Characterizing Activity-Dependent Processes with a Piecewise Exponential Model

C. F. Starmer

Biometrics, Volume 44, Issue 2 (Jun., 1988), 549-559.

Stable URL:
http://links.jstor.org/sici?sici=0006-341X%28198806%2944%3A2%3C549%3ACAPWAP%3E2.0.CO%3B2-%23

BIOMETRICS 44, 549–559
June 1988

Characterizing Activity-Dependent Processes with a Piecewise Exponential Model

C. F. Starmer

Departments of Medicine (Cardiology) and Computer Science,
P. O. Box 3181, Duke University Medical Center,
Durham, North Carolina 27710, U.S.A.

SUMMARY

The response of some biological processes is dependent on the frequency of stimulation. With first-order processes, the response is driven exponentially to an equilibrium determined by the value of the driving function. When the stimulus or driving function is viewed as switching between constant values the resulting response is piecewise exponential. With periodic excitation, the time course of a point fixed in time relative to the initiation time of each stimulus is shown to be exponential with a rate and steady state that are linearly dependent on the rates and equilibria associated with each component exponential. This linearity can be exploited and leads to a simple estimation procedure for the apparent state-dependent rates.

1. Introduction

When a packet of the neurotransmitter acetylcholine (ACh) is released in a synapse between two nerves, its lifetime is limited, resulting in a transient interaction between ACh and the post-synaptic ACh receptor. When a local anesthetic binds to an ion channel in a nerve or cardiac cell membrane, the interaction occurs transiently, as if the channel binding site were only temporarily accessible. In contrast to many ligand-receptor processes where both components are free to interact continuously, these two examples represent members of a class of processes described by what one might term packet or pulse chemistry, where the response is related to the periodic presence of a drug or state of activation as determined by the frequency of stimulation or excitation. Since electrical activation of the heart, and to some extent the nervous system, is periodic, it would be useful to characterize responses in these systems as a function of excitation frequency and to explore the role excitation frequency plays in cellular responses. Such processes have been described as use-, frequency-, or activity-dependent processes and are associated with memory, learning, and the efficacy of antiarrhythmic and anticonvulsant drugs (Courtney, 1975; Smith, 1987; Rankin and Carew, 1987; Magleby, 1973; Pinsker et al., 1970).

Recently, I developed a model of the periodic interaction of ion channel antagonists (local anesthetics, antiarrhythmic and anticonvulsant agents) with sodium (Na), potassium (K), and calcium (Ca) channels (Starmer, 1986). The configuration of many types of channel proteins is sensitive to the electrical potential existing across the cell membrane, so that periodic changes in membrane potential (repetitive nerve or cardiac action potentials) induce changes in the channel configuration. These agents appear to enter the ion

Key words: Activity-dependent; Anesthetics; Binding; Dose–response; Frequency-dependent; Ion channel; Ligand; Piecewise exponential; Receptor.

channel when the channel transiently passes through a bindable configuration and to physically plug the channel, thus preventing the flow of ions across the cell membrane. A simple sequential process involving inaccessible sites (I) accessible sites (A), and sites bound (B) to a drug (D) illustrates this model:

$$I \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} A \underset{l}{\overset{kD}{\rightleftharpoons}} B. \tag{1}$$

Here, assume that α and β are sensitive to membrane potential. Under "resting" conditions, the equilibrium defined in terms of the reaction rates (α and β) favors the inaccessible (I) state, whereas under "activated" conditions, the equilibrium favors the bindable (A) state. Interactions between the drug and the A state lead to bound sites (B). When the equilibration time between the I and A states is rapid in comparison to the drug binding equilibration time, the process can be simplified [see (2) or (3) below] using apparent rate constants $\alpha k/(\alpha + \beta)$ and l. With voltage-sensitive conformation transition rates, α and β, the apparent rates will change values as the membrane potential varies. This process can be viewed as one case of a general class of binding processes between an antagonist and a channel with switched apparent rate constants (reflecting the fraction of bindable channels) that change in response to external stimulation.

