Winter 12-1998

Development of Chronoamperometric Logarithmic Signatures with Application to Drug-Package Interactions and Mechanism Elucidation

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DEVELOPMENT OF CHRONOAMPEROMETRIC LOGARITHMIC SIGNATURES WITH APPLICATION TO DRUG-PACKAGE INTERACTIONS AND MECHANISM ELUCIDATION

by

Beth Sarsfield

December, 1998

Submitted to the Department of Chemistry of Seton Hall University in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.
We certify that we have read this thesis and that in our opinion it is adequate in scientific scope and quality as a dissertation for the degree of Doctor of Philosophy.

APPROVED

[Signatures]

In Charge of Major Work

Member of Dissertation Committee

Member of Dissertation Committee

Approved for the Chemistry Department Chairman, Department of Chemistry
DEDICATION

To Mum
ACKNOWLEDGMENTS

I am greatly appreciative of the mentoring which Dr. Joseph T. Maloy has extended. Besides technical discussions and advice throughout the research phase of my work, Dr. Maloy started by making sure that I had the tools I would need to complete the research. His direction, even when I couldn't see if it would lead anywhere, turned out to be exactly what was needed to complete the project.

Now that I am at the end of this particular work, I realize that there have been several mentors who have helped me and deserve special notice. These are Paul Kimmel, Tom Wood, George Reier, Henry Merkle, Herb Letterman, Ken Morris, and Alison Lukacsko. Each has provided invaluable technical direction, career advice, opportunities and friendship.

I have been lucky to also have several friends that I could count on. Among them are Harriet Behm, Beverly Bowman, Cindie Kura, Jerry Frunzi, Mildred Loprete, John Migton, Mike Nichols, Sunanda Ranadive, and Pat Werschulz. Also, I cannot think of one person who was a part of the chemistry or product development groups in Bristol-Myers Products, who hasn't at one time or another, helped me out and been a good friend. I need to especially thank David Chin for his computer hardware advice.

Above all, I am thankful for my family, especially my mother, Elizabeth, who made sure I had a foundation and who listened, encouraged, and understood the things I was doing. Also many thanks to D.G. and Judy, who I were both family and friends, and who taught me about beer.
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Abstract

Chronoamperometric logarithmic signatures are generated from experimental and theoretical transients by computing the dimensionless function:

\[ f(t) = \frac{\Delta (\ln i)}{\Delta (\ln t)} \]

Calculated over many orders of magnitude in time by employing digital smoothing techniques, this function may be used to identify the processes that control the current at any given time. During Cottrell time domains when current is proportional to \( t^{1/2} \), \( f(t) = -0.5 \). Analogously, during steady state time domains, \( f(t) = 0 \). For chronoamperometric experiments at a microelectrode, the diffusion limited current has been described as having Cottrell behavior, steady state behavior, or connecting behaviors. The method for computing \( f(t) \) from experiments at micro- and macroelectrodes for the reduction of ferricyanide will be presented. Analysis of \( f(t) \) over several time domains provided logarithmic signatures which were used to define steady state and Cottrell behaviors. Use of the defined time domains improved the accuracy of macroelectrode and microelectrode size determinations based on chronoamperometry experiments.

Using the method developed for ferricyanide reduction, logarithmic signatures were developed for the potential step studies of chlorpromazine HCl in acetate buffer, which has a non-reversible, kinetically complicated oxidation mechanism. Theoretical logarithmic signatures computed from finite difference simulations of possible mechanisms were compared to the experimental logarithmic signatures. Goodness-of-fit calculations
comparing the experimental and theoretical logarithmic signatures showed that, while an ece process is indicated, something other than the first order ece mechanism is operative. Results demonstrated that the experimental fit with the disproportionation mechanism was significantly better than with the first order ECE mechanism. However, the best fit between experimental and theoretical logarithmic signatures occurred with the buffer interaction mechanism.

A new electroanalytical technique based on scanning electrochemical microscopy was adopted to measure and predict solute sorption interactions with solid surfaces. By maximizing surface to volume ratios, this method significantly reduces the study time of drug-package interactions and allows prediction of possible long term effects. Chronoamperometry experiments were run in 40 microliter drops of solution containing drug placed on a solid substrate disk of about 7 mm diameter in a sample cell designed to accommodate a miniaturized three electrode set-up. Logarithmic signatures were used to define the optimum experimental conditions for chronoamperometric analysis. Results of sorption studies of chlorpromazine to glass, PP, HDPE, PET, EVA and PVC are presented. The small volume sorption experiments demonstrated that chlorpromazine interacts most quickly with PVC and HDPE and least with glass and PP. Long term stability tests confirmed the predictions of the small volume experiments.

The generation and analysis of the function, \( \Delta(\ln i)/\Delta(\ln t) \), improves the accuracy of analytical measurements of reversible and kinetically complicated electrode reactions, and extends the usefulness of the electroanalytical method to many drugs by accurately identifying time domains for steady state or Cottrell behavior.
INTRODUCTION

Interactions Between Drugs and Packages

Polymeric materials are used as parenteral and enteral administration sets, dialysis sets, syringes, and containers for injectables. Direct-to-consumer plastic packages are used for creams, ointments, otic suspensions, nasal solutions, and oral products including cough syrups, antibiotic suspensions and pediatric analgesics. With the known physical and chemical characteristics of hydrophobic drugs and polymeric packaging materials, it is not unexpected that drug-package interactions occur. The spectrum of drug/package interactions\(^1\) includes leaching of packaging ingredients into the drug product, adsorption of drugs or excipients to the surface of the package, absorption of the drugs or excipients by the polymer matrix, permeation through the packaging material, chemical reaction between the packaging materials and the drug product, or alteration in the physical properties of the package. Sorption of isosorbide dinitrate to injection catheters\(^2\) and to administration sets,\(^3\) amiodarone to infusion bags and administration sets,\(^4\) cyclosporine to indwelling catheters,\(^5\) chlorambucil to PVC infusion bags\(^6\) and numerous other drugs to various polymeric materials including containers and closures\(^7,8,9,10\) have been reported.

Pharmaceutical Product Development Process

An assessment of potential drug/package interactions is required during the product development process for new pharmaceuticals. The pharmaceutical product development process is comprised of five stages, with entrance to each new stage based
on obtaining the desired results from the previous stage. The first stage consists of finding a promising new chemical entity (NCE) based on *in vitro* and *in vivo* screening of numerous potential drugs. After an NCE is identified, it enters Phase 1 testing, during which the NCE's safety, bioavailability and pharmacologic activity is established in animals. Subsequently, the NCE enters Phase 2 clinical testing, which monitors safety and establishes the bioavailability of the NCE in healthy humans. During Phase 3, the activity of the NCE is established by treating diseased humans with the NCE. Upon successful completion of Phase 3, a New Drug Application (NDA) is submitted to the FDA. Approval of the NDA allows sale of the new drug so the drug enters Phase 4, which includes continuous post-marketing surveillance of the drug for safety and efficacy issues.

In the traditional pharmaceutical product development process, all stages are entered sequentially, with each investment in the NCE delayed to the latest possible stage. For example, an NCE could enter Phase 1 animal studies as a simple suspension or solution prepared with little regard to using an optimum formulation with a known long term stability profile. The NCE to be taken orally could then enter Phase 2 in a "simple" capsule formulation with limited stability and no relation to the final dosage form. Traditionally, the NCE is formulated into the potential marketed product once it is determined that there is a high likelihood of passing Phase 2. Thus, some Phase 2 studies may have to be repeated with the optimal formulation, and Phase 3 clinical studies need to wait at least for the formulation development, analytical method development, and drug stability testing. This traditional philosophy of drug development minimized
monetary risk at each stage, with little concern for the amount of time required for each activity. Thus, it was not unusual for it to take 15 years from identification of the NCE to approval of the NDA.

Recently, the philosophy of pharmaceutical companies has changed. It was realized that the time delays in the product development process had actually cost money by delaying introduction of the drug and thus delaying the potential for obtaining income from the new drug. Therefore, pharmaceutical companies are becoming less risk averse and are starting processes earlier in each stage, while finding ways of increasing the speed and output at each stage. Combinatorial chemistry techniques have monumentally increased the rate of developing NCEs. New in vitro screening techniques are used to complement the combinatorial chemistry techniques, which thus allows for more rapid identification of promising NCEs. Activities surrounding formulation and process development are being moved to earlier stages so that it is now common for the final formulation to be used in Phase 2 clinicals. There is a trend for NCEs to be more lipophilic than in the past, so the use of complicated formulations can be required to improve bioavailability of water insoluble drugs during the Phase 1 studies. These new processes have the goal of decreasing the time to obtain FDA approval in half.

Along with the speed-up of the pharmaceutical product development process comes a need to obtain the most information at the earliest possible point and to not repeat expensive animal or human studies. Thus, NCEs are characterized early in the process. This characterization includes determination of solubility parameters, intrinsic dissolution, degradation kinetics, and probable drug-excipient interactions. There is also
a need to study drug-package interactions. As already noted, there is a high potential for lipophilic drugs to interact with the polymeric films used in manufacturing equipment and packaging, including the syringes and injection administration tubing used in Phase 1 and Phase 2 studies. With the many choices of polymeric materials available for packaging and the small amount of NCEs available during early development, it is desirable to have a screening method for drug-package interactions that does not require large amounts of the NCE.

Mechanisms of drug-package interactions

The major drug-package interactions are classified\textsuperscript{11} as desorption of packaging ingredients into the drug product, as adsorption of drugs or excipients to the surface of the package, or as absorption of the drugs or excipients into the polymer matrix.

The adsorption process has been reported as the specific mechanism for loss of insulin on in-line filters\textsuperscript{12} and betamethasone to a latex.\textsuperscript{13} Adsorption processes have alternatively been used to understand the role of fibrinogen in platelet aggregation by measuring its adsorption to acrylates and other polymers.\textsuperscript{14} Adsorption is a surface phenomenon in which drug or excipient solutes adhere to the surface of the packaging polymer. Langmuir adsorption occurs when only one molecule of either solvent or solute can occupy each adsorption site. At equilibrium, the adsorption equilibrium constant, $K'$ is described by:
where $X_1$ is the fraction of adsorbed solvent, $X_2$ is the fraction of adsorbed solute, $a_1$ is the activity of the bulk solvent, and $a_2$ is the activity of the bulk solute. Equation 1.2 is a common representation of the Langmuir equation:

$$
K' = \frac{X_2 a_1}{X_1 a_2}
$$

where the fraction of the surface occupied by solute, $\theta$, approaches 1 as $K a_2$ increases. This implies the maximum of a single layer of solute adsorbed to the surface. In the interpretation of drug-package sorption isotherms, Langmuir-type adsorption is assumed when there is an initial loss of drug from solution followed by insignificant losses in the long term. It is expected that sorption isotherms which appear as Langmuir isotherms are empirical interpretations because the packaging polymer matrix surface is not normally homogeneous at the molecular level, few monolayers are ideal, few solute-solute or solute-solvent interactions are ideal, multiple solutes are present, and the drug concentrations of interest are not dilute. It is also possible for multiple layers to adsorb, which is experimentally demonstrated by continued loss of solute from solution or by solute loss to a constant value where $\theta > 1$.

Absorption of drug or excipient solutes into a packaging polymer matrix can occur by many mechanisms which depend on the characteristics of the drug and polymer.
matrix. Most pharmaceutical packaging materials are lipophilic polymer matrices so that
the solvent, which is normally water, does not interact with the package. Thus it is not
surprising that lipophilic drugs or un-ionized forms will have an affinity for the
packaging polymer matrices. Absorption occurs as a two stage process. The first is for
the drug to absorb into the polymer matrix at its surface. The second is for the drug to
diffuse through the polymer matrix thus creating a solute concentration gradient at the
surface allowing more solute to absorb. With packaging materials, it is assumed that the
third permeation event, release of solute at the opposite surface of the polymer matrix
(desorption of drug to the outside), does not occur unless the drug is volatile (e.g.
menthol). Solute mass transport through the polymer matrix can occur by diffusion
through the void space within the polymer matrix or by solvation in the polymer matrix.
Thus, important drug characteristics which relate to the potential for absorption into
packaging polymer matrices include pKa, solubility parameter, partition coefficients, and
molecular size. In fact, published reports demonstrate that lipophilicity as measured by
water/octanol partition coefficients, and amount unionized as measured by pH and
pKa,\(^{16,17}\) can be used to predict sorption of drugs by polyvinyl chloride (PVC) and other
plastic packaging materials.

The physical characteristics and chemical composition of packaging material
polymer matrices also influence the type and extent of interactions with drugs. Stern and
Frisch\(^{18}\) described three types of gaseous diffusion through polymers which depend on
polymer characteristics. Case I, Fickian diffusion of the solute, occurs with rubbery
polymer matrices, when the temperature is higher than the glass transition temperature,
of the polymer matrix. Fickian diffusion is controlled by the diffusion coefficient, $D$, of the solute in the polymer matrix. This diffusion coefficient is not concentration dependent, which leads to time-independent boundary conditions with no dependence on swelling kinetics. For glassy polymers at temperatures slightly less than the $T_g$, solutes often behave according to the dual-sorption model, which is a combination of Fickian diffusion and Langmuir adsorption. Stern and Frisch proposed that the Langmuir adsorption behavior is present because some solute molecules become partially or totally immobilized at fixed sites in the glassy polymer matrix. Non-Fickian or anomalous diffusion can also occur such that the penetrant interacts so strongly with the polymer matrix that swelling occurs and the diffusion coefficient becomes dependent upon history, time and concentration.

The presence of crystallinity within a polymer matrix can also affect the diffusion coefficient by:\(^\text{19}\)

\[
(\tau \beta) = \frac{D^*}{D}
\]  

(1.3)

where $D^*$ is the diffusion coefficient in a completely amorphous polymer and $D$ is the diffusion coefficient in the polymer containing crystallinity. The geometric impedance factor, $\tau$, accounts for the local reduction in the area available for diffusion and for the increased effective diffusion path length due to the presence of the crystallites. The second impedance factor, $\beta$, accounts for the decreased chain mobility caused by interference of movement from the crystallites.
Effects of glass transition temperature, void space and solubility on rates and extent of diffusion of drugs in rubbery and glassy polymers\textsuperscript{20,21,22} have been demonstrated. Vrentas and Vrentas\textsuperscript{29} studied the effect of the average hole free volume, \( V_{FH} \), on \( D \), the diffusion coefficient:

\[
D \propto \exp\left[\frac{-1}{V_{FH}}\right]
\]

(1.4)

where \( V_{FH} \) is affected by \( \alpha \), the thermal expansion coefficient for the equilibrium solute-polymer and by \( \alpha_c \), the thermal expansion coefficient for the sum of the occupied and free volumes of the polymer at temperatures above \( T_g \). At temperatures below \( T_g \), the thermal expansion coefficient for the glassy polymer, \( \alpha_g \), must also be taken into account. As a further complication, it is often assumed that \( \alpha \) is temperature independent. However, Vrentas and Vrentas showed that the \( \alpha \) for polystyrene is \( 5.3 \times 10^{-4} \text{ K}^{-1} \) above the glass transition temperature and is \( 3.5 \times 10^{-4} \text{ K}^{-1} \) below the \( T_g \).

Studies show that ingredients in the package matrix such as plasticizers\textsuperscript{23} affect the amounts and rates of drug sorption. Bray evaluated the equilibrium sorption isotherms for benzocaine in PVC plasticized with bis-2-ethylhexylphthalate (DEHP) or with acetyl tri-n-butyl citrate (ATBC) using:

\[
P = KD
\]

(1.5)

where \( P \) is the permeability coefficient, \( K \) is the partition constant, and \( D \) is the diffusion coefficient. Bray found that \( K \), determined from the slope of the benzocaine sorption
isothersms, was dependent upon the concentration of the plasticizer, and was greater for ATBC than for DEHP. Extending Equation 1.5, Bray demonstrated that:

\[ K_p = \frac{S_p}{S_w} = \frac{C_p}{C_w} \]  

where \( K_p \) is the partition coefficient dependent on the plasticizer content, \( S_p \) and \( S_w \) are the solubilities of the drug in the plasticizer and water, respectively, and \( C_p \) and \( C_w \) are the drug concentrations in the plasticizer and water obtained from equilibrium studies. This method is now commonly used for studying equilibrium sorption of drugs by packaging materials.

**Current methods for evaluating drug/package interactions**

Drug-package interactions are traditionally evaluated during stability testing of new pharmaceutical formulations. The formulation containing drug and excipients is filled into several types of glass and plastic containers and placed at various temperature and humidity stability conditions for up to 5 years. Along the way, packages with unacceptable drug-package stability profiles are eliminated. Choice of potential packages is usually made based on previous long-term stability studies, packaging costs, and the cost of running the stability tests over long time periods. All studies mentioned previously used an amount of drug sufficient to completely fill packages for determination of drug-package sorption isotherms. Drug solutions are filled into the package and placed at a stability condition of some controlled temperature and humidity.
The amounts of drug remaining in solution at specified times are measured and losses are assigned to the sorption of drug by the packaging materials. These methods also require significant amount of drug, which is usually unavailable early in the development process.

An alternative method, used by Komiyama\textsuperscript{24} and Shibusawa,\textsuperscript{25} used the film roll method to measure the amounts of dyes absorbed by Nylon. In this method, a roll of thin polymer film was analyzed directly for the amount of absorbed dye. This method is not useful for the measurement of drug-package sorption isotherms because packaging materials are not thin films and many do not have the flexibility to be rolled.

In addition, many investigators have studied the mechanisms, kinetics, and thermodynamic properties of drug-package interactions with the goal of generating data which can be used to understand the adsorption and absorption interactions between drugs and packaging materials.

Much of the theoretical adsorption concepts are based on experiments with activated carbon. In pivotal early studies, Graham\textsuperscript{26} demonstrated that there was a distribution of pore sizes in activated carbon and that the adsorption of dyes into the pores depended on the relative size of the pore and of the adsorbing molecule. Graham used B.E.T. (Brunnauer, Emmet and Teller), a method which measures multiple layers of gas adsorption to solid surfaces, to determine the activated carbon surface areas before and after dye adsorption took place. This was correlated this to the amounts of dye remaining after equilibrium adsorption was attained. Graham also showed that the ionic character of the adsorbent surface, as measured by acid-base titration, affected the adsorption of
anionic and cationic dyes to different extents. More recently Matsumoto, et. al. studied the adsorption of hydrocarbons to activated carbon fibers (ATFs). These fibers are manufactured to have slit-shaped pores of uniform widths. Though the best method for determining pore size is still adsorption of a gas such as \( \text{N}_2 \) (similar to the B.E.T. test), calorimetric methods for measuring the heats of adsorption and desorption are now commonly included. Matsumoto, et. al. confirmed that more adsorption occurred with larger pore widths by determining the microporosity of the ATFs, the equilibrium adsorption of hydrocarbons, and the Lennard-Jones (nonpolar interactions) potentials which can be related to the energy and the centered-point size of the hydrocarbons. Gusev and O'Brien used similar methods to determine the adsorption of ethane by activated carbons. However, they obtained a better estimate of hydrocarbon size and adsorption by using a two-center model. These molecular simulation techniques are difficult to extend to predicting drug-package adsorption interactions because drugs are more complicated chemical entities and accurate simulation techniques are not yet available.

For the adsorption of larger molecules on surfaces, atomic force microscopy (AFM) can be useful. There are no reports of the use of AFM to look at drug adsorption to packaging material surfaces, but there are several reports of measuring surfactant adsorption to surfaces. Bard, et. al., used AFM to measure the change in surface charge as an ionic surfactant adsorbs to the surface. Several other methods, including isothermal microcalorimetry, \( ^{30} \) NMR, \( ^{31} \) ellipsometry, \( ^{32} \) FTIR, \( ^{33} \) Raman, \( ^{34} \) ESR, \( ^{35} \) fluorescence decay\( ^{36} \) and neutron reflection\( ^{37} \) have also been used to characterize
adsorption of surfactants to surfaces. However, these methods have not yet been extended to the study of smaller molecule, non-surfactant adsorption phenomenon.

Absorption and unspecified sorption of drugs by packaging materials have received a great amount of study. Autian\textsuperscript{38} reviewed the current literature concerning sorption of many different drugs to nylon syringes, polyethylene, and poly(vinyl chloride) (PVC). Diffusion coefficients of various drugs in polyethylene and nylon range from $10^{-7}$ to $10^{-10}$ cm$^2$/s, as compared to about $10^{-5}$ cm$^2$/s in solution.

Illum, \textit{et. al.},\textsuperscript{22,39} used sorption isotherms to understand the sorption mechanism and advanced the theory that adsorption and absorption can occur together. Illum's method was based on Crank's equation for diffusion from a stirred solution of limited volume:\textsuperscript{40}

$$\frac{M_t}{M_\infty} = \frac{F_t - F_\infty}{1 - F_\infty} = \sum_{n=1}^{\infty} \frac{2\alpha(1 + \alpha)}{1 + \alpha + \alpha^2 q_n^2} \exp\left(-q_n^2 D t / l^2\right)$$

(1.7)

where $M_t$ is the solute amount in the plastic at time, $t$, $M_\infty$ is the solute amount in the plastic at infinite time, $F_t$ is the solute fraction remaining in solution at $t$, $F_\infty$ is the solute fraction remaining in solution at infinite time, $\alpha$ equals $F_\infty / (1 - F_\infty)$, $D$ is the diffusion coefficient of the solute in plastic, $l$ is the thickness of the plastic, and the values of $q_n$ are the non-zero positive roots of $\tan q_n = -\alpha q_n$ and can be obtained from Crank's Table 4.1. Semilogarithmic plots of the fraction of drug remaining versus time became linear at later times. This allowed determination $D/l^2$ from the slope. The experimental sorption isotherms were compared to the theoretical absorption isotherms generated using the $D/l^2$
data. There was good agreement for the sorption of diazepam and warfarin by PVC, which indicated that these were absorption processes controlled by diffusion of drug in the PVC.

Roberts et al. determined the loss of drugs from solution into PVC during “normal use” time intervals. This stability data was compared to proposed sorption mechanisms. For PVC infusion bags, the proposed diffusion model consisted of a constant concentration throughout the solution, with drug diffusing through the PVC layers with a concentration gradient as a driving force. The model comprised a constant concentration throughout the solution without a drug depletion layer adjacent to the modelled package surface, suggesting that the solution is stirred. However, the experiments were not conducted using stirred solutions. At time, t, the fraction of drug remaining in solution, $F_t$, is defined by:

$$F_t = e^{[S_{nt}]} \text{erfc} [\sqrt{S_{nt}t}]$$  \hspace{1cm} (1.8)

so that $F_t$ decreases as $S_{nt}t$ increases, either with long experimental times, or with $S_n$, the sorption number, defined by:

$$S_n = \left( \frac{K' A}{V} \right)^2 D = \left( \frac{KA}{V} \right)^2 f_u D$$  \hspace{1cm} (1.9)

where $K'$ is the apparent partition coefficient between the plastic and the solution, $K$ is the partition coefficient of the unionized fraction between the plastic and the solution, $A$ is the packaging material surface area, $V$ is the solution volume, $f_u$ is the unionized drug
fraction and D is the drug diffusion coefficient in the plastic. This work by Roberts, et. al., demonstrates that hydrophobic drug uptake by a polymeric packaging material is a function of the package surface area-to-solution volume ratio, the apparent partition coefficient, and the diffusion coefficient of the solute in the plastic. Roberts extended his work to predict sorption of solutes by tubing. The absorption of isosorbide dinitrate in PVC tubing compared well to the Roberts model, which was extended to include the assumption that an interfacial barrier existed at the solution-tube interface. This assumed that the solute concentration was zero at the interface, which is equivalent to assuming that the solution was unstirred. By appropriately choosing drugs which have a high affinity for PVC, the confirmatory experiments performed by Roberts, et. al., could each be completed within one week.

All of these methods for predicting absorption require knowledge of the diffusion coefficient of a drug in the plastic, which requires equilibrium absorption studies to be completed. For hydrophobic drugs in PVC, this is an easy task with equilibrium conditions attained within two weeks. However, for drug-package interactions with smaller diffusion coefficients, it requires much more time to attain equilibrium. Molecular modeling could eventually be used to estimate diffusion coefficients, but at this time, it is only being used in ideal situations to study adsorption phenomena. There is still a need for a screening method which can be used to determine short term drug-package interactions for prediction of long term drug-package interactions with several packaging materials.
Electrochemical Adsorption Method

Unwin and Bard\(^{45}\) have reported a new method for measuring adsorption isotherms based on techniques used in scanning electrochemical microscopy. In this method, an ultramicroelectrode was used to measure the loss of a dye, methylene blue, from 10 μl drops. Sorption isotherms were generated to reveal information about the adsorption processes of the dye to various graphite surfaces. Using a miniaturized two electrode system, the electrode was held at a potential which caused the reduction of methylene blue. The resultant diffusion limiting current at steady state, \(i_d\), was correlated to the bulk concentration, \(C_o\), of methylene blue by:

\[
i_d = 4nFD\,C_o\,r
\]

where \(n\) is the number of electrons transferred, \(F\) is the Faraday constant, \(D\) is the diffusion coefficient of the dye, and \(r\) is the radius of the disk microelectrode. During the experiment, the limiting current, \(i_d\), was measured over time and the loss of generated current over time was correlated to loss of dye from solution over time. This loss of dye was attributed to adsorption to graphite. The experiments demonstrated that the amount of methylene blue adsorbed to graphite depended on the particular crystal face used in the adsorption experiment. It was also demonstrated that there was no loss in \(i_d\) when adsorption did not occur, as when the dye was in contact with glass.

 Proposed Electrochemical Sorption Method

The work by Bard demonstrated that it was possible to monitor solute losses from
a small drop of solution. As seen by Equation 1.9, increases in the packaging surface area-to-solution volume ratio cause increases of $S_n$, which causes greater loss from solution. In the present study, Bard's concept is extended to the study of adsorption and absorption processes which occur in drug-package interactions. It is proposed that the loss of drug from small drops of solution can be correlated to the loss of drug from solution in standard containers. It is also proposed that the small volume experiments will demonstrate drug-plastic interactions at earlier time intervals than seen in conventional packages due to an increase in the packaging surface area-to-drug solution volume. Thus, this method provides a means of screening potential packages using the small drug volumes available during the preformulation stage. It also provides a method of observing slow drug-package interactions in a shorter time span.

