation of the drug and urine output in order to model another antiarrhythmic drug, procainamide. Simulations were done for hepatic clearance and for bolus (impulse) input to the model. The rate of uptake and rate of release for procainamide were found to be 9.35 min^{-1} . The rate of breakdown and urine output were 0.0053 min^{-1} and 0.0013 min^{-1} respectively.

Finally, a parameter sensitivity study was done for both lidocaine and its metabolites and procainamide in order to determine sensitivity of the model to the parameters used. The maximum values of rate constants for which the model can operate in stable range were determined.

A PHARMACOKINETIC MODEL
OF THE LIVER

by
Samirbhai Rameshbhai Patel

A Thesis
Submitted to the Faculty of
New Jersey Institute of Technology
in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Biomedical Engineering

Biomedical Engineering Committee

January 1995

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This thesis is dedicated to my grandparents
Maganbhai and Shantaben Patel

ACKNOWLEDGMENT

The author wishes to express his sincere gratitude to his advisor, Dr. Arthur Ritter, for his guidance, friendship, and moral support throughout this research.

The author is grateful and appreciates the timely help and suggestion by Dr. David Kristol. His advice and help were the basis of my education at NJIT.

Special thanks to Dr. Stanley S. Reisman for serving as a member of the committee.

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CHAPTER 1

INTRODUCTION

The liver is the primary organ for metabolism of a wide range of lipophilic compounds, including many drugs, aromatic hydrocarbons, and chlorinated compounds [1]. Within the liver, a number of different physiological processes combine to give observed differences in drug elimination. Net changes in concentration of these compounds are due to a series of steps [2] summarized as follows;

- (1) The net flow of blood (perfusion medium) in the vascular network of the organ.
- (2) Uptake of the substrate from the vasculature into the liver cells.
- (3) Enzyme mediated reactions within the cells.
- (4) Release of metabolic products and unconverted substrate from the cells into the sinusoids.

It is necessary to understand each of these processes to fully comprehend the overall process of drug elimination. Thus, a drug elimination model was developed by considering the above processes either individually or by grouping some of them with appropriate approximations. The major purpose of this model is to mathematically describe the dominant physiological processes that are occurring. The distribution of most drugs from the blood into highly perfused tissues such as liver and kidney is known to be quite rapid and that distribution in to moderately to poorly perfused tissues such as muscles and fat is rather slow [3]. This study is part of the whole body pharmacokinetic model for blood flow. Anesthetic and antiarrhythmic drug model of liver was developed.

1.1 Liver Physiology and Functions

The liver is located in the blood stream between the gastrointestinal tract and spleen and vena cava leading to the heart. The liver can be regarded as a three dimensional, slowly

moving lake of blood in which sheets of liver cells, or hepatocytes float [4]. Blood enters the organ through both the portal vein and the hepatic artery and leaves the liver via the hepatic vein (Figure 1.1). The portal vein, hepatic vein, and hepatic artery are all subject to branching. Individual branches serve each lobe of the liver [5]. The blood flow to the liver is normally about 25% of the cardiac output. The flow is derived from the two sources, the portal vein and the hepatic artery. The portal vein provides about three fourth of the blood flow, after passing through, the gastrointestinal capillary bed. The hepatic artery delivers the remaining one fourth of the blood [6].

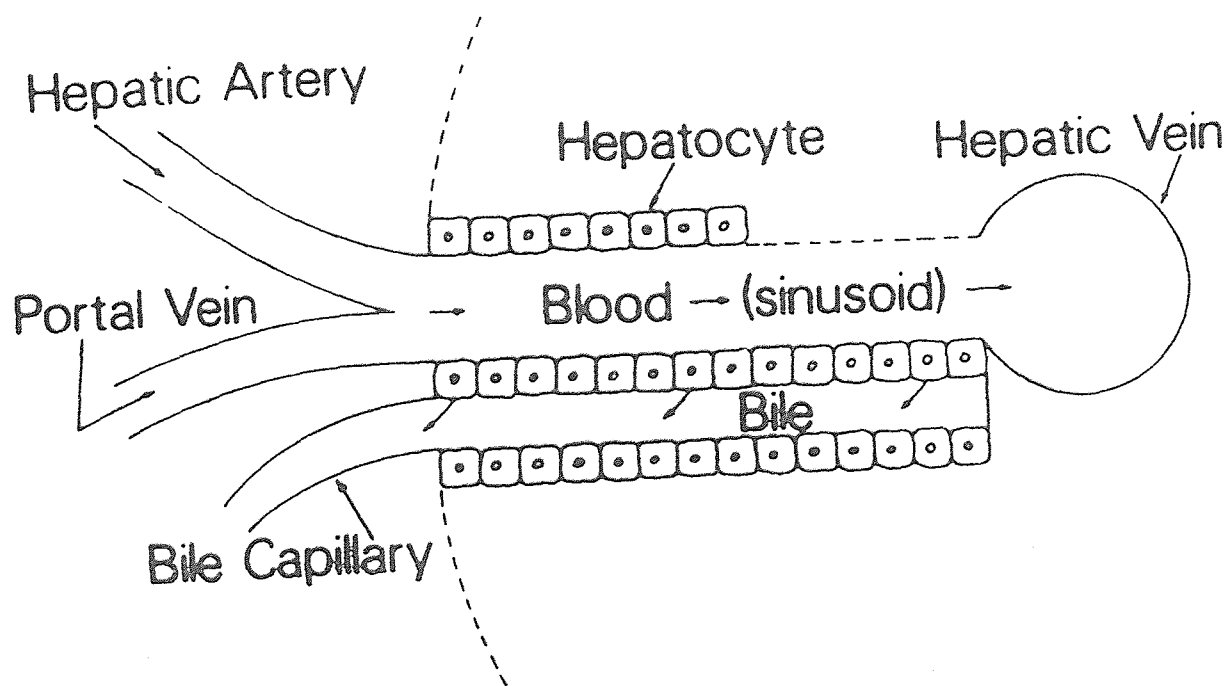


Figure 1.1 Schematic diagram of the Liver structure (From B. A. Saville, M. R. Gray, Y. K. Tam, "Models of Hepatic drug elimination", *Drug Metabolism Reviews*, 24(1), 49- 88, 1992)

1.1.1 Physiology of Liver

The basic functional unit of the liver is the liver lobule, which is a cylindrical structure. The human liver contains 50,000 to 100,000 individual lobules. The venous sinusoids are lined by two types of cells (1) Typical endothelial cells and (2) large kupffer cells, which are tissue microphages. The endothelial lining of the venous sinusoids has extremely

large pores. Beneath this lining, lying between the endothelial cells and hepatic cells, is a very narrow tissue space called the space of Disse. Because of the large pores in the endothelium, substances in the plasma move freely into the space of Disse. Kupffer cells are capable of phagocytizing bacteria and other foreign matter in the blood [7].

Orally administered substances are absorbed in the gastrointestinal tract, and enter the liver through the portal vein. Drugs administered intravenously circulate through the body and enter the liver through both hepatic artery and portal vein [2]. The liver contains about 15% of total blood volume of the body. The liver constitutes an important blood reservoir in humans.

The liver is a continuous meshwork of highly interconnected blood spaces. The sinusoidal channels are of varying length and are oriented in a nearly random fashion. Mixing can occur at various sites within the liver, especially at each node corresponding to the divergence and convergence of a number of sinusoids. Furthermore, back mixing within the organ occurs due to flow reversal in the sinusoids. Hepatic metabolism is highly dependent upon the physical properties of the substrate relative to the physical characteristics and intrinsic activity of the liver. Every hepatocyte is exposed to the blood, since the plates of hepatocytes are no more than two cells thick. The hepatocytes remove substances from the blood and secrete them in to biliary canaliculi lying between the adjacent hepatocytes. The countercurrent relationship between the bile flow and blood flow within the lobule minimizes the concentration to the liver's efficiency in extracting substances from the blood [8]. To investigate the vast range of phenomena that affect hepatic metabolism, several classes of compounds can be used as probes of intrahepatic mixing, interphase transport and elimination [2]. The intimate contact of a large fraction of the hepatocyte surface with blood contributes to the ability of the liver to clear the blood effectively of certain classes of compounds. The organ must be considered as a heterogeneous system to account for the transport between the vasculature and the cells [1].

1.1.2 Functions of Liver

The basic functions of the liver can be divided into (1) vascular functions for storage and filtration of blood (2) metabolic functions concerned with the majority of the metabolic systems of the body, and (3) secretory and excretory functions that are responsible for forming the bile that flows through the bile ducts into the gastrointestinal tract. The liver performs a wide variety of functions. Some of them are endocrine functions, clotting functions, digestive functions, organic and cholesterol metabolism, excretory and degradative functions [9]. The liver regulates the metabolism of carbohydrates, lipids and proteins. The liver transforms and excretes a large number of drugs and toxins. Drugs and toxins are frequently converted to inactive forms by reactions that occur in hepatocytes. Drug transformations that occur in hepatocytes are oxidative, acetylation, methylation, reduction, and hydrolysis. The transformation that occurs in the liver renders many drugs more water soluble, and thus they are more readily excreted by the kidneys. Some drug metabolites are secreted into bile. The liver has a very active chemical medium and this medium is well known for capability of detoxifying or excreting into the bile many different drugs including sulfonamides, penicillin, ampicillin, erythromycin, and many others. In a similar manner several of the different hormones secreted by the endocrine glands are either chemically altered or excreted by the liver, including thyroxine.

A heterogeneous model was used to study hepatic elimination of the lipophilic compound lidocaine and its metabolites. Simulations were done on a 486 based personal computer with the VisSim (Visual Solution Inc., Westford, MA) graphical modeling program. A sensitivity study was done which established ranges of kinetic constant values that can be used. The heterogeneous model had to be changed slightly to simulate the antiarrhythmic drug procainamide. Simulations were done for procainamide and range of kinetic constant values were determined.

CHAPTER 2

METHODS

The following chapter documents the methods available for modeling kinetics of liver metabolism. The method used is described in detail. Equations and parameter values are described. Simulations were done on VisSim software [10].

2.1 Types of Models Available

There are three types of models available for liver metabolism; which include

- (1) Non-parametric models,
- (2) Homogenous mixing models,
- (3) Heterogeneous models

Hepatic metabolism models may be classified according to the assumption made in the liver physiology and degree of mixing within the organ. Non-parametric models are the simplest kind of models. These models do not have any adjustable parameter to describe extent of mixing and interphase transport. A second class of models are homogenous and these models take into account the extent of intra hepatic mixing. However these models do not explicitly account for mass transfer between the cells and the vasculature. Both non-parametric models and homogenous models are described by first order ordinary differential equations. The heterogeneous models are divided into two types. The first type uses homogenous compartments to describe intrahepatic mixing and this type assumes complete mixing on a microscopic level. The second type assumes little or no mixing on a microscopic level [2]. Microscopic heterogeneous models (no mixing) use partial differential equations and are distributed parameter models. These models are more complex than the earlier types described.

2.1.1 Non-Parametric Models

The most commonly used and most extensively investigated models of hepatic elimination are the well stirred model and parallel tube model. Both models ignore the heterogeneous nature of the liver, assuming that compounds are equally and instantaneously distributed between the vascular and cellular regions of the liver. Both models can be mathematically described by the same Taylor series expansion [11]. A well mixed model is mathematically simple. However, it cannot describe the metabolism of materials which are limited by the transport into the hepatocytes. A parameter model is more complex mathematically. Pang and Rowland [12] demonstrated that weak dependence of the lidocaine metabolism upon flow rate was best described by the well mixed model. These types of models are mathematically simple and cannot be used to describe intra hepatic mixing. Well mixed and parallel tube model, require so many approximations as to limit their use to a small selected number of substrates. Non parametric models can be described by ordinary differential equations.

2.1.2 Homogenous Models

These types of models are mixing models, and are used to describe mixing phenomena that occur in the liver. There are two single parameter homogenous models for hepatic mixing (1) The axial dispersion model [11, 13-16]

(2) The series compartment model [17]

Both these models are based upon well established models for chemical reactors [18]. The axial dispersion model assumes that the liver is a packed bed in which different degrees of axial mixing can occur. The dispersion model is mathematically complex and is used mainly as an empirical model. The series compartment model is mathematically simple and is very general for species without transport limitations. Axial dispersion models are described by partial differential equations. The series compartment model

does not include the effect of transport processes between the vascular and cellular regions of the liver. The disadvantage with both types of homogenous models is that there is no direct means of accounting for physiological phenomena such as interphase mass transport and variable flow through the liver.

2.1.3 Heterogeneous Model

The heterogeneous model is required to properly investigate transport process in the liver [2]. Heterogeneous models are typically more complex than homogenous models. Several models for heterogeneous metabolism have been developed with varying degree of complexity. Heterogeneous models explicitly account for transport processes between species in the cells and the vasculature. The heterogeneous models proposed by Tsuji [19] were used for a variety of antibiotics but this model has drug specific assumptions and cannot be used as a general model. The Deans-Levich model [20] and the finite stage transport model [21] are promising but require modifications to be made before they can be used for liver metabolism. The compartment model proposed by Weisiger [22] has several advantages such as mathematical simplicity, requires minimum data and is easy to use as a predictive model for both drugs and metabolites. This model can account for several physiological processes such as cellular uptake and release as well as intracellular reactions. The compartment model proposed by Weisiger [22] and modified by Saville [1] comes closest to the ideal model for liver metabolism. The modified model can be used to describe time dependent profiles of a variety of compounds. Experimental evidence suggests that this is particularly effective for species subject to passive transport. Hence, this model was used for the liver metabolism. The model is mathematically simple, and can account for a wide variety of physiological phenomena and is easy to use both for correlating data and as a predictive model [2].

The heterogeneous model proposed by Weisiger [22] and modified by Saville [1] produced a best fit of the data and was used to model hepatic elimination of lidocaine and its metabolism. A similar model was used to model hepatic elimination of procainamide.

There are two types of enzyme inactivation. (1) Chemical moves in to the cell and enzymes breakdown chemical in the cell. (2) Enzymes moves outside cell and breakdown of chemical occurs outside cell. In lidocaine breakdown occurs inside cell. While in procainamide breakdown occurs outside cell.

2.2 Model for Lidocaine Metabolism

The liver model for the lipophilic compound lidocaine consists of two compartments: an extracellular compartment and a cellular compartment [1]. Experimental evidence indicates that the concentration of substances in the space of Disse is very close to the concentration of the substances within the sinusoids, since the fenestrates are large [22]. Lidocaine undergoes linear oxidative deethylation of the tertiary amine group and forms monoethylglycinexylidide represented as MEGX. Lidocaine also undergoes hydroxylation of the aromatic ring to form 3-hydroxylidocaine represented as 3-OHLID. These two are the important metabolites of lidocaine.

2.2.1 Assumptions and Equations

- (1) The general model consists of a series of repeating cellular-extracellular parallel compartments.
- (2) The sinusoids and the interstitial space of Disse are approximated as a single unit called the extracellular compartment.
- (3) The second compartment is the tissue or cellular compartment. This compartment is assumed to behave as a homogeneous pool for both reaction and efflux.
- (4) Mass transfer takes place between these two compartments by kinetic rate constants k_{12} and k_{21} .

- (5) Metabolites are formed in the cellular compartment.
- (6) The number of composite compartment units does not influence the effectiveness of this model in representing washout profiles of lidocaine and its metabolites. The reason for this is that time to complete cellular uptake and release is significantly longer than the time require to clear the extracellular network [1]. Therefore for our purpose we choose $N=1$.
- (7) Inputs and outputs are by way of the extracellular compartment only.