For a simple two-value stimulus function, the overall behavior of the channel ensemble can be described as a two-step process involving an activated channel mixture with a lifetime paralleling the excitatory phase of stimulation,

$$U + D \underset{g_a l}{\overset{f_a k}{\rightleftharpoons}} B \quad (\textit{activated mixture}), \tag{2}$$

and a rest channel mixture with a lifetime paralleling the recovery phase of stimulation,

$$U + D \underset{g_r l}{\overset{f_r k}{\rightleftharpoons}} B \quad (\textit{rest mixture}), \tag{3}$$

where U represents unbound channels, D is the antagonist concentration, and B represents bound channels. In the simplest characterization, the true binding rates, k and l, are considered independent of excitation, while the fraction of accessible sites (f_a, f_r) and the fraction of drug-receptor complexes able to dissociate (g_a, g_r) are considered sensitive to the stimulus. The true rates of binding and unbinding are represented by k and l, whereas the apparent rates are determined by the product of the true rate and the fraction of accessible sites (f_a, f_r) and the fraction of bound sites (g_a, g_r) capable of unbinding. These apparent rates are clearly sensitive to the nature of the stimulus protocol and thus are unsuitable for comparing drug-induced responses (except under identical conditions). However, if the apparent rates actually reflect the product of an access function and the true rate, and the access function could be experimentally determined, then the true binding rates could be extracted from the apparent values and used for comparing drugs. Here I develop a general characterization including pulsed release of neurotransmitter and present a simple procedure for estimating apparent rate constants. An example of the interaction of cibenzoline, an antiarrhythmic drug, with cardiac sodium channels is presented to demonstrate the procedure. The overall model is general for periodically excited systems and complements models of continuous drug-receptor models.

2. Model

To fix ideas, consider a pseudo–first-order drug-receptor interaction

$$U + D_i \underset{l_i}{\overset{k_i}{\rightleftharpoons}} B, \tag{4}$$

where i represents the "state" of the system, U represents unbound sites, B represents bound sites, D_i represents drug concentration, and k_i and l_i represent apparent rates of binding and unbinding. The time course of the fraction of bound sites, b, under condition i is described by

$$\frac{db}{dt} = k_i D_i(1 - b) - l_i b \tag{5}$$

with a solution

$$b(t) = b_{i,\infty} + (b_0 - b_{i,\infty})e^{-\lambda_i t} \tag{6}$$

where

$$b_{i,\infty} = [1 + l_i/(k_i D_i)]^{-1} \tag{7}$$

and

$$\lambda_i = k_i D_i + l_i, \tag{8}$$

and b_0 is the fraction of bound receptors at $t = 0$.

When the model parameters are constant, the time course of b is exponential. However, when the rates, k_i or l_i, or the drug concentration, D_i, switch values in response to stimulation, the time course of b is piecewise exponential.

Pulsed excitation of an excitable cell usually consists of two intervals: an activation interval, t_a, followed by a recovery or rest interval, t_r. In characterizing the response to pulsed excitation, two alternative conditions must be considered with respect to selecting the appropriate value of t_a: (1) do the switched model parameters (e.g., k_i, l_i, or D_i) dwell in their various states for intervals equal to t_a or t_r, or (2) do the switched model parameters have a dwell time or lifetime that differs from the stimulus intervals? As an example, the sodium channel is known to exhibit at least three states: a nonconducting rest and inactivated state, and a conducting, open state. Typically, the channel is in a rest state. Upon excitation, though, the channel protein changes to an open "conduit" conformation allowing the passage of ions down an electrochemical gradient. The lifetime of the conducting conformation, though, is only about 1 msec and is followed by a transition to a nonconducting, inactivated conformation. Thus, if the interval during which binding can take place is limited to that of the open conformation and is induced by the activation phase of the stimulus, then the binding interval will probably differ from that of the activated stimulus interval. Fortunately, the open channel lifetime of many types of channels can be characterized in terms of a first-order transition between a closed, C, and an open, O, state, i.e.,

$$C \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} O. \tag{9}$$

The resulting open channel lifetime is frequently modeled by an exponential distribution and has been verified by direct observation (Grant, Starmer, and Strauss, 1983; Coronado, Latorre, and Mautner, 1984). The lifetime of neurotransmitters such as ACh is also exponentially distributed. Let the lifetime be characterized by a transition rate, β. The expected fraction of bound sites, then, is

$$\mathrm{E}(b) = \int_0^\infty [b_\infty + (b_0 - b_\infty)e^{-\lambda t}]\beta e^{-\beta t}\, dt = b_\infty + (b_0 - b_\infty)\frac{\beta}{\beta + \lambda}. \tag{10}$$