To prove this concept, a drug which is known to interact with plastic packaging materials, known not to interact with glass, and known to be electrochemically detectable, needed to be selected. Chlorpromazine HCl (CPZ) was selected as the model drug to confirm the methodology. It is an antipsychotic drug that has been reported to sorb to various plastics materials but not to glass$^{46,47}$ and has been analyzed electrochemically.$^{48,49,50}$

Logarithmic Signatures

The oxidation of chlorpromazine is kinetically complicated by subsequent chemical reactions which could interfere in the electrochemical determination of CPZ concentration. A disproportionation mechanism$^{51,52}$ was proposed by Merkle for CPZ
oxidation under very acidic conditions; and a buffer interaction mechanism\textsuperscript{53,54} was proposed by McCreery for CPZ oxidation in buffered solutions nearer to neutral pHs. With either of these mechanisms, chronoamperometric measurements could be complicated by the following reactions. Thus, the experimental times for microelectrode experiments based on estimations for reversible systems may give erroneous data.

Analytical results for chronoamperometric experiments should be run at times during which the resultant current is proportional to $t^{-\alpha/2}$ (Cottrell region) for macroelectrode experiments or during which the resultant current has no time dependence (Steady State) for microelectrode experiments. It has been previously demonstrated by Therdeppitak that the function, $f(t) = \Delta(\ln i)/\Delta(\ln t)$, can be used to determine Cottrell and Steady State behaviors.\textsuperscript{55} The Cottrell time regime is indicated by $f(t) = -\alpha/2$ and the steady state time regime is indicated by $f(t) = 0$. It is proposed that $f(t)$ be determined over several orders of magnitude of time so that the time domains applicable to analytic interpretation (Cottrell or Steady State) can be determined. As performed on the first order ECE mechanism by Therdeppitak and Maloy,\textsuperscript{56} it may also be possible to provide some insight into the oxidation mechanism by evaluating experimentally and theoretically derived logarithmic signature, which is $f(t)$ over multiple time domains.
LOGARITHMIC SIGNATURE METHOD DEVELOPMENT

Introduction

Theory

Potential step techniques have recently been used to determine electrode sizes and diffusion coefficients,\textsuperscript{57} in scanning electrochemical microscopy,\textsuperscript{58} in analysis of a small drop with an ultramicroelectrode,\textsuperscript{45} for flow-through sensors,\textsuperscript{59} as biosensors\textsuperscript{60} and to characterize microelectrode arrays.\textsuperscript{61} To interpret the data obtained during chronoamperometric experiments at either macroelectrodes or microelectrodes, it is necessary to know the prevailing mechanism for diffusion control during the experimental time frame.

The limiting current, $i_\ell$, produced from diffusion controlled reactions at planar macroelectrodes (or microelectrodes at very short times) during chronoamperometric (single potential step) experiments are described by the Cottrell Equation:

$$i_d(t) = \frac{nFAD^{1/2}C^*}{\pi^{1/2}t^{1/2}}$$

where $n$ is the number of electrons, $F$ is the Faraday constant, $A$ is the area of the electrode, $D$ is the diffusion coefficient, $C^*$ is the bulk concentration, and $t$ is experiment time. Thus, for potential step experiments at planar macroelectrodes, the resultant current is normally described as proportional to $t^{-1/2}$. Deviations from current proportionality to $t^{-1/2}$ for Cottrell behavior can be caused by double-layer charging at the beginning of
experiments, convection caused by the migration of reduced and oxidized species in response to concentration gradients, and convection caused by uncontrolled vibrations. Chemical reactions following electrode reactions can produce either positive or negative deviations from Cottrell behavior. Experiments run under ideal conditions are often used to determine $n, A, D$ or $C^*$ by evaluating the slope of $i_d(t)$ vs $t^{1/2}$. Deviations can be determined by non-linearity or intercepts other than zero.

The limiting current produced from diffusion controlled reactions at planar microelectrodes, using longer experimental times than those described by the Cottrell Equation, are described by the Steady State Equation:

$$i_d(t) = 4nFrD C^*$$

where $r$ is the radius of the planar disk microelectrode. Thus chronoamperometric experiments using microelectrodes can also be used to determine $n, A, D$ or $C^*$, except that this is accomplished by evaluating the intercept of $i_d(t)$ vs $t^{1/2}$. Deviations from this steady state behavior are caused by the same conditions which cause deviations to Cottrell behavior and are normally determined by nonlinearity of the $i_d(t)$ vs $t^{1/2}$ line and slopes other than zero.

Diffusion controlled reactions at a disk electrode inlaid in an infinitely large insulator have been shown by Shoup and Szabo to follow the chronoamperometric relationship
\[
\frac{i_d(t)}{4nFrDC^*} = 0.7854 + 0.2146e^{-0.7823\tau^{-1/2}} + \left(\frac{\tau^{1/2}}{2}\right)\tau^{-1/2} \tag{2.3}
\]

where \(\tau = 4Dt/r^2\) and the numerical equivalent of \(\pi^{1/2}/2\) was given in the original text.

When \(\tau^{1/2} > 10\), the exponential term in Equation (2.3) vanishes and the current-time curve is given by

\[
i_d(t) = 0.7854(4nFrDC^*) + \frac{nFAD^{1/2}C^*}{\tau^{1/2}} \tag{2.4}
\]

Thus, at very short times the concentration may be determined from the slope of \(i_d(t)\) vs \((t^{1/2})\) using Equation (2.1). On the other hand, when \(\tau^{1/2} < 0.05\) the exponential part of Equation (2.3) may be expanded using the approximation \(e^x \approx (1-x)\) to obtain a somewhat different linear form for the current-time curve

\[
i_d(t) = 4nFDC^*r + 0.8103 \frac{nFAD^{1/2}C^*}{\pi^{1/2}t^{1/2}} \tag{2.5}
\]

where 0.8103 = \((8/\pi^2)\). Equation (2.5) shows that, at long times, the reactant concentration may be determined from the intercept of the \(i_d(t)\) vs \(t^{1/2}\) curve using Equation (2.2).

At intermediate times (for \(10 > \tau^{1/2} > 0.05\)), both the slope and the intercept of the linear form of Equation (2.3) will depart from the ideal values given in Equation (2.1) and Equation (2.2), and some decision must be made whether to determine the concentration...
from the slope or the intercept of the $i_d(t)$ vs $t^{1/2}$ plot. This report will demonstrate that the calculation of the logarithmic signature, $\Delta(\ln i)/\Delta(\ln t)$, provides independent guidance as to which method to employ.

**Initial Experiments for Reversible System**

Baur and Wightman determined $D$ and $r$ for various systems, including ferricyanide reduction, by choosing to maintain $\tau > 55$ for chronoamperometric experiments and by calculating the intercepts from Equation (2.5). This is equivalent to assuming steady state behavior described by Equation (2.2) where the current has no time dependence, the slope of $i_d(t)$ vs $t^{1/2}$ is zero, and the intercept can provide information about $n, D, r,$ or $C^*$. The choice of $\tau > 55$ was based on a report by Hepel and Osteryoung which demonstrated that Equation (2.5) is 99% accurate when $\tau > 3.2$. Higher $\tau$ values, obtained by increasing the experimental time or by decreasing the electrode size, increase the experimental accuracy by increasing the likelihood that the steady state time domain has been achieved.

Initial chronoamperometric experiments for chlorpromazine HCl oxidation, a kinetically complicated and irreversible system, produced results which did not provide good agreement with chlorpromazine HCl concentration. The conditions for these initial experiments, were selected based on subjective choices. With the aim of understanding chronoamperometric experimentation better, the reduction of ferricyanide,

$$Fe(CN)_6^{3-} + e \rightleftharpoons Fe(CN)_6^{4-}$$

$$E^\circ = 0.69 \ V \ vs \ NHE \quad (2.6)$$
a reversible system, was chosen for additional studies, and for development of the logarithmic signature method.

Methods

Electrochemical methods

A BAS 100B/W electrochemical analyzer (Bioanalytical Systems, West Lafayette, IN) was used for all electrochemical experiments. The BAS 100B/W, Version 1, software was used to set test conditions and to collect data using the BAS 12-bit A/D converter. All microelectrode experiments were run using the BAS Amplifier and a Faraday cage.

All electrodes were obtained from Bioanalytical Systems. Traditional three-electrode systems were used for analysis with both macroelectrode and microelectrode experiments. In all cases, the auxiliary electrode was a platinum wire. The reference electrode for all ferricyanide experiments was the Ag/AgCl electrode (BAS model RE-5). Platinum disk macroelectrodes had nominal diameters of 1 mm with 7 mm o.d. including the Kel-F insulator. Platinum disk microelectrodes had nominal diameters of 10 μm with 4 mm o.d. including the glass insulator. Carbon disk macroelectrodes were glassy carbon electrodes with nominal diameters of 3 mm with 7 mm o.d. including the Kel-F insulator. Carbon disk microelectrodes were carbon fiber electrodes with nominal diameters of 9 μm to 13 μm with 4 mm o.d. including the glass insulator. Working macroelectrodes were polished with 0.05 mm polishing alumina and working microelectrodes were
polished with 1 μm diamond paste, both supplied by BAS.

Cyclic voltammetry and chronoamperometry experiments were run on K₃Fe(CN)₆ in 0.5 M KCl adjusted to pH 3.0 with HCl. Ferricyanide electrochemical experiments were run using N₂ purged solutions with an N₂ blanket maintained throughout the experiments. The potential jump for ferricyanide reduction experiments was from 0.60 V to -0.10 V vs Ag/AgCl.

Microscopic Electrode Size Determination

The macroelectrodes were also inspected visually to determine electrode sizes. A RAM Optics system was used to determine the diameters of the disks. The instrument provides magnification of 10x to 40x for viewing the disk electrodes. Once the magnification is set, the object is viewed on a video screen. The instrument, which is normally used to determine the dimensions of packages (bottles, tubes, etc.), contains software which can be used to determine diameters. With this software, three points on the edge of the disks were chosen at random using a mouse and selecting points on the video screen. From these three points, the software can calculates the diameters of disk macroelectrodes. Microelectrodes are too small to be measured accurately using the RAM Optics Equipment.

Reagents

All chemicals were used as received from commercial sources. K₃Fe(CN)₆ (A.C.S. reagent grade, Fisher) was 99.9% pure as per certificate of analysis. The
supporting electrolyte for ferricyanide experiments was prepared using Milli-Q (Millipore) filtered water, KCl (A.C.S. reagent grade, Aldrich) and 1.0 M HCl (Mallinkrodt). Ferricyanide solutions were purged and blanketed with Ultra High Purity grade N₂ obtained from JWS Inc.

Method Development for Chronoamperometry of Ferricyanide

Initial Experiments

Cyclic voltammetry of 0.1 mM K₃Fe(CN)₆ in 0.5 M KCl maintained at pH 3 was performed using all four types of electrodes (macro and microelectrodes of Pt and carbon) described above. Figure 1 shows typical cyclic voltammetry curves for experiments using glassy carbon disk macroelectrodes and carbon fiber microelectrodes. Cyclic voltammetry curves for experiments using platinum disk electrodes were similar. From this data, it was determined that the potential jump from 0.60 V to -0.10 V vs Ag/AgCl would be used for all ferricyanide reduction chronoamperometric experiments.

The minimum time for the microelectrode experiments were initially calculated using the guidelines suggested by Hepel and Osteryoung⁶⁴ of setting the experimental chronoamperometric run time such that \( \tau > 3.2 \) to attain steady state. Thus, for an 11 μm diameter electrode, \( t \) is 0.047 s with \( D = 7.17 \times 10^{-6} \text{ cm}^2/\text{s} \) for ferricyanide in 0.5 M KCl at pH 3. To improve the chances of steady state behavior, the chronoamperometric experiments for ferricyanide reduction were run for 0.1 s. The choice of run time for
Figure 1. Cyclic voltammetry of 0.1 mM K$_3$Fe(CN)$_6$ in 0.5 M KCl (pH 3.0) at: (A) graphite disk macroelectrode, 0.1 V/s and (B) carbon fiber microelectrode, 0.01 V/s
macroelectrode experiments were chosen empirically to be 32 s, which is the maximum run time included in the BAS software for chronoamperometry.

For the macroelectrode experiments, the slope was determined using the BAS software which estimates the slope of the $i_d(t)$ vs $r^{1/2}$ line from the last 20% of the data. Using Equation (2.1), the BAS-calculated slope, $7.17 \times 10^{-6}$ cm$^2$/s as $D$, and $9.99 \times 10^{-7}$ mol/cm$^3$ as $C^*$, it was determined that the diameter of one glassy carbon electrode (electrode designated as CB) was 2.24 cm (%RSD = 3.0%) and for a second glassy carbon electrode (electrode designated as CC) was 3.12 cm (%RSD = 3.6%). These electrodes were visually inspected using the RAM Optics to determine the diameters of these two electrodes. By this visual test, the diameter of CB was found to be 3.002 mm $\pm$ 0.033 mm, and the diameter of CC was found to be 2.986 mm $\pm$ 0.013 mm. Comparing the two sets of data, it appears that the chronoamperometric results for glassy carbon macroelectrode CC compared favorably to the microscopic measurement results. This was not true for glassy carbon macroelectrode CB, which appears to have its diameter underestimated based on the chronoamperometric method. No specific reason for the unexpected results for the size of macroelectrode CB was immediately apparent.

For the microelectrode, the intercept was determined using the BAS software which estimates the intercept of $i_d(t)$ vs $r^{1/2}$ using approximately the last 20% of the data. Assuming that Equation (2.2) holds for the microelectrode, the sizes of the four different carbon fiber microelectrodes were calculated to be $5.34 \times 10^{-5}$ cm, $8.62 \times 10^{-5}$ cm, $9.88 \times 10^{-5}$ cm and $2.11 \times 10^{-4}$ cm, each with %RSD between 10 and 15%. This did not compare favorably to the electrode sizes reported by BAS, which were within the range
of $9 \times 10^4$ to $1.3 \times 10^3$ cm. The microelectrode sizes were not confirmed by other methods because available light microscopy methods did not work and SEM was unavailable. It was hypothesized that the disparity between the chronoamperometrically determined and reported electrode sizes could occur if the chronoamperometric experiments were not run under steady state conditions.

**Experimental Logarithmic Signature Development**

It has been previously reported that, for chronoamperometric experiments under Cottrell behavior, the value of $f(t) = \Delta(\ln i)/\Delta(\ln t)$ is -0.5 due to diffusion limited current proportionality to $r^{1/2}$. Under steady state conditions, $\Delta(\ln i)/\Delta(\ln t)$ is equal to zero. As a dimensionless function, $\Delta(\ln i)/\Delta(\ln t)$ is completely independent of concentration, electrode dimensions, and mass transport parameters. Therefore, this function can be used to correlate experiments run over several orders of magnitude in time domain. It also may be used to follow current-time transients which represent double-layer charging, Cottrell behavior, steady state behavior, and all transitional or kinetically complicated behaviors. The chronoamperometric transient described by $\Delta(\ln i)/\Delta(\ln t)$ has been used as signature working-curves for kinetically complicated mechanisms. Therefore, a method to determine the logarithmic signature, $f(t) = \Delta(\ln i)/\Delta(\ln t)$, from experimental chronoamperometric data was developed with the aim of determining the optimum experimental time domain for macroelectrode and microelectrode experiments of the reversible ferricyanide reduction, thus improving the accuracy of determining disk electrode sizes.
Electrochemical methods

As with the previous experiments, the BAS 100B/W electrochemical analyzer (Bioanalytical Systems, West Lafayette, IN) was used for all electrochemical experiments to produce the logarithmic signature. The BAS 100B/W software limits the run times and number of points collected during chronoamperometric experiments. Thus, the logarithmic signature curves, \( f(t) = \Delta \ln(i) / \Delta (\ln t) \), were developed from series of experiments run during the time scales of 0.1 msec to 0.1 sec, 0.3 msec to 0.3 sec, 1 msec to 1 sec, 3 msec to 3 sec, 10 msec to 10 sec and 30 msec to 30 sec. In each time domain, 1000 evenly spaced data points were collected and the interval between points was equal to the minimum time point. This strategy allowed collection of the maximum allowable number of data points per run, and allowed collection of chronoamperometric data over all the time domains available in the BAS chronoamperometry software.

Several chronoamperometric experiments which varied the sensitivity (gain) were run for each time domain. Data could be collected by setting sensitivities increments of \( 10^x \). Figures 2, and 3 demonstrate the effect of sensitivity selection on the chronoamperometric experiments at various time domains using macroelectrodes. Chronoamperometry experiments with 0.1 second run times showed that when the sensitivity is set at \( 1 \times 10^{-6} \) A/V (Figure 2E), the signal is maxed out and reads 0.01 mV throughout the experiment. At the next lowest sensitivity selection (Figure 2D), about 18% of the signal is at the limit, and at the sensitivity set to \( 1 \times 10^{-4} \) A/V (Figure 2C), less than 1% of the signal is over the limit. At sensitivity selections of \( 1 \times 10^{-3} \) (Figure 2B) and \( 1 \times 10^{-2} \) (Figure 2A), the complete experiment is within measurable range. Comparison
Figure 2. CA of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt macroelectrode, run time 0.0001 s to 0.1 s, $\Delta E$ = 0.6 V to -0.1 V vs Ag/AgCl. Sensitivities are (A) $1 \times 10^{-2}$ A/V, (B) $1 \times 10^{-3}$ A/V, (C) $1 \times 10^{-4}$ A/V, (D) $1 \times 10^{-5}$ A/V, and (E) $1 \times 10^{-6}$ A/V.
Figure 3. CA of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt macroelectrode, run time 0.001 s to 1 s, \( \Delta E = 0.6 \text{ V} \) to -0.1 V vs Ag/AgCl. Sensitivities are (A) $1\times10^{-2}$ A/V, (B) $1\times10^{-3}$ A/V, (C) $1\times10^{-4}$ A/V, (D) $1\times10^{-5}$ A/V, and (E) $1\times10^{-6}$ A/V.
of Figures 2C to 2E with Figures 3C to 3E show that, as the run time increases, less data is at the upper measurable limit. As the run time is increased, the earliest times for collecting data become longer. Since the current generated at early times of chronoamperometric experiments are mostly due to capacitive current, and the current generated at later times of chronoamperometric experiments is due to Faradaic processes, the trend seen in Figures 2 and 3 are not unexpected. The experiments with longer run times also have initial data collection times that are later, accounting for the detection of smaller currents.

For the experiments with run times of 0.1 seconds, $1 \times 10^{-4}$ A/V (Figure 2C) was selected as the sensitivity. This was done to obtain a signal with the smallest amplitude of digital noise while assuring that at least 95% of the collected current data for each run was within a range recognizable by the BAS system. Using this criteria, $1 \times 10^{-5}$ A/V was selected as the sensitivity for chronoamperometric experiments with run times of 1 second (Figure 3D). Similar trends were seen for microelectrode experiments. Table 1 shows the sensitivity selected for each disk electrode size and experimental time domain.

Data analysis was performed using locally written software on a 486/DX2-66 computer. Calculation of \( \Delta(\ln i)/\Delta(\ln t) \) and smoothing techniques were written using PowerBASIC (Spectra).

**Signature Curve Generation**

The logarithmic signature curve, \( f(t) = \Delta(\ln i)/\Delta(\ln t) \), for the reduction of 1.0 mM ferricyanide at disk macroelectrodes (Figure 4) and microelectrodes (Figure 5) were
TABLE 1
Sensitivities selected for chronoamperometric experiments using macroelectrodes and microelectrodes to study the reduction of ferricyanide

<table>
<thead>
<tr>
<th>Graphite or Platinum Macroelectrode</th>
<th>Carbon Fiber or Platinum Microelectrode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run Time</td>
<td>Sensitivity (A/V)</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>0.1 ms to 0.1 s</td>
<td>$1 \times 10^{-4}$</td>
</tr>
<tr>
<td>0.3 ms to 0.3 s</td>
<td>$1 \times 10^{-4}$</td>
</tr>
<tr>
<td>1 ms to 1 s</td>
<td>$1 \times 10^{-4}$</td>
</tr>
<tr>
<td>3 ms to 3 s</td>
<td>$1 \times 10^{-5}$</td>
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<tr>
<td>10 ms to 10 s</td>
<td>$1 \times 10^{-5}$</td>
</tr>
<tr>
<td>30 ms to 30 s</td>
<td>$1 \times 10^{-5}$</td>
</tr>
<tr>
<td>Run Time</td>
<td>Sensitivity (A/V)</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>0.1 ms to 0.1 s</td>
<td>$1 \times 10^{-7}$</td>
</tr>
<tr>
<td>0.3 ms to 0.3 s</td>
<td>$1 \times 10^{-7}$</td>
</tr>
<tr>
<td>1 ms to 1 s</td>
<td>$1 \times 10^{-8}$</td>
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<td>30 ms to 30 s</td>
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</tbody>
</table>
Figure 4. Chronoamperometry (CA) of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5 M KCl @ pH 3, at a Pt macroelectrode, Sensitivity = $1 \times 10^{-5}$ A/V, $\Delta E = 0.6$ V to -0.1 V vs Ag/AgCl, run time = 3 s: (A) CA current-time transient, (B) $\Delta(\ln i)/\Delta(\ln t)$ calculated using adjacent points from (A) without smoothing.
Figure 5. Chronoamperometry (CA) of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt microelectrode, Sensitivity = $1 \times 10^{-9}$ A/V, $\Delta E = 0.6$ V to -0.1 V vs Ag/AgCl, run time = 30 s: (A) CA current-time transient, (B) $\Delta(\ln i)/\Delta(\ln t)$ calculated using adjacent points from (A) without smoothing.
initially calculated by determining the natural log of the current and time values for each data point collected during a chronoamperometric experiment. The differences between \( \ln(i) \) and \( \ln(t) \) for neighboring points were used to calculate \( \Delta(\ln i)/\Delta(\ln t) \) which was assigned on the time scale to the midpoints of each interval. This method magnifies noise in the data because differences between neighboring points are confounded by digitalization noise levels in the amplitude of the signal which are exaggerated by being divided by a very small number which represents the time interval between points. Thus, a traditional chronoamperometric experiments (Figures 4A and 5A) produce unacceptable logarithmic signature curves (Figures 4B and 5B). Obviously, the purpose of generating \( f(t) = \Delta(\ln i)/\Delta(\ln t) \) is to distinguish between Cottrell, steady state and connecting behaviors. Consequently, the logarithmic signatures should be able to distinguish between \( \Delta(\ln i)/\Delta(\ln t) = -0.5 \) for Cottrell behavior and \( \Delta(\ln i)/\Delta(\ln t) = 0 \) for steady state behavior. Figure 4B shows a range of \( \Delta(\ln i)/\Delta(\ln t) \) from about -50 to +50, and Figure 5B shows a range of \( \Delta(\ln i)/\Delta(\ln t) \) from -11 to +10. Linear regression analysis of the logarithmic signatures in Figures 4B and 5B provide correlation coefficients \( (r^2) \) of \( 3.6 \times 10^{-5} \) for this macroelectrode experiment, and \( 1.3 \times 10^{-4} \) for this microelectrode experiment. This treatment clearly provides unacceptable data since it cannot distinguish between Cottrell behavior, steady state behavior or any connecting behaviors.

**Smoothing Protocol Development**

Other options for managing the experimental data to produce meaningful logarithmic signature curves were explored. Smoothing the experimental data,
TABLE 2
Smoothing and $\Delta(\ln i)/\Delta(\ln t)$ calculation techniques evaluated. Phase 1 smooths original data, Phases 2a or 2b calculate $\Delta(\ln i)/\Delta(\ln t)$, Phase 3 smooths the calculated logarithmic signature.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Smoothing or Calculation Technique</th>
<th>Technique Performed on:</th>
<th>Total Points (N) per Smooth or Calculation Investigated</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Savitzky-Golay</td>
<td>Original Current vs Time experimental data</td>
<td>0, 7, 11, 15, 21, or 25</td>
<td>Linear/quadratic least squares fit</td>
</tr>
<tr>
<td>2a</td>
<td>Interval $\Delta(\ln i)/\Delta(\ln t)$</td>
<td>Current vs Time data smoothed in Phase 1</td>
<td>2, 10, 25, 50, or 100</td>
<td>Calculates sliding $\Delta(\ln i)/\Delta(\ln t)$ with midpoint = N/2</td>
</tr>
<tr>
<td>2b</td>
<td>Interval skip $\Delta(\ln i)/\Delta(\ln t)$</td>
<td>Current vs Time data smoothed in Phase 1</td>
<td>10, 25, 50 or 100</td>
<td>Calcs $\Delta(\ln i)/\Delta(\ln t)$ deleting points not used in calcs with midpoint = N/2</td>
</tr>
<tr>
<td>3</td>
<td>Savitzky-Golay</td>
<td>$\Delta(\ln i)/\Delta(\ln t)$ vs Time data calculated by Phase 2a or 2b</td>
<td>0, 7, 15, or 25</td>
<td>Linear/quadratic least squares fit</td>
</tr>
</tbody>
</table>
smoothing the calculated logarithmic signature, and various methods of calculating $\Delta (\ln i)/\Delta (\ln t)$ were investigated. Table 2 contains a summary of the smoothing and calculation techniques which were evaluated.

Various smoothing algorithms were considered as candidates, with certain requirements placed on the smoothing optimization process. The smoothed data should be based on the best fit to the original data. As much data as possible must be conserved so that maximum overlap of data sets from consecutive time domains could be maintained and so that the electrode behaviors between and surrounding the Cottrell and steady state regions can be observed. Most importantly, visual inspection of the logarithmic signature should be able to distinguish the characteristic chronoamperometric time domains for Cottrell or steady state behavior. There was also a desire not to distort the logarithmic signature so that the time regimes for important chronoamperometric behaviors are not shifted.