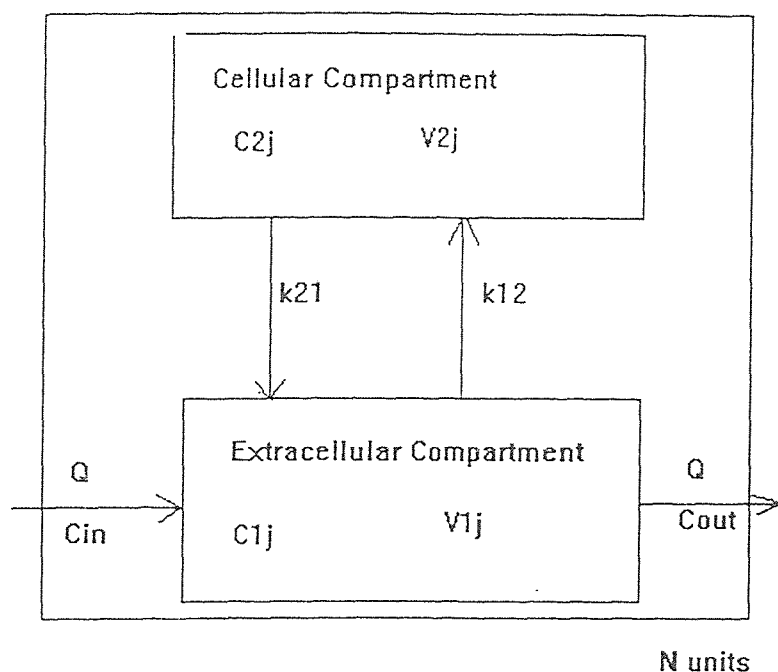


Figure 2.1 Compartment model for hepatic elimination of lidocaine and its metabolites (From B.A. Saville, M.R. Gray, and Y. K. Tam, "Experimental studies of transient mass transfer and reaction in the liver, Interpretation using a heterogeneous compartmental model", *J. Pharm. Sci.*, 81(3), 265-271, 1992)

The model shown in Figure 2.1 to describe liver metabolism was first proposed by Weisiger [22] and then modified by Saville [1]. There are 'N' number of extracellular and cellular compartments arranged in series parallel order. Compartments '1' and '2' represent the cellular and extracellular compartments respectively. The concentration of

cellular and extracellular compartments is represented as C_{1j} and C_{2j} respectively. 'Q' is the blood flow in to and out of the cellular compartment. C_{in} is the input to the cellular compartment. As seen in Figure 2.1 'j' is the number of compartments. For lidocaine 'j'=1. Mass transfer equations for Figure 2.1 are given as

$$V_{1j} [dC_{1j}/dt] = Q(C_{in} - C_{1j}) - k_{12} V_{1j} C_{1j} + k_{21} V_{2j} C_{2j} \quad (1)$$

$$V_{2j} [dC_{2j}/dt] = k_{12} V_{1j} C_{1j} - k_{21} V_{2j} C_{2j} - V_{2j} k_r C_{2j} + V_{2j} k_f C_{p2j} \quad (2)$$

Where:

V_{1j} = Volume of extracellular compartment (mL)

V_{2j} = Volume of cellular compartment (mL)

Q = Volumetric flow rate through organ (L/min)

C_{in} = Input concentration (μM)

C_{1j} = Concentration in extracellular compartment (μM)

C_{2j} = Concentration in cellular compartment (μM)

C_{p2j} = Precursor concentration in the cellular compartment (μM)

C_{m2j} = Metabolite concentration in the cellular compartment (μM)

k_{12} = Rate constant of uptake in to liver cells from extracellular space (min^{-1})

k_{21} = Rate constant of release in to liver cells from extracellular space (min^{-1})

k_f = Rate constant for intracellular formation (min^{-1})

k_r = Rate constant for intracellular reaction (min^{-1})

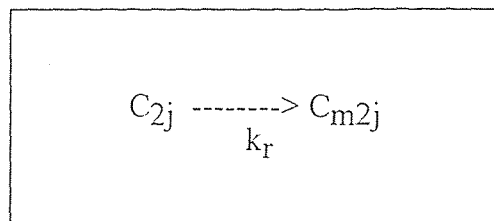


Figure 2.2 Metabolites formation of lidocaine.

Figure 2.2 shows the reactions occurring in the cellular space when the species of interest C_{2j} reacts to form metabolites C_{m2j} . Metabolites are formed in the cellular compartment by the kinetic rate constant k_r . Depending on the rate constant, metabolite formation occurs. If k_r increases then metabolites form quickly and if k_r decreases then metabolites form slowly.

2.2.2 Calculations

V_{1j} and V_{2j} are calculated as ;

$$V_{1j} = V_v / N; \quad V_{2j} = V_c / N \quad (3)$$

N is the number of compartmental units

$N = 1$ for Lidocaine and its metabolites

V_v is extracellular volume (mL)

V_c is Cellular volume (mL)

$$V_{tot} = V_c + V_v \quad (4)$$

Where V_{tot} is the total physiologic volume of the liver (mL)

The volume of the cellular region is nearly six times that of the extracellular region [1].

$$V_{2j} = 6 * (V_{1j}) \quad (5)$$

$$V_{tot} = Wl / fl \quad (6)$$

Where Wl = Liver weight (g)

fl = Density of liver (g/L)

All experiments used rat livers isolated from male Sprague-Dawley rats [1]. Rats were anesthetized with diethyl ether, and the liver was isolated by surgical cannulation of the hepatic and portal veins and inferior vena cava. The bile duct was not cannulated. During experiment, the organ was kept moist and at a physiological temperature. Concentrated lidocaine was infused with a syringe pump. Samples of the inlet concentration were taken every 10 min to verify the infusion rate and to ensure that a constant concentration at the inlet was maintained. For washout experiments, lidocaine was infused until steady state was reached. Drug infusion was then stopped. Samples of the liver effluent were optioned every 6 seconds. Parameters for this model were estimated from the experimental data [1, 22] at a standard set of conditions.

$$Wl = 10 \text{ gms} \quad fl = 1 \text{ g/L}$$

Therefore, $V_{tot} = 10 \text{ mL}$ (from equation (6))

Using equations (3), (4), and (5)

$$V_{1j} = 1.4285 \text{ mL and } V_{2j} = 8.571 \text{ mL}$$

From [22] at standard test condition

$$Wl/Q = 0.33 \text{ but } Wl = 10 \text{ g Therefore } Q = 30.30 \text{ L/min}$$

Next kinetic rate constants were estimated. The most important consideration in modeling the metabolism of lipophilic compounds in the liver is the proper estimation of the kinetic time constant values. When the model was simulated on a 486 based personal computer with VisSim (Visual solution Inc.,) [10] software with kinetic constant values published in reference [1], it was found that the system was unstable. Kinetic rate

constants values given in reference [1] for k_{12} and k_{21} were $1206 \pm 830 \text{ min}^{-1}$ and $46 \pm 39 \text{ min}^{-1}$ respectively for lidocaine. When model was simulated with these kinetic rate constant washout profile were unstable. Concentration was getting very high value in range of thousands of micomolar. Also concentration was achieving negative values which is impossible. With kinetic constant values published in reference [1] for lidocaine metabolites MEGX and 3-OHLID concentration reached very high value and also negative values.

2.2.3 Data Analysis

We then used the exponential peeling method [24] to obtain parameters which characterized the experimental curves presented in reference [1]. We used these values in the heterogeneous model.

Model equations (1) and (2) were solved analytically for $N = 1$. This solution was compared with the exponential peeling equations and kinetic constants were estimated which then allowed us to fit the experimental data. Table 2.1 gives the comparison of the kinetic constant values which are given in the reference and values which were obtained by the exponential peeling method. It is seen that there is vast difference in the values between the two.

Table 2.1 Comparison of kinetic constants values for lidocaine given in the reference and predicted after exponential peeling method

Values given in the reference	Predicted value
$k_{12} = 1206 \pm 83 \text{ min}^{-1}$	$k_{12} = 9.7 \text{ min}^{-1}$
$k_{21} = 46 \pm 39 \text{ min}^{-1}$	$k_{21} = 0.48 \text{ min}^{-1}$
$k_r = 0.49 \pm 0.16 \text{ min}^{-1}$	$k_r = 0.49 \text{ min}^{-1}$

By comparing this results, it was seen that the values for k_{12} and k_{21} were 100 times less than those reported in reference [1]. Difference in the values of kinetic rate constant may be due to typographical error. This was then repeated to obtain kinetic constant values for the lidocaine metabolites. The rate constant values were changed accordingly and new predicted values were obtained are shown in table 2.2.

Table 2.2 Predicted rate constant values for lidocaine metabolites

Rate constant	MEGX	3-OHLID
$k_{12} \text{ (min}^{-1}\text{)}$	0.38	2.2
$k_{21} \text{ (min}^{-1}\text{)}$	0.03	0.08
$k_r \text{ (min}^{-1}\text{)}$	0.24	0.35

Simulation was done using these parameters on a 486 based personal computer using VisSim software [10]. It was observed that the system behaved in a predictable way. These parameters values were then used in a sensitivity study and a range of values were determined for lidocaine and each of its metabolites.

The results obtained were compared with the experimental results or data presented in reference [1]. It was found that the washout profile was very similar to the one given in the reference. Simulation curves are kept in the appendix A. It was found that the heterogeneous model accounts for the slow elution of the drug and its metabolites.

Encainide is a highly effective, well tolerated antiarrhythmic agent [25]. We tried to model metabolism of encainide in the liver but were unsuccessful due to reasons stated below; (1) There are few models available for modeling encainide metabolism. (2) The models that are available contain so many simplifying assumptions that they are not

useful for a heterogeneous organ such as liver [26,27]. Therefore, another antiarrhythmic drug procainamide was modeled [28-30].

2.3 Model for Procainamide

The model which was previously described for lidocaine was used to model procainamide with appropriate changes. Figure 2.4 describes the model and it is represented by differential equations (7) and (8). 'u' is the amount of procainamide present in urine. This parameter is taken in to account as procainamide is excreted in urine with sufficient quantity so that it must be considered. It should be noted that metabolism and breakdown occurs in the extracellular compartment. Therefore rate constant for breakdown is included in the extracellular concentration equation. Breakdown of procainamide in the extracellular compartment is due to the enzymes which inactivates it. These are the changes which differ from the lidocaine model.

$$V_{1j} [dC_{1j} / dt] = Q (C_{in} - C_{1j}) - k_{12} V_{1j} C_{1j} + k_{21} V_{2j} C_{2j} - k_r V_{1j} C_{1j} - u C_{1j} \quad (7)$$

$$V_{2j} [dC_{2j} / dt] = k_{12} V_{1j} C_{1j} - k_{21} V_{2j} C_{2j} \quad (8)$$

Values for the kinetic constants and other parameters used in equations (7) and (8) were obtained from [3,28]. However, the same values of Q, V_{1j} , V_{2j} were used as in the lidocaine model. The reason for this is that the extracellular and cellular volumes and flow are expected to be similar for both drugs.

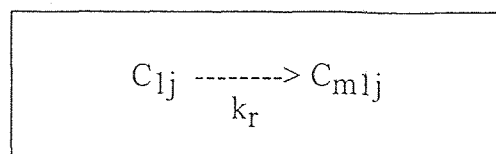


Figure 2.3 Metabolite Formation of Procainamide

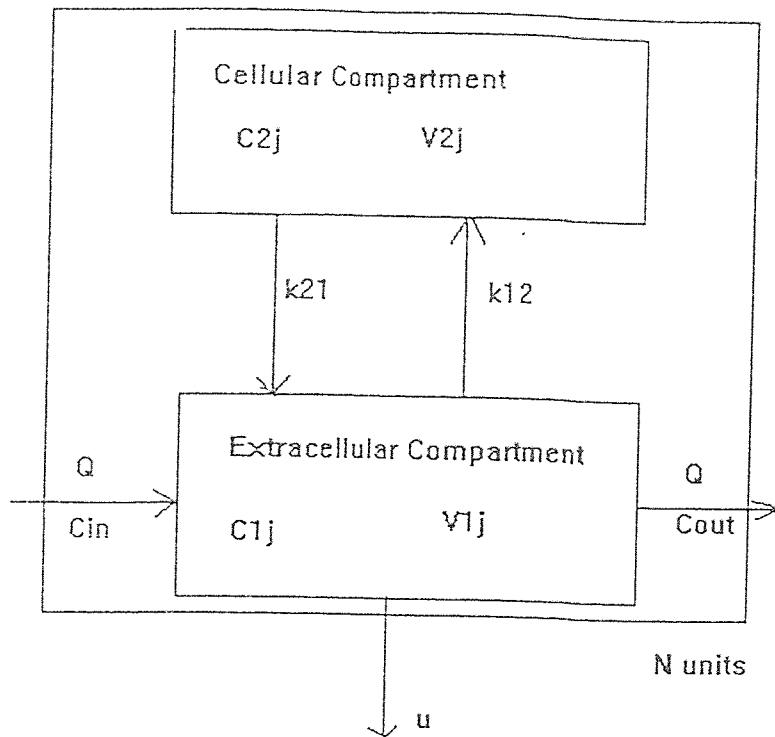


Figure 2.4 Compartmental model for hepatic elimination of procainamide

2.3.1 Calculations

C_{m1j} is the metabolite of C_{1j}

k_r is the rate constant for metabolite formation

$$k_{12} = 9.35 \text{ min}^{-1}$$

$$k_{21} = 9.35 \text{ min}^{-1}$$

$$k_r = 0.0053 \text{ min}^{-1}$$

$$u = 0.0013 \text{ ml/min/mole}$$

$$C_{in} = 20, 50, 70 \text{ mg/kg (single impulse injection)}$$

u is the concentration of Procainamide in urine output

C_{in} is converted from mg/kg to μM .

Molecular weight of Procainamide hydrochloride = 271.79

$$\text{mg/kg} \rightarrow 10^{-3} \mu\text{g/kg (mol. wt.)} \rightarrow \mu\text{M}$$

Using this formula different values of C_{in} are obtained;

5.4358 μM for 20 mg/kg

13.5895 μM for 50 mg/kg

19.0253 μM for 70 mg/kg

Using these data and equations (7) and (8) simulations of the pharmacokinetics of the procainamide in the liver were done using VisSim software [10] on a 486 based personal computer. A parameter sensitivity study was also done to determine the range of values for the kinetic rate constants for which the model is stable. Results are placed in chapter 3.

CHAPTER 3

RESULTS AND DISCUSSION

The following chapter discusses the results of the simulations. The range of kinetic constants which can be used in the stable operating range and sensitivity study are described in detail. The simulation results and block diagram of differential equations are kept in appendix A.

3.1 Lidocaine and its Metabolites

3.1.1 Washout Simulations

The clearance of lidocaine and its metabolites MEGX and 3-OHLID from the liver were simulated by loading the system with an initial concentration of each drug. For each case an initial condition was set in the integration block [step(hepatic loading)] and no input was given to the model to simulate washout experiments. It was observed that the concentration decreased exponentially with time. These results matched the data [1] from washout experiments after cessation of drug administration. Curve 1 shows these results. The simulation profiles indicate that the concentration of lidocaine and its metabolites declined in a first order fashion (Curve 2, 3, and 4). These results are consistent with the results obtained by radiolabeled lidocaine and supports the conclusion that drug transport and release in the liver are linear.

It is observed that lidocaine concentration is higher than its metabolites in both the cellular and extracellular compartments because lidocaine is the major chemical (drug) while MEGX and 3-OHLID are its metabolites. All three drugs take nearly the same amount of time to "washout" of the liver. The model also predicts that MEGX and 3-OHLID are eliminated faster than lidocaine.

3.1.2 Sensitivity Study

A parameter sensitivity study establishes the range of kinetic constants for which the model is stable. It was determined that, if the sensitivity range is exceeded, the cellular and/or extracellular concentrations become negative or approach zero. The sensitivity study was done by using a steady state (step input) input along with an initial condition (hepatic loading). This is similar to the experimental setup in which the perfused liver is first infused with drug to reach a steady state condition and then the drug is administered at a constant rate after some predetermined time period. The maximum values of the kinetic constants were determined at the stage where the system response was different from the normal behavior. A step input was given, the kinetic constant value of one parameter was either increased or decreased and kinetic constant values of other parameters were unchanged. Simulations were done and these steps were repeated until abnormal behavior in the model was observed. When the cellular and extracellular concentration decreased or diminished, instead of increasing, this define the maximum value and sets the upper limit for the kinetic constants for the model. Similarly, the lower limit is set when simulated extracellular and cellular concentrations approached zero or became negligible. It was seen that the rate constant for uptake was significantly different for each drug and was lowest for MEGX and highest for lidocaine. This shows that lidocaine is the drug which is taken in from compartment 1 to 2 very fast compared with its metabolites. Similarly, the rate constant for release of the drug from the cells differed for each drug. It was lowest for MEGX and highest for lidocaine. This shows that MEGX takes the longest time to come out of compartment 2 to 1 and lidocaine takes the shortest time. Curve 5.A shows the washout profile of lidocaine and its metabolites taken from reference [1]. Curve 5.B shows the simulation results of washout profiles for lidocaine and its metabolites (no input). It is seen that Curve 5.A and Curve 5.B looks similar. Curve 5.C shows simulation results with a step input and with initial conditions. The

extracellular concentrations increased and attained a new steady state value in a short period of time. Thereafter, the extracellular concentration remained constant. The cellular concentration remained unchanged for a step input because input does not affect cellular concentration directly.

3.1.2(a) Sensitivity Study of Lidocaine

Curves 6.A and Curve 6.B (cellular concentration of lidocaine with less effective change) show a simulation in which the liver is loaded with an initial concentration of lidocaine and then a step input is applied at some predetermined time. It is observed that for nominal values of the parameters the extracellular concentration first decreases exponentially and then increases exponentially to attain a steady state value after a long time. When the kinetic constants are set at their maximum values, it is seen that extracellular concentration starts decreasing. Using minimum values of the kinetic constants the extracellular concentration reaches a value nearly equal to the step input in a very short period of time. When the kinetic constants are increased to their maximum values, the cellular concentration decreases to a very low value (Curve 6.B). When the minimum values of the kinetic constants were used there was no effect of the step input on the cellular concentration. It remained constant for all time. Thus, no significant changes were observed for cellular concentration with input. Hence, cellular concentration curves are not included for lidocaine metabolites.

3.1.2(b) Sensitivity Study for MEGX and 3-OHLID

Curves 7, and 8 show the simulation for lidocaine metabolites MEGX and 3-OHLID respectively. When the maximum value of the kinetic constants were used the extracellular concentration of both metabolites starts decreasing, while cellular concentration approached zero. At the lower limit for the kinetic constants the extracellular concentration of both metabolites reached very high values equal to the

steady state input, whereas the cellular concentration of both metabolites remained unchanged for the entire simulation time period. The reason for the unchanged cellular concentration is that the kinetic constants are so low that they do not affect the cellular concentration. In other words nothing comes in and nothing goes out of the cellular compartment. The maximum values of the kinetic constant represent very fast rates of uptake and release. This leads to concentrations in the extracellular compartment below their initial value and negative values for the extracellular concentration. The ranges of the kinetic constants are summarized in table 3.1. Table 3.1 shows the summary of values of k_{12} , k_{21} , k_r .