Thus, if the "true" activation time is taken as $t_a = 1/\beta$, then the expected fraction of bound sites under stochastic conditions is a first-order approximation of that encountered under

a fixed interval determined by the mean dwell time since

$$e^{-\lambda/\beta} \approx \frac{\beta}{\beta + \lambda}. \tag{11}$$

In addition to identifying the correct value for t_a, we must deal with the difference between the true and stimulus values of t_a. Here we assume that the difference between the apparent (excitation-induced) activated interval and the true activated interval (as determined by the chemistry) can be neglected.

Consider a periodic stimulus. During each interval of the stimulus, equation (6) describes the time course of drug-receptor interaction. Thus, with repetitive stimulation, blockade follows a piecewise exponential time course. Blockade just prior to each transition of the stimulus function can be described by a sequence of recurrence equations. Here we will derive a closed-form representation of the fraction of bound sites just prior to each time the stimulus switches state. Let r_n and a_n represent the fraction of bound sites before the two transition steps in the stimulus (Figure 1). Further, let k_r, l_r, k_a, and l_a represent the apparent binding rates associated with the two states. Then

$$r_n = a_{n-1}e^{-\lambda_r t_r} + r_\infty(1 - e^{-\lambda_r t_r}); \tag{12}$$

$$a_n = r_n e^{-\lambda_a t_a} + a_\infty(1 - e^{-\lambda_a t_a}); \tag{13}$$

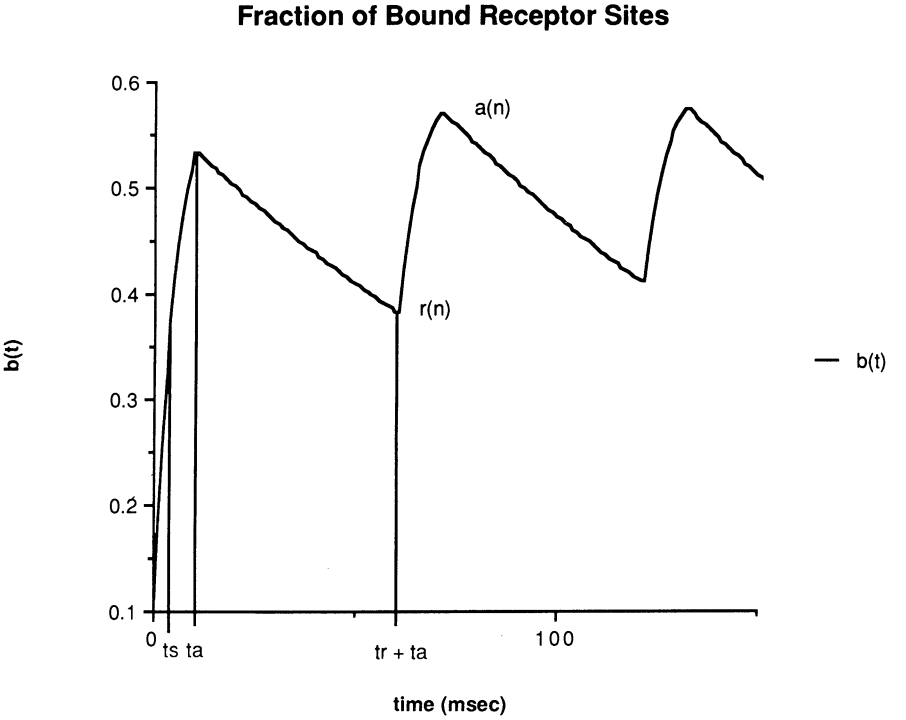

Figure 1. Piecewise exponential binding. With periodic stimulation, drug receptor binding follows an exponential time course during each constant phase of the stimulus. The values of bound sites just prior to stimulation are represented by r_n, those values just after stimulation by a_n, and those values sampled during the stimulus by s_n. All three sequences (r_n, a_n, s_n) follow an exponential pattern with an apparent rate determined by a linear combination of the state-dependent rates.