The Savitzky-Golay smoothing algorithms were selected as the preferred smoothing technique because they perform linear and quadratic regression analysis on segments of data and predict the best-fit center point for each data segment. The first/second order Savitzky-Golay algorithms (BASIC program SMOOTH02.BAS, Appendix 1) were chosen because it was assumed that the curvature of $\Delta (\ln i)/\Delta (\ln t)$ within each time domain was minimal and thus could be best estimated by first order or second order algorithms. The smoothing algorithms outlined in Table 2 as Phase 1 were performed on the original current-time results shown in Figures 4A and 5A followed by calculation of $\Delta (\ln i)/\Delta (\ln t)$ using sequential points (BASIC program DLNILNT2.BAS,
Figure 6. Logarithmic signature of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt macroelectrode, Sensitivity = $1 \times 10^{-5}$ A/V, $\Delta E = 0.6$ V to -0.1 V vs Ag/AgCl, run time = 3 s, with Savitzky-Golay (A) 7 point, (B) 11 point, (C) 15 point, (D) 21 point, and (E) 25 point linear/quadratic smooth of data represented in Figure 4A followed by calculation of $\Delta (\ln i)/\Delta (\ln t)$ using adjacent points.
Figure 7. Logarithmic signature of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt microelectrode, Sensitivity = $1 \times 10^{-9}$ A/V, $\Delta E = 0.6$ V to -0.1 V vs Ag/AgCl, run time = 30 s, with Savitzky-Golay (A) 7 point, (B) 11 point, (C) 15 point, (D) 21 point, and (E) 25 point linear/quadratic smooth of data represented in Figure 5A followed by calculation of $\Delta(ln i)/\Delta(ln t)$ using adjacent points.
Appendix 2). The BAS data collection system records time in milliseconds for some experiments, but not for others. Therefore, the recorded times for many data sets were first converted to seconds prior to any further calculations (BASIC program MSECSEC.BAS, Appendix 3). Figures 6 and 7 show the results of the various smoothing operations on the logarithmic signatures from macroelectrode and microelectrode experiments. In general, smoothing of the original data produces logarithmic signatures with less noise. More specifically, increasing the number of points used in the smoothing calculation decreases the noise in the logarithmic signature, which can be seen by the progressively smoother logarithmic signatures in Figures 6 and 7. However, Figures 6E and 7E show that even the 25 point Savitzky-Golay smoothing method did not produce acceptable results where the chronoamperometric time domains could be distinguished. Thus, subsequent changes in the method of calculating $\Delta(\ln i)/\Delta(\ln t)$ were required to obtain meaningful logarithmic signatures, and the calculations outlined as Phases 2a and 2b in Table 2, were investigated.

Sliding interval (Table 2, Phase 2a) and interval skip (Phase 2b) algorithms with various point spreads were used to calculate $f(t) = \Delta(\ln i)/\Delta(\ln t)$. As with the Savitzky-Golay smoothing techniques, the center point of each interval was assigned the newly calculated $\Delta(\ln i)/\Delta(\ln t)$ values. Since the most aggressive smooth in Phase 1 had not produced a meaningful logarithmic signature, all the calculations in Phase 2a or Phase 2b were performed on data previously smoothed using the 25 point Savitzky-Golay linear/quadratic method.

The sliding interval method was performed by calculating $f(t) = \Delta(\ln i)/\Delta(\ln t)$
Logarithmic signature of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt macroelectrode, Sensitivity = 1×10$^{-5}$ A/V, ΔE = 0.6 V to -0.1 V vs Ag/AgCl, run time = 3 s, original data with (A) 10 point, (B) 25 point, (C) 50 point, and (D) 100 point sliding interval calculations of Δ(ln i)/Δ(ln t).
Figure 9. Logarithmic signature of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt microelectrode, Sensitivity = $1 \times 10^{-9}$ A/V, $\Delta E = 0.6$ V to -0.1 V vs Ag/AgCl, run time = 30 s, original data with (A) 10 point, (B) 25 point, (C) 50 point, and (D) 100 point sliding interval calculations of $\Delta (\ln i)/\Delta (\ln t)$. 

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using two data points separated by either 10, 25, 50 or 100 points followed by a subsequent similar calculation sliding to adjacent points. Thus, the first logarithmic signature point is calculated by using the first and tenth points, and the second logarithmic signature point is calculated by using the second and eleventh points. The BASIC program used to perform this calculation, DLNT3.BAS, is in Appendix 4.

Figures 8 and 9 show the results for a macroelectrode and a microelectrode experiment, respectively. Each frame in Figures 8 and 9 show two dotted lines, one for \( f(t) = \frac{\Delta (\ln i)}{\Delta (\ln t)} = 0 \) and one for \( f(t) = -0.5 \). For both the macroelectrode and microelectrode experiments, a 10 point sliding interval (Figures 8A and 9A) on original data is not enough to distinguish between Cottrell and steady state behavior. As the interval is increased to 100 points (Figure 8D) for the macroelectrode experiments, it can be seen that the time domain of a 3 second run is near Cottrell behavior, where \( f(t) = -0.5 \). This data still has significant noise such that \( f(t) \) ranges from -0.6 to -0.25. Thus, it could be difficult to use other time domains to graphically visualize connecting behaviors between Cottrell and steady state behavior. With the chosen microelectrode experiments, it becomes obvious that the experimental time domain is near steady state behavior starting with 25 point sliding interval calculations (Figure 9B). With the use of 100 point sliding intervals (Figure 9D), it appears that the noise in the logarithmic signature is reduced to an acceptable level where it might be possible to also observe connecting behaviors.

Based on the macroelectrode data (Figure 8), it is still necessary to obtain further noise reduction if this is to be used as a general method for calculating \( \frac{\Delta (\ln i)}{\Delta (\ln t)} \) for
Figure 10. Logarithmic signature of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt macroelectrode, Sensitivity = $1 \times 10^{-5}$ A/V, $\Delta E = 0.6$ V to -0.1 V vs Ag/AgCl, run time = 3 s, original data with (A) 7 point, (B) 11 point, (C) 15 point, (D) 21 point, and (E) 25 point Savitzky-Golay smooth, all followed by 100 point sliding interval calculations of $\Delta (\ln i)/\Delta (\ln t)$. 
Figure 11. Logarithmic signature of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt microelectrode, Sensitivity = 1×10$^9$ A/V, ΔE = 0.6 V to -0.1 V vs Ag/AgCl, run time = 30 s, original data with (A) 7 point, (B) 11 point, (C) 15 point, (D) 21 point, and (E) 25 point Savitzky-Golay smooth, all followed by 100 point sliding interval calculations of $\Delta(\ln i) / \Delta(\ln t)$. 

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all data sets. Figures 10 and 11 show the results of using the 100 point sliding interval method on data smoothed using different intervals. Both sets demonstrate that the logarithmic signature becomes smoother when the 100 point sliding interval calculation of $\Delta(\ln i)/\Delta(\ln t)$ is performed on smoothed data. For this microelectrode experiment (Figure 11), it appears that the data manipulation is complete and it is obvious that this time domain is in the steady state region. There is still some noise in the logarithmic signature of for the macroelectrode experiment (Figure 10) even with the 25 point smooth on the original data.

The sliding interval method uses all points in the smoothed data set for the logarithmic signature calculation. However, the method shortens the time domain actually plotted because it attributes the calculation of $\Delta(\ln i)/\Delta(\ln t)$ to the midpoint of each interval. This is demonstrated as fewer plotted points at the beginning and end of each data set as the interval is increased (Figures 8A→8D and 9A→9D).

As an alternative to the sliding interval method, an interval skip method (Table 2, Phase 2b) was also investigated. This method calculates $\Delta(\ln i)/\Delta(\ln t)$ using the data points separated by the defined interval. It is different from the sliding interval method in that the calculations do not use all points. As an example, for a 10 point interval skip, the first calculation of $\Delta(\ln i)/\Delta(\ln t)$ uses data from the first and tenth points. However, the second calculation uses the eleventh and twentieth points. The results of Phase 2b calculations are shown in Figures 12 through 15. The 10, 25, 50 and 100 point interval skip method was used to calculate $f(t) = \Delta(\ln i)/\Delta(\ln t)$ on the same original current-time data for the macroelectrode (Figure 12) and microelectrode (Figure 13) experiments.
Figure 12. Logarithmic signature of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt macroelectrode, Sensitivity = $1 \times 10^{-5}$ A/V, $\Delta E = 0.6$ V to -0.1 V vs Ag/AgCl, run time = 3 s, original data with (A) 10 point, (B) 25 point, (C) 50 point, and (D) 100 point interval skip calculations of $\Delta \ln i/\Delta \ln t$. 
Figure 13. Logarithmic signature of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt microelectrode, Sensitivity = $1 \times 10^4$ A/V, $\Delta E = 0.6$ V to -0.1 V vs Ag/AgCl, run time = 30 s, original data with (A) 10 point, (B) 25 point, (C) 50 point, and (D) 100 point interval skip calculations of $\Delta (\ln i)/\Delta (\ln t)$. 
Figure 14. Logarithmic signature of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt macroelectrode, Sensitivity = $1 \times 10^{-5}$ A/V, $\Delta E = 0.6$ V to -0.1 V vs Ag/AgCl, run time = 3 s, original data with (A) 7 point, (B) 11 point, (C) 15 point, (D) 21 point, and (E) 25 point Savitzky-Golay smooth all followed by a 25 point interval skip calculation of $\Delta (\ln i)/\Delta (\ln t)$. 

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Figure 15. Logarithmic signature of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt microelectrode, Sensitivity = $1 \times 10^9$ A/V, $\Delta E = 0.6$ V to -0.1 V vs Ag/AgCl, run time = 30 s, original data with (A) 7 point, (B) 11 point, (C) 15 point, (D) 21 point, and (E) 25 point Savitzky-Golay smooth all followed by a 25 point interval skip calculation of $\Delta(\ln i)/\Delta(\ln t)$. 

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With the microelectrode experiments, it appeared that the 25 point interval skip (Figure 13B) effectively demonstrated that the system was at steady state. For the macroelectrode experiments, only the 100 point interval skip method (Figure 12D) seemed to show that the \( f(t) \) was at -0.5.

Since the 25 point interval skip method provided some useful data for the microelectrode experiment, it was studied further and some results are shown in Figures 14 and 15. In these figures, the 25 point interval skip method of calculating \( f(t) \) was performed on previously smoothed data. As with the sliding interval method, this set of microelectrode results was improved with the use of only a 7 point smooth on the original data (Figure 15A). However, the macroelectrode experiment required either the 21 point or 25 point smooth followed by the 25 point interval skip method (Figure 14D and 14E). This appeared to have more noise associated with it than did the 100 point sliding interval (Figure 10D and 10E). The 100 point, 50 point, 25 point and 10 point interval skip methods used just 2\%, 4\%, 8\% and 20\%, respectively, of the original data points to calculate the logarithmic signature. It appeared from these sets of data that the 25 point interval skip method might produce readable logarithmic signatures, but with so much data not included in the calculations, it did not seem reasonable to continue considering this technique.

Because the 100 point sliding interval on smoothed current-time data appeared as the best candidate for calculating the logarithmic signature, it was studied further. For the macroelectrode experiments, this produced a logarithmic signature with some bounce in the data, which subsequent smoothing could reduce. Therefore, Phase 3 (Table 2),
smoothing of the calculated logarithmic signature, needed to be considered. Figures 16
and 17 show the effects of smoothing subsequent to calculation of $\Delta(\ln i)/\Delta(\ln t)$. The
macroelectrode (Figure 16) and microelectrode (Figure 17) data were originally smoothed
with a 25 point interval followed by calculation of $f(t)$ using the 100 point sliding
interval. In these two figures, the 7 point (frame B), 15 point (frame C) and 25 point
(frame D) final smoothing algorithms are compared to the data without the final smooth
(frame A). For the macroelectrode experiment, the additional final smoothing helped to
show that this data set starts out with $\Delta(\ln i)/\Delta(\ln t)$ slightly less than -0.5, and ending at
slightly greater than -0.5. Thus, only a portion of this data set is in the Cottrell time
domain. For the microelectrode experiments, the additional smoothing does not
significantly change the appearance of the logarithmic signature. Therefore, the final
choice of a method for calculating $f(t) = \Delta(\ln i)/\Delta(\ln t)$ consists of an initial 25 point
smooth on the experimentally generated current-time data, followed by the 100 point
sliding interval method to calculate $f(t)$, with a final 25 point smooth on the calculated
$f(t)$.

Results and Discussion

Chronoamperometry of Ferricyanide Reduction and Logarithmic Signatures

The selected technique for generating $\Delta(\ln i)/\Delta(\ln t)$ signature curve for the
reduction of Fe(CN)$_6^{3-}$ was performed on data collected from experiments over the
several time domains described previously. The generated results from experiments
Figure 18. Logarithmic signatures of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt macroelectrode, run at sensitivities listed in Table 1, calculated using initial 25 point smooth on current-time data, 100 point sliding interval calculation of $\Delta (\ln i)/\Delta (\ln t)$ and final 25 point smooth for run times of (A) 0.1 s, (B) 0.3 s and (C) 1 s.
Figure 19. Logarithmic signatures of 1.0 mM Fe(CN)₆³⁻ in 0.5M KCl @ pH 3, at a Pt macroelectrode, run at sensitivities listed in Table 1, calculated using initial 25 point smooth on current-time data, 100 point sliding interval calculation of $\Delta(\ln i)/\Delta(\ln t)$ and final 25 point smooth for run times of (A) 3 s, (B) 10 s and (C) 30 s.
using a platinum macroelectrode are shown in Figures 18 and 19. Each of the frames in
these figures uses a different time scale, starting with a run time of 0.1 second for Figure
18A to a run time of 30 seconds for Figure 19C. These figures show that Cottrell
conditions occur during the time domain of about one to three seconds (Figure 19A). At
times earlier than that (Figures 18A, 18B and 18C), the $\Delta (\ln i)/\Delta (\ln t)$ results are below
and steadily increase to the Cottrell value of -0.5. These values below -0.5 are probably
due to recovery from capacitive current and double-layer charging. The values after three
seconds (Figures 19B and 19C) seem to increase to slightly above -0.5 with a possible
trend towards steady state conditions. However, the trend could not be clearly
determined since the equipment did not allow significantly longer experiments and the
deviations due to digitization noise are not significantly different than -0.5.

Similar experiments using platinum microelectrodes were analyzed to generate
Figures 20 and 21. These show that the system recovers from capacitive current up to
0.03 seconds followed by electrode behavior between Cottrell and steady state (Figures
20A, 20B, 20C, 21A and 21B). The system appears to be at steady state behavior from
10 to 30 seconds (Figure 21C). None of the experimental time domains are fast enough
to achieve Cottrell behavior with microelectrodes.

While visually analyzing six time domains for each experiment, two issues
develop. First, it is inconvenient to view all the time domains as separate graphs.
Second, is the question of whether or not the $\Delta (\ln i)/\Delta (\ln t)$ results from the time domains
overlap. Thus, the time domains were accumulated on one logarithmic time scale to form
the cumulative logarithmic signature for the reduction of ferricyanide. Figure 22 shows
Figure 20. Logarithmic signatures of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt microelectrode, run at sensitivities listed in Table 1, calculated using initial 25 point smooth on current-time data, 100 point sliding interval calculation of $\Delta(\ln i)/\Delta(\ln t)$ and final 25 point smooth for run times of (A) 0.1 s, (B) 0.3 s and (C) 1 s.
Figure 21. Logarithmic signatures of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a Pt microelectrode, run at sensitivities listed in Table 1, calculated using initial 25 point smooth on current-time data, 100 point sliding interval calculation of $\Delta \ln i/\Delta \ln t$ and final 25 point smooth for run times of (A) 3 s, (B) 10 s and (C) 30 s.
Cumulative logarithmic signatures of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at (A) Pt microelectrode, run over six time domains as in Figures 20 and 21, and (B) Pt macroelectrode, run over six time domains as in Figures 18 and 19. All calculated using initial 25 point smooth on current-time data, 100 point sliding interval calculation of $\Delta (\ln i)/\Delta (\ln t)$ and final 25 point smooth for each run time.
this cumulative logarithmic signature for the data presented above. Curve A is the cumulative logarithmic signature using a platinum disk microelectrode, and Curve B is the cumulative logarithmic signature using a platinum disk macroelectrode. As seen with the individual curves in Figures 18 and 19, the macroelectrode experiments (Curve B) reach Cottrell behavior between 1 and 3 seconds, with earlier times having \[ \frac{\Delta(\ln i)}{\Delta(\ln t)} < -0.5 \] and later times having \[ \frac{\Delta(\ln i)}{\Delta(\ln t)} > -0.5. \] Also as expected from the individual curves in Figures 20 and 21, the microelectrode experiments (Curve A) reach steady state behavior from 10 to 30 seconds, and the majority of the time before that is in a region between Cottrell and steady state behaviors. For both sets of data, there is excellent overlap of consecutive time domains. Interestingly, the cumulative logarithmic signature for the microelectrode experiments shows an local minimum from about 0.1 to 1 second within the intermediate range between the Cottrell and steady state regions. The reason for this behavior in this region was not investigated.

Figure 23 shows the cumulative logarithmic signature for the reduction of ferricyanide at a carbon fiber disk microelectrode (Curve A) and at a glassy carbon disk macroelectrode (Curve B). As with the platinum electrode experiments, the time domains overlap. However, even with use of the aggressive smoothing algorithm discussed previously, the logarithmic signatures are not as smooth as with the platinum electrode experiments. Still, the trends in the cumulative logarithmic signatures can be observed. Neither the macroelectrode nor microelectrode cumulative logarithmic signatures show the high negative values less than -0.5. Thus, it appears that recovery from capacitive current occurs earlier with the carbon based electrodes. As with the platinum
Cumulative logarithmic signatures of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at (A) carbon fiber disk microelectrode, run over six time domains, and (B) graphite disk macroelectrode, run over six time domains. All calculated using initial 25 point smooth on current-time data, 100 point sliding interval calculation of $\Delta(ln \, i)/\Delta(ln \, t)$ and final 25 point smooth for each run time.
Figure 24. Cumulative logarithmic signatures of 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at (A) platinum disk microelectrode, run over six time domains, and (B) platinum disk macroelectrode, run over six time domains (both different electrodes than in Figure 22). All calculated using initial 25 point smooth on current-time data, 100 point sliding interval calculation of $\Delta(\ln i)/\Delta(\ln t)$ and final 25 point smooth for each run time.
The Cottrell region for the reduction of ferricyanide using a glassy carbon macroelectrode is between 1 and 3 seconds, and the steady state region using a carbon fiber microelectrode is from 10 to 30 seconds. The carbon fiber microelectrode experiments also show a local minimum in the intermediate region between Cottrell and steady state behaviors, however this region is from 0.03 to 1 second, which is a longer time period than with use of a platinum microelectrode. The cumulative logarithmic signature for the reduction of ferricyanide using platinum macro- and microelectrodes were confirmed using different electrodes of similar size (Figure 24).

The cumulative logarithmic signatures can be interpreted as unique for each specific mechanism, and will be discussed in Chapter 4. As discussed above, they can also be used to define analytic regions for running chronoamperometric experiments, such as the Cottrell region and the steady state region. Using an alternate plotting method for the cumulative logarithmic signature, it is possible to determine the \( \tau \) values, where \( \tau = \frac{4D\ln t}{r^2} \), for the reduction of ferricyanide run using a microelectrode under the specific experimental conditions run for these studies. Figure 25 shows a plot of the cumulative logarithmic signature with respect to \( \tau \). It shows that the steady state region, which occurred from 10 to 30 seconds, is equivalent to \( \tau = 1200 \) to 2600. At earlier values of \( \tau \), such as 55 as suggested by Baur and Wightman57 and 3.2 as suggested by Hepel and Osteryoung64, the cumulative logarithmic signature shows that this specific experimental system is not at steady state. In Chapter 4, a possible reason for the unanticipated requirement for \( \tau \) values as compared to those used by other investigators will be discussed.
Figure 25. Cumulative logarithmic signatures versus $\tau$ for 1.0 mM Fe(CN)$_6^{3-}$ in 0.5M KCl @ pH 3, at a platinum disk microelectrode (same as in Figure 24A), run over six time domains, and calculated using initial 25 point smooth on current-time data, 100 point sliding interval calculation of $\Delta \ln i/\Delta \ln t$ and final 25 point smooth for each run time.
Measurement of Electrode Sizes

The steady state region for the microelectrode studies and the Cottrell region for the macroelectrode systems are obvious from the $\Delta(\ln i)/\Delta(\ln t)$ signature curves. These signature curves relate the experimental conditions necessary for the system to remain in regions where the most information can be obtained.

From evaluation of Figures 22, 23, and 24, ferricyanide reduction experiments to determine platinum and glassy carbon macroelectrode sizes were run from 3.0 msec to 3.0 sec. Unsmoothed data from 1.0 sec to 3.0 sec were evaluated assuming Cottrell behavior and using Equation (2.1). Macroelectrode sizes were determined from the slopes of current vs. $t^n$, with $C_0$ equal to 0.998 mM and $D$ equal to $7.17\times10^{-6}$ cm$^2$s$^{-1}$. The correlation coefficients for these unsmoothed lines had values of $0.996 \leq r^2 \leq 0.9997$. Electrode sizes calculated previously, determined during time domains determined from inspection of cumulative logarithmic signatures, and from use of the RAM Optics are presented in Table 3.

The data from the chronoamperometric experiments using the platinum disk electrodes (electrodes PA and PB) correlate well with the optically generated data. The chronoamperometric results for the glassy carbon disk sizes (electrodes CB and CC) seem to have a low bias when compared to the optically generated data, but are consistent and different than the electrode sizes determined previously. For the glassy carbon macroelectrode measurements, the initially calculated diameters were calculated from experiments at run times of 30 seconds. Evaluation of the logarithmic signatures show
<table>
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<th>Electrode</th>
<th>Supplier's Listed Diameter</th>
<th>Initial Calculated Diameter</th>
<th>Final Calculated Diameter</th>
<th>Microscopic Diameter</th>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>PA</td>
<td>1 mm</td>
<td>---</td>
<td>1.61 mm</td>
<td>1.657 ± 0.0021 mm</td>
</tr>
<tr>
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<td>---</td>
<td>1.77 mm</td>
<td>1.664 ± 0.0083 mm</td>
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<td>---</td>
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<td>---</td>
</tr>
<tr>
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<td>10 μm</td>
<td>---</td>
<td>10.15 μm</td>
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<td><strong>Carbon</strong></td>
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<td>2.75 mm</td>
<td>3.002 ± 0.033 mm</td>
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<td>3.12 mm</td>
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<td>C1</td>
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<td>0.53 μm</td>
<td>8.25 μm</td>
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<tr>
<td>C2</td>
<td>9 - 13 μm</td>
<td>0.86 μm</td>
<td>10.59 μm</td>
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</tr>
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</table>

*a* Obtained from chronoamperometric experiments with run times determined empirically or based on \( \tau > 55 \).

*b* Obtained from chronoamperometric experiments with run times determined from logarithmic signatures.

*c* Microscopic Diameter determined only for macroelectrodes (PA, PB, CB, CC) using RAM Optics dimension analysis system.
that there is a slight deviation from Cottrell behavior at this run time and that the most appropriate run time should be between 1 and 3 seconds. Thus, the platinum macroelectrode sizes are very close to the microscopically measured sizes, and possibly more accurately represent the apparent size of the glassy carbon macroelectrodes, even though there appears to be a low bias.

Ferricyanide reduction experiments to determine platinum and carbon fiber microelectrode sizes were run from 30 msec to 30 sec. As with the macroelectrode data, unsmoothed data could be used, but for these experiments, from the 10 sec to 30 sec region. The intercepts of these data sets were evaluated assuming steady state behavior using Equation (2.2). The calculated electrode diameters are compared to the diameters reported by the supplier in Table 3. These electrodes were too small to be measured by the optical systems available. The data from the chronoamperometric experiments using the platinum disk microelectrodes (electrodes P1 and P2) and the carbon fiber microelectrodes (electrodes C1 and C2) correlate well with the supplier's estimates. It is also clear that the results from the carbon fiber disks based on the time domain selected from investigation of the logarithmic signatures are much closer to the electrode sizes reported by the supplier than the initial electrode sizes determined from experiments with time domains selected based on keeping $\tau$ slightly greater than 55.
Conclusions

Ferricyanide reduction, which is an electrochemically reversible system, was used to develop the method for developing cumulative logarithmic signatures. These logarithmic signatures identify Cottrell, steady state, capacitive current recovery, and intermediate behaviors. To overcome digitalization noise and amplification of that noise by dividing by small $\Delta t$, an aggressive smoothing and logarithmic signature calculation technique was developed. The sizes of microelectrodes and macroelectrodes were determined prior to the development of the logarithmic signature and found to be inaccurate. The sizes were recalculated based on experiments determined to be within Cottrell and steady state regions by evaluation of logarithmic signatures. The greatly improved accuracy of the results validated the use of logarithmic signatures to determine chronoamperometrically analytic time domains.
SHORT-TERM CHRONOAMPEROMETRIC SCREENING OF CHLORPROMAZINE-PACKAGE INTERACTIONS

Introduction

The electrochemical method for generating adsorption isotherms developed by Unwin and Bard\textsuperscript{45} used a two electrode system, with a microelectrode as the working electrode, to measure the loss of methylene blue from 10 µl drops placed on various graphite crystal surfaces. Because the method did not include a reference electrode, loss from solution was determined by decreases in the diffusion limited current generated by a single potential step. The losses of methylene blue were measured in the time scale of hours. The methylene blue loss rates were related to the hydrophilic/hydrophobic character of the graphite crystal face.

It was hypothesized that a significant increase in the ratio of the packaging material surface area to the drug solution volume would increase the apparent rate of sorption. This would provide a means of observing absorption or adsorption interactions of drug with packaging materials in a shorter time span than with the normal long term stability study. This hypothesis is supported by Equations 1.8 and 1.9, which show that, during absorption, the surface-to-volume ratio is inversely proportional the amount of solute remaining in solution.

Unwin and Bard's method for electrochemically determining the adsorption isotherm was employed as the method for measuring loss of a drug from solution over
several days. To control the volume of the drop, however, a three electrode system was employed. This was small enough to fit into a small drop in order to provide the capability of making accurate concentration measurements that can be compared with data generated on several different days, weeks, or months.

Because the oxidation of chlorpromazine HCl (CPZ) was selected for proof of principle, this method would have the additional complications occurring from the kinetically complicated oxidation mechanism of CPZ. Even with a kinetically complicated mechanism, it was hypothesized that currents generated from time domains where current is proportional to $t^{1/2}$ or where current has no time dependence, then the Cottrell (Equation 2.1) and steady state (Equation 2.2) estimations, respectively, could be used to accurately determine CPZ solution concentrations. Thus, it was expected that logarithmic signatures would be able to identify Cottrell and steady state behavior for CPZ oxidation.