Table 3.1. The range of values for k_{12} , k_{21} , and k_r for lidocaine and its metabolites

Chemical	$k_{12} \text{ min}^{-1}$		$k_{21} \text{ min}^{-1}$		$k_r \text{ min}^{-1}$	
	Min	Max	Min	Max	Min	Max
Lidocaine	0.0	18.1	0.0	8.75	0.0	11.75
MEGX	0.0	18.4	0.0	16.45	0.0	12.35
3-OHLID	0.0	18.58	0.0	13.0	0.0	2.75

Maximum values of k_{12} and k_{21} which can be used simultaneously are given in Table 3.2. k_r value denotes the rate constant of breakdown which can be used along with these maximum values to give a stable model response.

Table 3.2 Maximum values of both k_{12} and k_{21} which can be used together

Chemical	$k_{12} \text{ min}^{-1}$	$k_{21} \text{ min}^{-1}$	$k_r \text{ min}^{-1}$
Lidocaine	10.7	5.25	0.49
3-OHLID	10.7	7.76	0.35
MEGX	12.58	6.35	0.24

The volume of the cellular compartment is nearly six times that of the extracellular compartment. Thus, at steady state there is close to thirty times more material in the cellular space than in the extracellular space. This shows that cells can act as a large reservoir for the drug and its metabolites. Hence, it takes time to fill the extracellular compartment (drug uptake). It takes time to empty the cellular compartment (drug washout). Normal values are ones for which results of simulation are consistent with the results published. Table 3.3 summarizes the normal values of kinetic rate constants.

Table 3.3 Normal value of kinetic constant for lidocaine and its metabolites

Chemical	$k_{12} \text{ min}^{-1}$	$k_{21} \text{ min}^{-1}$	$k_r \text{ min}^{-1}$
Lidocaine	9.7	0.48	0.49
MEGX	2.2	0.08	0.35
3-OHLID	0.38	0.03	0.24

It is seen that changing flow (Q) has no effect on extracellular or cellular concentrations. The reason for this is that the transport process is barrier limited. There are two types of transport processes (1) flow limited and (2) barrier limited.

Flow limited:

Transport out of the compartment into the extracellular space is very rapid. Therefore if flow is increased more material is brought to the transport site and increases the amount of material transported.

Barrier limited :

Transport out of the compartment into the extracellular space is very slow so it does not change very much if more material is brought to the transport site by increasing flow.

3.2 Procainamide Simulations

For the antiarrhythmic drug procainamide the heterogeneous model used is similar to that used for lidocaine. For procainamide, metabolism occurs in the cells and hence the differential equations for the cellular and extracellular compartments are modified accordingly. Procainamide elimination occurs in urine [30] and that factor is included in the model. Urine output is added to the extracellular compartment. Procainamide metabolites are not important so they were not considered. With these changes differential equations (8) and (9) were simulated on a 486 based personal computer using VisSim (Visual Solution Inc.) software. Procainamide simulations are divided into washout profiles, simulations with input and sensitivity study of different kinetic rate constant parameters. Each of them is described in detail.

3.2.1 Washout Profile

Washout of procainamide is simulated using an initial condition in the integration block (similar to the lidocaine washout simulation). Curve 9 shows the simulation. As time increases the extracellular and cellular concentrations of procainamide decrease exponentially in a first order fashion. It is seen that drug elimination is faster in the extracellular compartment than the cellular compartment, because more concentration leaves the compartment than enters the compartment. The rate of cellular uptake and the rate of cellular release are assumed to be same for procainamide because it is not lipid soluble. Hence, the same amount of time is taken by cellular compartment to take up procainamide and to release procainamide.

3.2.2 Simulation with Input

Curve 10 shows the simulation of a bolus injection of procainamide. This input is similar to a pulse of very short duration. Both cellular and extracellular concentrations are shown

along with the input. In this simulation no procainamide is present initially in either of the compartments. It is seen that the extracellular compartment acts as a reservoir and its concentration increases rapidly with the impulse (bolus injection). The maximum value attained by the extracellular compartment is nearly equal to the peak of the impulse and thereafter, extracellular concentration decreases suddenly to a zero value. The rise in concentration is exponential but the fall in concentration is not exponential. The reason for this is that before the concentration reaches saturation level in the extracellular region the impulse starts to decrease causing the extracellular concentration to decrease. The cellular concentration acts exactly as any linear system should act. The cellular concentration increases exponentially and reaches its steady state value during the time period of the impulse. When the impulse starts decreasing the cellular concentration also starts to decrease in an exponential way. The amount of procainamide in the cellular compartment is smaller than that in the extracellular compartment, because the cellular compartment volume is greater than the extracellular compartment volume. It is also seen that the time taken to reach saturation level during the impulse is higher in the extracellular compartment than in the cellular compartment.

3.2.3 Sensitivity Study for k_{12}

Curves 11.A and 11.B show the results of the sensitivity study done on the liver model for procainamide for k_{12} . It shows the range rate of uptake from the extracellular compartment to the cellular compartment for extracellular concentration and cellular concentration respectively. Within the given range the Curve 11.A shows the simulations of extracellular compartment for which model is stable. The minimum and maximum curves represent the lower and upper limit of k_{12} . It is seen that when k_{12} is reduced significantly with respect to k_{21} , the extracellular concentration reaches a value above the impulse amplitude value. This is not a realistic occurrence, hence this sets the lower limit for k_{12} . During the decreasing portion of the impulse it is seen that the extracellular

concentration decreases, then increases and then decays exponentially. This is similar to an overshoot in an electrical system. On the other hand when k_{12} is increased and made much larger than k_{21} , it is seen that the extracellular concentration reaches negative values when the impulse starts decreasing. This is not physically possible so this sets the upper limit for k_{12} . Curve 10.B shows the curve for cellular concentration with different values of k_{12} with respect to k_{21} . It is observed that for lower value of k_{12} cellular concentration becomes very low, while for higher values of k_{12} , cellular concentration reaches very high values.

3.2.4 Sensitivity Study for k_{21}

Curves 12.A and 12.B show the effects of changes in the rate constants k_{21} with an impulse as input, with no initial condition on cellular and extracellular concentrations respectively. Curve 12.A shows the simulation results when the kinetic constant k_{21} is changed for the extracellular compartment (k_{21} is decreased compare to k_{12}). This is physically represented as a longer time for the drug to be eliminated from the cellular compartment. Simulating this condition, it was found that during the increasing part of the impulse the cellular concentration increased in a linear manner and during the decreasing phase of the impulse the cellular concentration decreased exponentially. It was seen that a longer time was taken before the whole drug was completely eliminated from the cellular compartment (Curve 12.B). This is consistent with the physical interpretation. With k_{21} increased it is seen that during the increasing phase of the impulse period, the cellular concentration reaches its steady state value quickly and then the cellular concentration remains constant. During the decreasing phase of the impulse the cellular concentration decreases rapidly. When the nominal value of k_{21} was used, cellular concentration increases exponentially, attains a steady state value at the end of the impulse period and then decreases exponentially with the decreasing period of the impulse. This is similar to any stable linear system response.

Curve 12.A shows the effect of k_{21} for different ranges of extracellular concentration. At the maximum value of rate constant k_{21} , the extracellular concentration increases to a higher value than the input, while for the minimum value of k_{21} the extracellular concentration attains negative values. For the nominal value of k_{21} , the extracellular concentration increases during the increasing phase of the impulse and then decreases during the decreasing phase of the impulse.

3.2.5 Sensitivity Study for 'u'

Curve 13 shows the results of the simulations for the range of the kinetic constant 'u' (urine). For increasing values of 'u' the extracellular concentration increases exponentially and before it reaches its steady state value, the impulse starts decreasing. The extracellular concentration then drops and returns to zero. At this value of 'u' the extracellular concentration attains higher value than the input. We consider this to define the maximum value of 'u' for this model. The curve for the nominal value of 'u' shows the action of a stable linear system. There is no lower limit of 'u' for extracellular concentration. Cellular concentration changes less than 5% with changes in the value of 'u', since 'u' does not effect cellular concentration directly.

3.2.6 Sensitivity Study for k_r

The results of the sensitivity study of the rate constant of breakdown of the drug (k_r) are shown in Curve 14. It is seen that when k_r is made very high the extracellular concentration attains negative values for the decreasing phase of the impulse. This is overshoot and it is the characteristic of an underdamped system. Concentration can never attain negative values, thus this sets the upper limit for K_r . Physically increasing k_r means that the breakdown of the drug is taking place faster than it is being formed. There is no lower limit for k_r because, if k_r is made very small a longer time is taken for its

metabolites to form and hence this will delay the formation of other metabolites. Cellular concentration is less affected by changes in the rate constant of breakdown k_r .

Thus, we have range of kinetic constants for procainamide which can be used for stable simulation of the model. Also there are normal limits during which the model behavior was similar to the predicted one. Table 3.4 summarizes the range of values for parameters for procainamide.

Table 3.4 Procainamide simulations results with different ranges.

	Minimum	Normal	Maximum
$k_{12} \text{ min}^{-1}$	2.95	9.35	14.25
$k_{21} \text{ min}^{-1}$	0.5	9.35	20.5
$u \text{ ml/min/mole}$	0	0.0013	6.78
$k_r \text{ min}^{-1}$	0	0.0053	4.65

CHAPTER 4

CONCLUSIONS AND SUGGESTIONS

4.1 For Lidocaine and its Metabolites

The heterogeneous model represented by equations (1) and (2) is appropriate to describe the metabolites of the lipophilic compound lidocaine and its metabolites. Simulations were done for lidocaine and its metabolites and results obtained were consistent with published data [1]. Washout profiles of lidocaine and its metabolites exhibited a first order decline. With a step input the model behaved in a linear manner, for lidocaine and its metabolites. The kinetic constant for cellular uptake of lidocaine was higher than the kinetic constant for extracellular uptake. This states that lidocaine and its metabolites are distributed faster in the cellular region than in the blood compartment (since lidocaine is lipid soluble). The rate of conversion of lidocaine within the cells is much slower than the rate of release from the cells. Thus, the amount of lidocaine converted to metabolites will be significantly less than the amount of lidocaine transported from the cellular compartment.

4.2 For Procainamide

For the antiarrhythmic drug procainamide, it was found that the rate constant of uptake from the extracellular compartment to the cellular compartment and the rate of release were identical (procainamide is not lipid soluble). Sensitivity study estimated the upper and lower limits for each rate constants. The simulations done provided insight of kinetic constants and metabolism of procainamide in liver.

4.3 Future Work

The heterogeneous model presented in this thesis can be readily modified to include enzyme inactivation. Also the model can be used to study the interactions of two or more drugs if the interaction constants can be obtained. It will be interesting for the model to be tested for simulating concentrations of toxic chemicals such as halogenated hydrocarbons as well as other critical drugs. The heterogeneous model developed for local anesthetic drug lidocaine can be used along with other models developed for cardiovascular, respiratory and cerebral systems to simulate the overall effect of lidocaine on the body. In this manner other drugs and toxic chemicals such as halogenated hydrocarbon metabolism can be modeled and their effects can be simulated. The heterogeneous model is capable of describing the time dependent profile of a variety of compounds.

APPENDIX A

SIMULATION CURVES

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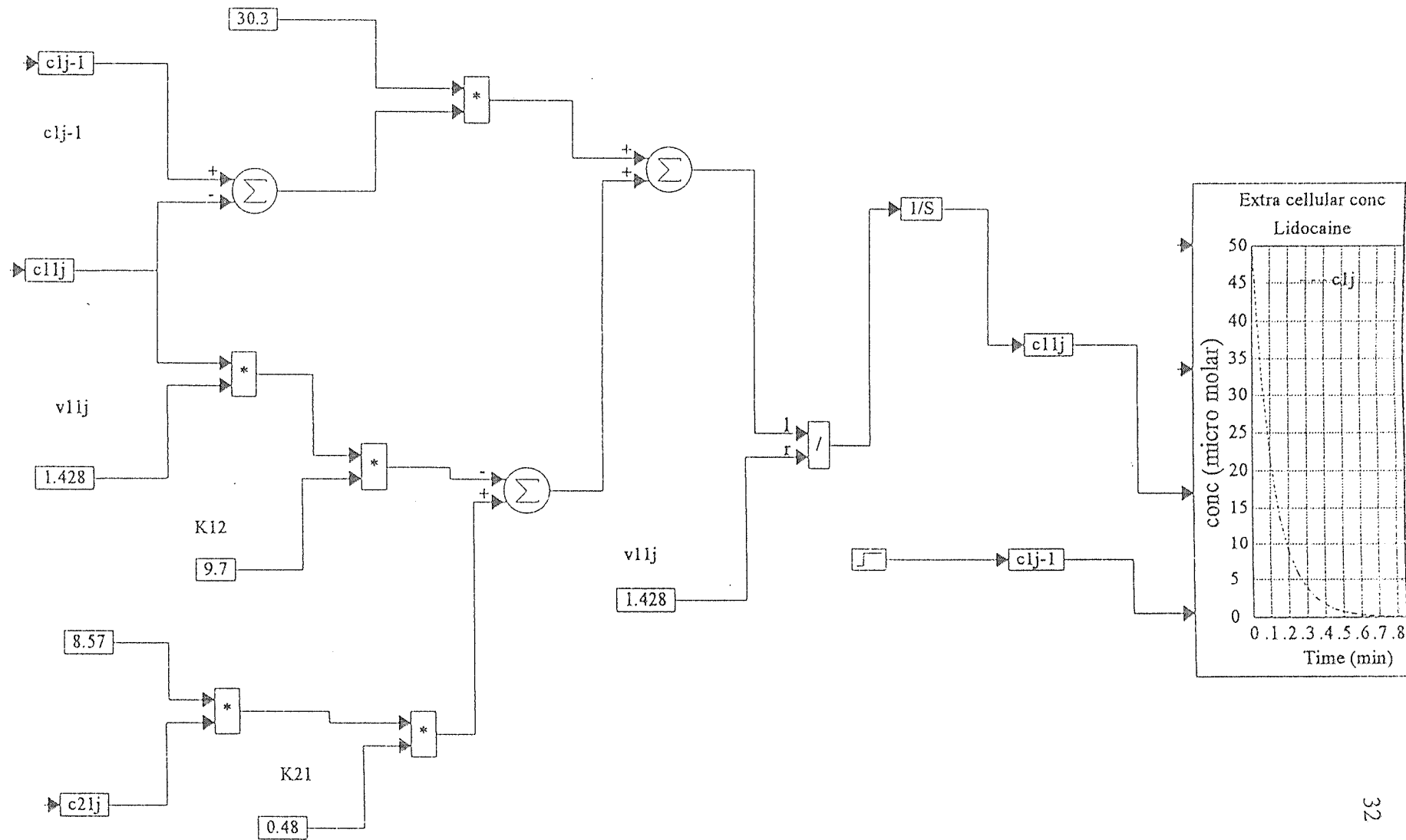
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Block Diagram of Extracellular Compartment for Lidocaine