where

$$\lambda_r = k_r D + l_r; \tag{14}$$

$$r_\infty = \left(1 + \frac{l_r}{k_r D}\right)^{-1}; \tag{15}$$

$$\lambda_a = k_a D + l_a; \tag{16}$$

$$a_\infty = \left(1 + \frac{l_a}{k_a D}\right)^{-1}. \tag{17}$$

Equations (12) and (13) can be combined to yield relationships that are homogeneous in r_n or a_n, yielding

$$r_n = r_{n-1}e^{-\lambda} + a_\infty(1 - e^{-\lambda_a t_a})e^{-\lambda_r t_r} + r_\infty(1 - e^{-\lambda_r t_r}), \tag{18}$$

$$a_n = a_{n-1}e^{-\lambda} + r_\infty(1 - e^{-\lambda_r t_r})e^{-\lambda_a t_a} + a_\infty(1 - e^{-\lambda_a t_a}), \tag{19}$$

where

$$\lambda = \lambda_a t_a + \lambda_r t_r. \tag{20}$$

These can be solved, yielding the periodic pulsed equivalent to the continuous representation of binding:

$$r_n = r_{ss} + (r_0 - r_{ss})^{-n\lambda}, \tag{21}$$

$$a_n = a_{ss} + (a_0 - a_{ss})e^{-n\lambda}, \tag{22}$$

where

$$r_{ss} = a_\infty + \gamma_r(r_\infty - a_\infty), \tag{23}$$

$$a_{ss} = r_\infty + \gamma_a(a_\infty - r_\infty), \tag{24}$$

$$\gamma_r = \frac{1 - e^{-\lambda_r t_r}}{1 - e^{-\lambda}}, \tag{25}$$

$$\gamma_a = \frac{1 - e^{-\lambda_a t_a}}{1 - e^{-\lambda}}. \tag{26}$$

Thus, the points just prior to stimulus transitions of a periodic piecewise exponential process follow an exponential sequence [equations (21) and (22)] with a rate that is a linear function of the state-dependent rates [equation (20)] and a steady state that is a linear function of the state-dependent equilibria [equations (23) and (24)]. Generalization to three or more states is straightforward, with the linearity expressed by equations (20), (23), and (24) holding.

If data are recorded at arbitrary times, t_s (Figure 1) after the initiation of each stimulus, these points will follow an exponential pattern with rate λ. The steady-state value observed at t_s will also remain a linear function of the two equilibria. Let $0 \leqslant t_s \leqslant t_a$, then the recurrence relations are

$$r_n = a_{n-1}e^{-\lambda_r t_r} + r_\infty(1 - e^{-\lambda_r t_r}); \tag{27}$$

$$s_n = r_n e^{-\lambda_a t_s} + a_\infty(1 - e^{-\lambda_a t_s}); \tag{28}$$

$$a_n = s_n e^{-\lambda_a(t_a - t_s)} + a_\infty[1 - e^{-\lambda_a(t_a - t_s)}]. \tag{29}$$

The solution for s_n is

$$s_n = s_{ss} + (s_0 - s_{ss})e^{-n\lambda}, \tag{30}$$

where

$$s_{ss} = a_\infty + \gamma_s(r_\infty - a_\infty) \tag{31}$$

and

$$\gamma_s = \frac{(1 - e^{-\lambda_r t_r})e^{-\lambda_a t_s}}{1 - e^{-\lambda}}. \tag{32}$$

3. Analysis

Pulse train stimulation yields observations of a sequence of samples of the fraction of bound sites, $s_0, s_1, \ldots, s_n$. For each different stimulation frequency, a different sequence of sample values is observed. A straightforward method for estimating k_a, l_a, k_r, and l_r is to fit equation (30) utilizing parameter definitions of equations (14)–(17), (20), (23), and (25) using a nonlinear iterative least squares procedure.