**Theory**

**Potential Step Methods**

Analysis of oxidation and reduction electrode processes is often complicated by subsequent chemical reactions. Non-electrochemical methods, including spectroscopic methods, are often used to elucidate reaction mechanisms and determine rate constants. Cyclic voltammetry is a technique often used as a qualitative method for understanding
complex electrode processes. The shape of cyclic voltammograms can be confounded by the rate of the follow-up chemical reaction, the rate of heterogeneous electron transfer, the charging of the electric double layer, uncompensated resistance, and inadequate potential control.⁶⁶

Potential step methods reduce the effects of the confounding factors present with sweep voltammetry methods. A single potential step (Figure 26A) produces a resultant current transient (Figure 26B) which is characterized by high current levels early in the transient followed by current due to Faradaic processes. The initially high current is attributed to the electrolysis of material in the vicinity of the electrode and to the capacitive current from double layer charging. Traditionally, potential step methods have been used to analytically evaluate the parameters in the Cottrell and steady state equations, and to evaluate rate constants by choosing voltage jumps which produce steady state or Cottrell behavior.

Potential step experiments over several time domains, including those time domains outside of steady state or Cottrell behavior, can be used to compute the logarithmic signature, \( f(t) = \Delta \ln i / \Delta \ln t \), as discussed in Chapter 2. It has been suggested that each rate limiting process produces a unique logarithmic signature.⁵⁶
Figure 26. Chronoamperometry of 1.0 mM Fe(CN)$_6$$^{3-}$ in 0.5M KCl @ pH 3, at a platinum disk macroelectrode: (A) Potential step from 600 mV to -100 mV and (B) resultant current.
Chlorpromazine HCl Oxidation

Chlorpromazine HCl is a drug classed as a phenothiazene used mainly as a sedative.

The oxidation of chlorpromazine HCl (CPZ) is nonreversible, as demonstrated by its cyclic voltammogram in Figure 27. The first oxidation occurs at 0.68V vs SCE and the second oxidation occurs at 1.2 V vs SCE. A small reduction peak occurs at 0.55 V vs SCE. The same reduction peak occurs when the oxidation is limited to the first oxidation step. The oxidation of chlorpromazine has been well studied, with Richards and Bard\textsuperscript{67} reporting electrochemiluminescence associated with the second oxidation.

Two mechanisms were previously proposed for the reactions following the first oxidation step of chlorpromazine. The Disproportionation Mechanism, proposed by Merkle and Discher, was studied in highly acidic conditions.\textsuperscript{51} An alternative mechanism is the Buffer Interaction mechanism proposed by McCreery, \textit{et. al.}, which describes the nonreversible chlorpromazine oxidation mechanism in the presence of buffer.\textsuperscript{53} Both mechanisms propose that, for every two CPZ molecules consumed by oxidation, one CPZ is reformed and two CPZ\textsuperscript{+} are consumed.

Whether the oxidative mechanism of CPZ includes the disproportionation mechanism, the buffer interaction mechanism, or a combination of mechanisms, it is clear
Figure 27. Cyclic voltammetry of 2.8 mM CPZ in 0.25M acetate buffer @ pH 6, at a platinum disk macroelectrode, v = 0.05 V/s.
that the oxidation of CPZ is not reversible. For chronoamperometric studies at macroelectrodes, the Cottrell equation assumes that the electrode process is reversible. The Shoup and Szabo equation, which describes the full range of processes for chronoamperometric studies at microelectrodes, also assumes reversibility. The question for chlorpromazine HCl oxidation was whether or not time domains exist where the resultant current is proportional to the concentration of CPZ. Even though CPZ oxidation is not reversible, it was hypothesized that time domains which have apparent Cottrell behavior or steady state behavior, as indicated by $\Delta \frac{\ln i}{\Delta \ln t} = -0.5$ or 0, respectively, would be time domains during which the resultant current is proportional to the CPZ bulk concentration.

**Methods**

**Materials** - All chemicals were used as received from commercial sources. Chlorpromazine HCl (Aldrich), CPZ, was 98% pure as per certificate of analysis. The supporting electrolyte for chlorpromazine experiments was prepared using Milli-Q filtered water, sodium acetate, trihydrate (Baker Reagent grade) and glacial acetic acid (HPLC grade, Fisher).

The pretreatment for carbon electrodes was immersion in 0.1 N NaOH (Mallinkrodt) for at least one minute. This was to assure that current response was consistent between runs. As demonstrated in Figure 28, soaking the carbon electrodes in acidic (Figure 28A) or neutral solutions (Figure 28B) changed electrode behavior for consecutive cyclic voltammetry (CV) experiments. However, soaking the carbon
Figure 28. Cyclic voltammetry of 2.8 mM CPZ in 0.25M acetate buffer @ pH 6, at a platinum disk macroelectrode, $v = 50 \text{ V/s}$. Sequential runs after soaking glassy carbon working electrode with (A) pH 4, (B) pH 7, or (C) pH 10 standard buffer solutions between each run.
electrodes in basic solution provided consistent responses from CV experiments (Figure 28C). Since the CPZ test solutions were standardized at pH 6, electrodes were soaked in pH 10 buffer for one minute prior to each chronoamperometric experimental run.

The packaging materials used as solid substrates for determining CPZ sorption interactions, as well as the surface areas and internal package surface area-to-CPZ volume ratios, are described in Table 4. The chosen packaging materials are commonly used for shelf packages or IV administration. Glass was selected as a reference material that does not interact with CPZ. Also listed in Table 4 are the interior surface areas of each package which was in contact with the CPZ test solution during the large volume stability experiments. The surface/volume ratios calculate in the last column of Table 4 were derived from the fill volume used in the large volume experiments described herein.

**Small Volume Experiments** - The small volume sample cell using a three electrode setup, which was developed for the small volume experiments and was based on the two electrode cell design described by Unwin and Bard, is shown in Figure 29. The cell was blown from a glass tube and designed to fit the top of a commercial sample cell (Bioanalytical Systems, Inc. (BAS), West Lafayette, IN). The working, reference and auxiliary electrodes were shaped to fit into a 40 μl drop of solution placed on an 6.74 mm diameter disk cut from actual package materials using a size 3 cork borer. This provided a surface to volume ratio of 8.92 cm⁻¹, which is one order of magnitude larger than for the large volume studies (Table 4, last column). The tip of the SCE reference electrode was extended to 1 mm o.d. and a piece of cotton was placed in the tip. The platinum wire electrode (BAS) was cut and bent to reach the drop. The working
Table 4
Packaging Materials

<table>
<thead>
<tr>
<th>Material</th>
<th>Material Description</th>
<th>Surface (cm²)</th>
<th>Surface/Volume&lt;sup&gt;a&lt;/sup&gt; (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>Polypropylene with colorant and with stearates as lubricants</td>
<td>53.4</td>
<td>1.53</td>
</tr>
<tr>
<td>PVC</td>
<td>PVC plasticized with bis-2-ethylhexyl phthalate (Viaflex from Baxter)</td>
<td>428</td>
<td>0.76</td>
</tr>
<tr>
<td>EVA</td>
<td>Ethylene vinyl acetate (Clintec)</td>
<td>477</td>
<td>0.86</td>
</tr>
<tr>
<td>PET</td>
<td>Polyethylene terephthalate, extruded</td>
<td>109</td>
<td>0.95</td>
</tr>
<tr>
<td>HDPE (Semi-opaque)</td>
<td>High density polyethylene semi-opacified with TiO₂ and lubricated with stearates</td>
<td>153</td>
<td>1.09</td>
</tr>
<tr>
<td>HDPE (Opaque)</td>
<td>High density polyethylene, opacified with TiO₂ and lubricated with stearates</td>
<td>185</td>
<td>0.92</td>
</tr>
<tr>
<td>Glass&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Borosilicate glass</td>
<td>62</td>
<td>1.24</td>
</tr>
</tbody>
</table>

<sup>a</sup> Small volume experiments used 6.74 mm diameter disks cut from each of these packaging materials. Small volume surface/volume is 8.92 cm⁻¹.

<sup>b</sup> Glass disks for small volume experiments were ground to size with a diamond file.
Figure 29. Small volume cell.

Solid substrate disk with 40 μL drop
electrode (BAS) was a carbon fiber disk microelectrode with a nominal diameter of 9 - 13 µm. The distance of the working electrode from the top of the solid substrate was set to about 0.15 mm manually. The glass surrounding this electrode, initially 3 mm x 4 mm o.d. oval, was filed down to 1.0 mm x 1.5 mm o.d. using diamond roughing and polishing files. The solid substrate was placed on a sample holder using double sided tape. The oval sample holders were used to ease the solid substrate disk insertion and removal from the small volume cell. All microelectrode experiments were run in a Faraday cage.

Forty microliter drops of CPZ solutions were placed on solid substrate disks attached to sample holders. The disks were stored at room temperature away from light in 93% relative humidity chambers prepared with saturated solutions of NH₄H₂PO₄. Enough samples were prepared so that three samples of each CPZ concentration on each substrate could be sampled daily. Due to evaporation which was accelerated by the Kelvin Effect, the samples lost water and were replenished daily with 10 µl of water. At lower humidities (76% RH using saturated sodium acetate, NaC₂H₃O₂, or 37% using saturated magnesium chloride, MgCl₂), the daily loss was about 25 µl of water daily. At 100% humidity, small temperature changes caused rain in the chamber which unpredictable changes in water loss or gain for each 40 µl sample drop. Each sample was weighed before and after storage to correct for changes in water content. Samples were placed in the small volume cell, the electrodes were placed into the CPZ drop and the chronoamperometric electroanalytical method was run.

Large Volume Experiments - Chlorpromazine HCl solutions were also tested during storage in the original packages. Solutions were prepared to the same
specifications as the solutions in the small volume experiments. Chronoamperometric experiments for the large volume experiments also used a three electrode setup with a platinum wire auxiliary electrode and SCE reference electrode (BAS). Most experiments were run with carbon fiber disk microelectrodes similar to those used in the small volume experiments, but with the original glass sheath intact. Some experiments used a platinum disk microelectrode with a 10 μm diameter as the working electrode.

**Electrochemical methods and Logarithmic Signature Development** - All chronoamperometry and cyclic voltammetry experiments were run using a BAS 100B/W Electrochemical Analyzer with a low current module (BAS). Experimental conditions were set and data was collected using the 12-bit A/D converter and software included in the BAS 100B/W system. Sensitivity (gain), which is available at increments of 10^x, was selected for each experiment by maximizing S/N while ensuring that at least 95% of the data collected was within detectable range for the selected sensitivity. Appropriate experimental time scales for chronoamperometric measurements during steady-state behavior (for microelectrodes) were determined by calculating f(t) = Δ(ln i)/Δ(ln t) for each time domain and observing the cumulative logarithmic signature curve over several overlapping orders of magnitude of time. Data analysis was performed using locally written software on a 486/DX2-66 computer. Calculation of Δ(ln i)/Δ(ln t) and smoothing techniques were written using PowerBASIC (Spectra) programs in Appendices 1 through 4 and described in Chapter 2. Linear least squares best fit calculations for standard curves were performed using Origin 4.1 (Microcal).

Solutions were prepared to contain 2.8 mM and 28 μM chlorpromazine HCL in
0.25M sodium acetate/acetic acid buffer at pH 6.0. This isotonic acetate buffer system was selected because it was reported to provide acceptable stability to CPZ and to have the least solute-buffer interactions. As already seen in Figure 27, the first oxidation is at 0.65 V vs SCE, followed by a second oxidation at 1.2 V vs SCE. The potential jump for chronoamperometry experiments was selected to be from 0.3 V to 0.83 V vs SCE.

The Δ(ln i)/Δ(ln t) signature curve was generated using the method developed in Chapter 2 for ferricyanide reduction. Therefore, multiple experiments run at the time scales of 0.1 msec to 0.1 sec, 0.3 msec to 0.3 sec, 1 msec to 1 sec, 3 msec to 3 sec, 10 msec to 10 sec, and 30 msec to 30 sec and the resulting cumulative logarithmic signature curve was generated.

The cumulative logarithmic signatures for macroelectrode and microelectrode experiments were used to identify the Cottrell and steady state regions, respectively. A standard curve was developed using the steady state time domain for a series of microelectrode chronoamperometric experiments in which the CPZ concentrations varied from 2.8 μM to 2.8 mM. The standard curve and all subsequent electroanalytical experiments were analyzed using Equation (2.5). Each steady state region data segment was plotted as current vs \( r^{1/6} \) from which the intercept \( (4nFDC \cdot r) \) was determined from a linear least squares fit. A typical example of Cottrell Plots, current vs \( r^{1/6} \), for five different CPZ concentrations is shown in Figure 30. Standard curves (Table 5) of the current intercept vs. concentration were generated using the direct proportionality of CPZ concentration to the intercept as shown in Equations 2.2 and 2.5, with a standard curve shown in Figure 31 which uses the intercepts determined from Figure 30.
Figure 30. Cottrell plots for oxidation of (A) 0.02 mg/ml, (B) 0.04 mg/ml, (C) 0.06 mg/ml, (D) 0.08 mg/ml, and (E) 0.1 mg/ml CPZ in 0.25 M acetate buffer @ pH 6, at a carbon fiber microelectrode.
Figure 31. Standard curve with data from Cottrell Plots in Figure 30.
### TABLE 5

Typical Calibration Data Curves for CA of CPZ

<table>
<thead>
<tr>
<th>Micro-Electrode</th>
<th>Sample Cell Volume</th>
<th>Sensitivity&lt;sup&gt;a&lt;/sup&gt; (Amps/M [(\omega)])</th>
<th>Intercept&lt;sup&gt;b&lt;/sup&gt; (Amps [(\omega)])</th>
<th>LOQ (mole/L)</th>
<th>Accuracy (Mean % Recovery of (n) samples)</th>
<th>Precision (% RSD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>40 (\mu)l</td>
<td>(-1.06 \times 10^{-6}) [1.24 \times 10^{-7}]</td>
<td>(-4.71 \times 10^{-11}) [5.39 \times 10^{-12}]</td>
<td>5.09 \times 10^{-4}</td>
<td>100.29 ((n=5))</td>
<td>1.9436</td>
</tr>
<tr>
<td>Carbon</td>
<td>15 ml</td>
<td>(-1.09 \times 10^{-6}) [2.10 \times 10^{-8}]</td>
<td>(-1.50 \times 10^{-11}) [3.92 \times 10^{-12}]</td>
<td>3.58 \times 10^{-4}</td>
<td>104.51 ((n=10))</td>
<td>2.7139</td>
</tr>
<tr>
<td>Platinum</td>
<td>15 ml</td>
<td>(-7.68 \times 10^{-7}) [1.54 \times 10^{-8}]</td>
<td>(-6.64 \times 10^{-11}) [2.72 \times 10^{-12}]</td>
<td>3.55 \times 10^{-4}</td>
<td>100.03 ((n=14))</td>
<td>0.0283</td>
</tr>
</tbody>
</table>

<sup>a</sup> Slope of Current Intercept of Eq (2.5) vs CPZ concentration

<sup>b</sup> Intercept of calibration curve
Results and Discussion

Signature Curve Generation - The cumulative logarithmic signature curves for the oxidation of chlorpromazine HCl at a carbon fiber microelectrode and a glassy carbon macroelectrode was developed by calculating \( \frac{\Delta (\ln i)}{\Delta (\ln t)} \) using the method developed in Chapter 2 for ferricyanide reduction. Thus, the original current-time transients were smoothed using a 25 point least-squares linear/quadratic smooth, followed by the calculation of \( \frac{\Delta (\ln i)}{\Delta (\ln t)} \) over a 100 point sliding interval. This was subjected to final smoothing. The results generated from experiments using a carbon fiber microelectrode are shown in Figure 32, curve A. This shows that closest approach to steady state conditions occur during a time domain of about ten to thirty seconds. At time points earlier than that, the logarithmic signature results are well below zero indicating the approach toward the steady state as \( t \to \infty \). None of the experimental time domains are short enough to measure Cottrell behavior with microelectrodes. Similar experiments using a glassy carbon disk macroelectrode were analyzed to generate curve B in Figure 32. With this macroelectrode, the system achieves Cottrell behavior from about 0.05 sec to 0.1 sec. Prior to that, the \( \frac{\Delta (\ln i)}{\Delta (\ln t)} \) signature is below -0.5, a value indicative of the recovery from non-Faradaic processes (double layer charging and/or potentiostat rise-time). After 0.1 seconds, the \( \frac{\Delta (\ln i)}{\Delta (\ln t)} \) signature is in the region between steady state and Cottrell behavior. This behavior, which is indicative of current control resulting from
Figure 32. Cumulative logarithmic signatures of 2.8 mM CPZ in 0.25 M acetate buffer @ pH 6, at (A) carbon fiber disk microelectrode, run over six time domains, and (B) glassy carbon macroelectrode, run over six time domains. All calculated using initial 25 point smooth on current-time data, 100 point sliding interval calculation of $\Delta (\ln i) / \Delta (\ln t)$ and final 25 point smooth for each run time.
the chemical reactions that follow CPZ oxidation rather than CPZ mass transport, is not observed at the microelectrode where steady state is readily attained. This implies that the three dimensional mass transport associated with the microelectrode contributes more significantly to the current that is observed at that electrode; the microelectrode is, therefore, superior for the measuring CPZ concentration.

Calibration curves were developed from chronoamperometric experiments using a series of concentrations of CPZ in 40 μl drops on glass disks using the small volume cell. For large volume experiments, calibration curves were developed using cell volumes up to 15 ml. As suggested by the Δ(ln i)/Δ(ln t) signature, experiments were run from 0.3 sec to 30 sec and unsmoothed data from 10 to 30 seconds were analyzed as discussed in the Methods section. The concentrations of CPZ were varied from 2.6 μM to 2.8 mM CPZ in 0.25 M pH 6 acetate buffer. The intercepts \( 4nFDC_o \cdot r \) of \( i_d vs r^{1/2} \) at each concentration were plotted against the known concentration to produce the calibration curves. Because the cumulative logarithmic signature identified the approach to steady state so well, the current vs \( r^{1/2} \) were analyzed using regression analysis without any smoothing (Figures 30 and 31). Table 5 shows typical standard calibration data for the various systems. The limit of quantification (LOQ) was calculated as the CPZ concentration corresponding to ten standard deviations from the intercept.

**Sorption Isotherms** - Small volume sorption experiments for 2.8 mM CPZ and 28 μM CPZ on small disks of the seven packaging materials (Table 4) were run for fourteen days. The results (Figure 33 and Table 6) demonstrate that no losses were detected for 2.8 mM CPZ on glass, polypropylene (PP), ethylene vinyl acetate (EVA) or
Figure 33. Small volume sorption isotherms for 2.8 mM CPZ onto packaging material disks of (A) glass, (B) PET, (C) PP, (D) EVA, (E) HDPE (Opaque), (F) HDPE (semi-opaque), and (G) PVC with DEHP.
Table 6
Gross Heterogeneous Rate Constants for CPZ/Package Interaction Studies

<table>
<thead>
<tr>
<th></th>
<th>Small Volume 2.8×10⁻³ M CPZ</th>
<th>Small Volume 2.8×10⁻³ M CPZ</th>
<th>Large Volume 2.9×10⁻³ M CPZ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial (^c) (cm/sec)</td>
<td>Overall (^d) (cm/sec)</td>
<td>Initial (^c) (cm/sec)</td>
</tr>
<tr>
<td>Glass</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PET</td>
<td>8.68×10⁻¹⁴</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PP</td>
<td>1.37×10⁻¹³</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>EVA</td>
<td>4.71×10⁻¹⁴</td>
<td>4.64×10⁻¹⁴</td>
<td>0</td>
</tr>
<tr>
<td>HDPE (^a)</td>
<td>1.84×10⁻¹⁴</td>
<td>6.09×10⁻¹⁴</td>
<td>0</td>
</tr>
<tr>
<td>HDPE (^b)</td>
<td>1.40×10⁻¹³</td>
<td>4.98×10⁻¹⁴</td>
<td>0</td>
</tr>
<tr>
<td>PVC</td>
<td>2.89×10⁻¹³</td>
<td>1.25×10⁻¹³</td>
<td>8.72×10⁻¹⁴</td>
</tr>
</tbody>
</table>

\(^a\) Semi-opaque.
\(^b\) Opaque.
\(^c\) Loss rate after first day.
\(^d\) Overall loss rates for 14 days (small volume) or 56 days (large volume).
polyethylene terephthalate (PET) (Figure 33). Figure 33 does show small losses detected for 2.8 mM CPZ on semi-opaque and opaque high density polyethylene (HDPE). For 2.8 mM CPZ on polyvinyl chloride with the plasticizer bis-2-ethylhexyl phthalate (PVC with DEHP), up to 60% is lost in fourteen days. The CPZ loss on PVC appears to exhibit an exponential decay \((Ae^{-mt})\) where \(A\) is 2.8\(\times\)10\(^{-3}\) M and \(m\) is 8.7\(\times\)10\(^{-7}\) s\(^{-1}\).

Interactions of CPZ with packaging materials were further distinguished by the experiments with 28 \(\mu\)M CPZ (Figure 34). At this lower concentration of CPZ, only in glass was there no loss of CPZ over fourteen days of experimentation. This is consistent with the current practice of selling CPZ solutions only in glass. In PET and PP, approximately a 10% loss of CPZ was observed during the first day, but minimal losses occurred thereafter. Data for EVA, semi-opaque HDPE and opaque HDPE demonstrated 50 - 70% loss of CPZ over fourteen days. In PVC, the CPZ concentration decreased to such an extent that the limit of quantification was reached in six days, with no CPZ detected by ten days.

The effects observed on CPZ concentration using actual packages are shown in Figure 35. The time scale for this experiment is eight weeks, which is four times longer than the small volume experiments. As predicted by the sorption experiments using the small disks of packaging materials, PVC showed significant losses quickly, with 99.7% CPZ loss in two weeks. PET and glass showed no detectable loss during the two month stability test. PP showed a slight loss of about 2% in the first four days, and only an additional loss of 1% over the next 7.5 weeks. EVA produced a CPZ loss isotherm similar to PP, with about 4% loss in the first four days and an additional 3% over the next
Figure 34. Small volume sorption isotherms for 28 μM CPZ onto packaging material disks of (A) glass, (B) PET, (C) PP, (D) EVA, (E) HDPE (Opaque), (F) HDPE (semi-opaque), and (G) PVC with DEHP.
Figure 35. Large volume sorption isotherms for 2.9 mM CPZ in actual packages of (A) glass, (B) PET, (C) PP, (D) EVA, (E) HDPE (Opaque), (F) HDPE (semi-opaque), and (G) PVC with DEHP.
7.5 weeks. The two HDPE packages produced essentially consistent CPZ losses over the 8 weeks, ending at about 14% loss. PP showed no detectable change over the first two weeks and then began to produce small losses in CPZ concentration.

**Heterogeneous Rate Constants:** Table 6 shows gross heterogeneous rate constants for initial CPZ losses (after one day), which may be due to Langmuir adsorption or absorption under sink conditions; also shown in this table are long term losses, which can have multiple causes. The gross rate constants were determined by dividing the rate of CPZ uptake per unit area (moles/cm²/sec) by the bulk CPZ concentration (moles/cm³).

The large volume and small volume sorption isotherms shown in Figures 34 and 35 suggest that Langmuir type adsorption may occur with PP and PET. The initial loss rates for PP and PET are significant in the large volume experiments ($2.3 \times 10^{-8}$ and $9.2 \times 10^{-9}$ mol/cm²/day respectively) and in the small volume experiments using $2.8 \times 10^{-3}$M CPZ ($3.2 \times 10^{-10}$ and $2.0 \times 10^{-10}$ mol/cm²/day respectively). The small volume experiments show no subsequent loss of CPZ. This is indicative of either Langmuir type adsorption, which is a surface phenomenon that allows only one CPZ molecule to adsorb to each sorption site on the packaging material; or absorption of unionized CPZ into the packaging material followed by slow diffusion of CPZ through the package; or saturation of the package with CPZ. The large volume experiments confirmed the Langmuir adsorption pattern for PET and PP by showing relatively high initial rates of CPZ loss followed by no subsequent CPZ loss (for PET) or a relatively slower rate loss (for PP). The slower long term rate of loss for CPZ in contact with PP is indicative of a diffusion
process of CPZ in this packaging material. The other materials tested did not show significantly different initial and total chlorpromazine loss rates.

**Sorption Processes:** Absorption processes can occur by the diffusion of unionized CPZ into the polymer matrix, solvation of CPZ by the polymer matrix, or by capillary forces pulling the CPZ into the matrix. Solutes may diffuse more easily through a polymer above its glass transition temperature, $T_g$, due to regional mobility of the polymer molecules. The addition of plasticizers can enhance the diffusion rate of a drug in a polymer material by solubilizing the drug or by lowering the glass transition temperature of the polymer matrix. The two flexible packaging materials, PVC and EVA, have glass transition temperatures below room temperature, while all the other packaging materials have glass transition temperatures above room temperature. This may provide part of the explanation for the relatively rapid CPZ losses from interactions between CPZ and both PVC and EVA, as compared to interactions between CPZ and glass, PP or PET.

The greatest drug-package interaction found in these experiments was between CPZ and PVC which was plasticized with DEHP. The high rate of interaction between CPZ and PVC could be due to a high diffusion rate of CPZ in the PVC/DEHP matrix. The high affinity between CPZ and PVC has been related to the CPZ octanol/water partitioning ($\text{P}_{\text{o/w}} = 5.00$)\textsuperscript{39} of unionized CPZ ($\text{PK}_a = 9.4$, 0.04% unionized at pH 6). An additional factor which may cause the high rate of CPZ loss in contact with PVC is possible solubilization of CPZ by DEHP, as observed with other drugs.\textsuperscript{4} The effect of $T_g$ on solubility in polymers does not explain the relatively rapid CPZ loss due to
interactions between CPZ and the two HDPE packages. Though polyolefins, like HDPE, are normally inert with respect to drug sorption, it is possible that some additive in these HDPE packages may enhance diffusion of solubilization of CPZ in the polyethylene.