Figure A1 Block Diagram of Extracellular Compartment of Lidocaine

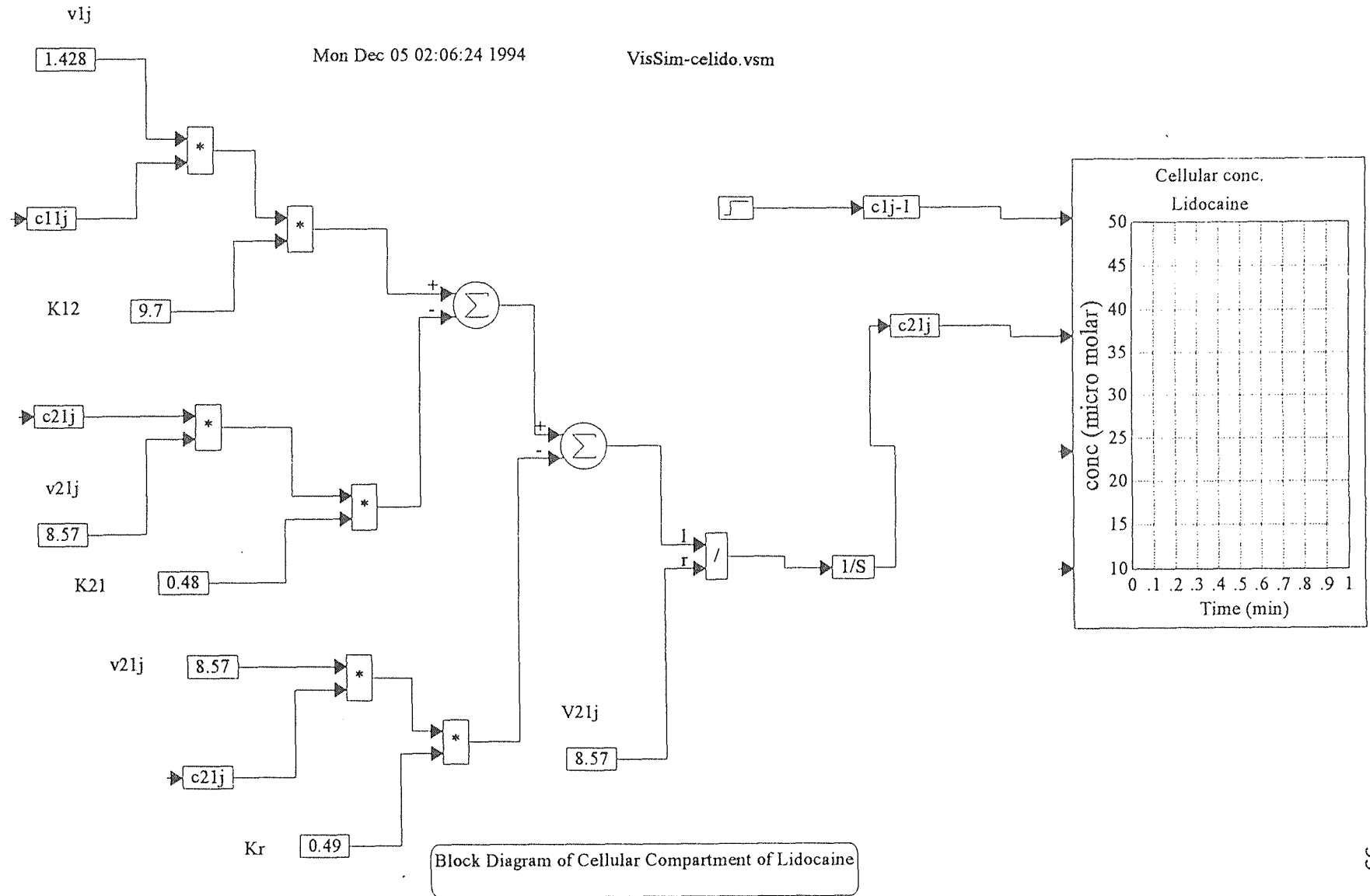


Figure A2 Block Diagram of Cellular Compartment of Lidocaine

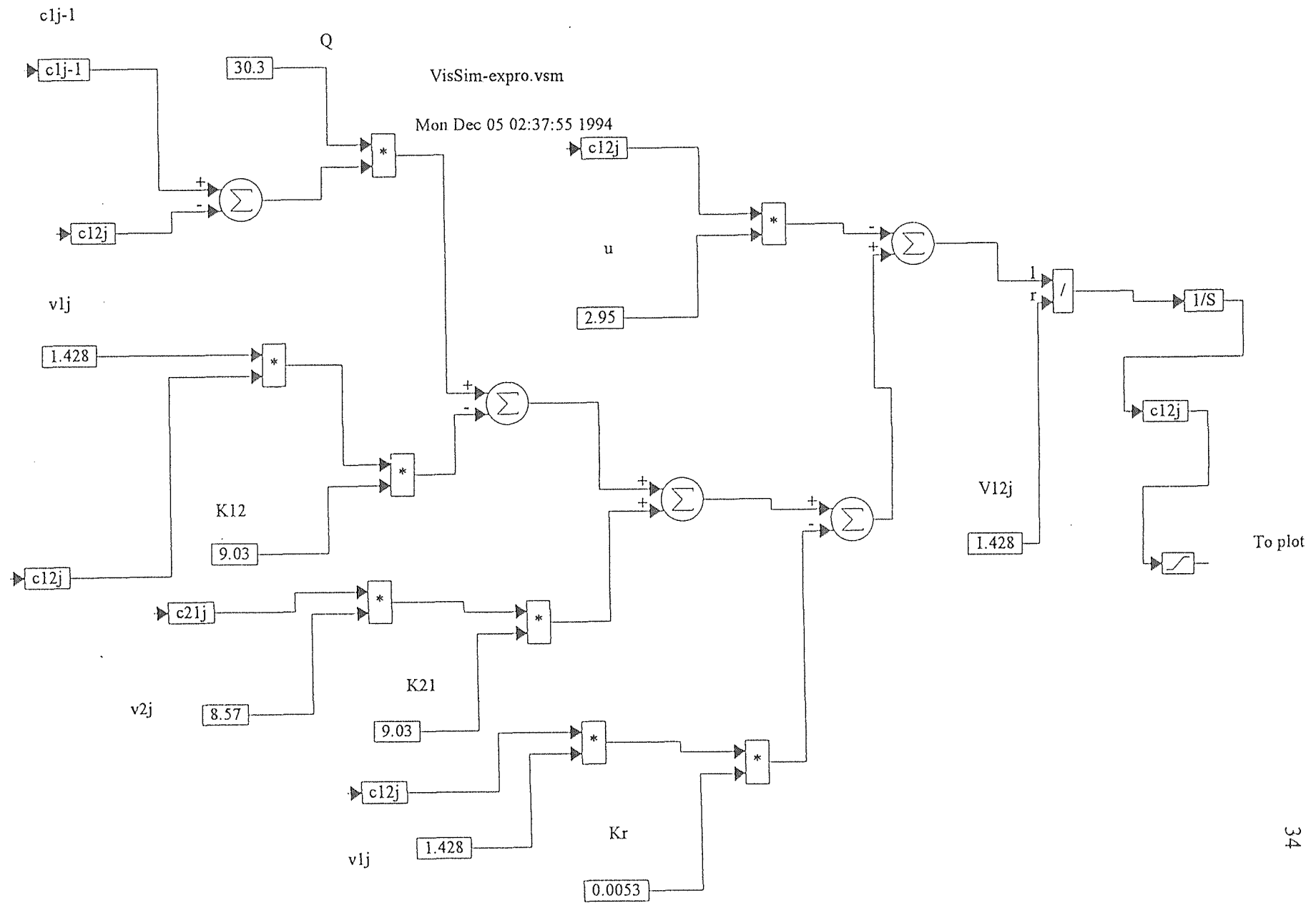


Figure A3 Block Diagram of Extracellular Compartment of Procainamide

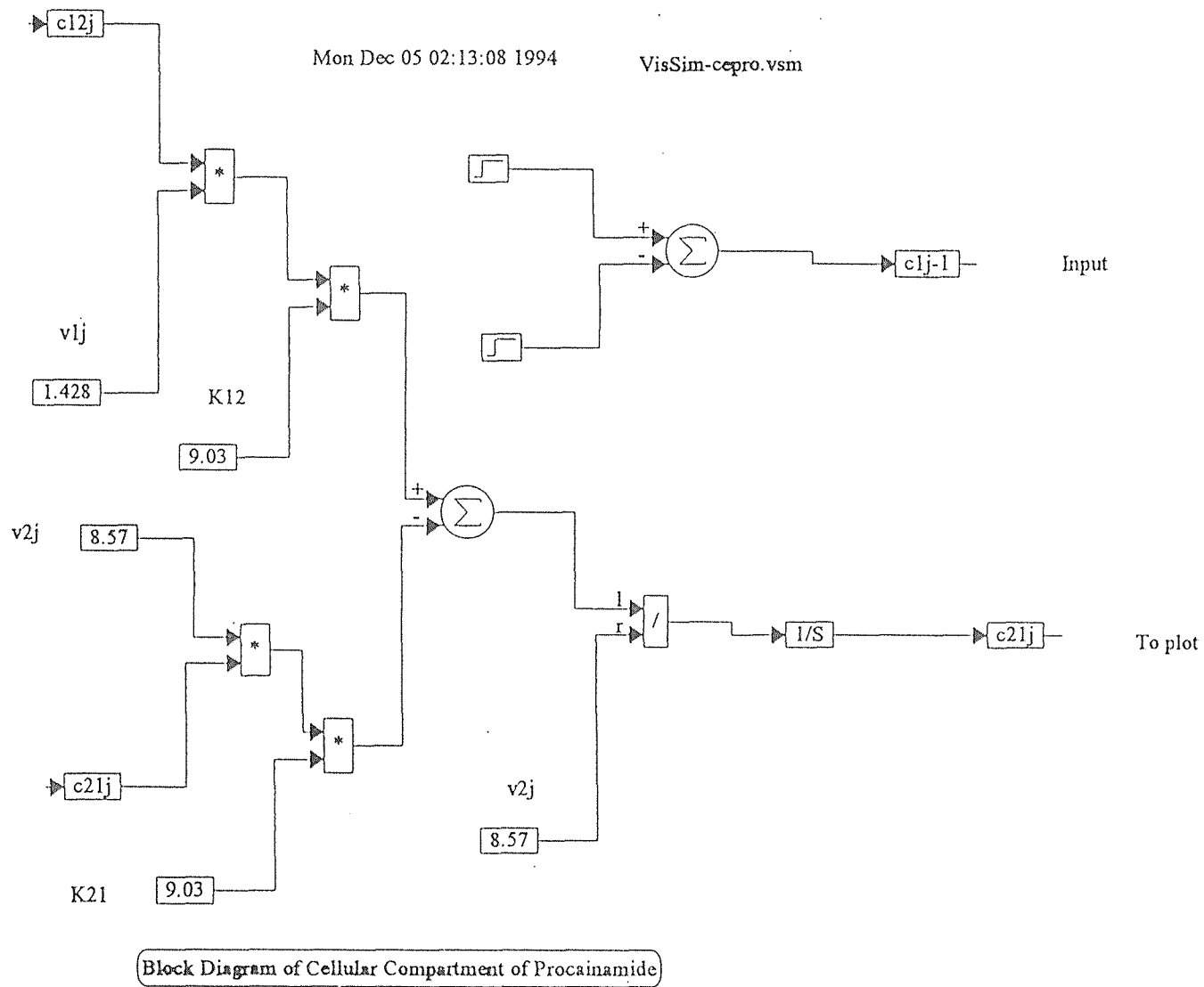
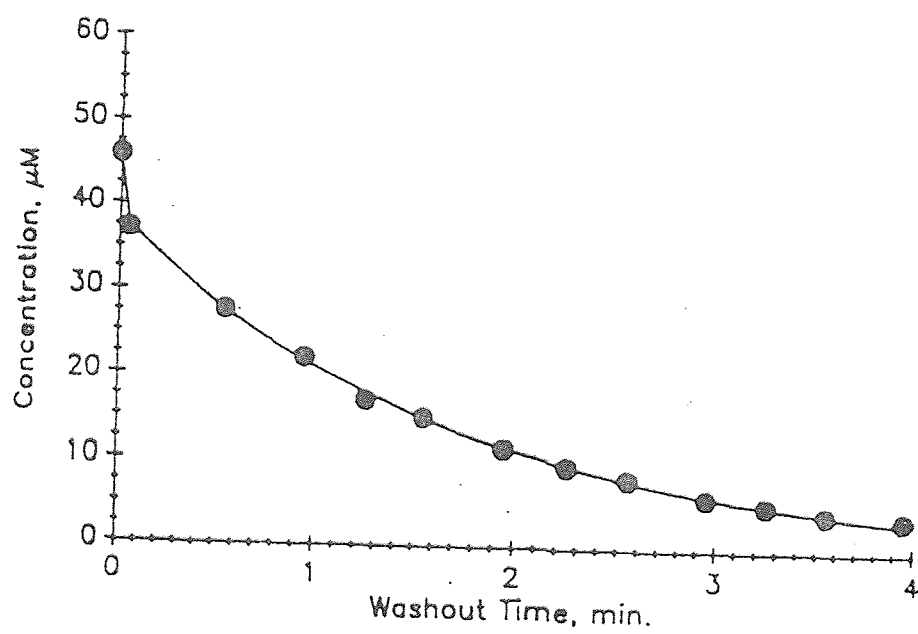
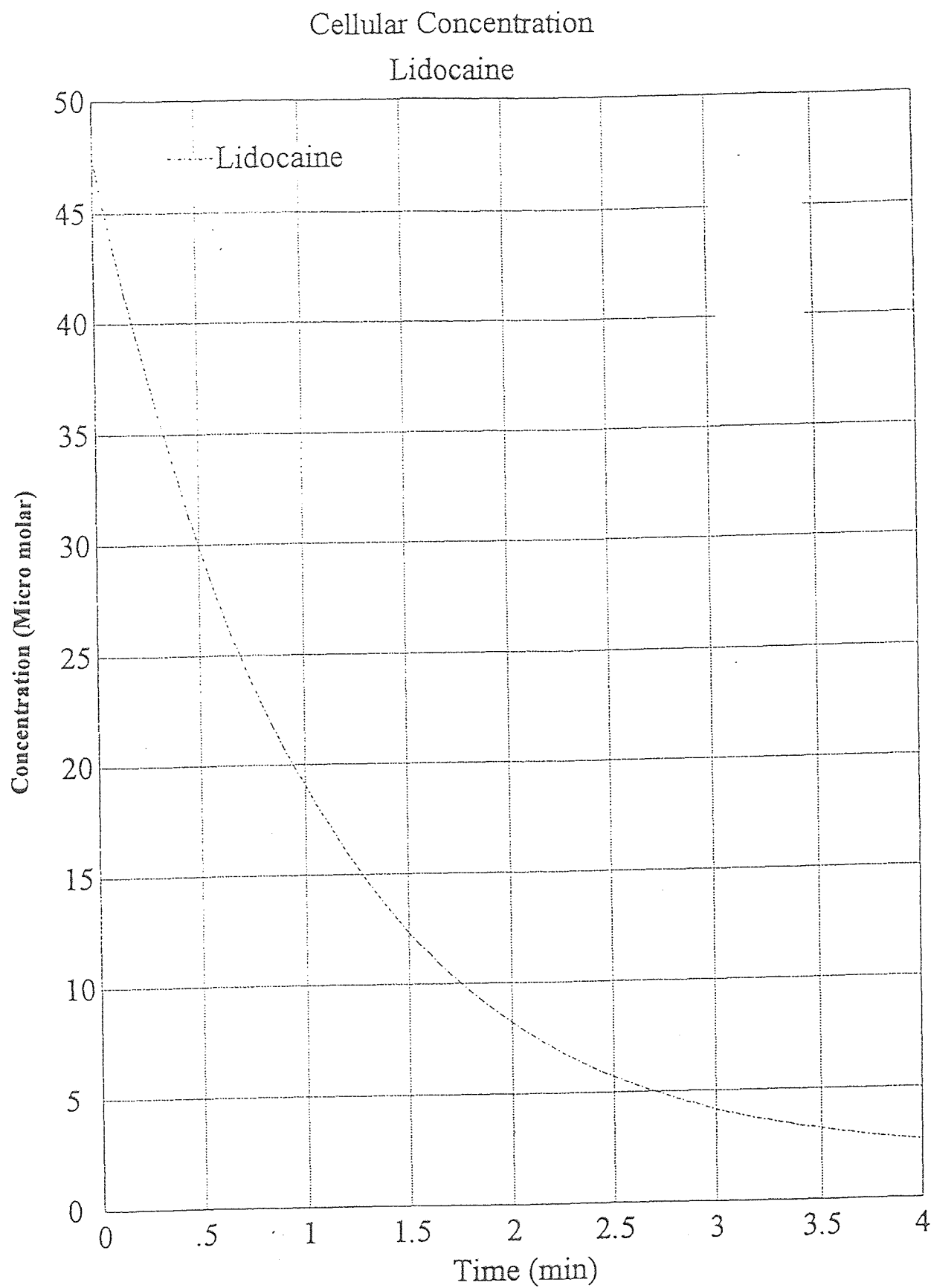


Figure A4 Block Diagram of Cellular Compartment of Procainamide



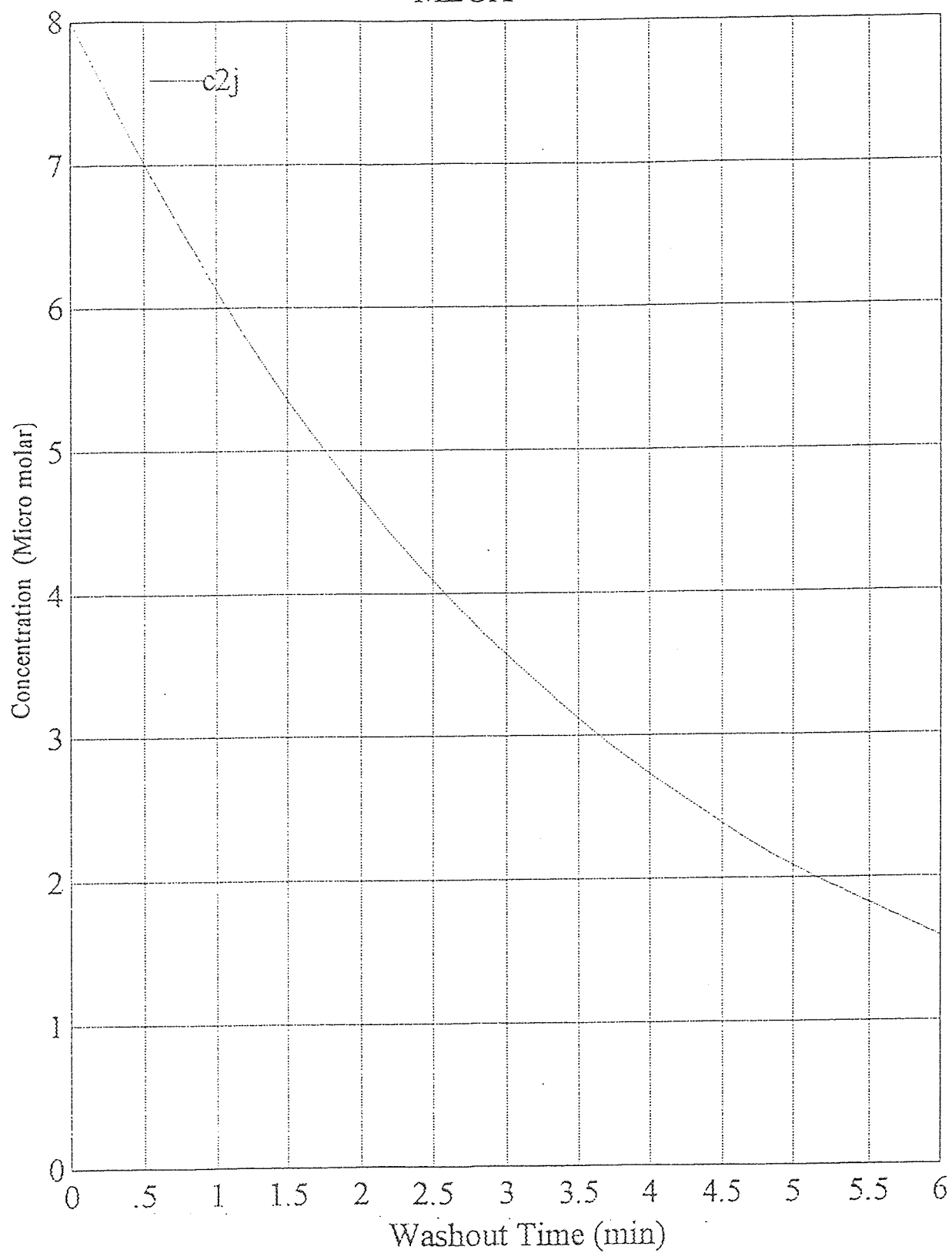
Curve 1 Washout Profile of MEGX from reference [1]