An alternate and easily visualized estimation procedure is to capitalize on the linear relations defining the exponential rate, λ, and the steady-state fraction of bound sites, s_{ss}. Variations in the apparent exponential rate, λ, yield estimates of λ_a and λ_r when variation is induced by manipulating t_a or t_r in the stimulus protocol. An appropriate experimental protocol, then, is to generate, using pulse train excitation, a sequence of s_i for a fixed value of t_a and a fixed value of t_r. The t_r interval is then changed. Pulse train excitation is used to generate another sequence of s_i. From each sequence of s_i, equation (30) is fit, yielding estimates of s_0, s_{ss}, and λ. A regression of λ against t_r yields $\lambda_a t_a$ as an intercept and λ_r as the slope. A regression of s_{ss} against γ_s (determined from the estimates of λ_r and λ_a) then yields estimates of a_∞ (intercept) and $r_\infty - a_\infty$ (slope). From these values, k_a, l_a, k_r, and l_r are readily determined. Extending the analysis to recovering the "true" rate constants requires a detailed model of the access function (f and g). Several models of the voltage dependence of channel conformation have been used by others (Courtney, 1975; Strichartz, 1973) and could be applied here.

4. Example

In studies of nerve or cardiac membrane, the macroscopic channel current is measured by a microelectrode inserted through the cell membrane. From the channel current (I) and driving potential (V), the channel conductance, g, can be computed. Channels blocked by drugs during the channel open interval reduce channel conductance so that Ohm's law, reflecting channel blockade, is written as

$$I = g(1 - b)V. \tag{33}$$

With repetitive stimulation, the fraction of blocked channels progressively increases, reducing the observed current

$$I_n = gV[1 - b_{ss} - (b_0 - b_{ss})e^{-n\lambda}]. \tag{34}$$

For cardiac cells, it is difficult to measure membrane current directly. In this case, the maximum first derivative of the membrane potential, $\dot{V}_{\max}$, is frequently used to assess membrane current, because it is theoretically proportional to transmembrane current.

Recent studies of the interaction of the antiarrhythmic drug cibenzoline with cardiac cells demonstrated frequency-dependent binding (Figure 2). Table 1 reflects stimulus-to-

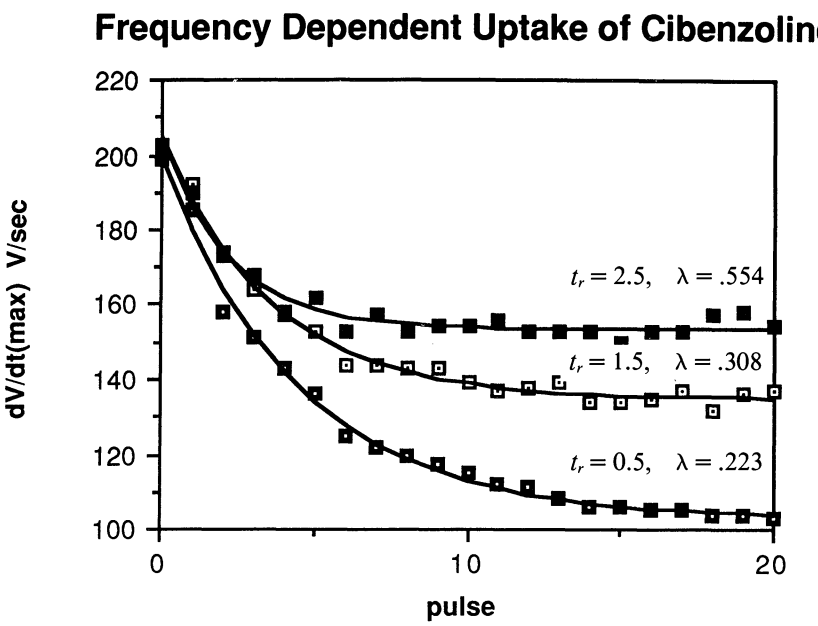

Figure 2. Frequency-dependent reduction in $\dot{V}_{max}$ associated with 16 μM cibenzoline interacting with cardiac muscle. Stimulus rates ranged from 2 Hz to .4 Hz. Each curve was fit to equation (29). Here, three typical curves are illustrated. The boxes represent the observed points; the lines represent the least squares predicted curves.