**Predictive Value of Small Volume Studies:** Comparison of CPZ loss rates (Table 6) between the different experimental conditions provide insight into the small volume sorption isotherm method. By testing a lower CPZ concentration, 28 μM, in the small volume cell, small losses could be measured for each package, excluding glass. The heterogeneous rates for the initial losses and overall losses for small volume and large volume experiments were on the order of $10^{-16}$ - $10^{-13}$ cm/sec (Table 6), with glass and PET showing the slowest heterogeneous rate losses, and PVC with DEHP providing the fastest heterogeneous rate losses. Heterogeneous loss rates determined from the large volume experiments at high concentration correlated well with the small volume experiments using the lower CPZ concentration, as shown in Figure 36. The linearity of this plot demonstrates the feasibility of using the results of the small volume low concentration experiments to predict the solute sorption by containers of higher solute concentrations over longer time intervals. No correlation could be found between the small volume experiments using the higher CPZ concentration and either the small volume with the low CPZ concentration or the large volume experiments. This is because the small volume high CPZ concentration experiments did not produce CPZ concentration changes significant enough to be measured during the brief duration of the accelerated test. The small volume, short term experiments demonstrated the order of suitability of packaging materials for storage of CPZ, and correlated well to the CPZ loss.
Figure 36. Comparison of overall heterogeneous rate constants for 56 day large volume sorption studies using 2.9 mM CPZ with 14 day small volume sorption studies using 28 μM CPZ. Regression analysis gives intercept = -7.40 x 10^{-16} \text{ cm/sec}, slope = 0.504, r^2 = 0.857. Packaging materials: (A) glass, (B) PET, (C) PP, (D) EVA, (E) HDPE (Opaque), and (F) HDPE (semi-opaque).
rates in the large volume studies. With the specific packages tested, the order of chlorpromazine HCl stability starting at the most stable was glass ≥ PET > PP > EVA > HDPE (semi-opaque) ≥ HDPE (opaque) >> PVC with DEHP.

Conclusions

A small volume electroanalytical method has been developed to detect losses of solutes due to solute/solid interactions such as adsorption and absorption. By maximizing the packaging material surface to drug solution volume, the drug-package interactions are exaggerated. Thus, this technique provides a short experiment which can predict which packaging materials may provide adequate long term stability. Because very small amounts of solute are used, this technique can be used in the early stages of product development when little drug is available and drug characterization is not complete.

To determine the correct time scale for the chronoamperometric experiments, the method developed for the ferricyanide reduction studies was extended to use for the analysis of a kinetically complicated system. Examination of $\Delta(\ln i)/\Delta(\ln t)$ signature curves prior to analysis simplifies data analysis by identifying the time domains over which the system exhibits limiting apparent Cottrell or steady state behaviors. This extends the utility of microelectrode chronoamperometry to the electroanalysis of non-reversible, kinetically complicated systems.
Mechanism Studies Using Experimental and Simulated
Chronoamperometric Logarithmic Signatures

Introduction

Interpretation of electrochemical processes is sometimes complicated by the effects of following homogeneous chemical reactions of the species that are involved in the electrode reaction. Investigations of these homogeneous reaction mechanisms over the past half century using a wide variety of electroanalytical methods have been well-documented. Cyclic voltammetry is frequently used to gain a qualitative understanding of these following reaction mechanisms. However, the shape of cyclic voltammograms can be complicated by the complexity of the homogeneous mechanism, the rate of heterogeneous electron transfer, the charging of the electric double layer, uncompensated solution resistance, and inadequate potential control. Thus, even though there have been recent advances in the development of explicit and implicit software for the digital simulation of theoretical cyclic voltammetry under the influence of following reaction mechanisms, the complexity of the experimental results under the influence of the variables enumerated above places considerable limitation on the validity of comparisons between experiment and theory using this electrochemical technique.

Potential step methods may be used to eliminate or reduce the effects of many of the confounding factors that are present in sweep voltammetry. In addition, the digital
simulation of chronoamperometry is much less complicated than that of cyclic voltammetry, and given the more reliable experimental data in the case of potential steps, these constant potential methods have become the preferred means to investigate the kinetics of following chemical reactions. Indeed, compilations of theoretical results for a wide variety of mechanisms have been obtained for chronoamperometry using finite difference methods. Early investigations of homogeneous reaction kinetics used a digital simulation technique to develop theoretical "working curves" that displayed some kinetic variable such as a current ratio as a function of time rendered dimensionless by the rate constant associated with the homogeneous kinetics. These theoretical working curves were then compared with their experimental counterparts in order to make mechanistic assignments and evaluation of rate constants based upon the degree of agreement between experiment and theory. More recently it has been suggested that in the case of the first order ece mechanism (an electron transfer reaction followed by a chemical reaction followed by a second electron transfer reaction), traditional chronoamperometric working curves may be replaced by a logarithmic signature, \( f(t) = \Delta(\ln i)/\Delta(\ln t) \), that may be compared with its experimental equivalent to elucidate that mechanism. Heretofore, however, the comparison of experimental and theoretical logarithmic signatures in this context has not been attempted. Only recently has the extent of aggressive smoothing that is necessary to evaluate the experimental logarithmic signature been realized (Chapters 2 and 3).

Finite difference algorithms can be used to model diffusion and chemical reactions associated with complicated redox behavior and have been well described
previously. Briefly, finite difference algorithms calculate the theoretical concentration of each material in each theoretical volume element, which represents distance from the electrode surface where the first volume element (box) is $J = 1$. For diffusion controlled, reversible systems (Figure 37), the boundary conditions include starting with reactant only in each volume element ($J = n$), the redox occurs only in the first volume element ($J = 1$), and the amount of product and reactant in each volume element at each iteration ($K$) is determined by the diffusion of each material into and out of adjacent volume elements, with all diffusion rates determined by a dimensionless diffusion model coefficient. The current is determined throughout the reaction only by the occurrences in the first volume element. For more kinetically complicated systems (Figure 38), the amount of each material in each volume element is calculated at each iteration ($K$) by first determining the amount in each volume element due to diffusion and then determining the effect of the kinetics on all materials within each volume element. The input variables are dimensionless time and kinetic parameters specific to the mechanism. Due to program design and computer memory limits, it is normal to set the maximum number of iterations, $L$, to 1000. It is possible to calculate a theoretical logarithmic signature from these 1000 points; however, a single simulation run does not include enough information to form a complete theoretical logarithmic signature. As suggested by the experimental cumulative logarithmic signatures, it was hypothesized that appropriate choice of several overlapping dimensionless time and/or kinetic input parameters might generate a theoretical cumulative logarithmic signatures in a manner similar to the generation of the experimental cumulative logarithmic signatures discussed in Chapters 2 and 3. These
Figure 37. Finite difference simulation technique for $R \rightarrow O + ne$ under diffusion control. The left side is the theoretical electrode surface, $L$ is the maximum number of iterations, $J$ is the volume element.
Figure 38. Finite difference simulation technique for $R \rightarrow O + ne$ with kinetic complications, where $x$ corresponds to products other than $O$, and some combination of products can reform $R$. The left side is the theoretical electrode surface, $L$ is the maximum number of iterations, $J$ is the volume element.
theoretical cumulative logarithmic signatures could also be compared with experimental
cumulative logarithmic signatures which could aid in the elucidation of the mechanism.
This chapter presents the cumulative signature generation from the explicit simulation of
reversible redox behavior and the finite difference models of two possible mechanisms
for chlorpromazine HCl oxidation. The simulated logarithmic signatures are then
compared with the experimentally derived logarithmic signatures.

**Theory For Reversible Reactions**

**Diffusion Controlled Processes** The chronoamperometric current generated by
reversible systems is explicitly described by the exponential function developed by Shoup
and Szabo (Equation 2.3 and below as 4.1)

\[
\frac{i_d(t)}{4nFrDC} = 0.7854 + 0.2146e^{-0.7823r^{-1/2}} + \frac{(\frac{\pi^{1/2}}{2})r^{-1/2}}
\]

where \( r = 4Dt/r^2 \) with D as the diffusion coefficient, \( t \) as the experimental time, and \( r \) as
the radius of the electrode. As discussed in Chapter 2, when \( r \leq 0.01 \), the logarithmic
signature curve approaches Cottrell behavior where \( r(t) = 0.5 \); when \( r \geq 400 \) the
logarithmic signature approaches steady state behavior where \( r(t) = 0 \). Since \( r \) is
inversely proportional to \( r^2 \), Cottrell behavior for macroelectrode experiments are
described by the linearized form based on low \( r \) values (Equation 2.4) and steady state
behavior for microelectrode experiments are based on the linearized form for high \( r \)
values (Equation 2.5). By calculating the theoretical chronoamperometric current generated over several orders of magnitude of \( \tau \), it is possible to generate a theoretical logarithmic signature for \( f(\tau) = \Delta(\ln Z)/\Delta(\ln \tau) \) where \( Z \) is the designation for theoretically derived current \( i_d \) in Equation 4.1. If the appropriate domains of \( \tau \) are used to generate the logarithmic signature, then \( f(\tau) \) should progress from Cottrell behavior where \( f(\tau) = -0.5 \) to steady state behavior where \( f(\tau) = 0 \).

Comparison of \( f(\tau) \) with \( f(\tau) \) from an experimentally reversible system is then possible by calculating \( f(\tau) \) for the experimental system. This requires knowledge of the electrode size used to generate the experiments. In Chapter 2, Table 3, the electrode sizes determined from chronoamperometric reduction of ferricyanide are presented. Therefore, \( \tau \) can be determined for the experimental data from the ferricyanide experiments. It was hypothesized that the experimentally derived logarithmic signature for the macroelectrode experiments for ferricyanide reduction should compare to the Shoup and Szabo simulated logarithmic signature in the region where \( f(\tau) = -0.5 \). Also, the experimentally derived logarithmic signature for the microelectrode experiments for ferricyanide reduction should compare to the Shoup and Szabo simulated logarithmic signature in the region where \( f(\tau) = 0 \). It was also hypothesized that the intermediate regions from the experimental data should compare to the intermediate regions from the Shoup and Szabo simulation.

The BASIC program developed to calculate the Shoup and Szabo equation over several orders of magnitude of \( \tau \), and to generate a theoretical logarithmic signature for \( f(\tau) = \Delta(\ln Z)/\Delta(\ln \tau) \), is included in Appendix 5.
Chlorpromazine HCl Oxidation - The cyclic voltammetry of chlorpromazine HCl (CPZ) in 0.25 M acetate buffer at pH 6 was previously shown in Figure 27. The first oxidation occurs at 0.68 V vs SCE while the second oxidation peak is at 1.2 V vs SCE. The small reduction peak occurring at 0.55 V vs SCE on the reverse scan is indicative of the presence of following chemical reactions after the initial oxidation. Similar behavior is observed when the scan is stopped at the end of the oxidation. The homogeneous kinetics of these following chemical reactions have received much attention over the past four decades. Nearly that long ago, Merkle and Discher proposed a disproportionation mechanism involving the product of the first oxidation. Subsequently, McCreery, et al. used spectroelectrochemical methods to postulate a buffer interaction mechanism for the products of the same reaction. Either of these mechanisms may be viewed as higher order ece sequence, i.e., a process where a homogeneous reaction sequence follows an electrode reaction to produce additional electroactive species. The mechanistic speculation that follows is associated with the ece processes that accompany the first oxidation wave of chlorpromazine.

First Order ece Mechanism - In the classic ece mechanism the product of the initial electrode reaction is converted via a first order homogeneous reaction to a second species that is also electroactive at the applied potential. When both species react at the electrode under diffusion control, the current is described by
\[ i(t) = (nFAD^{1/2}C^+) (2 - e^{-kt}) (\pi t)^{-1/2} \]  \hspace{1cm} (4.2)

where all factors have the usual electrochemical significance. It has been previously demonstrated that this chronoamperometric relationship yields a characteristic logarithmic signature that is given by

\[ f(kt) = (kt/(2e^{kt} - 1)) - 1/2 \]  \hspace{1cm} (4.3)

The graphical representations of this equation were produced by the plotting program, Origin 4.1, which was used to evaluate Equation 4.3 directly over the desired time domains.

This well-defined signature for the first order ece mechanism provides a basis of comparison for the other two mechanistic signatures described below. These were obtained, however, using finite difference simulations.

**Disproportionation Mechanism** - Merkle and Discher proposed the following mechanism to describe the CPZ oxidation mechanism in acidic conditions (Figure 39).

\[
\begin{align*}
\text{CPZ} & \rightarrow \text{CPZ}^+ + e \\
\text{CPZ}^+ & \rightarrow \text{CPZ}^{2+} + e \\
2\text{CPZ}^+ & \rightarrow \text{CPZ}^{2+} + \text{CPZ} \\
\text{CPZ}^{2+} + \text{H}_2\text{O} & \rightarrow \text{CPZO} + 2\text{H}^+
\end{align*}
\]  \hspace{1cm} (Reaction 1, 2, 3, 4)
Chlorpromazine (CPZ); \( R = \text{CH}_2\text{(CH}_2\text{)}_2\text{N(CH}_3\text{)}_2 \)

Figure 39. Disproportionation Mechanism, where I = Reaction 3.1, II = Reaction 3.2, III = Reaction 3.3, and IV = Reaction 3.4.
Reactions 1 and 2 correspond to the first and second oxidations, respectively. Reaction 3 is the disproportionation reaction, in which two cation radicals, CPZ\(^+\) produced by the first oxidation, combine to form a divalent cation and the starting material, CPZ. The divalent cation reacts with the solvent to form a sulfoxide, which does not react subsequently. Merkle proposed that Reaction 4 is quite fast. Thus, the disproportionation reaction produces the dication which quickly becomes non-reactive, and additional CPZ which can undergo further oxidation.

**Buffer Interaction Mechanism** - McCreery, *et al.* studied the reaction of the products of chlorpromazine oxidation in the presence of buffer.\(^5\) As with the disproportionation mechanism, for every two CPZ molecules consumed by oxidation, the buffer interaction mechanism reforms one CPZ and consumes two CPZ\(^+\).

\[
\begin{align*}
\text{CPZ} & \rightarrow \text{CPZ}^+ + e \\
\text{CPZ}^+ + \text{B}^- & \rightarrow \text{CPZB} \\
\text{CPZ}^+ + \text{CPZB} & \rightarrow \text{CPZB}^+ + \text{CPZ} \\
\text{CPZB}^+ + \text{H}_2\text{O} & \rightarrow \text{CPZO} + \text{HB} + \text{H}^+ 
\end{align*}
\]

(Reaction 5)

(Reaction 6)

(Reaction 7)

(Reaction 8)

This mechanism is more complicated to model because it is possible that Reaction 8 may be slow enough to allow the reverse of Reaction 7 be significant. Also, there are two separate reactions consuming CPZ\(^+\) (Reactions 6 and 7) instead of the one disproportionation reaction (Reaction 3).
Methods

Finite Difference Simulation - The explicit finite difference method for simulating this mechanism has been described in detail. The simulation technique divides the diffusion layer into a large number of volume elements and the calculates the change in $f_i(J)$, the fractional concentration of each species, $i$, in each volume element, $J$, due to mass transport (diffusion) and chemical reaction due to the disproportionation or buffer interaction mechanism. Boundary conditions are set for the first and final volume elements, $J(1)$ and $J(∞)$, respectively. $J(1)$ is theoretically adjacent to the electrode surface and is the volume element where the oxidation of CPZ to CPZ$^+$ also occurs. The characteristic diffusion algorithm is used to model mass transport for all species:

$$f_i(J) = f_i(J) + D_{M_i}[f_i(J+1) - 2f_i(J) + f_i(J-1)]$$  \hspace{1cm} (4.4)

A defined dimensionless parameter $D_{M_i}$, the model diffusion coefficient for each species, controls the material flux between volume elements. This diffusion algorithm calculates the new fractional concentration of each species, $f_i$, in each volume element as a function of $i$ diffusing into the $J$ volume element from the previous volume element, $J-1$, and from the next volume element, $J+1$, as well as diffusion out of volume element $J$ in two directions. This diffusion algorithms was used for both the disproportionation mechanism and buffer interaction mechanism simulations.

Finite Difference Simulation of the Disporportionation Mechanism - The fractional concentration of each species in each volume element due to the disproportionation
mechanism described above is computed using the following equations

\[ f_{CPZ}(J) = f_{CPZ}(J) + \left( \frac{k_3 t_k [CPZ^+]}{L} \right) \times (f_{CPZ^+}(J))^2 \]  

\[ f_{CPZ^+}(J) = f_{CPZ^+}(J) + \left( \frac{k_3 t_k [CPZ^+]}{L} \right) \times (f_{CPZ^+}(J))^2 \]  

\[ f_{CPZ^+}(J) = f_{CPZ^+}(J) - 2 \left( \frac{k_3 t_k [CPZ^+]}{L} \right) \times (f_{CPZ^+}(J))^2 \]

where \( k_3 \) is the disproportionation rate constant, \( t_k \) is a known time corresponding to the last iteration in a given simulation, \([CPZ^+]\) is the bulk concentration of CPZ, and \( L \) is the total number of iterations in that simulation. Following Merkle's proposal that the hydrolysis of \( CPZ^{2+} \) to \( CPZO \) is quite rapid, Equation 4.7 combines the effects of Reaction 2 and Reaction 3. These equations show that for every two CPZ molecules consumed by oxidation, the disproportionation reaction reforms one CPZ, consumes two \( CPZ^+ \) and forms one \( CPZO \). It should be noted that the specification of the dimensionless rate constant \( k_3 t_k [CPZ^+] \) at the outset of a given run also defines all time intervals within that simulation in terms of \( k_3 [CPZ^+] \); thus, it is possible to use the explicit method employed in this work piecewise in order to obtain results over many orders of time.
The dimensionless current, $Z$, is determined for each iteration, $K$, by assuming that all the CPZ in the first volume element is oxidized to CPZ$^-$. 

$$Z(K) = \left( \frac{L}{D_{M-CPZ}} \right)^{1/2} \times \left( \left( D_{M-CPZ} \times f_{CPZ}(2) \right) + \left( \frac{k_3 f_{CPZ}^*}{L} \right) \times f_{CPZ}(1)^2 \right)$$ \hspace{1cm} (4.8)

The CPZ in the first volume element comes from diffusion of CPZ from the second volume element and from the disproportionation of the CPZ$^-$ that is present in that element. The theoretical logarithmic signature for the disproportionation reaction is represented by $\Delta(\ln Z(K))/\Delta(\ln t(K))$ vs. $k_3 f[CPZ^-]$.

A description of the variables used in the disproportionation simulation and the associated BASIC program, DISP3.BAS, are located in Appendix 6. In DISP3.BAS, the values of each form of CPZ were calculated by accounting for diffusion followed by the disproportionation mechanism at each iteration. The dimensionless current, $Z(K)$, was calculated after each iteration from the values in the first volume element, $J(1)$. As a check to assure that the simulation was working as expected, the fraction of each form of CPZ, and the sum of all forms of CPZ, in each volume element was determined when the simulation was 40%, 80% and 100% completed (Figure 40). It is important to note that the sum of all forms of CPZ should equal one throughout the simulation. Figure 40 also demonstrates that experimentally meaningful variables relating to distance from the electrode surface can be obtained from the simulation variables by
Figure 40. Disproportionation Simulation with $D_{M, CPZ} = D_{M, CPZ^+} = D_{M, CPZ^{++}} = 0.49$, $L = 1000$, $MKAT = k_{34}[CPZ^+] = 1$. Comparison of values of CPZ, CPZ+, and CPZ++ with distance from the theoretical electrode surface at 40% ($L=400$), 80% ($L=800$) and 100% ($L=1000$) completion of the simulation. The dotted line at Fractional Concentration = 1 is the cumulation of all fractions of CPZ at L=1000.
where \( x \) is the distance from the electrode, \( D \) is the diffusion coefficient, \( t \) is the experimental time, and both fractions are dimensionless. The boundary conditions of no CPZ present at the electrode surface and 100% CPZ present in the bulk are evident in Figure 40. As theoretical time increases, as denoted by increases in the number of iterations, the fraction of CPZ near the electrode surface decreases. Figure 40 also shows that, even though the second oxidation step does not occur, CPZ\(^{2+}\) is formed due to the disproportionation reaction. In this simulation, due to the Merkle proposal that Reaction 4 is very fast, it is assumed that all CPZ\(^{2+}\) is hydrolyzed to become the sulfoxide, CPZO. Thus, the profiles for CPZ\(^{2+}\) are the same as the profiles for CPZO.

**Finite Difference Simulation of the Buffer Interaction Mechanism** - Finite difference methods used to model the buffer interaction mechanism used the same mass transport simulation technique represented in Equation 4.4. Rate equations were developed to account for the equilibrium conditions in Reactions 6 and 7 (\( K_e \) and \( K_r \)) and for the forward rates of Reactions 6, 7, and 8 (\( k_6, k_r \) and \( k_g \)). Thus, five dimensionless input parameters are necessary to specify the mechanism completely. Computation of the changes in fractional concentration of all species may be facilitated by computing the mass balance parameters \( W(J) \), \( X(J) \), and \( Y(J) \) for each volume element. This results in the following mechanistic sequence:
\[ f_{\text{CPZ}}(J) = f_{\text{CPZ}}(J) + X(J) \quad (4.10) \]
\[ f_{\text{CPZ}^+}(J) = f_{\text{CPZ}^+}(J) - W(J) - X(J) \quad (4.11) \]
\[ f_{\text{CPZB}}(J) = f_{\text{CPZB}}(J) + W(J) - X(J) \quad (4.12) \]
\[ f_{\text{CPZB}^-}(J) = f_{\text{CPZB}^-}(J) + X(J) - Y(J) \quad (4.13) \]
\[ f_{\text{CPZD}}(J) = f_{\text{CPZD}}(J) + Y(J) \quad (4.14) \]

where:
\[ W(J) = (k_{d1}[B]/L) * (f_{\text{CPZ}^+}(J) - (f_{\text{CPZB}^-}(J)/K_6)) \quad (4.15) \]
\[ X(J) = (k_{-t1}[\text{CPZ}^+]/L) * ((f_{\text{CPZB}^-}(J) * f_{\text{CPZ}^+}(J)) - (f_{\text{CPZB}^-}(J) * f_{\text{CPZ}}(J)/K_6)) \quad (4.16) \]
\[ Y(J) = (k_8 t_4/L) * f_{\text{CPZB}^-}(J) \quad (4.17) \]

With the buffer interaction mechanism, CPZ arrives at the electrode volume element, \( J(l) \), by diffusion of CPZ from the second volume element and by its generation via Reaction 7. Thus, the dimensionless current, \( Z(K) \), is given by
\[ Z(K) = (\frac{L}{D_{M-CPZ}^{1/2}}) * ((D_{M-CPZ} * f_{\text{CPZ}}(2)) + X(1)) \quad (4.18) \]

Similar to the disproportionation mechanism, the logarithmic signature for the buffer interaction mechanism may be represented by plotting \( \Delta(\ln Z(K))/\Delta(\ln t(K)) \) vs. \( k, t[\text{CPZ}^+] \). While any of the three forward rate constants employed in the simulation (Equations 4.15 to 4.17) could have been used to render time dimensionless in this signature, the rate constant for Reaction 7 has been used below.

The BASIC program, CPZ104.BAS, and a description of the variables used in the
buffer interaction simulation are located in Appendix 7. In CPZ104.BAS, the values of each form of CPZ were calculated by accounting for diffusion followed by the buffer interaction mechanism at each iteration. The dimensionless current, $Z(K)$, was calculated after each iteration from the values in the first volume element, $J(I)$. Using a check similar to that used for the disproportionation simulation, the fraction of each form of CPZ as a function of the distance from the electrode surface was evaluated. The individual fractions and the sum of all forms of CPZ in each volume element were determined when the simulation was 40%, 80% and 100% completed (Figure 41). From this figure, it can be seen that the sum of all fractions equals 1 throughout the simulation. The boundary conditions of no CPZ present at the electrode surface and 100% CPZ present in the bulk are evident in Figure 41. Similar to the disproportionation model, as theoretical time increases, as denoted by increased K value, the fraction of CPZ in volume elements near the electrode surface decreases. Figure 41 also shows that, at the theoretical electrode surface and as theoretical time increases, the fraction of CPZ\(^+\) decreases while the fractions of CPZB\(^-\), CPZB\(^+\), and CPZO increase.

**Electrochemical methods** - Electrochemical methods for chronoamperometry (CA) and cyclic voltammetry (CV) experiments, solution preparation, materials, and experimental cumulative logarithmic signature development for ferricyanide reduction and CPZ oxidation were described in Chapters 2 and 3, respectively.
Figure 41. Buffer Interaction Simulation with $D_{M-CPZ} = D_{M-CPZ^*} = D_{M-CPZB} = D_{M-CPZB^*} = D_{M-CPZO} = 0.49$, $L = 1000$, $k_{6k}[B] = k_{7k}[CPZ^*] = k_{4k} = 1$, $K_6 = 10$, and $K_7 = 0.4$. Comparison of values of (A) CPZ, (B) CPZ*, (C) CPZB, (D) CPZB*, and (E) CPZO with distance from the theoretical electrode surface at 40% ($K=0.4L$), 80% ($K=0.8L$) and 100% ($K=L$) completion of the simulation. (F) is the sum of all CPZ fractions.
Results and Discussion

Simulation of Reversible System - The experimental cumulative logarithmic signatures for the reduction of ferricyanide were developed in Chapter 2, with examples shown in Figures 22, 23, and 24. The solution to the Shoup and Szabo equation (Equation 4.1) over 10 orders of magnitude of \( \tau \) is represented in Figure 42 as the smooth curve starting with Cottrell behavior and ending with steady state behavior. This figure also shows the experimental cumulative logarithmic signatures for macroelectrode and microelectrode experiments originally represented in Figure 22. However, the experimental logarithmic signatures were transformed to functions of \( \tau \), where \( \tau = 4Dt/r^2 \). Thus, the original time scale for the experimental data was multiplied by \( 4D/r^2 \), where \( D = 7.17 \times 10^{-6} \text{ cm}^2/\text{s} \), and the sizes of the macroelectrode and microelectrode are 1.61 mm and 10.35 \( \mu \)m, respectively (\( 4D/r^2 \) to be \( 1.1 \times 10^{-3} \text{ s}^{-1} \) for the macroelectrode and \( 27 \text{ s}^{-1} \) for the microelectrode.) Interestingly, the logarithmic signature for the microelectrode experiments and for the theoretical line each reach \( f(\tau) = \Delta(\ln Z \ or \ i)/\Delta(\ln \tau) = 0 \) when \( \tau \) is approximately 1000. This corresponds well to the work discussed in Chapter 2 (Figure 25) and leads to the question as to why others previously considered running experiments at times less than or equal to \( \tau = 55 \). Even more confusing is the fact that the diffusion coefficient, \( D \), for ferricyanide under the experimental conditions used in this work, were obtained at \( \tau = 55 \). It is noteworthy that the use of this \( D \) to calculate platinum electrode sizes based upon chronoamperometric experiments seemed to lead to macroelectrode sizes comparable to sizes obtained from microscopy and to microelectrode sizes similar
Figure 42. The solid smooth curve is the solution to Shoup and Szabo Equation. The experimental logarithmic signatures from Figure 22 were transformed to functions of $\tau = 4D_\tau r^2$ using $D = 7.17 \times 10^{-6}$ and the experimentally derived electrode sizes for PA and P1 (Table 3).
Comparison of the experimental and simulated data shows that the experimental time for the microelectrode experiments attaining steady state behavior correspond with the simulation. However, the behavior of the microelectrode in the intermediate region does not match the intermediate behavior of the simulation. The reason for the mismatch prior to steady state behavior was not identified. There are several possible reasons for this mismatch. One is that mass transport also occurs by convection, which is not included in the theory. Some labs isolate electrochemical cells from vibration, which was not done for these experiments. It is also possible that this microelectrode system, which was run in the same cell as the macroelectrode experiments, has a longer time for recovery from capacitive current than expected. From the dip which showed up in three separate microelectrode logarithmic signatures (Figures 22, 23 and 24), one is lead to the hypothesis that the system overshoots the recovery from capacitive current and then rebounds. Since the intermediate portions of the experimental logarithmic signatures match do not compare with the Shoup and Szabo theory, it is also possible that other ferricyanide reactions are complicating the reversible assumption. This could also contribute to the difference in the Cottrell region between simulated and macroelectrode experimental logarithmic signatures.