Curve 2 Simulation of Washout Profile of Lidocaine

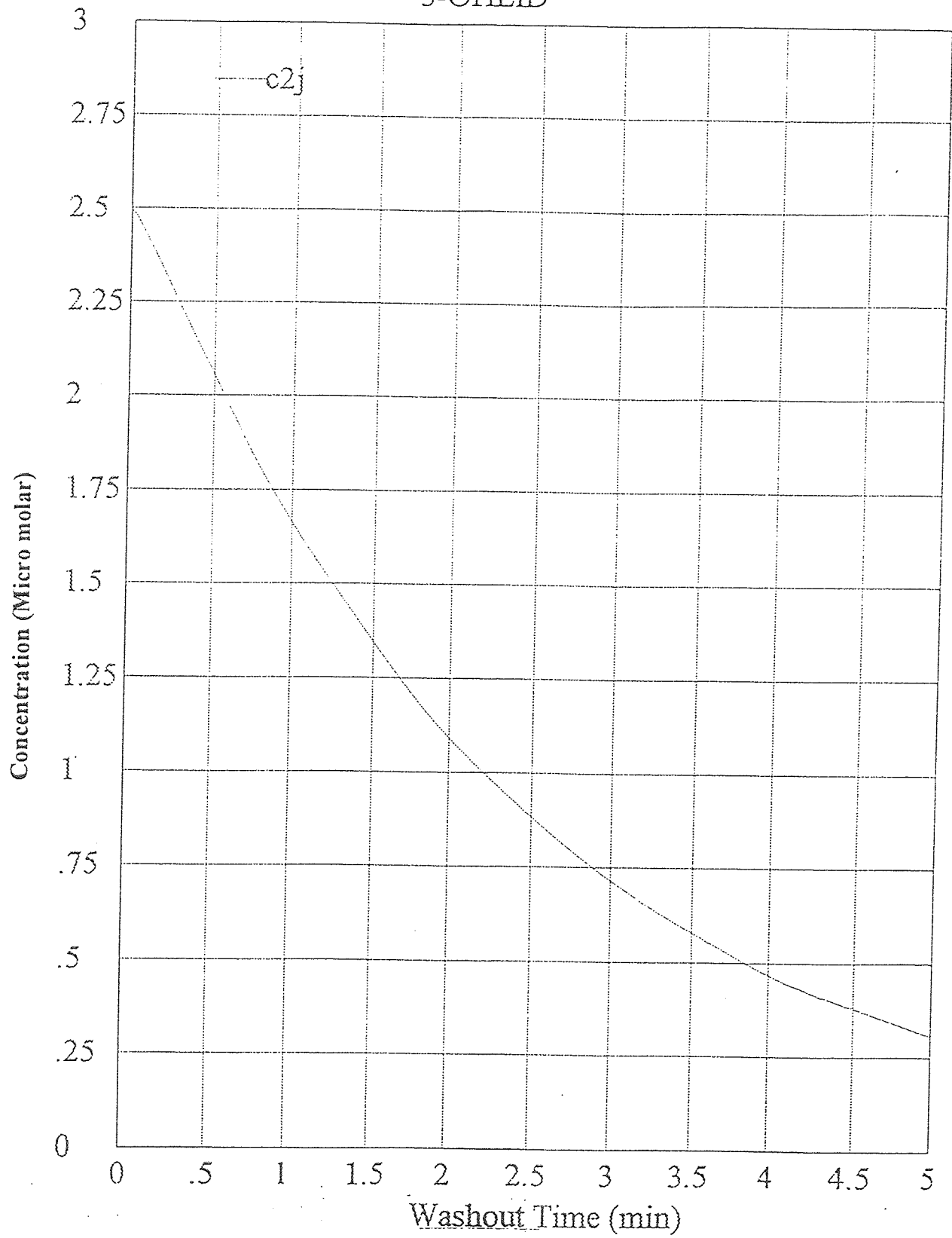
Cellular Concentration

MEGX

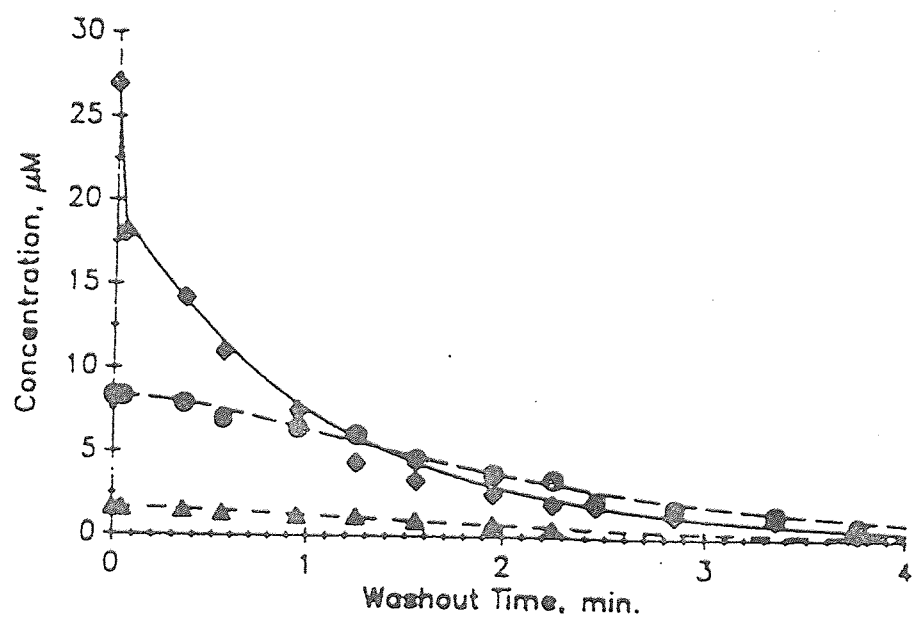


Curve 3 Simulation of Washout Profile of MEGX .

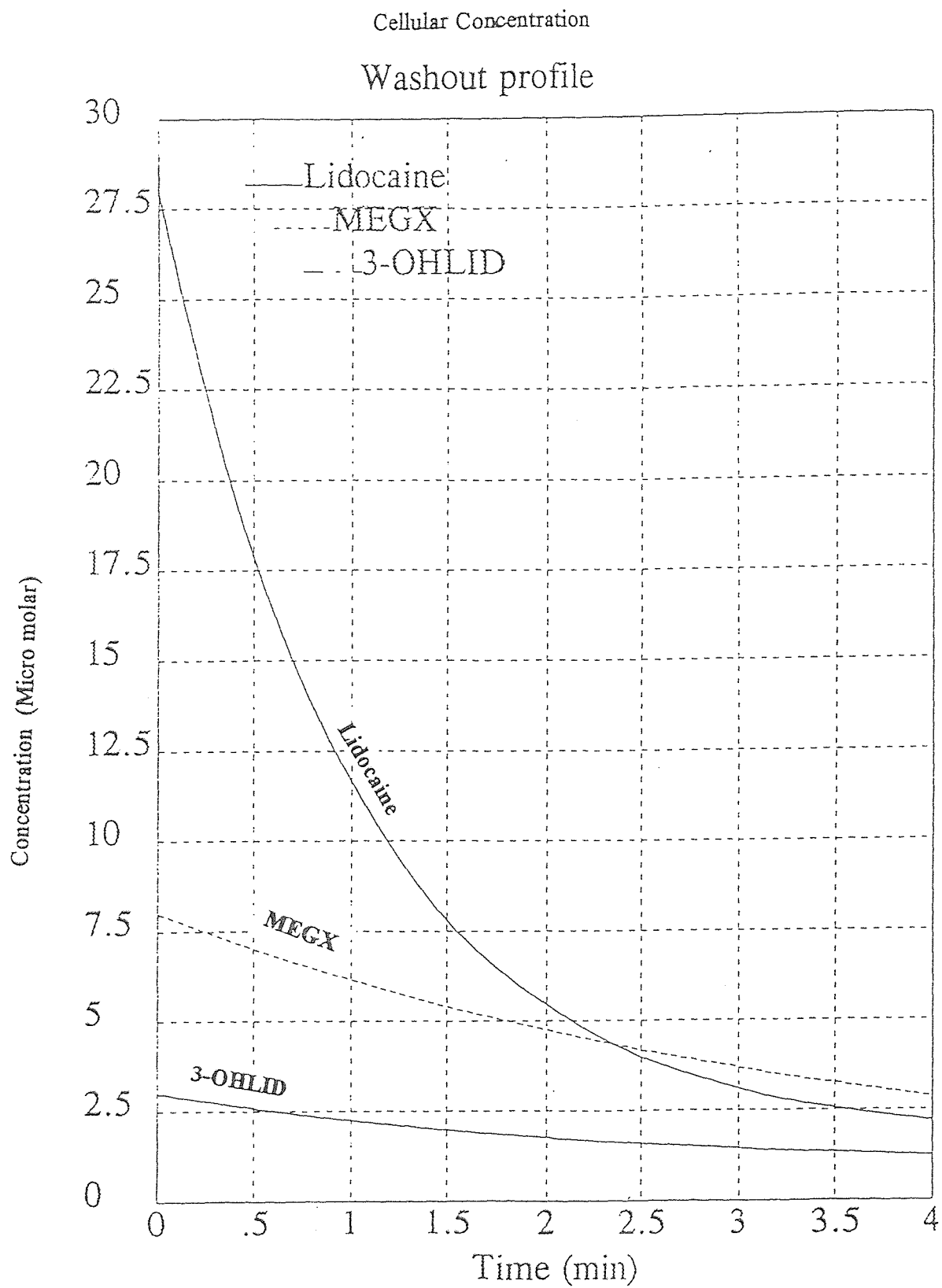
3-OHLID



Curve 4 Simulation of Washout Profile of 3-OHLID



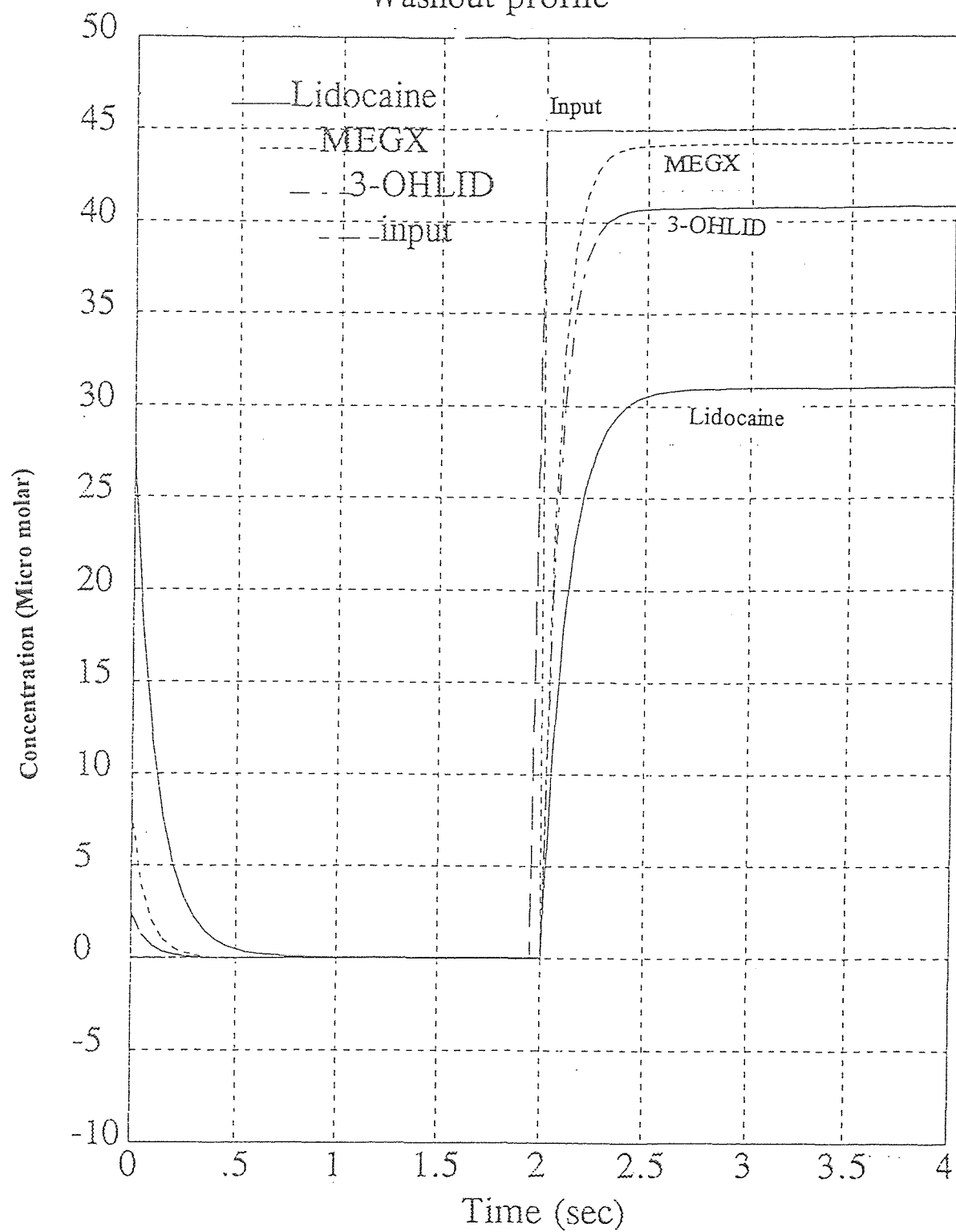
Curve 5.A Washout Profile of Liodcaine and its Metabolites from reference [1]



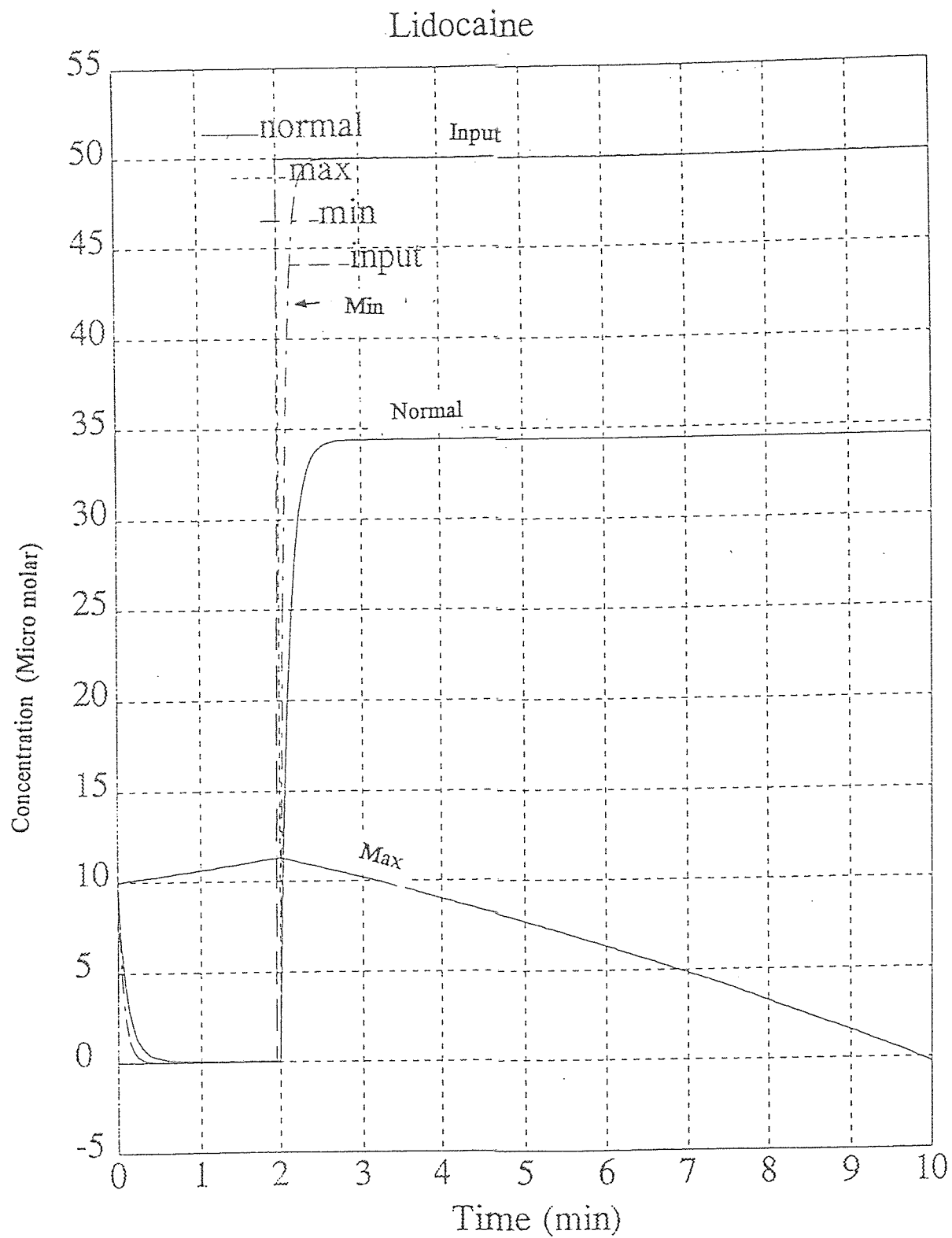
Curve 5.B Simulation of Washout Profile of Lidocaine and its Metabolites