Table 1
dV/dt(max) V/sec

	Stimulus interval				
Pulse	.5	1.0	1.5	2.0	2.5
0	185	188	192	194	190
1	158	170	173	173	174
2	151	160	164	162	168
3	143	147	158	164	157
4	136	148	153	161	162
5	125	138	144	155	153
6	122	131	144	155	157
7	120	132	143	156	153
8	117	129	143	153	154
9	115	129	139	149	154
10	112	130	137	152	156
11	111	124	138	151	153
12	108	123	139	150	153
13	106	121	134	149	153
14	106	124	134	150	150
15	105	121	135	149	153
16	105	124	137	150	153
17	104	126	132	149	157
18	104	123	136	150	158
19	103	119	137	149	154
Control	199	201	203	203	203
t_r(sec)	.5	1.0	1.5	2.0	2.5
λ(pulse^{-1})	.230	.277	.308	.437	.554
b_{ss}	.482	.388	.335	.261	.241

stimulus reduction in $\dot{V}_{max}$ for several stimulus frequencies using a concentration of 16 μM. Each sequence of values was fit to

$$\dot{V}(n) = \dot{V}_{ss} + (\dot{V}_0 - \dot{V}_{ss})e^{-n\lambda} \tag{35}$$

in order to estimate $\dot{V}_{ss}$, $\dot{V}_0$, and λ. Steady-state block was estimated from

$$b_{ss} = (\dot{V}_c - \dot{V}_{ss})/\dot{V}_c, \tag{36}$$

where $\dot{V}_c$ is the control observation made in the absence of drug. The estimated parameters are shown at the bottom of the table.

For sodium channel blockade, the mean channel access time, t_a, is about 1 msec and independent of stimulus interval (Grant et al., 1983). Figure 3a illustrates the quality of the predicted linear relationship between apparent event rate, λ, and the rest interval, t_r. From this relationship, λ_r was estimated as .1616/sec (slope). The value of $\lambda_a t_a$ was .1189. Figure 3b illustrates the quality of the predicted linear relationship between steady-state block, b_{ss},

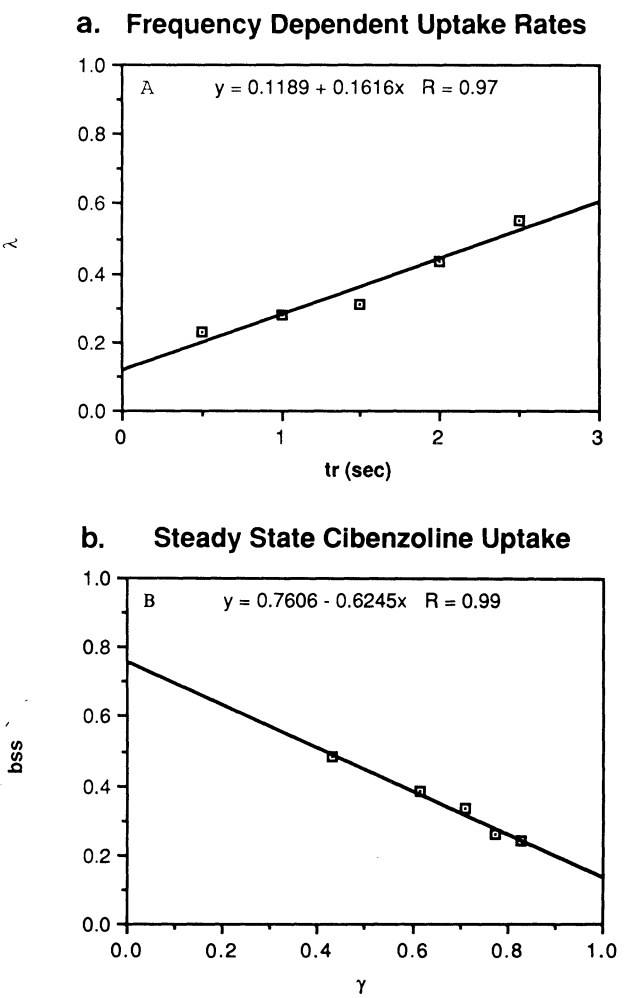

Figure 3. (**a**) Apparent binding rate as a function of recovery interval. Note that both the slope and intercept are nonzero as required by the model. (**b**) Steady-state block as a function of the stimulus parameter, γ. Note that the intercept is positive, the slope is negative, and its absolute value is less than the intercept as required by the model.