Figure 43 shows the same data with the experimental logarithmic signatures shifted to coincide with the simulation. This leads to the estimation of $4D/r^2$ to be $5.5 \times 10^{-4} \text{ s}^{-1}$ for the macroelectrode and $0.27 \text{ s}^{-1}$ for the microelectrode. If the same diffusion coefficient is assumed, then the macroelectrode and microelectrode should have
The solid smooth curve is the solution to Shoup and Szabo Equation. The experimental logarithmic signatures from Figure 40 were shifted to increase overlap with the simulation. New $4D/r^2 = 2.2 \times 10^{-3} \text{ s}^{-1}$ for macroelectrode and $0.11 \text{ s}^{-1}$ for microelectrode.
diameters of 2.3 mm and 1.0×10⁻² cm, respectively, in order to achieve the estimated τ values. Thus, the apparent electrode sizes are larger than expected. Alternately, the apparent diffusion coefficient could be 3.6×10⁻⁶ cm²s⁻¹ and 7.2×10⁻⁸ cm²s⁻¹ for the macroelectrode and microelectrode, respectively, if the electrode diameters are assumed to be as specified. However, since the times to reach steady state match so well between the experimental and theoretical logarithmic signatures, and because D and τ are constant (τ 4D/τ²) then it initially appears that shifting the experimental values in the τ domain is not a valid option. But there may be reasons for these apparently anomalous results. The apparent diffusion coefficient may be different than D in the presence of an additional mass transport phenomenon, such as migration due to ionic interactions in the double layer near the electrode surface. It is possible that the electrode double layer for the microelectrode experiments may be larger than expected and thus affect the diffusion of the ferricyanide ion, leading to erroneous D values. Another option is that the apparent electrode radii are larger than the actual surfaces of the electrodes. With these possibilities and others including possible additional following reactions and electrode kinetics effects, it is important to take care when interpreting data using extremely small electrodes such as in scanning electrochemical microscopy (SECM). More work needs to be done to fully understand these issues.

**Theoretical First Order ece Signature** - The theoretical logarithmic signature for the first order ece mechanism is shown in Curve B of Figure 44. This line was constructed using Equation 4.3 by setting \( k = 660 \text{ s}^{-1} \) in order to obtain the best possible agreement.
Figure 44. Logarithmic signature curves for (A) 2.8 mM chlorpromazine HCL in 0.25 M acetate buffer at pH 6, (B) ECE mechanism with $k = 660 \text{ s}^{-1}$ and (C) disproportionation simulation with $DM_{CPZ} = DM_{CPZ^+} = DM_{CPZ^{++}} = 0.49$, $L = 1000$ and $k_3 = 0.019 \text{ L/mol-s}$. 
with Curve A. Due to the semi-log nature of this plot, the optimum value for the first order rate constant can be determined by merely adding the necessary constant to the log-time variable to bring experiment and theory into coincidence. Since the linear ordinate of each plot is invariant, a direct comparison of the two ordinates may be used to measure the goodness-of-fit. (Short time experimental values for f(t) below -0.5 are indicative of non-faradaic processes, e.g., capacitive current due to double layer charging; these points were not used in the comparison of experiment and theory.) This comparison can be made by computing the experimental to theoretical ratio, $f_{exp}(t)/f_{theo}(t)$, at each point and then computing the mean value of this ratio for the two signatures under consideration. Goodness-of-fit may be assessed by determining the relative standard deviation of this mean; the higher the %RSD, the poorer the fit. The comparison of Curve A and Curve B in Figure 44 yields a mean value of $f_{exp}(t)/f_{theo}(t) = 1.072$ with a relative standard deviation of 19.61%, thereby confirming the visual observation of the mismatch between these two signatures. These results are summarized in Table 7.

Theoretical Disproportionation Signature - Digital simulations were used to obtain the theoretical logarithmic signature for the disproportionation mechanism. In each of these simulations, the model diffusion coefficients, $D_{Mi}$, of all species were set equal to 0.49 while the maximum iteration number, $L$, was set equal to 1000. The dimensionless rate constant for disproportionation, $k_3t_0[CPZ^+]$, was varied by several orders of magnitude domains to obtain dimensionless current and time values. Dimensionless time was expressed parametrically in terms of the rate constant $k_3$ by multiplying the known time...
Table 7
Theoretical Chronoamperometric Logarithmic Signature Parameter Values

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Parameter</th>
<th>Parameter Value</th>
<th>Mean $f_{exp}(t)/f_{theo}(t)$</th>
<th>%RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Order ECE</td>
<td>$k$</td>
<td>660 s⁻¹</td>
<td>1.072</td>
<td>19.61</td>
</tr>
<tr>
<td>Figure 44B</td>
<td>$k_j$</td>
<td>190 L mol⁻¹s⁻¹</td>
<td>1.019</td>
<td>5.96</td>
</tr>
<tr>
<td>[CPZ*]</td>
<td>2.8 mM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disproportionation</td>
<td>$k_r$</td>
<td>713 L mol⁻¹s⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Figure 44C</td>
<td>[CPZ*]</td>
<td>2.8 mM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffer Interaction I</td>
<td>$K_6$</td>
<td>10</td>
<td>1.001</td>
<td>2.96</td>
</tr>
<tr>
<td>Figure 45B</td>
<td>$K_7$</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffer Interaction II</td>
<td>$k_6[B]/k_7[CPZ*]$</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Figure 45C</td>
<td>$k_6/k_7[CPZ*]$</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffer Interaction II</td>
<td>$k_6$</td>
<td>713 L mol⁻¹s⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Figure 45C</td>
<td>[CPZ*]</td>
<td>2.8 mM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffer Interaction II</td>
<td>$K_6$</td>
<td>10</td>
<td>0.998</td>
<td>5.84</td>
</tr>
<tr>
<td>Figure 45C</td>
<td>$K_7$</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffer Interaction II</td>
<td>$k_6[B]/k_7[CPZ*]$</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Figure 45C</td>
<td>$k_6/k_7[CPZ*]$</td>
<td>10.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ratio, K/L, by the dimensionless rate constant, k₃tₖ[CPZ'], to obtain k₃t[CPZ']. The theoretical logarithmic signature curve was then obtained by plotting 
\[ \Delta(\ln Z(K))/\Delta(\ln t(K)) \] vs. k₃t[CPZ'] for each dimensionless rate constant that was used.

In this manner, the entire signature could be constructed piecemeal over several orders of time magnitude. However, because the explicit simulation algorithms cause oscillations in dimensionless current in the early stages of the simulation, the first 15% of each data set was not used for signature curve development. The resulting theoretical signature for the disproportionation mechanism is displayed as Curve C in Figure 44. Once again, the best agreement between experiment and theory was obtained by sliding the semi-log theoretical curve along the experimental plot until good agreement was obtained. At the bulk CPZ concentration of 2.8 mM, this best fit was obtained with \( k_j = 190 \text{ L mol}^{-1}\text{s}^{-1} \).

Goodness-of-fit was once again determined by computing the mean value for \( f_{\text{exp}}(t)/f_{\text{theo}}(t) \) and its %RSD. These were 1.019 and 5.96%, respectively, for the coincidence of Curve A and Curve C, thereby indicating much better agreement between the experimental data and the theoretical values for the disproportionation mechanism compared to the first order ece mechanism.

**Theoretical Buffer Interaction Signature** - The finite difference simulation for the buffer interaction mechanism has five different kinetic input parameters: \( k_s t_s[B^+] \), \( k_s t_k[CPZ'] \), \( k_s t_s \), \( K_s \), and \( K_s \). The parameter \( k_s t_k[CPZ'] \) was selected as the kinetic variable used to render time dimensionless in the logarithmic signature; it was the only time dependent input parameter used in these simulations. The other time-dependent
parameters, $k_{6t_k[B^1]}$ and $k_{8t_k}$, were computed from $k_{t_k[CPZ^*]}$ and the two time-independent parameters, $K_6$, and $K_8$, were also specified as input parameters. As in the disproportionation simulations, the dimensionless model diffusion coefficients of all species were set to 0.49, and the maximum number of iterations for each run was set at 1000. Figure 45 shows the comparison of the experimental CPZ signature, Curve A, with the results of two different theoretical curves for the buffer interaction mechanism, each obtained by finite difference simulation using two different sets of the input parameters. These input parameters are specified in Table 7; they are identical except for $k_{7k-[CPZ^*]}$. Curve B was obtained using $k_{7k-[CPZ^*]} = 1.0$, while Curve C was obtained using $k_{7k-[CPZ^*]} = 10$. Thus, the observed difference between the two theoretical curves for the buffer interaction mechanism is a ten-fold increase in the rate of Reaction 8 (as compared to Reaction 7). The mean values for $f_{exp}(t)/f_{theo}(t)$ and the corresponding relative standard deviations are shown in Table 7. These results indicate that the buffer interaction mechanism with $k_{7k-[CPZ^*]} = 10$ (Curve C) agrees with the experimental signature to the same degree that the disproportionation mechanism does. (It should be noted that an increase in the rate of Reaction 8 results in the additional formation of CPZO, the inert product of the disproportionation mechanism.) The best agreement between experiment and theory is obtained, however, when $k_{7k-[CPZ^*]} = 1.0$ (Curve B). In this case, $f_{exp}(t)/f_{theo}(t) = 1.001$ and the %RSD = 2.96%. Here, it is clearly demonstrated that decreasing the rate of CPZO production (by allowing reversible buffer interaction) improves the theoretical agreement.

It is not surprising that five adjustable parameters can produce better agreement.
Figure 45. Logarithmic signature curves for (A) 2.8 mM chlorpromazine HCl in 0.25M acetate buffer at pH 6, (B) buffer interaction simulation with $DM_{CPZ} = DM_{CPZ-} = DM_{CPZ++} = 0.49$, $L = 1000$, $k_6 t_k[B^+] = k_7 t_k[CPZ^*] = k_8 t_k$, $K_6 = 10$, and $K_7 = 0.4$ and (C) buffer interaction simulation same as (B) except $10k_6 t_k[B^+] = 10k_7 t_k[CPZ^*] = k_8 t_k$. 
between experiment and theory than one adjustable parameter. Moreover, the preceding discussion is by no means intended to be an exhaustive elucidation of the buffer interaction mechanism. Rather, it illustrates how one might use logarithmic signatures in this study. The results reported above did not require extensive computation to bring about the reported comparisons. For example, with all other variables remaining the same, $K_-$ increased the amount of CPZ that was regenerated and available for subsequent oxidation. This has a direct effect on height of the first peak of the theoretical logarithmic signature, and with $K_- = 0.4$, the peak heights of the two signatures match.

The most important feature of the buffer interaction logarithmic signature is the presence of a second peak. The valley and second peak seen in the simulation closely match the experimental tailing noted in the experimental logarithmic signature. This cannot be replicated in the disproportionation signature because CPZO forms immediately in disproportionation.

**Conclusion**

The utility of chronoamperometric logarithmic signatures in the elucidation of the ece mechanism of the homogeneous chemical reactions following the oxidation of CPZ has been clearly demonstrated, providing that aggressive digital smoothing is employed in the construction of the experimental signature. However, due to the immutable acquisition characteristics of the electrochemical instrumentation used in this study, the experimental signature for the oxidation of CPZ had to be constructed piecemeal from
separate 1000 point blocks of data acquired over different time ranges. The agreement between the overlapping portions of the signature obtained during different runs confirms the validity of the computation, and offers the hope that the mechanistic subtleties can be discerned in the signature. This hope has been realized in the mechanistic comparisons. The first order ece description of the observed results can easily be rejected in favor of either of the two second order mechanisms that have been proposed. While the disproportionation mechanism gives good agreement with the experiment, the buffer interaction mechanism is capable of giving the same level of agreement or better. The mechanistic subtleties seen in the piecemeal explicit finite difference simulation of the buffer interaction mechanism are clearly evident in the experimental signature. This is a very useful method for investigating ece reactions, i.e., systems that lend themselves to investigation with single potential step chronoamperometry.

It is probable that the utility of employing chronoamperometric signatures goes far beyond the investigation of one particular kind of homogeneous reaction sequence. It is hypothesized that every electrochemical process exhibits its own unique logarithmic signature than can easily be compared with its theoretical counterpart using the same semi-log interpretation methods that are employed in this work. Identification of different current-controlling processes can be carried out numerically using the same goodness-of-fit criteria used in this work. Given the proper data acquisition strategy with current autoranging, one can easily envision the digitally acquired logarithmic signature of the current as the basis for a universal sensor for electrochemical processes.
CONCLUSIONS AND COMMENTS

This work started with a simple idea: to develop an analytical method which accelerates the detection of drug-package interactions by increasing the surface-to-volume ratio. A cell was previously designed to contain two electrodes and to measure loss from small drops. This concept was extended to a three electrode system to enable the collection of analytical (ie. reproducible, accurate and precise) data. Chlorpromazine Hcl (CPZ) was selected as the model drug because it was known to interact with plastics but not with glass, thus providing a control. So, a small cell was built and experiments began. Using the usual techniques for determining chronoamperometric run times, it was impossible, no matter what the cell size or the electrode dimensions, to develop an electroanalytical method with errors less than +/- 20% in one day and completely non-reproducible over several days. Questions as to whether or not the tests were being run correctly lead to the investigation of a simple, reversible system. Because there is so much data available for ferricyanide reduction, experiments began based on experiments found in the literature. It was soon discovered that the usual techniques for determining chronoamperometric run times were not working for this simple system, either.

At this point, there was nothing to do but to figure out why I was obtaining erroneous results were being obtained for the reversible system. Assurance was sought that the run times were within the Cottrell region for the macroelectrode experiments and within the steady state region for the microelectrode experiments. The usual ways of “run for as long as possible” to achieve Cottrell conditions and “run to $4Dt/r^2 > 3$, with 55
being adequate" to achieve steady state conditions did not seem to work. It was already known that the calculation of $f(t) = \Delta(\ln i)/\Delta(\ln t)$ should be equal to -0.5 for Cottrell region and 0 for steady state region. And so, the experiments and calculation of $f(t)$ began. It was immediately obvious that the act of performing this calculation magnified the noise greatly. After the development of a smoothing and calculation protocol which used aggressive smoothing, the $f(t)$ values became somewhat meaningful. It also became apparent that one chronoamperometric experiment could not provide enough information to truly understand the $f(t)$ trends. Thus, multiple experiments over multiple time domains were run, each using an optimized data collection (sensitivity) method, and each requiring aggressive smoothing. The multiple $f(t)$ calculations were then put on one graph using a semi-log plot. Finally, the complete $f(t)$ trend could be visualized, and this became known as the cumulative logarithmic signature.

This cumulative logarithmic signature was initially used to determine Cottrell and steady state time domains, which were subsequently shown to be the correct time domains for obtaining analytical results for both reversible and non-reversible systems. This allowed for the accurate determination of electrode sizes using ferricyanide reduction and for the development of a successful accelerated drug-package interaction method.

Further analysis of the logarithmic signature showed that the cumulative logarithmic signatures were specific to the electrode process. Besides having different times for Cottrell and steady state behaviors, the reversible and non-reversible systems had different connecting (intermediate) behaviors. Two possible mechanisms for the
oxidation of CPZ had been identified in the literature. Using the finite difference simulation technique, it was known that complicated mechanisms could be modeled to obtain dimensionless current ($Z$) and dimensionless time ($\tau$) data. This simulation technique, however, was limited as to the range of dimensionless time that could be used in each simulation. The concept of developing a logarithmic signature from experimental data obtained over several time domains was then extended to the simulated data. By appropriately choosing dimensionless time and dimensionless rate constants, the cumulative simulated logarithmic signatures for the various mechanisms were developed. It was then possible to use chemometric techniques to determine which mechanism simulation modeled the experimental data best. This demonstrated that, not only is each logarithmic signature unique to the mechanism, but also to the kinetics.

**Suggestions for the Future:** The instrumental methods to gather experimental data could be improved which will lead to less aggressive smoothing algorithms for the calculation of the logarithmic signature. Most importantly, the gain should be based on powers of 2 rather than powers of 10 so that finer control of the noise can be obtained. The next priority would be to develop an instrumental method that allows a change in gain throughout the experiment so that the gain could be continuously optimized. And lastly, it would be beneficial if data from multiple time domains could be obtained in a single experiment. With the use of logarithmic signatures and these instrumental changes, I see no reason why chronoamperometry could become an analytical method of choice in many labs.

The most interesting data was obtained from the logarithmic signatures.
Investigation of the differences between the experimental and theoretical logarithmic signatures for the reversible reduction of ferricyanide would be quite interesting. Why do the curves not overlap in the connecting regions? What is the cause of the local minimum in the connecting region for the experimental data when no such local minimum is suggested by the theoretical logarithmic signature? Do these apparent anomalies mean that the electrode size can be apparently different than the true electrode size? Or does it mean that the diffusion coefficient is not constant? Or does a long time kinetic process for ferricyanide affect the logarithmic signature? For the CPZ oxidation, what is the optimized set of kinetic parameters, and does this match the data obtained by other authors using spectroscopic methods? Is there another mechanism which matches the experimental logarithmic signature? It is hoped that all these things will be wondered about by someone else in the future.
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51. Merkle, F. H.; Discher, C. A. Electrochemical Oxidation of Chlorpromazine


‘SMOOTH01.BAS BY BETH SARSFIELD, May, 1995

‘Adopted from SAVGOL.BAS, AUGUST, 1990
‘Abraham Savitzky and Marcel Golay method
‘Smoothing and Differentiation of Data by Simplified Least

‘Smooth errors from outside files. X-axis must have constant
intervals. Error must be in Y-axis (ordinate). Curves must
be continuous.

‘smooth01.bas provides choice to retain or discard the initial and final
points, and performs quadratic smoothing only.

DIM NDATA##(2001) 'NDATA = ORIGINAL DATA, EXTENDED PRECISION
DIM MDATA##(2001) 'MDATA = MODIFIED DATA, SMOOTHED OR
  'START/END ORIGINAL
DIM NP##(25) 'NP IS USED IN LOOPS TO HELP ORGANIZE DATA
DIM TIME##(2001) 'TIME IS TIME (X=AXIS DATA).
DEFINT A-Z 'DEFINE AS INTEGERS A THROUGH Z FOR COUNTING, ETC.

PRINT " SMOOTH01.BAS"
PRINT " THIS PROGRAM SMOOTH DATA FROM DATA FILES"
PRINT:PRINT:PRINT

MAIN:
L=1
INPUT "ENTER FILE (xxxxxxxx.xxx) TO BE MANIPULATED ";F1$
INPUT "ENTER FILE NAME FOR SMOOTHED DATA (XXXXXXXX.XXX) ";F2$
INPUT "ENTER SMOOTHING NUMBER (ODD NUMBER, 5 TO 25) ";P
INPUT "DO YOU WANT TO RETAIN THE ORIGINAL BEGINNING AND ENDING
  POINTS? ";YN1$ 
YN1$=UCASE$(YN1$)

OPEN F1$ FOR INPUT AS #1 'THIS LOOP INPUTS RAW DATA
  'WHILE NOT EOF(1)
    INPUT #1,TIME##(L),NDATA##(L)
  L=L+1
WEND
CLOSE #1
L = L - 1

IF P = 5 THEN
    GOSUB QCSMOOTH5
ELSEIF P = 7 THEN
    GOSUB QCSMOOTH7
ELSEIF P = 9 THEN
    GOSUB QCSMOOTH9
ELSEIF P = 11 THEN
    GOSUB QCSMOOTH11
ELSEIF P = 13 THEN
    GOSUB QCSMOOTH13
ELSEIF P = 15 THEN
    GOSUB QCSMOOTH15
ELSEIF P = 17 THEN
    GOSUB QCSMOOTH17
ELSEIF P = 19 THEN
    GOSUB QCSMOOTH19
ELSEIF P = 21 THEN
    GOSUB QCSMOOTH21
ELSEIF P = 23 THEN
    GOSUB QCSMOOTH23
ELSEIF P = 25 THEN
    GOSUB QCSMOOTH25
END IF

OUTPUTFILE:
OPEN F2$ FOR OUTPUT AS #2
IF YN1$ = "Y" OR YN1$ = "YES" THEN
    FOR H = 1 TO L
        WRITE #2, TIME##(H), MDATA##(H)
    NEXT H
ELSE
    FOR H = Y TO Z
        WRITE #2, TIME##(H), MDATA##(H)
    NEXT H
END IF
CLOSE #2
PRINT F2$ " IS COMPLETE"
PRINT
L = 1
APPENDIX 1

INPUT "Is there another file to smooth? ";YN2$
YN2$=UCASE$(YN2$)
IF YN2$="Y" OR YN2$="YES" THEN GOSUB MAIN
END

QCSMOOTH5:
Y=(P+1)/2 'Y=MIDPOINT OF SMOOTH RANGE, P=5(THIS SUBROUTINE)
Z=L-Y+1 'Z=LAST MIDPOINT NO FOR 5 PT SMOOTH, L=LAST POINT
FOR J=1 TO L ' J, K ARE COUNTERS IN FOR LOOPS
  IF J<Y OR J>Z THEN 'THIS IF/THEN SAVES THE INITIAL AND FINAL
    MDATA##(J)=NDATA##(J) 'POINTS THAT ARE NOT REPLACED BY
  ELSE
    FOR K=1 TO P 'THIS ELSE STATEMENT CALCULATES THE LEAST-
      I=J+K-Y 'SQUARES REGRESSION FOR EACH SMOOTHING RANGE
      NP##(K)=NDATA##(I) 'AND REPLACES THE MIDPOINT WITH A
    NEXT K
    NSUM##=17*NP##(3)+12*(NP##(2)+NP##(4))-3*(NP##(1)+NP##(5))
    MDATA##(J)=NSUM##/35
  END IF
NEXT J
GOSUB OUTPUTFILE

QCSMOOTH7:
Y=(P+1)/2 'Y=MIDPOINT OF SMOOTH RANGE, P=7(THIS SUBROUTINE)
Z=L-Y+1 'Z=LAST MIDPOINT NO FOR 7 PT SMOOTH, L=LAST POINT
FOR J=1 TO L ' J, K ARE COUNTERS IN FOR LOOPS
  IF J<Y OR J>Z THEN 'THIS IF/THEN SAVES THE INITIAL AND FINAL
    MDATA##(J)=NDATA##(J) 'POINTS THAT ARE NOT REPLACED BY
  ELSE
    FOR K=1 TO P 'THIS ELSE STATEMENT CALCULATES THE LEAST-
      I=J+K-Y 'SQUARES REGRESSION FOR EACH SMOOTHING RANGE
      NP##(K)=NDATA##(I) 'AND REPLACES THE MIDPOINT WITH A
    NEXT K
    NSUM##=7*NP##(4)+6*(NP##(3)+NP##(5))+3*(NP##(2)+NP##(6))-2*(NP##(1)+NP##
      #7))
    MDATA##(J)=NSUM##/21
APPENDIX 1

END IF
NEXT J
GOSUB OUTPUTFILE

QCSMOOTH9:
Y=(P+1)/2   'Y=MIDPOINT OF SMOOTH RANGE, P=9(THIS SUBROUTINE)
Z=L-Y+1     'Z=LAST MIDPOINT NO FOR 9 PT SMOOTH, L=LAST POINT
FOR J=1 TO L   'J, K ARE COUNTERS IN FOR LOOPS
    IF J<Y OR J>Z THEN   'THIS IF/THEN SAVES THE INITIAL AND FINAL
        MDATA##(J)=NDATA##(J)  'POINTS THAT ARE NOT REPLACED BY
                                   'QCSMOOTH
    ELSE
        FOR K=1 TO P   'THIS ELSE STATEMENT CALCULATES THE LEAST-
            I=J+K-Y  'SQUARES REGRESSION FOR EACH SMOOTHING
            'RANGE
            NP##(K)=NDATA##(I)  'AND REPLACES THE MIDPOINT WITH A
                                   'NEW VALUE
        NEXT K
        ANSUM##=59*NP##(5)+54*(NP##(4)+NP##(6))+39*(NP##(3)+NP##(7))
        BNSUM##=14*(NP##(2)+NP##(8))-21*(NP##(1)+NP##(9))
        NSUM##=ANSUM##+BNSUM##
        MDATA##(J)=NSUM##/23
    END IF
NEXT J
GOSUB OUTPUTFILE