Extracellular Concentration

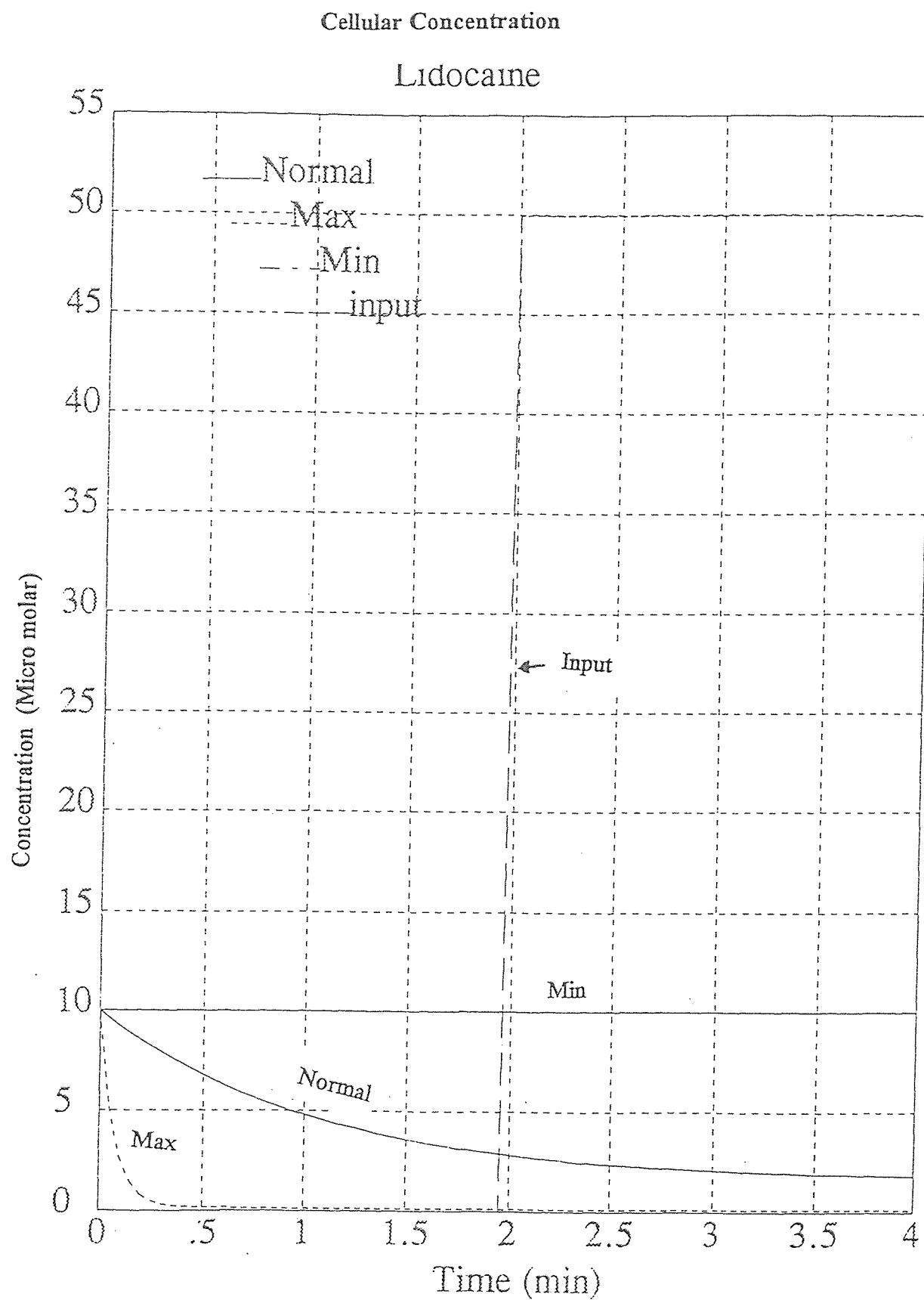
Washout profile



Curve 5.C Simulation of Washout Profile of Lidocaine and its Metabolites with Input