QCSMOOTH11:
Y=(P+1)/2   'Y=MIDPOINT OF SMOOTH RANGE, P=11(THIS SUBROUTINE)
Z=L-Y+1     'Z=LAST MIDPOINT NO FOR 11 PT SMOOTH, L=LAST POINT
FOR J=1 TO L   'J, K ARE COUNTERS IN FOR LOOPS
    IF J<Y OR J>Z THEN   'THIS IF/THEN SAVES THE INITIAL AND FINAL
        MDATA##(J)=NDATA##(J)  'POINTS THAT ARE NOT REPLACED BY
                                   'QCSMOOTH
    ELSE
        FOR K=1 TO P   'THIS ELSE STATEMENT CALCULATES THE LEAST-
            I=J+K-Y  'SQUARES REGRESSION FOR EACH SMOOTHING
            'RANGE
            NP##(K)=NDATA##(I)  'AND REPLACES THE MIDPOINT WITH A
                                   'NEW VALUE
        NEXT K
        ANSUM##=89*NP##(6)+84*(NP##(5)+NP##(7))+69*(NP##(4)+NP##(8))
APPENDIX 1

BNSUM## = 44*(NP##(3)+NP##(9))+9*(NP##(2)+NP##(10))-36*(NP##(1)+NP##(11))
NSUM## = ANSUM## + BNSUM##
MDATA##(J) = NSUM##/429
END IF
NEXT J
GOSUB OUTPUTFILE

QCSMOOTH13:
Y=(P+1)/2   'Y=MIDPOINT OF SMOOTH RANGE, P=13 (THIS SUBROUTINE)
Z=L-Y+1   'Z=LAST MIDPOINT NO FOR 15 PT SMOOTH, L=LAST POINT
FOR J=1 TO L   'J, K ARE COUNTERS IN FOR LOOPS
  IF J<Y OR J>Z THEN   'THIS IF/THEN SAVES THE INITIAL AND FINAL
    MDATA##(J)=NDATA##(J)   'POINTS THAT ARE NOT REPLACED BY
    QCSMOOTH
  ELSE
    FOR K=1 TO P   'THIS ELSE STATEMENT CALCULATES THE LEAST-
      I=J+K-Y   'SQUARES REGRESSION FOR EACH SMOOTHING
      'RANGE
      NP##(K)=NDATA##(I)   'AND REPLACES THE MIDPOINT WITH A
      'NEW VALUE
    NEXT K
    ANSUM## = 25*NP##(7)+24*(NP##(6)+NP##(8))+21*(NP##(5)+NP##(9))+
                   16*(NP##(4)+NP##(10))
    BNSUM## = 9*(NP##(3)+NP##(11))-11*(NP##(1)+NP##(13))
    NSUM## = ANSUM## + BNSUM##
    MDATA##(J) = NSUM##/143
  END IF
NEXT J
GOSUB OUTPUTFILE

QCSMOOTH15:
Y=(P+1)/2   'Y=MIDPOINT OF SMOOTH RANGE, P=15 (THIS SUBROUTINE)
Z=L-Y+1   'Z=LAST MIDPOINT NO FOR 15 PT SMOOTH, L=LAST POINT
FOR J=1 TO L   'J, K ARE COUNTERS IN FOR LOOPS
  IF J<Y OR J>Z THEN   'THIS IF/THEN SAVES THE INITIAL AND FINAL
    MDATA##(J)=NDATA##(J)   'POINTS THAT ARE NOT REPLACED BY
    QCSMOOTH
  ELSE
    FOR K=1 TO P   'THIS ELSE STATEMENT CALCULATES THE LEAST-
      I=J+K-Y   'SQUARES REGRESSION FOR EACH SMOOTHING
      'RANGE

APPENDIX 1

NP##(K)=NDATA##(I) ' AND REPLACES THE MIDPOINT WITH A
' NEW VALUE

NEXT K
ANSUM##=167*NP##(8)+162*(NP##(7)+NP##(9))+147*(NP##(6)+NP##(10))
BNSUM##=122*(NP##(5)+NP##(11))+87*(NP##(4)+NP##(12))+
42*(NP##(3)+NP##(13))
CNSUM##=-13*(NP##(2)+NP##(14))-78*(NP##(1)+NP##(15))
NSUM##=ANSUM##+BNSUM##+CNSUM##
MDATA##(J)=NSUM##/1105
END IF
NEXT J
GOSUB OUTPUTFILE

QCSMOOTHI7:
Y=(P+1)/2 'Y=MIDPOINT OF SMOOTH RANGE, P=17(THIS SUBROUTINE)
Z=L-Y+1 'Z=LAST MIDPOINT NO FOR 17 PT SMOOTH, L=LAST POINT
FOR J=1 TO L ' J, K ARE COUNTERS IN FOR LOOPS
  IF J<Y OR J>Z THEN ' THIS IF/THEN SAVES THE INITIAL AND FINAL
    MDATA##(J)=NDATA##(J) 'POINTS THAT ARE NOT REPLACED BY
                      'QCSMOOTH
  ELSE
    FOR K=1 TO P ' THIS ELSE STATEMENT CALCULATES THE LEAST-
                  'SQUARES REGRESSION FOR EACH SMOOTHING
      I=J+K-Y ' RANGE
      NP##(K)=NDATA##(I) ' AND REPLACES THE MIDPOINT WITH A
                          'NEW VALUE
    NEXT K
    ANSUM##=43*NP##(9)+42*(NP##(8)+NP##(10))+39*(NP##(7)+NP##(11))
    BNSUM##=34*(NP##(5)+NP##(12))+27*(NP##(4)+NP##(13))+
            18*(NP##(4)+NP##(14))
    CNSUM##=7*(NP##(3)+NP##(15))-6*(NP##(2)+NP##(16))-21*(NP##(1)+NP##(17))
    NSUM##=ANSUM##+BNSUM##+CNSUM##
    MDATA##(J)=NSUM##/323
  END IF
NEXT J
GOSUB OUTPUTFILE

QCSMOOTHI9:
Y=(P+1)/2 'Y=MIDPOINT OF SMOOTH RANGE, P=19(THIS SUBROUTINE)
Z=L-Y+1 'Z=LAST MIDPOINT NO FOR 19 PT SMOOTH, L=LAST POINT
FOR J=1 TO L ' J, K ARE COUNTERS IN FOR LOOPS
  IF J<Y OR J>Z THEN ' THIS IF/THEN SAVES THE INITIAL AND FINAL
    MDATA##(J)=NDATA##(J) 'POINTS THAT ARE NOT REPLACED BY
                      'QCSMOOTH
  ELSE
    FOR K=1 TO P ' THIS ELSE STATEMENT CALCULATES THE LEAST-
                  'SQUARES REGRESSION FOR EACH SMOOTHING
      I=J+K-Y ' RANGE
      NP##(K)=NDATA##(I) ' AND REPLACES THE MIDPOINT WITH A
                          'NEW VALUE
    NEXT K
    ANSUM##=43*NP##(9)+42*(NP##(8)+NP##(10))+39*(NP##(7)+NP##(11))
    BNSUM##=34*(NP##(5)+NP##(12))+27*(NP##(4)+NP##(13))+
            18*(NP##(4)+NP##(14))
    CNSUM##=7*(NP##(3)+NP##(15))-6*(NP##(2)+NP##(16))-21*(NP##(1)+NP##(17))
    NSUM##=ANSUM##+BNSUM##+CNSUM##
    MDATA##(J)=NSUM##/323
  END IF
NEXT J
GOSUB OUTPUTFILE
APPENDIX 1

IF \( J < Y \) OR \( J > Z \) THEN \\
\( \text{THIS IF/THEN SAVES THE INITIAL AND FINAL} \) \\
\( \text{POINTS THAT ARE NOT REPLACED BY} \) \\
\( \text{QCSMOOTH} \) \\
ELSE \\
FOR \( K = 1 \) TO \( P \) \\
\( \text{THIS ELSE STATEMENT CALCULATES THE LEAST-} \) \\
\( \text{SQUARES REGRESSION FOR EACH SMOOTHING} \) \\
\( \text{RANGE} \) \\
\( \text{NP##(K)} = \text{NDATA##(I)} \) \\
\( \text{AND REPLACES THE MIDPOINT WITH A} \) \\
\( \text{NEW VALUE} \) \\
NEXT \( K \) \\
\( \text{ANSUM##=269*NP##(10)+264*(NP##(9)+NP##(11))+249*(NP##(8)+NP##(12))} \) \\
\( \text{BNSUM##=224*(NP##(7)+NP##(13))+189*(NP##(6)+NP##(14))+} \) \\
\( 144*(NP##(5)+NP##(15)) \) \\
\( \text{CNSUM##=89*(NP##(4)+NP##(16))+24*(NP##(3)+NP##(17))-} \) \\
\( 51*(NP##(2)+NP##(18)) \) \\
\( \text{DNSUM##=-136*(NP##(1)+NP##(19))} \) \\
\( \text{NSUM##=ANSUM##+BNSUM##+CNSUM##+DNSUM##} \) \\
\( \text{MDATA##(J)} = \text{NSUM##/2261} \) \\
END IF \\
NEXT \( J \) \\
GOSUB OUTPUTFILE

QCSMOOTH21:
\( Y = (P+1)/2 \) \\
\( \text{Y=MIDPOINT OF SMOOTH RANGE, P=21 (THIS SUBROUTINE)} \) \\
\( Z = L-Y+1 \) \\
\( \text{Z=LAST MIDPOINT NO FOR 21 PT SMOOTH, L=LAST POINT} \) \\
FOR \( J = 1 \) TO \( L \) \\
\( \text{J, K ARE COUNTERS IN FOR LOOPS} \) \\
IF \( J < Y \) OR \( J > Z \) THEN \\
\( \text{THIS IF/THEN SAVES THE INITIAL AND FINAL} \) \\
\( \text{POINTS THAT ARE NOT REPLACED BY} \) \\
\( \text{QCSMOOTH} \) \\
ELSE \\
FOR \( K = 1 \) TO \( P \) \\
\( \text{THIS ELSE STATEMENT CALCULATES THE LEAST-} \) \\
\( \text{SQUARES REGRESSION FOR EACH SMOOTHING} \) \\
\( \text{RANGE} \) \\
\( \text{NP##(K)} = \text{NDATA##(I)} \) \\
\( \text{AND REPLACES THE MIDPOINT WITH A} \) \\
\( \text{NEW VALUE} \) \\
NEXT \( K \) \\
\( \text{ANSUM##=329*NP##(11)+324*(NP##(10)+NP##(12))+309*(NP##(9)+NP##(13))} \) \\
\( \text{NSUM##=284*(NP##(8)+NP##(14))+249*(NP##(7)+NP##(15))+} \) \\
\( 204*(NP##(6)+NP##(16)) \) \\
\( \text{CNSUM##=149*(NP##(5)+NP##(17))+84*(NP##(4)+NP##(18))+} \) \\
\( 9*(NP##(3)+NP##(19)) \) \\
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APPENDIX 1

DNSUM##=-76*(NP##(2)+NP##(20))-171*(NP##(1)+NP##(21))
NSUM##=ANSUM##+BNSUM##+CNSUM##+DNSUM##
MDATA##(J)=NSUM##/3059
END IF
NEXT J
GOSUB OUTPUTFILE

QCSMOOTH23:
Y=(P+1)/2 'Y=MIDPOINT OF SMOOTH RANGE, P=23(THIS SUBROUTINE)
Z=L-Y+1 'Z=LAST MIDPOINT NO FOR 23 PT SMOOTH, L=LAST POINT
FOR J=1 TO L ' J, K ARE COUNTERS IN FOR LOOPS
  IF J<Y OR J>Z THEN ' THIS IF/THEN SAVES THE INITIAL AND FINAL
    MDATA##(J)=NDATA##(J) ' POINTS THAT ARE NOT REPLACED BY
  ELSE
    FOR K=1 TO P ' THIS ELSE STATEMENT CALCULATES THE LEAST-
      I=J+K-Y ' SQUARES REGRESSION FOR EACH SMOOTHING
      NP##(K)=NDATA##(I) ' RANGE
    NEXT K
  END IF
NEXT J
GOSUB OUTPUTFILE

QCSMOOTH25:
Y=(P+1)/2 'Y=MIDPOINT OF SMOOTH RANGE, P=25(THIS SUBROUTINE)
Z=L-Y+1 'Z=LAST MIDPOINT NO FOR 25 PT SMOOTH, L=LAST POINT
FOR J=1 TO L ' J, K ARE COUNTERS IN FOR LOOPS
  IF J<Y OR J>Z THEN ' THIS IF/THEN SAVES THE INITIAL AND FINAL
    MDATA##(J)=NDATA##(J) ' POINTS THAT ARE NOT REPLACED BY
  END IF
NEXT J
GOSUB OUTPUTFILE
APPENDIX I

ELSE
  FOR K=1 TO P  ' THIS ELSE STATEMENT CALCULATES THE LEAST-
  I=J+K-Y  ' SQUARES REGRESSION FOR EACH SMOOTHING
  ' RANGE
  NP##(K)=NDATA##(I)  ' AND REPLACES THE MIDPOINT WITH A
  ' NEW VALUE
  NEXT K
ANSUM##=467*NP##(13)+462*(NP##(12)+NP##(14))+447*(NP##(11)+NP##(15))
BNSUM##=422*(NP##(10)+NP##(16))+387*(NP##(9)+NP##(17))+
  322*(NP##(8)+NP##(18))
CNSUM##=287*(NP##(7)+NP##(19))+222*(NP##(6)+NP##(20))+
  147*(NP##(5)+NP##(21))
DNSUM##=62*(NP##(4)+NP##(22))-33*(NP##(3)+NP##(23))-138*(NP##(2)+NP##(24))
ENSUM##=-253*(NP##(1)+NP##(25))
NSUM##=ANSUM##+BNSUM##+CNSUM##+DNSUM##+ENSUM##
MDATA##(J)=NSUM##/5175
END IF
NEXT J
GOSUB OUTPUTFILE
APPENDIX 2

REM DLNLNT2.BAS: TAKES CURRENT/TIME DATA FROM **10** OTHER FILES AND OUTPUTS **10** NEW FILES WITH dlni/dlnt vs time (in seconds only) 7/2/95 BY B. SARSFIELD

REM FROM OLD FILES: T=TIME, Z=CURRENT, #=DOUBLE PRECISION
REM FOR NEW FILES: TN=NEW TIME(MIDPOINT), DZT=dlni/dlnt
DEFINT L, M, N

PRINT:PRINT:PRINT
PRINT "THIS PROGRAM CALCULATES dlni/dlnt vs t FROM **10** FILES CONTAINING"
PRINT "ARRAYS OF CURRENT VS TIME DATA [IN SECONDS ONLY]." 
PRINT:PRINT
INPUT "ENTER FILE NAME OF CURRENT/TIME DATA #1"; F1$
INPUT "" #2$; F2$
INPUT "" #3$; F3$
INPUT "" #4$; F4$
INPUT "" #5$; F5$
INPUT "" #6$; F6$
INPUT "" #7$; F7$
INPUT "" #8$; F8$
INPUT "" #9$; F9$
INPUT "" #10$; F10$
PRINT

FOR N=1 TO 10 
  ' COUNT FILE NUMBERS
  IF N=1 THEN 
    L=1
    OPEN F1$ FOR INPUT AS #1 
    ' OPEN OLD FILE AND READ DATA
  
  OPEN F#$(N) FOR OUTPUT AS #N 
  ' OPEN NEW FILE AND WRITE DATA
  
  FOR I=1 TO 2000 
    INPUT #1; T#, Z#
    TN#=T# + D#(N-1) / 2
    DZT#=D#(N) / (T# - D#(N-1))
    PRINT #N; TN#; DZT#
    PRINT 
  NEXT I 
  CLOSE #1, #N 

NEXT N
APPENDIX 2

WHILE NOT EOF(1)
   INPUT #1, T#(L), Z#(L)
   Z#(L)=ABS(Z#(L))
   L=L+1
WEND
CLOSE #1
L=L-1
GOSUB DLNIDLNT
OPEN G1$ FOR OUTPUT AS #2 'SAVE DATA TO NEW FILE
   FOR M=1 TO (L-1)
      WRITE #2, TN#(M), DZT#(M)
   NEXT M
CLOSE #2
PRINT G1$ " IS SAVED"
ELSEIF N=2 THEN
   L=1
   OPEN F2$ FOR INPUT AS #3 'OPEN OLD FILE AND READ DATA
   WHILE NOT EOF(3)
      INPUT #3, T#(L), Z#(L)
      Z#(L)=ABS(Z#(L))
      L=L+1
   WEND
   CLOSE #3
   L=L-1
   GOSUB DLNIDLNT
   OPEN G2$ FOR OUTPUT AS #4 'SAVE DATA TO NEW FILE
   FOR M=1 TO (L-1)
      WRITE #4, TN#(M), DZT#(M)
   NEXT M
   CLOSE #4
   PRINT G2$ " IS SAVED"
ELSEIF N=3 THEN
   L=1
   OPEN F3$ FOR INPUT AS #5 'OPEN OLD FILE AND READ DATA
   WHILE NOT EOF(5)
      INPUT #5, T#(L), Z#(L)
      Z#(L)=ABS(Z#(L))
      L=L+1
   WEND
   CLOSE #5
   L=L-1
APPENDIX 2

GOSUB DLNIDLNT
OPEN G3$ FOR OUTPUT AS #6 ' SAVE DATA TO NEW FILE
FOR M=1 TO (L-1)
    WRITE #6, TN#(M), DZT#(M)
NEXT M
CLOSE #6
PRINT G3$ " IS SAVED"
ELSEIF N=4 THEN
    L=1
    OPEN F4$ FOR INPUT AS #7 ' OPEN OLD FILE AND READ DATA
    WHILE NOT EOF(7)
        INPUT #7, T#(L), Z#(L)
        Z#(L)=ABS(Z#(L))
        L=L+1
    WEND
    CLOSE #7
    L=L-1
    GOSUB DLNIDLNT
    OPEN G4$ FOR OUTPUT AS #8 ' SAVE DATA TO NEW FILE
    FOR M=1 TO (L-1)
        WRITE #8, TN#(M), DZT#(M)
    NEXT M
    CLOSE #8
    PRINT G4$ " IS SAVED"
ELSEIF N=5 THEN
    L=1
    OPEN F5$ FOR INPUT AS #9 ' OPEN OLD FILE AND READ DATA
    WHILE NOT EOF(9)
        INPUT #9, T#(L), Z#(L)
        Z#(L)=ABS(Z#(L))
        L=L+1
    WEND
    CLOSE #9
    L=L-1
    GOSUB DLNIDLNT
    OPEN G5$ FOR OUTPUT AS #10 ' SAVE DATA TO NEW FILE
    FOR M=1 TO (L-1)
        WRITE #10, TN#(M), DZT#(M)
    NEXT M
    CLOSE #10
    PRINT G5$ " IS SAVED"
ELSEIF N=6 THEN
  L=1
  OPEN F6$ FOR INPUT AS #11 ' OPEN OLD FILE AND READ DATA
  WHILE NOT EOF(11)
    INPUT #11, T#(L), Z#(L)
    Z#(L)=ABS(Z#(L))
    L=L+1
  WEND
  CLOSE #11
  L=L-1
  GOSUB DLNIDLNT
  OPEN G6$ FOR OUTPUT AS #12 ' SAVE DATA TO NEW FILE
  FOR M=1 TO (L-1)
    WRITE #12, TN#(M), DZT#(M)
  NEXT M
  CLOSE #12
  PRINT G6$ " IS SAVED"
ELSEIF N=7 THEN
  L=1
  OPEN F7$ FOR INPUT AS #13 ' OPEN OLD FILE AND READ DATA
  WHILE NOT EOF(13)
    INPUT #13, T#(L), Z#(L)
    Z#(L)=ABS(Z#(L))
    L=L+1
  WEND
  CLOSE #13
  L=L-1
  GOSUB DLNIDLNT
  OPEN G7$ FOR OUTPUT AS #14 ' SAVE DATA TO NEW FILE
  FOR M=1 TO (L-1)
    WRITE #14, TN#(M), DZT#(M)
  NEXT M
  CLOSE #14
  PRINT G7$ " IS SAVED"
ELSEIF N=8 THEN
  L=1
  OPEN F8$ FOR INPUT AS #15 ' OPEN OLD FILE AND READ DATA
  WHILE NOT EOF(15)
    INPUT #15, T#(L), Z#(L)
    Z#(L)=ABS(Z#(L))
    L=L+1
  WEND
  CLOSE #15
  GOSUB DLNIDLNT
  OPEN G8$ FOR OUTPUT AS #16 ' SAVE DATA TO NEW FILE
  FOR M=1 TO (L-1)
    WRITE #16, TN#(M), DZT#(M)
  NEXT M
  CLOSE #16
  PRINT G8$ " IS SAVED"
WEND
CLOSE #15
L=L-1
GOSUB DLNIDLNT
OPEN G8$ FOR OUTPUT AS #16 ' SAVE DATA TO NEW FILE
FOR M=1 TO (L-1)
    WRITE #16, TN#(M), DZT#(M)
NEXT M
CLOSE #16
PRINT G8$ " IS SAVED"
ELSEIF N=9 THEN
    L=1
    OPEN F9$ FOR INPUT AS #17 ' OPEN OLD FILE AND READ DATA
    WHILE NOT EOF(17)
        INPUT #17, T#(L), Z#(L)
        Z#(L)=ABS(Z#(L))
        L=L+1
    WEND
    CLOSE #17
    L=L-1
    GOSUB DLNIDLNT
    OPEN G9$ FOR OUTPUT AS #18 ' SAVE DATA TO NEW FILE
    FOR M=1 TO (L-1)
        WRITE #18, TN#(M), DZT#(M)
    NEXT M
    CLOSE #18
    PRINT G9$ " IS SAVED"
ELSEIF N=10 THEN
    L=1
    OPEN F10$ FOR INPUT AS #19 ' OPEN OLD FILE AND READ DATA
    WHILE NOT EOF(19)
        INPUT #19, T#(L), Z#(L)
        Z#(L)=ABS(Z#(L))
        L=L+1
    WEND
    CLOSE #19
    L=L-1
    GOSUB DLNIDLNT
    OPEN G10$ FOR OUTPUT AS #20 ' SAVE DATA TO NEW FILE
    FOR M=1 TO (L-1)
        WRITE #20, TN#(M), DZT#(M)
    NEXT M
APPENDIX 2

NEXT M
CLOSE #20
PRINT G10$ " IS SAVED"
END IF
NEXT N
END

DLNIDLNT: ' CALCULATE TN AND DZT
FOR M=1 TO (L-1)
    TN#(M)=((T#(M+1) - T#(M))/2)+T#(M) ' CALC TN
    DZ#=LOG(Z#(M+1))-LOG(Z#(M)) ' delta(lni)
    DT#=LOG(T#(M+1))-LOG(T#(M)) ' delta(lnt)
    DZT#(M)=DZ#/DT# ' delta(lni)/delta(lnt)
NEXT M
RETURN
'MSECSEC.BAS: CONVERTS MSEC TO SEC FOR TIME(X) VS Y FILES
' BY B. SARSFIELD, 6/95

DIM T(2001), Y(2001)

PRINT:PRINT
PRINT " MSECSEC.BAS"
PRINT
GOSUB MAIN

MAIN: 
INPUT "Do you want to translate X data in a file from msec to secs: "; YN$ 
YN$=UCASE$(YN$)
IF YN$="Y" OR YN$="YES" THEN GOSUB TRANSLATE
 END

TRANSLATE:
L=1
INPUT "Enter FILE NAME with X value in msec: "; FILENAME$
OPEN FILENAME$ FOR INPUT AS #1
 WHILE NOT EOF(1)
 INPUT #1, T(L), Y(L)
 T(L)=T(L)/1000
 L=L+1
 WEND
L=L-1
CLOSE #1
PRINT "msec data in **";FILENAME$;"** is translated to seconds"

OPEN FILENAME$ FOR OUTPUT AS #1
 FOR M=1 TO L
 WRITE #1, T(M), Y(M)
 NEXT M
 CLOSE #1
PRINT "Data with time in seconds is saved in **";FILENAME$;"**"
GOSUB MAIN
APPENDIX 4

' DLNT3.BAS as described/written by J.T.Maloy on 4/27/95 in written notes
' prepared by B. Sarsfield, 4/28/95

' ** from 1 file, does 100, 50, 25 & 10 point intervals for data with
time in seconds only ***

DIM DELNIDELNT##(200 1)
DIM T(200 1), I##(200 1)
DEFINT J-M
PRINT
PRINT
" DLNI/DLNT VS T WITH DATA POINT REMOVAL."
INPUT "Enter file name containing data to be manipulated: ";£$
INPUT "Enter file name for smoothed data(100 pt): ";g1$
INPUT "Enter file name for smoothed data(50 pt): ";g2$
INPUT "Enter file name for smoothed data(25 pt): ";g3$
INPUT "Enter file name for smoothed data(10 pt): ";g4$
L=1

OPEN £$ FOR INPUT AS #1
WHILE NOT EOF(1)
  INPUT #1, T(L), I##(L)
  I##(L) = abs(I##(L)) , absolute value of current L=L+1
WEND
CLOSE #1
LMAX=L-1
FOR M=1 TO 4
  LMAX=L-1
  IF M=1 THEN
    L=100
    GOSUB DLNIDLNT
    OPEN g1$ FOR OUTPUT AS #1
    FOR L=2 to NMAX
      WRITE #1, T(L), DELNIDELNT##(L)
    NEXT L
    CLOSE #1
    PRINT "**** ";g1$;" is saved with ";NMAX-1;"data points ****"
  ELSEIF M=2 THEN
    L=50
    GOSUB DLNIDLNT
    OPEN g2$ FOR OUTPUT AS #1
  ELSEIF M=3 THEN
    L=25
    GOSUB DLNIDLNT
    OPEN g3$ FOR OUTPUT AS #1
  ELSEIF M=4 THEN
    L=10
    GOSUB DLNIDLNT
    OPEN g4$ FOR OUTPUT AS #1
  END IF

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FOR L=2 to NMAX
    WRITE #1, t(L), delnidelnt##(L)
NEXT L
CLOSE #1
PRINT "*** ;G2$;" is saved with";NMAX-1;"data points ***"
ELSEIF M=3 THEN
    I=25
    GOSUB DLNIDLNT
    OPEN g3$ FOR OUTPUT AS #1
    FOR L=2 to NMAX
        WRITE #1, t(L), delnidelnt##(L)
    NEXT L
    CLOSE #1
    PRINT "*** ;G3$;" is saved with";NMAX-1;"data points ***"
ELSEIF M=4 THEN
    I=10
    GOSUB DLNIDLNT
    OPEN g4$ FOR OUTPUT AS #1
    FOR L=2 to NMAX
        WRITE #1, t(L), delnidelnt##(L)
    NEXT L
    CLOSE #1
    PRINT "*** ;G4$;" is saved with";NMAX-1;"data points ***"
END IF
NEXT M
END

DLNIDLNT:
    NMAX=LMAX-(LMAX/I)
    j=1
    for n=2 to NMAX
        if ((n-I*j)>=0) then j=j+1
            delnidelnt##(n)=(log(i##(n+j))-log(i##(n-j)))/(log(t(n+j))-log(t(n-j)))
    next n
RETURN
APPENDIX 5

REM SHOUP05.BAS -
REM SIMULATES SHOUP AND SZABO DIFFUSION CONTROL CURRENT
REM January, 1998 - by Beth Sarsfield and J.T. Maloy
rem this version works for several orders of time magnitude
rem this version saves the data to a named file
rem this version uses the dimensionless value tau

print:print:print
print "Shoup and Szabo Diffusion Control Simulation"
print "using DimensionlessTau"
print
input "Enter the number of points per decade (10000 total max): ";pd
input "Enter file name for saved time-z data: ";fl$
input "Enter file name for saved time - dlnz/dln(t) data: ";f2$
PRINT

rem z(t) = (i(t)/4πFrDC) = 0.7854 + 0.2146e^(-x) + (1.2778*sqr(π)/2)*x
rem i(t)=4πFrDC(0.7854 + 0.2146e^(-x) + (1.2778*sqr(π)/2)*x)
rem τ^(-0.5) = r/(2*sqr(Dt)) where t = time

deltat% = 0                              ' initializes at 0 so 10^0 = 1
tau1 = 1E-7                             ' starting tau

print tab(6) "tau" tab(20) "z" tab(40) "dlnz/dln(tau)"
open fl$ for output as #1
open f2$ for output as #2

for deltat% = 0 to 11 step 1             ' 11 orders of magnitude for tau
tau01 = (10^(deltat%))*tau1             'sets where to end nested for/next loop and subtracts a small constant so program won't divide by zero
tau03 = (10*tau01)-(tau01/100)         ' sets step size

'stop
stp = tau01/(pd/10)
for tau = tau01 to tau03 step stp
  x = 0.39115/(sqr(tau))                  ' x = 0.7823tau^(-0.5)
  ex = EXP(-x)
  z = 0.7854 + (0.2146*ex) + (1.1324*x)
  write #1, tau, z
if tau > tau1 then
    dlnz = (log(z) - (log(ztold))
    dlnlnt = log(tau) - log(tauold)
    dlnzdlnt = dlnz/dlnlnt
    write #2, tau, dlnzdlnt
end if
print tab(5) tau tab(19) z tab(39) dlnzdlnt
    tauold = tau
    ztold = z
next tau
next deltat%
close #1
close #2
print "time-z data is stored in ";f1$
print "time-dlnz/dlnlnt data is stored in ";f2$
print "Program Shoup05.bas completed"
END
Simulation of Disproportionation Mechanism

\[
\text{CPZ} \leftrightarrow \text{CPZ}^+ + e^- \quad \text{Oxidation}
\]
\[
2\text{CPZ}^+ \rightarrow \text{CPZ} + \text{CPZ}^{++} \quad \text{Disproportionation}
\]

Model Constants:
- \(L\): Total number of iterations
- \(K\): Specific iteration number
- \(J\): Number of volume elements
- \(f_x\): Fraction of CPZ, CPZ\(^+\) or CPZ\(^{++}\)
- \(D\text{Mx}\): Model Diffusion Coefficient for CPZ, CPZ\(^+\) or CPZ\(^{++}\)
- \(k\): Disproportionation Rate Constant
- \(t_k\): Known time in physical experiment
- \(C^*\): Bulk concentration of CPZ
- \(\text{MKAT}\): Model Disproportionation Rate Coefficient \((k_t C^*)\)
- \(x/(D\text{t}_k)^{1/2}\): Dimensionless distance
  \[
  A = \text{CPZ} \quad B = \text{CPZ}^+ \quad C = \text{CPZ}^{++}
  \]

Diffusion Algorithm:
\[
f_x(J) = f_x(J) + D\text{Mx}(f_x(J+1) - 2f_x(J) + f_x(J-1))
\]

Disproportionation Algorithms:
\[
\begin{align*}
  f_A(J) &= f_A(J) + [(\text{MKAT}/L) \ast (f_B(J))^2] \\
  f_B(J) &= f_B(J) - 2[(\text{MKAT}/L) \ast (f_B(J))^2] \\
  f_C(J) &= f_C(J) + [(\text{MKAT}/L) \ast (f_B(J))^2]
\end{align*}
\]

Dimensionless current: \(Z(K) = (L/D\text{MA})^{1/2} \ast ((D\text{MA} \ast f_A(2)) + \text{FCDISP})\)
  where \(\text{FCDISP} = (\text{MKAT}/L) \ast f_B(1)^2\)

Simulation Technique (For each iteration \(K\)):
1. Calculate new concentrations in each volume element \(J\) due to diffusion.
2. Calculate revised concentrations in each volume element \(J\) due to disproportionation mechanism.
3. Repeat steps 1 and 2 until complete \(L\) iterations.
'DISP3.BAS: Simulates CA for disproportionation, modification of
'COTTRELL.BAS by J. T. Maloy (simulated a Cottrell Experiment)

DIM FAOLD(136), FBOLD(136), FCOLD(136)
DIM FANEW(136), FBNEW(136), FCNEW(136)
DIM Z(1001), T(1001)
DEFINT J, K, L

PRINT:PRINT:PRINT
PRINT TAB(30) "DISPR3.BAS"
PRINT:PRINT
PRINT "Simulation of chronoamperometric experiments for the following mechanism:

PRINT TAB(20) "A +/- e => B" TAB(45) "Reduction/Oxidation"
PRINT TAB(20) "B + B => C + A" TAB(45) "Disproportionation"
PRINT
PRINT "Enter the following variables:"
PRINT 
PRINT "(Select values for MKAT and L such that ** 0 <= MKAT <= L **)"
PRINT
INPUT "L (number of iterations, [up to 1000]): 
INPUT "MKAT (model disproportionation rate coefficient): 
INPUT "DMA (model diffusion coefficient for A, [up to 0.5]): 
INPUT "DMB (model diffusion coefficient for B, [up to 0.5]): 
INPUT "DMC (model diffusion coefficient for C, [up to 0.5]): 

PRINT:PRINT

K4=0.4*L ' SET K VALUES FOR STORAGE OF FRACTION/DISTANCE DATA
K8=0.8*L

FOR J=1 TO 136 ' Initialize volume element arrays for time = 0
FAOLD(J)=1!
FBOLD(J)=0!
FCOLD(J)=0!
NEXT J

K=1 ' First Iteration: Calc first current-time point
FAOLD(1)=0!
FBOLD(1)=1.2*(MKAT/L)
IF FBOLD(1)<0 THEN FBOLD(1)=0!
FCOLD(1)=(MKAT/L)
APPENDIX 6

\[ T(1)=0.5/L \]
\[ Z(1)=\sqrt{L/DMA}(1+FCOLD(1)) \]

FOR \( K=2 \) TO \( L \)  ' START OF ALL SUBSEQUENT ITERATIONS [\( K=2 \) TO \( L \)]

FANEW(1)=0!  ' ELECTRODE BOUNDARY CONDITIONS FOR \( K=2 \) TO \( K=L \)
FBNEW(1)=FBOLD(1)+DMA*FAOLD(2)-DMB*(FBOLD(1)-FBOLD(2))
FCDISP=(MKAT/L)*FBNEW(1)*FBNEW(1)

' DISPROPORTIONATION EFFECT
FANEW(1)=FCOLD(1)-DMC*(FCOLD(1)-FCOLD(2))+FCDISP
FBNEW(1)=FBNEW(1)-2*FCDISP+FCDISP
IF FBNEW(1)<0 THEN FBNEW(1)=0!

T(K)=(K-0.5)/L  ' CURRENT-TIME BEHAVIOR CALCULATED
Z(K)=\sqrt{L/DMA}*(DMA*FAOLD(2)+FCDISP)

JMAX=3*\sqrt{2K}+1  ' CALC MAXIMUM VALUE OF J FOR GIVEN VALUE ' OF \( K \)

FOR \( J=2 \) TO JMAX

' NEW CONCENTRATIONS CALC'D BY DIFFUSION ALGORITHM
FANEW(J)=FAOLD(J)+DMA*(FAOLD(J+1)-2*FAOLD(J)+FAOLD(J-1))
FBNEW(J)=FBOLD(J)+DMB*(FBOLD(J+1)-2*FBOLD(J)+FBOLD(J-1))
FCNEW(J)=FCOLD(J)+DMC*(FCOLD(J+1)-2*FCOLD(J)+FCOLD(J-1))

' NEW CONCENTRATIONS AFFECTED BY DISPROPORTIONATION
FANEW(J)=FANEW(J)+(MKAT/L)*FBNEW(J)*FBNEW(J)
FCNEW(J)=FCNEW(J)+(MKAT/L)*FBNEW(J)*FBNEW(J)
FBNEW(J)=FBNEW(J)-2*(MKAT/L)*FBNEW(J)*FBNEW(J)
IF FBNEW(J)<0 THEN FBNEW(J)=0!

NEXT J

IF K4=K THEN  ' STORAGE OF FRACTION/DISTANCE DATA AT 40% OF L
OPEN "K4.DAT" FOR OUTPUT AS #1
FOR J=1 TO JMAX
    WRITE #1, J, FANEW(J), FBNEW(J), FCNEW(J)
NEXT J
CLOSE #1
PRINT "FRACTION/DISTANCE DATA AT 40% OF L IS STORED IN 'K4.DAT'"
ELSEIF K=K8 THEN

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APPENDIX 6

' STORAGE OF FRACTION/DISTANCE DATA AT 80% OF L
OPEN "K8.DAT" FOR OUTPUT AS #1
FOR J=1 TO JMAX
    WRITE #1, J, FANEW(J), FBNEW(J), FCNEW(J)
NEXT J
CLOSE #1
PRINT "FRACTION/DISTANCE DATA AT 80% OF L IS STORED IN 'K8.DAT'"
ELSEIF K=L THEN
    ' STORAGE OF FRACTION/DISTANCE DATA AT 100% OF L
OPEN "L.DAT" FOR OUTPUT AS #1
FOR J=1 TO JMAX
    WRITE #1, J, FANEW(J), FBNEW(J), FCNEW(J)
NEXT J
CLOSE #1
PRINT "FRACTION/DISTANCE DATA AT 100% OF L IS STORED IN 'L.DAT'"
END IF

FOR J=1 TO JMAX
    ' TRANSFORM NEW ARRAYS TO OLD ARRAYS FOR NEXT ITERATION
    FAOLD(J)=FANEW(J)
    FBOLD(J)=FBNEW(J)
    FCOLD(J)=FCNEW(J)
NEXT J

NEXT K
    ' ITERATION FEEDBACK FOR K=2 TO K=L

OPEN "DISP.DAT" FOR OUTPUT AS #1
FOR K=1 TO L
    WRITE #1, T(K), Z(K)
NEXT K
PRINT "T(K) VS Z(K) DATA IS STORED IN 'DISP.DAT'"
PRINT "PROGRAM COMPLETE"
PRINT
APPENDIX 7

Proposed Buffer Interaction Mechanism for Chlorpromazine Oxidation in Buffered Solutions*

* All reaction numbers, rate constants and equilibrium constants listed below and in program CPZ9.BAS are as represented in J.S. Mayausky, H. Y. Cheng, P. H. Sackett, and R. L. McCreery, Advances in Chemistry Series, 1982, No. 201, p. 443-456.

\[
\begin{align*}
\text{CPZ} & \rightarrow \text{CPZ}^+ + e^- \\
\text{CPZ}^+ + \text{B}^- & \leftrightarrow (\text{CPZB})^- \\
(\text{CPZB}) + \text{CPZ}^+ & \leftrightarrow (\text{CPZB})^+ + \text{CPZ} \\
\text{H}_2\text{O} + (\text{CPZB})^+ & \rightarrow \text{CPZO} + \text{HB} + \text{H}^+ \\
\end{align*}
\]

\[
\begin{align*}
K_8 &= \frac{k_8}{k_{-8}} = \frac{[\text{CPZB}^-]}{[\text{CPZ}^+][\text{B}^-]} \\
K_9 &= \frac{k_9}{k_{-9}} = \frac{[\text{CPZB}^-][\text{CPZ}]}{[\text{CPZB}^+][\text{CPZ}^+]}
\end{align*}
\]

Simulation of
Buffer Interaction Mechanism

Model Constants:

\begin{align*}
\text{L:} & \quad \text{Total number of iterations} \\
\text{K:} & \quad \text{Specific iteration number} \\
\text{J:} & \quad \text{Number of volume elements} \\
\text{f_i:} & \quad \text{Fraction of CPZ, CPZ^+, CPZB^-, CPZB^+, or CPZO} \\
\text{DMx:} & \quad \text{Model Diffusion Coefficient for each species} \\
\text{t_k:} & \quad \text{Known time in physical experiment} \\
\text{C^*:} & \quad \text{Bulk concentration of CPZ} \\
\text{[B^-]:} & \quad \text{Buffer anion concentration} \\
\frac{x}{(Dt_i)^{1/2}}: & \quad \text{Dimensionless distance} \\
\end{align*}

\[
\begin{align*}
\alpha &= k_8 t_k [\text{B}^-] \\
\beta &= k_9 t_k C^* \\
\gamma &= k_{10} t_k \\
K_8 &= k_{8}/k_{-8} \\
K_9 &= k_{9}/k_{-9}
\end{align*}
\]

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APPENDIX 7

Diffusion Algorithm:
\[ f_x(J) = f_x(J) + DMx(f_x(J+1) - 2f_x(J) + f_x(J-1)) \]

Buffer Interaction Algorithms:
- \[ f_A(J) = f_A(J) + X \]
- \[ f_B(J) = f_B(J) - W - X \]
- \[ f_c(J) = f_c(J) + W - X \]
- \[ f_D(J) = f_D(J) + X - Y \]
- \[ f_E(J) = f_E(J) + Y \]

Where:
- \[ W = (\alpha/L) * (f_{CPZ_1}(J) - (f_{CPZ_2}(J)/K_x)) \]
- \[ X = (\beta/L) * ((f_{CPZ_1}(J) * f_{CPZ_2}(J)) - (f_{CPZ_2}(J) * f_{CPZ_1}(J)/K_y)) \]
- \[ Y = (\gamma/L) * f_{CPZ_2}(J) \]

Dimensionless current: \[ Z(K) = \text{SQR}(L/DMA) * ((DMA * f_{CPZ}(2)) + X) \]

Simulation Technique (For each iteration (K)):
1. Calculate new concentrations in each volume element (J) due to diffusion.
2. Calculate revised concentrations in each volume element (J) due to Buffer Interaction mechanism.
3. Repeat steps 1 and 2 until complete L iterations.
APPENDIX 7

'CPZ104.BAS: Simulates CA for redox/chem rxns as described by McCreery
'October, 1996 by B.A. SARSFIELD and J.T. MALOY
'Based on CPZ103.BAS, but now also calc's dlni/dlint
'Based on CPZ102.BAS, but now calc's Z up to L=1000
'Based on CPZ101.BAS but includes [B-] in ALPHA
'WITHOUT STEADY STATE ASSUMPTION OR K8 SUBSTITUTIONS

DIM FAOLD(136), FBOLD(136), FCOLD(136), FDOLD(136), FEOLD(136)
DIM TOLD(136)
DIM FANEW(136), FBNEW(136), FCNEW(136), FDNEW(136), FENEW(136)
DIM TNEW(136)
DIM Z(1002), T(1002), TN(1002), DZT(1002)
DEFINT J, K, L, M, N
DEF FNW = ((ALPHA/L)*(FBNEW(J)-(FCNEW(J)/EK8)))
DEF FNX = ((BETA/L)*(FCNEW(J)*FBNEW(J)-(FDNEW(J)*FANEW(J)/EK9)))
DEF FNY = (GAMA/L)*FDNEW(J)

PRINT
PRINT:PRINT:PRINT
PRINT TAB(30) "CPZ104.BAS"
PRINT:LPRINT
PRINT "Simulation of chronoamperometric experiments for the following mechanism:
PRINT
PRINT TAB(5) "CPZ => 'CPZ+ + e' TAB(45) "Electrode Reaction"
PRINT TAB(5) "'CPZ+ + B <=> 'CPZB.' TAB(45) "K8 = Equilibrium Const."
PRINT TAB(5) "'CPZ+ + 'CPZB.' <=> 'CPZB+ + CPZ" TAB(45) "K9 = Equilibrium Const."
PRINT TAB(5) "H20 + 'CPZB+ => CPZO + HB + H" TAB(45) "k10 = Pseudo 1st Order"
PRINT
PRINT "Enter the following variables:"
PRINT
LPRINT:LPRINT:LPRINT
LPRINT TAB(30) "CPZ104.BAS"
LPRINT:LPRINT
LPRINT "Simulation of chronoamperometric experiments for the following mechanism:"
LPRINT
LPRINT TAB(5) "CPZ => 'CPZ+ + e' TAB(45) "Electrode Reaction"
LPRINT TAB(5) "'CPZ+ + B <=> 'CPZB.' TAB(45) "K8 = Equilibrium Const."
LPRINT TAB(5) "'CPZ+ + 'CPZB.' <=> 'CPZB+ + CPZ" TAB(45) "K9 = Equilibrium Const."
APPENDIX 7

LPRINT TAB(5) "H2O + 'CPZB+' => CPZO + HB + H" TAB(45) "k10 = Pseudo 1st Order"
LPRINT
LPRINT "Enter the following variables:"
LPRINT
INPUT "L (number of iterations, [up to 1000]): " ; L
INPUT "ALPHA (kp8*t{known}*[B-]), [SET ALPHA < or = L]: " ; ALPHA
INPUT "BETA (kp9*t{known}*[CPZbulk]), [SET BETA < or = L]: " ; BETA
INPUT "GAMA (kp10*t{known}), [SET GAMA < or = L]: " ; GAMA
INPUT "EK8 (kp8/kn8): " ; EK8
INPUT "EK9 (kp9/kn9): " ; EK9
INPUT "FILE NAME FOR COMPLETION, L AS *.DAT " ; LF$
INPUT "FILE NAME FOR Z (DIMENSIONLESS CURRENT) AS *.DAT " ; ZF$
INPUT "FILE NAME FOR DLNZ/DLINT VS TIME AS *.DAT " ; DZTF$
LPRINT "L (number of iterations, [up to 1000]): " ; L
LPRINT "ALPHA (kp8*t{known}*[B-]), [SET ALPHA < or = L]: " ; ALPHA
LPRINT "BETA (kp9*t{known}*[CPZbulk]), [SET BETA < or = L]: " ; BETA
LPRINT "GAMA (kp10*t{known}), [SET GAMA < or = L]: " ; GAMA
LPRINT "EK8 (kp8/kn8): " ; EK8
LPRINT "EK9 (kp9/kn9): " ; EK9
LPRINT "FILE NAME FOR COMPLETION, L AS *.DAT " ; LF$
LPRINT "FILE NAME FOR Z (DIMENSIONLESS CURRENT) AS *.DAT " ; ZF$
LPRINT "FILE NAME FOR DLNZ/DLINT VS TIME AS *.DAT " ; DZTF$

LPRINT:

DMA=0.49
DMB=0.49
DMC=0.49
DMD=0.49
DME=0.49
K2=0.2*L
K4=0.4*L
K6=0.6*L
K8=0.8*L

FOR J=1 TO 136 ' Initialize volume element arrays for time = 0
FAOLD(J)=1! ' Old [CPZ]
FBOLD(J)=0! ' Old [CPZ+]
FCOLD(J)=0! ' Old [CPZB.]

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APPENDIX 7

FDOLD(J)=0! ' Old [CPZB+]
FEOLD(J)=0! ' Old [CPZO]

NEXT J

K=1 ' First Iteration: Calc first current-time point

J=1 ' Set J=1 for first groups of calculations

FAOLD(J)=0
FBOLD(J)=1
W = ((ALPHA/L)*(FBOLD(J)-(FCOLD(J)/E0))
X = ((BETA/L)*(FCOLD(J)*FBOLD(J)-(FDOLD(J)*FAOLD(J))/E0))
Y = (GAMA/L)*FDOLD(J)
FBOLD(J)=FBOLD(J)-W ' INCLUDES +W FOR FANEW(J) THAT WOULD BE ' PRODUCED
FCOLD(J)=FCOLD(J)+W-X ' Y HAS FAOLD=0. THIS MAY CAUSE PROBS W/ ' BOUNDARY
FDOLD(J)=FDOLD(J)+X-Y
FEOLD(J)=FEOLD(J)+Y
TOLD(J)=FAOLD(J)+FBOLD(J)+FCOLD(J)+FDOLD(J)+FEOLD(J)

T(1)=0.5/L
Z(1)=SQR(L/DMA)*(1+X)

FOR K=2 TO L ' START OF ALL SUBSEQUENT ITERATIONS [K=2 TO L]
J=1 ' CALC'S FOR FIRST BOX (BOUNDARY CONDITIONS)

'ELECTRODE BOUNDARY CONDITIONS FOR K=2 TO K=L FROM DIFFUSION
FANEW(J)=0!
FANEW(J)=FBOLD(J)+DMA*FAOLD(J+1)-DMB*(FBOLD(J)-FBOLD(J+1))
FCNEW(J)=FCOLD(J)-DMC*(FCOLD(J)-FCOLD(J+1))
FDNEW(J)=FDOLD(J)-DMD*(FDOLD(J)-FDOLD(J+1))
FENEW(J)=FEOLD(J)-DME*(FEOLD(J)-FEOLD(J+1))
TNEW(J)=FANEW(J)+FCNEW(J)+FDNEW(J)+FENEW(J)

'ELECTRODE BOUNDARY CONDITIONS FOR K=2 TO K=L FROM KINETICS
W=FNW
X=FNX
Y=FNY
FANEW(J)=FANEW(J)-W ' INCLUDES +X FOR FANEW(J) THAT WOULD BE ' PRODUCED
FCNEW(J)=FCNEW(J)+W-X  ' Y HAS FAOLD=0. THIS MAY CAUSE PROBS W/ ' BOUNDARY
FDNEW(J)=FDNEW(J)+X-Y
FENEW(J)=FENEW(J)+Y
TNEW(J)=FANEW(J)+FBNEW(J)+FCNEW(J)+FDNEW(J)+FENEW(J)

IF FBNEW(J)<0 THEN FBNEW(J)=0!

T(K)=(K-0.5)/L  ' CURRENT-TIME BEHAVIOR CALCULATED
Z(K)=SQR(L/DMA)*((DMA*FAOLD(2))+X)

JMAX=3*SQR(2*K)+1  ' CALC MAXIMUM VALUE OF J FOR GIVEN VALUE ' OF K

FOR J=2 TO JMAX  ' NEW CONCENTRATIONS CALC'D BY DIFFUSION ALGORITHM
  FANEW(J)=FAOLD(J)+DMA*(FAOLD(J+1)-2*FAOLD(J)+FAOLD(J-1))
  FBNEW(J)=FBOLD(J)+DMB*(FBOLD(J+1)-2*FBOLD(J)+FBOLD(J-1))
  FCNEW(J)=FCOLD(J)+DMC*(FCOLD(J+1)-2*FCOLD(J)+FCOLD(J-1))
  FDNEW(J)=FDOLD(J)+DMD*(FDOLD(J+1)-2*FDOLD(J)+FDOLD(J-1))
  FENEW(J)=FEOLD(J)+DME*(FEOLD(J+1)-2*FEOLD(J)+FEOLD(J-1))
  TNEW(J)=FANEW(J)+FBNEW(J)+FCNEW(J)+FDNEW(J)+FENEW(J)
NEXT J

FOR J=2 TO JMAX  ' NEW CONCENTRATIONS AFFECTED BY MCCREERY KINETICS
  W=FNW
  X=FNX
  Y=FNY
  FANEW(J)=FANEW(J)+X
  FBNEW(J)=FBNEW(J)-W-X
  FCNEW(J)=FCNEW(J)+W-X
  FDNEW(J)=FDNEW(J)+X-Y
  FENEW(J)=FENEW(J)+Y
  TNEW(J)=FANEW(J)+FBNEW(J)+FCNEW(J)+FDNEW(J)+FENEW(J)
NEXT J

FOR J=1 TO JMAX  ' TRANSFORM NEW ARRAYS TO OLD ARRAYS FOR ' NEXT ITERATION
APPENDIX 7

FAOLD(J)=FANEW(J)
FBOLD(J)=FBNEW(J)
FCOLD(J)=FCNEW(J)
FDOLD(J)=FDNEW(J)
FEOLD(J)=FENEW(J)

NEXT J

IF K2=K THEN
  PRINT "20% COMPLETE"
ELSEIF K4=K THEN
  PRINT "40% COMPLETE"
ELSEIF K6=K THEN
  PRINT "60% COMPLETE"
ELSEIF K8=K THEN
  PRINT "80% COMPLETE"
END IF

NEXT K

' STORAGE OF FRACTION/DISTANCE DATA AT 100% OF L
OPEN LF$ FOR OUTPUT AS #1
FOR J=1 TO JMAX
  WRITE #1, J, FANEW(J), FBNEW(J), FCNEW(J), FDNEW(J), FENEW(J), TNEW(J)
NEXT J
CLOSE #1
PRINT "FRACTION/DISTANCE DATA AT 100% OF L IS STORED IN "; LF$

OPEN ZF$ FOR OUTPUT AS #1
FOR K=1 TO L
  WRITE #1, T(K), Z(K)
  Z(K) = ABS(Z(K))
NEXT K
PRINT "T(K) VS Z(K) DATA IS STORED IN "; ZF$
CLOSE #1

OPEN DZTF$ FOR OUTPUT AS #2
FOR M=1 TO (L-1)
  TN(M)=((T(M+1) - T(M))/2)+T(M) ' CALC TN
  DZ# = LOG(Z(M+1)) - LOG(Z(M)) ' delta(lni)
  DT# = LOG(T(M+1)) - LOG(T(M)) ' delta(int)
  DZT(M)=DZ#/DT# ' delta(lni)/delta(int)

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WRITE #2, TN(M), DZT(M)
NEXT M
CLOSE #2
PRINT "d(ln Z)/d(ln t) IS STORED IN ";DZTFS$

PRINT "PROGRAM COMPLETE"
LPRINT "PROGRAM COMPLETE"