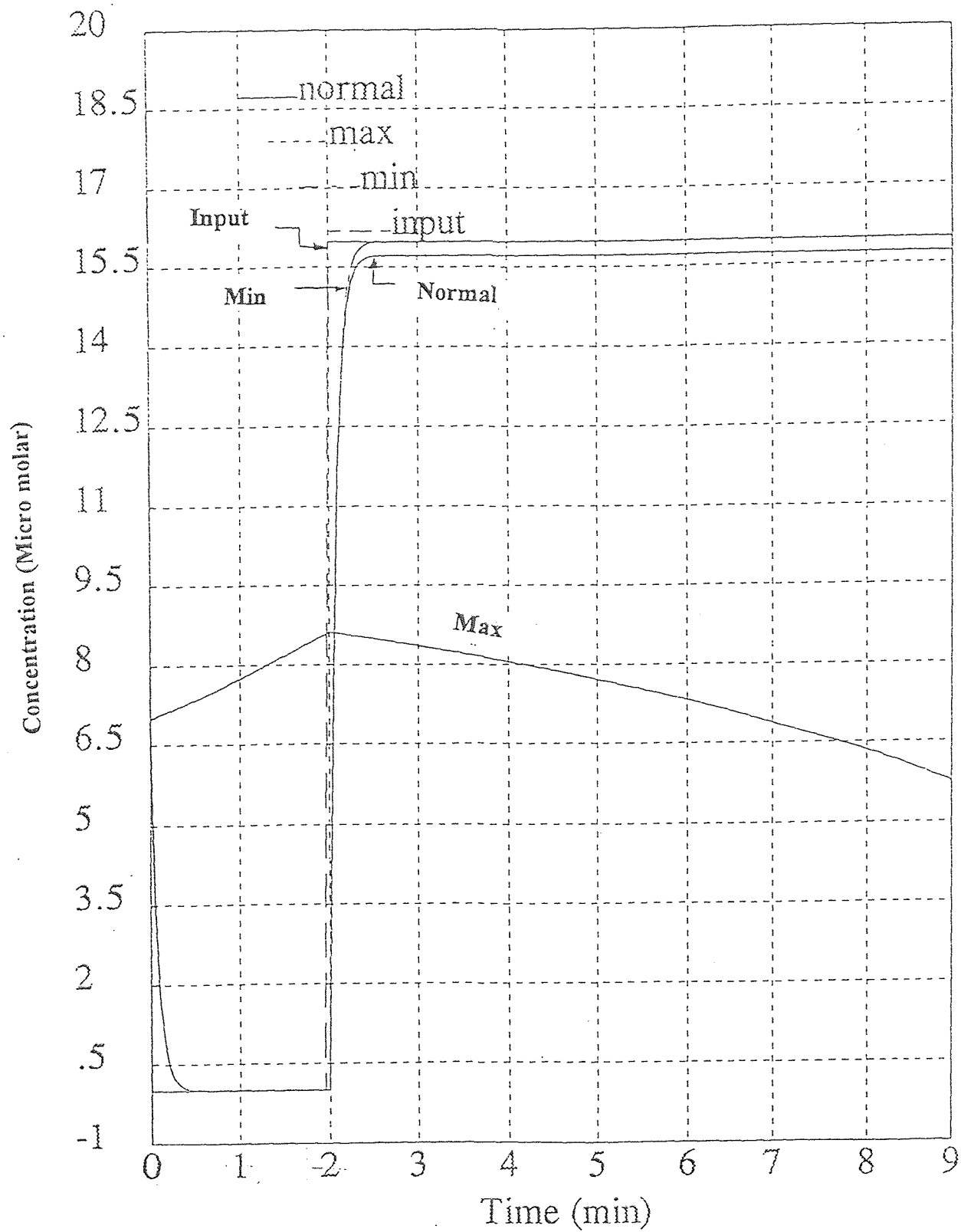


Curve 6.A Sensitivity Study of Lidocaine for Extracellular Compartment



Curve 6.B Sensitivity Study of Lidocaine for Cellular Compartment

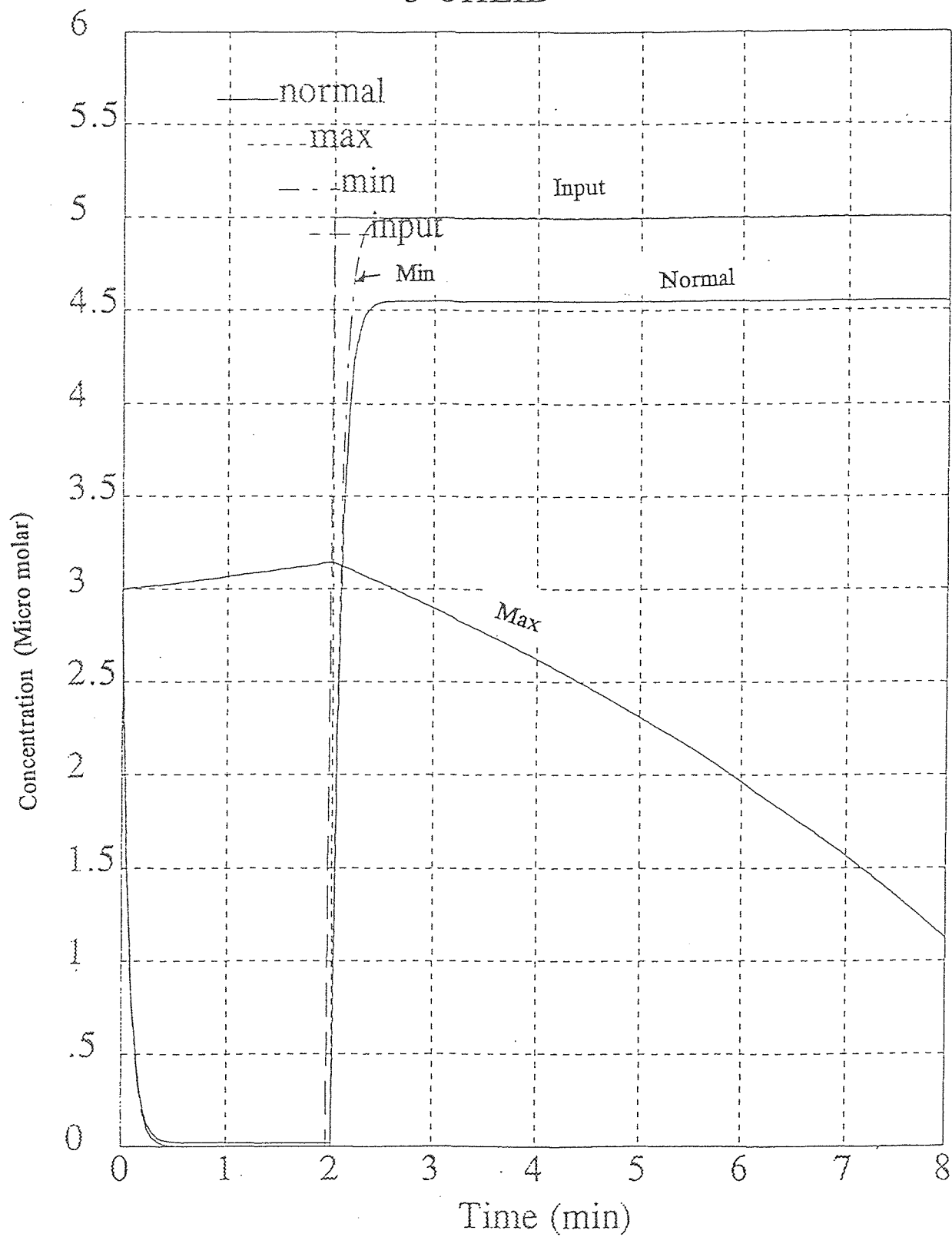
MEGX



Curve 7 Sensitivity Study of MEGX

Extracellular Concentration

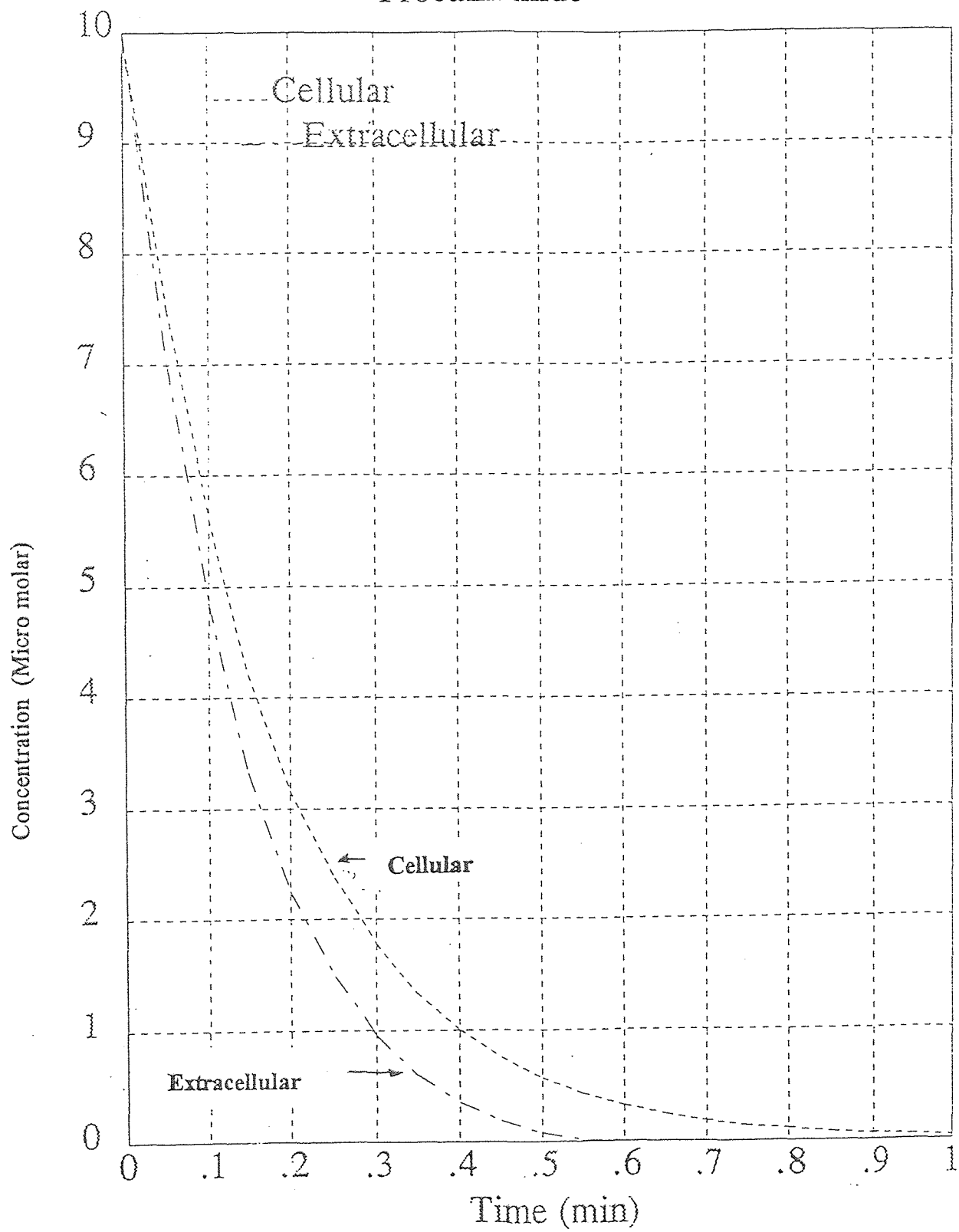
3-OHLID



Curve 8 Sensitivity Study of 3-OHLID

Extracellular and Cellular Concentration

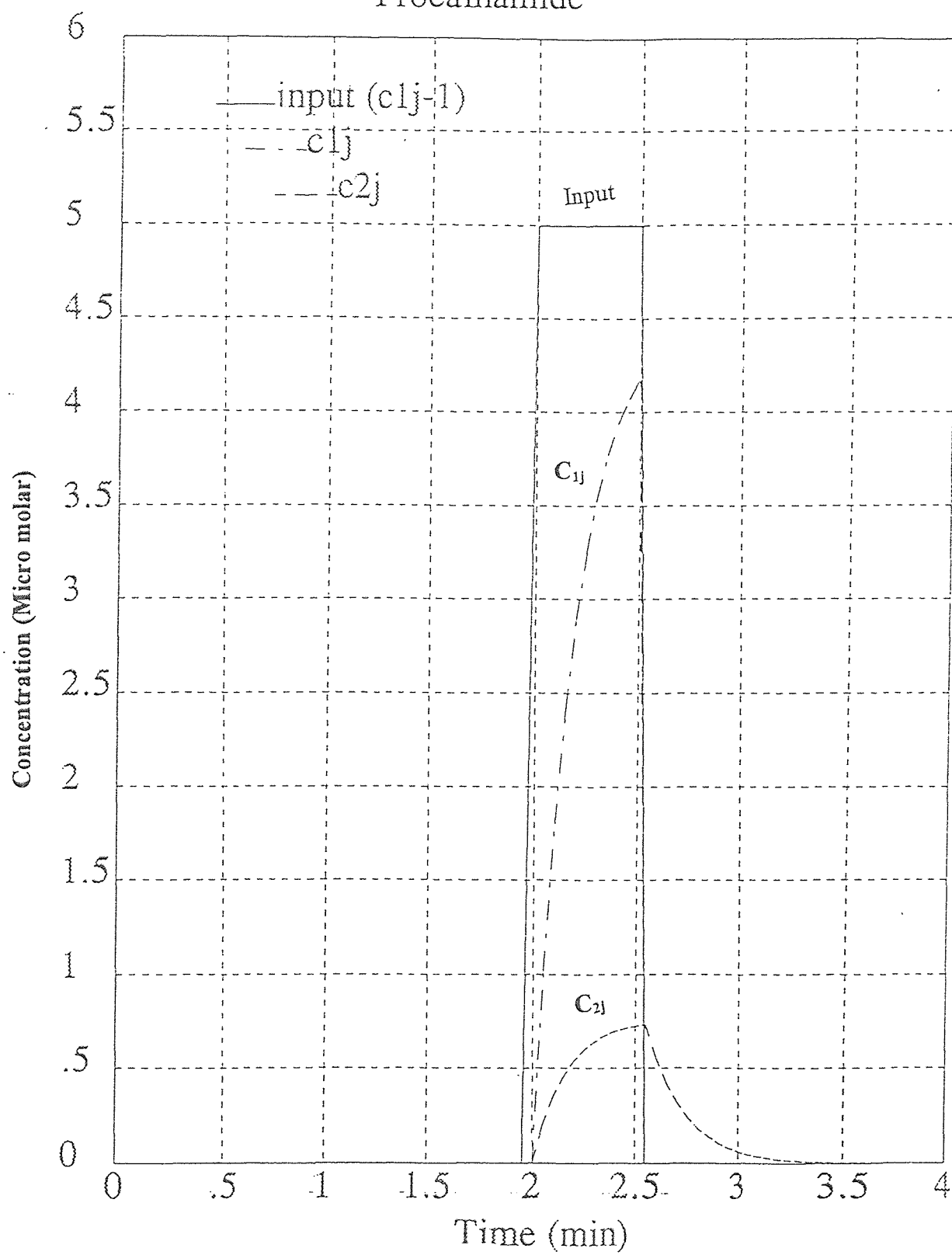
Procainamide



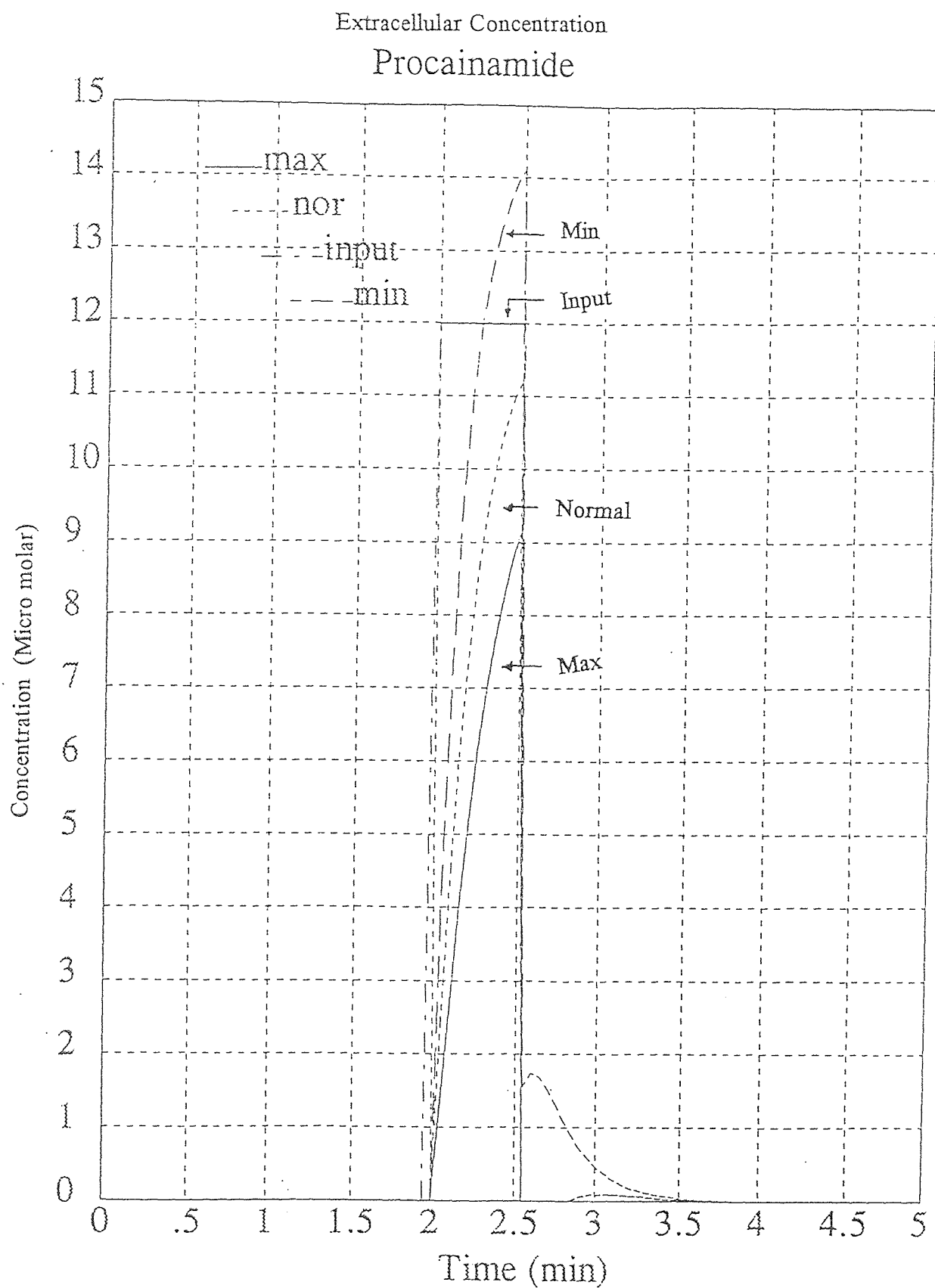
Curve 9 Washout Profile for Procainamide

Extracellular Concentration

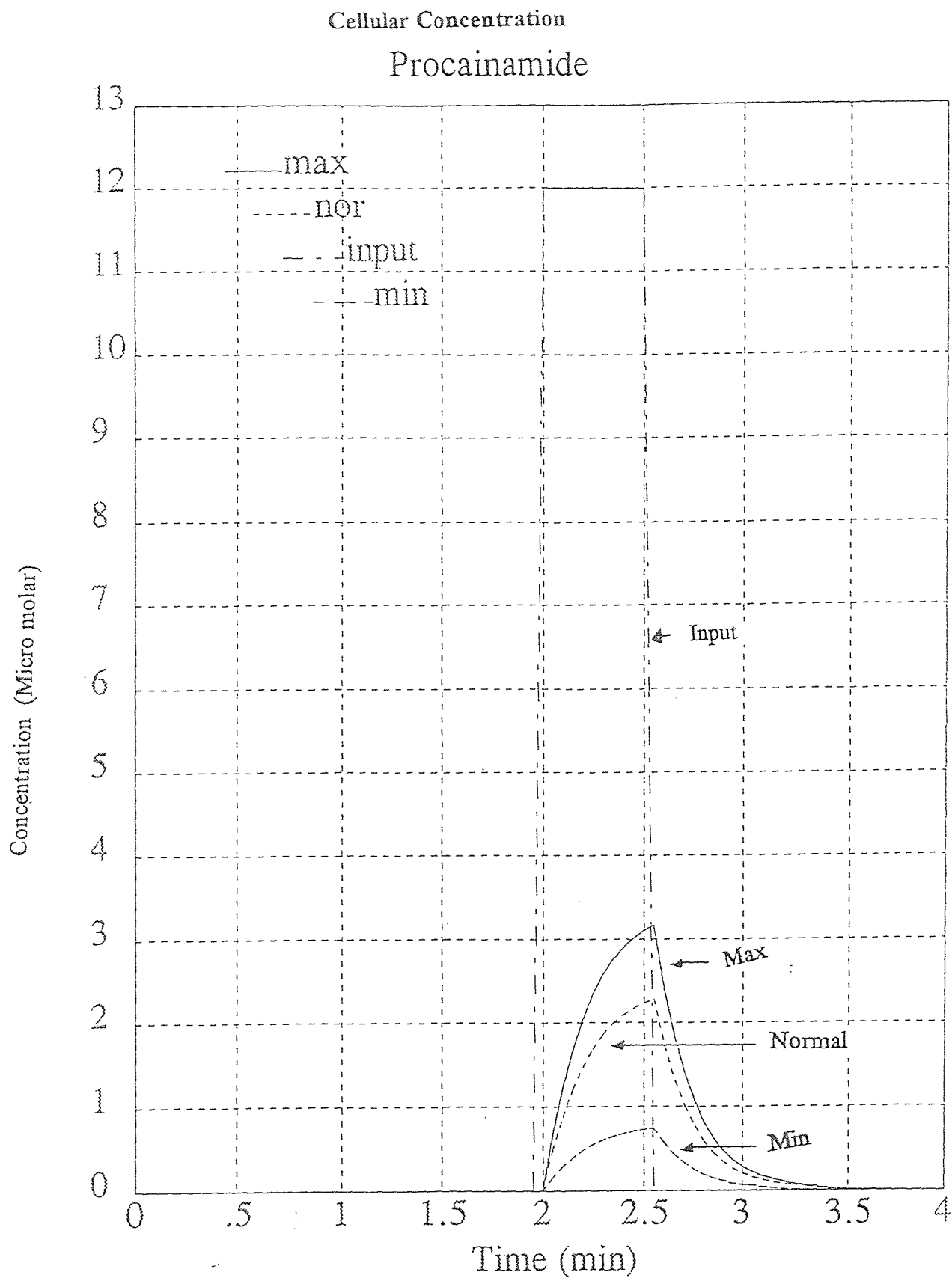
Procainamide



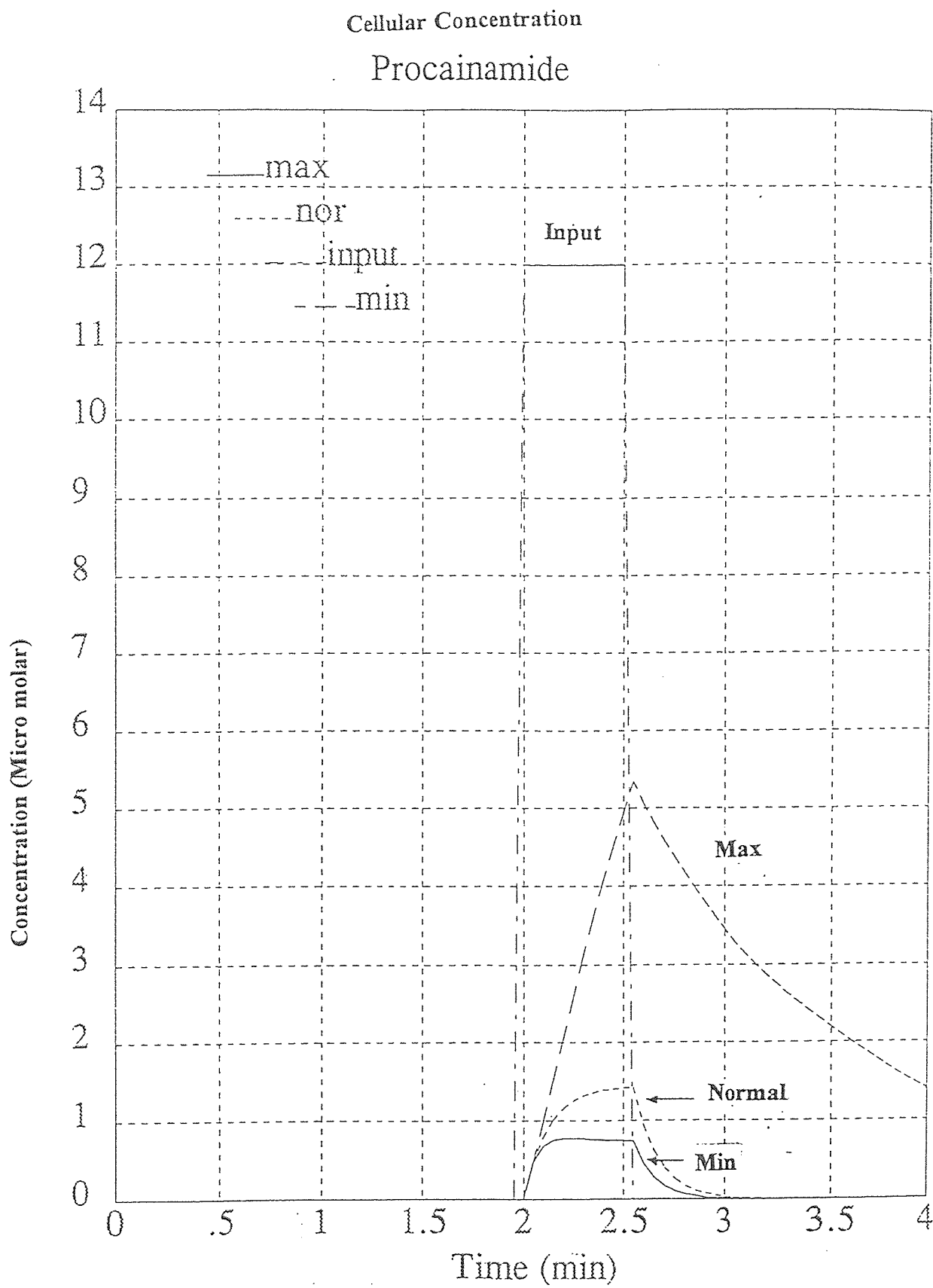
Curve 10 Simulation of Bolus Injection to Extracellular Compartment for Procainamide



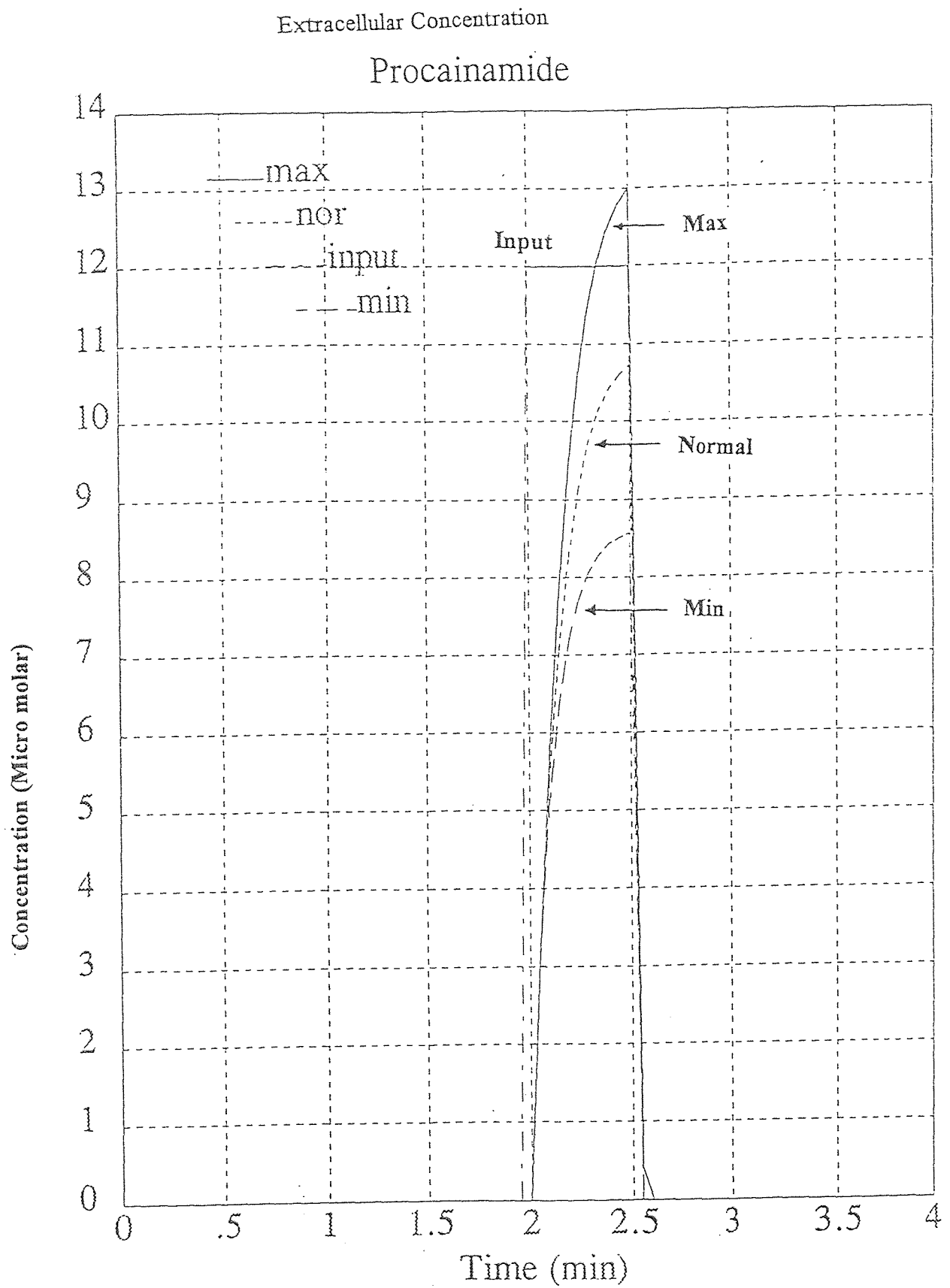
Curve 11.A Sensitivity Study of k_{12} for Procainamide for Extracellular Concentration



Curve 11.B Sensitivity Study of k_{12} for Procainamide for Cellular Concentration



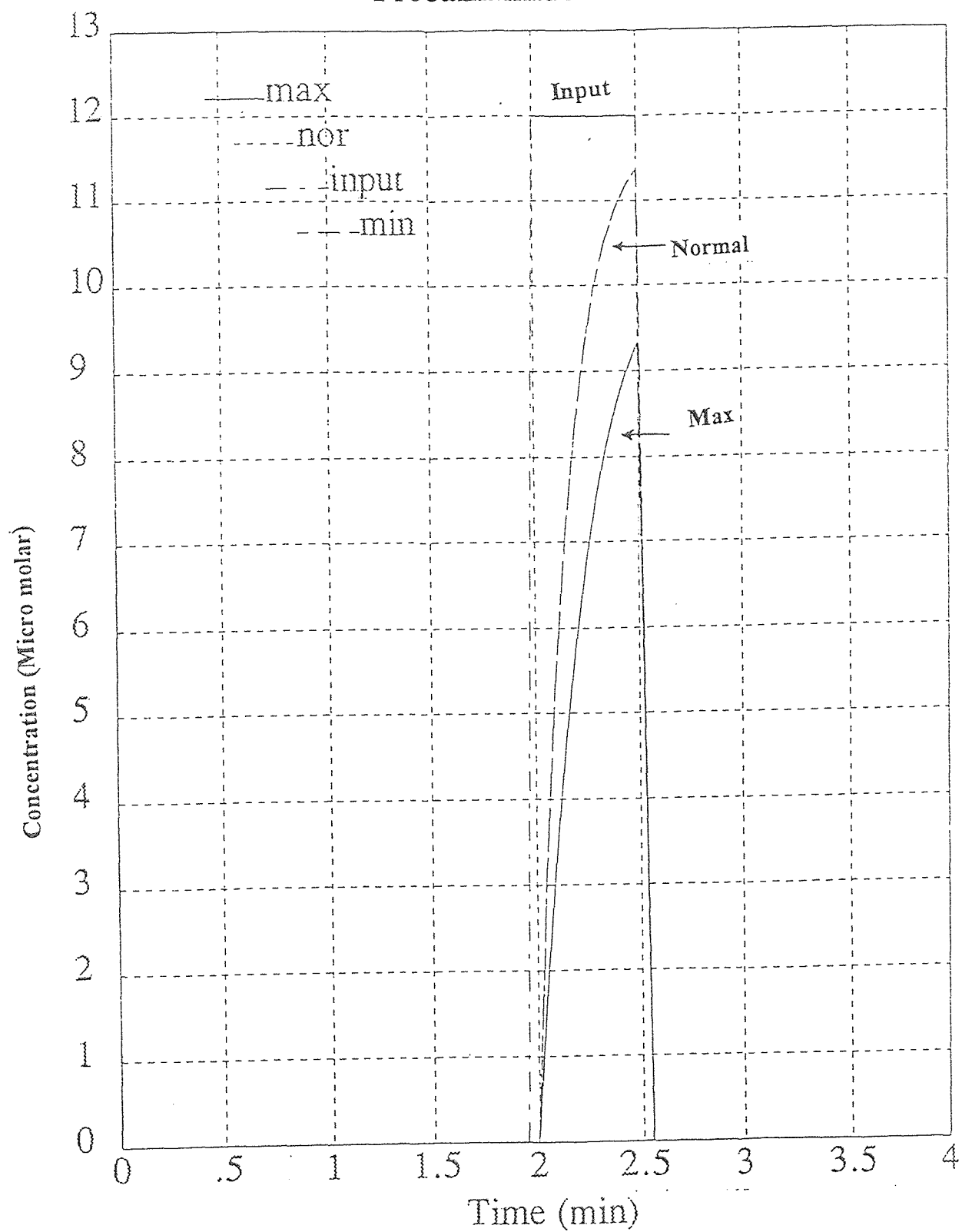
Curve 12.A Sensitivity Study of k_{21} for Procainamide for Cellular Concentration



Curve 12.B Sensitivity Study of k_{21} for Procainamide for Extracellular Concentration

Extracellular Concentration

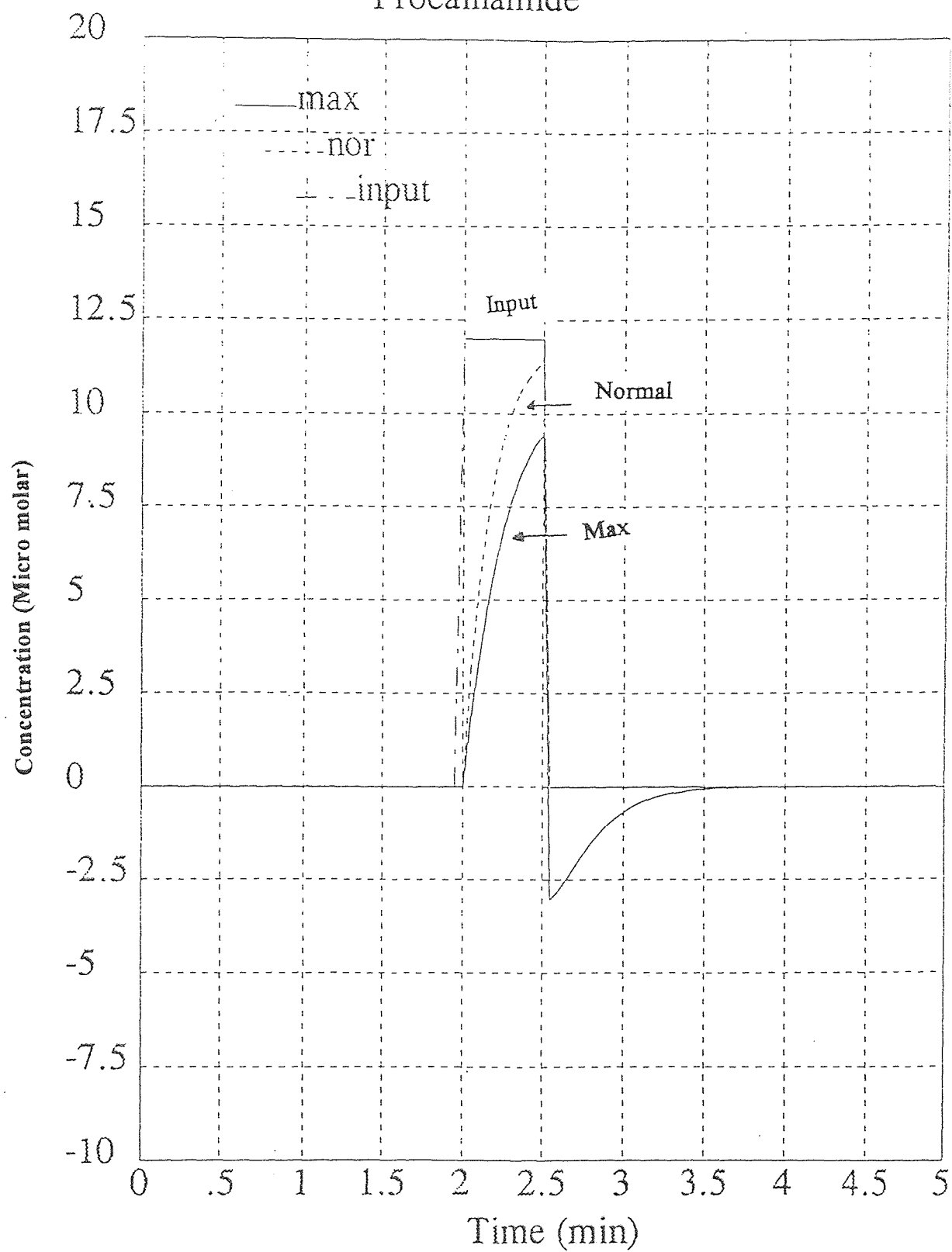
Procainamide



Curve 13 Sensitivity Study of 'u'

Extracellular Concentration

Procainamide

Curve 14 Sensitivity Study of k_T

APPENDIX B

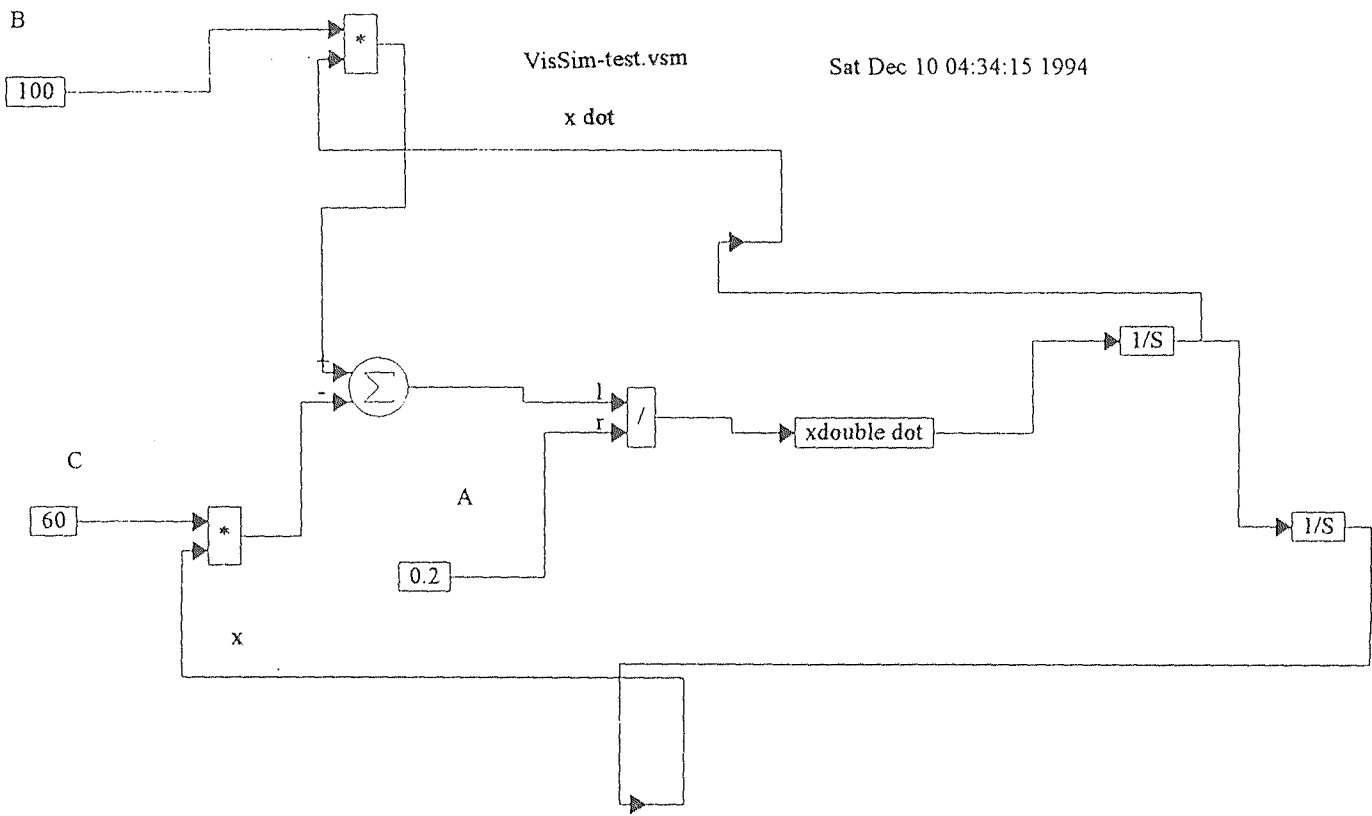
VISSIM DESCRIPTION

VisSim (Visual Solution Inc., Westford, M.A.) is a powerful set of software with the ability to design, simulate, plot, and debug within a single interactive environment. Models and systems are built using blocks. Blocks are connected to each other and to displays using flex wires. Blocks and flex wires are the primary tools of VisSim.

There are two types of blocks (1) standard blocks and (2) compound blocks. Standard blocks includes (1) Addition block, (2) Arithmetic block, (3) Integration, (4) Non-linear, (5) Boolean etc. A compound block is the combination of more than one standard block. There are also signal producing and signal consuming blocks. The signal consuming block include plot which is the output of any system in the form of a graph with time, frequency or parameter varying on 'y' axis. Signal producer block includes step, sinusoids, unknown etc. Any of these blocks can be used to represent a physical situation or to produce a signal. An example of this is that a bolus injection of a drug can be mathematically represented as an impulse. Consider the case, where a bolus injection is given between time 3 to 5 sec. For any other time the signal produced is zero. This is represented mathematically as shown below;

$$\begin{aligned} y &= 1 \text{ for } 3 < t < 5 \\ \text{else } y &= 0 \end{aligned}$$

This condition can be simulated using two step blocks and a summer block. By setting the proper time for the step block and adding one block (with $t=3$) and subtracting one (with $t=5$) a pulse of fixed duration of 2 second is produced. A step input can be used whenever the input is constant to the system after some predetermined time period. There are output connector tabs with triangular shapes which helps the user to view the direction of the signal. Each block has two



Block Diagram of $A \frac{d^2x}{dt^2} - B \frac{dx}{dt} + C x = 0$

types of signals (1) input signal or coming in signal and (2) output signal or exiting out signal.

In modeling the hepatic system for drug elimination, there are two differential equations; one for the cellular compartment and one for the extracellular compartment. These equations were represented by blocks on the VisSim (Visual Simulation Inc., Westford, M.A.) software. VisSim has the ability to solve several types of differential equations, including ordinary differential equations (ODE's). VisSim solves ODE's by using an integration operator. The example below shows how VisSim solves a second order differential equation. Let the equation be;

$$A(d^2x / dt^2) - B(dx/dt) + Cx = 0$$

Since integration is more numerically stable than differentiation, the above equation can be represented in terms of integrators. If we use $1/S$ (Laplace Operator) as a short hand notation for an integrator, then $x(t)$ can be represented by;

$$x(t) = 1/S [dx/dt] = (1/S) [1/S (d^2x) / (dt^2)]$$

The original equation can be written in modified form as;

$$d^2x / dt^2 = 1 / A [B (dx/dt) - Cx]$$

Figure on the opposite page shows block diagram of this differential equation. This equation is implemented on VisSim by wiring the output of the x and dx/dt variable blocks through two gain blocks (which represent 'C' and 'B' respectively). These two are then given as input to the summing block with a negative sign on the signal coming from the 'x' variable and a positive sign on the signal coming from the 'dx' variable. The output

of the summing block is divided by the constant block whose value is equal to 'A'. The output of this block is d^2x/dt^2 . This diagram represents a closed loop system. From this loop values for $x(t)$, dx/dt , d^2x/dt^2 can be tapped off and displayed using the signal consumer plot. Different values can be entered in appropriate blocks to simulate different sets of initial condition and system parameters.

The procedure to built a file and simulate a differential equation is as follows;

- (1) From file menu create a new file
- (2) From blocks in the menu create appropriate blocks, then connect them properly using flex wires so that they represent the differential equation.
- (3) Insert proper values for parameters and initial conditions in the appropriate blocks.
- (4) Check that the system is closed loop and all signs are properly matched.
- (5) Create plot from the block menu and connect the outputs of the differential equations to the plot.
- (6) Go to edit menu and simulate the differential equation.

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