and γ_r (we assume the sampling time, $t_s = 0$). The intercept was found to be .7606, and the slope was found to be −.6245. Note that these values are consistent with the model constraint requiring the absolute value of the slope ($r_\infty - a_\infty$) to be less than the intercept (a_∞). Since

$$\lambda_i = k_i D + l_i \tag{37}$$

and

$$b_{i,\infty} = \left(1 + \frac{l_i}{k_i D}\right)^{-1}, \tag{38}$$

the values of the four model parameters are readily estimated as $k_a = 5.65 \times 10^6$ $M^{-1}sec^{-1}$, $l_a = 28.46$ sec^{-1}, $k_r = 1{,}375$ $M^{-1}sec^{-1}$, and $l_r = .1396$ sec^{-1}.

These values were used as initial estimates for a nonlinear least squares fit of equation (30), utilizing the definitions specified in equations (14)–(17), (20), (23), and (25). This procedure refined the initial estimates slightly, resulting in values of $k_a = 7.49 \times 10^6$ $M^{-1}sec^{-1}$, $l_a = 43.19$ sec^{-1}, $k_r = 1{,}439$ $M^{-1}sec^{-1}$, and $l_r = .1148$ sec^{-1}.

5. Discussion

Increasingly, biomedical investigators are uncovering processes that exhibit use-dependent, frequency-dependent, or activity-dependent behavior where the response of a system is related to the frequency of excitation (Courtney, 1975; McCarren and Alger, 1985; McLean and MacDonald, 1986). These observations have not been limited to simple preparations. For instance, recently Snead and Hosey (1985) noted that in children subject to seizures with spike-and-wave discharges greater than 2.5–3 cycles per sec as measured by the EEG, the anticonvulsant carbamazepine made seizures worse.

Though there is a rich literature dealing with drug-receptor interactions where the interaction occurs continuously in time, there is little in the way of formal characterization of biochemical processes that occur periodically or transiently in time. The interaction of local anesthetics, antiarrhythmic and anticonvulsant agents with ion channels in excitable cells is an example of an observed frequency-dependent process. Since the electrical activity is frequently periodic in these systems, the binding will not reach an equilibrium. Rather, it will reach a steady state that is possibly frequency-dependent. Without a formal model of these processes, it is difficult to characterize with a few parameters the frequency-dependent nature of the interaction. Moreover, developing appropriate stimulus protocols to explore frequency-dependent processes is more of a trial-and-error process.

The study of continuous drug-receptor processes avoids many of these problems by utilizing the simple time course and equilibrium properties of a bimolecular chemical model. Specifically, experiments designed to monitor the time course of binding and eventual equilibrium provide enough data to estimate unambiguously the rates of binding and unbinding. Further, equilibrium dose–response curves provide data for estimating the equilibrium dissociation constant (ratio unbinding rate to binding rate) that is frequently used in comparing different hormones or drugs.

Here I have developed a minimal model of a frequency-dependent process where either apparent rates switch or drug concentration switches in response to external stimulation. The model demonstrates that with periodic stimulation, the fraction of bound sites follows a piecewise exponential pattern where the apparent rate of drug binding is a linear function of stimulus-induced state rates and the steady state is a linear function of state-dependent equilibria.

Several interesting issues are raised. In particular, what is an optimal stimulus protocol? Two constraints are: (1) how many data points during the transient exponential phase are

required to accurately fit an exponential function to a single pulsatile drug binding curve; and (2) how much variation in apparent uptake rate $\lambda = \lambda_a t_a + \lambda_r t_r$ must be induced (by holding t_a fixed and varying t_r) in order to estimate λ_a and λ_r reliably?

This class of model appears to have considerable generality. In studies of stimulation-induced transmitter release at a frog neuromuscular junction, Magleby and Zengel (1982) found that facilitation, the progressive increase in the amplitude of successive excitatory post-synaptic potentials during repetitive stimulation, could be accurately described by a first-order differential equation with switched parameters. In particular, they assumed that facilitation, F_1^*, decayed at a rate, k_{F_1}, and that each nerve impulse induced a fixed increment, f_1^*, in facilitation. The rate of change in facilitation was then described by

$$\frac{dF_1^*}{dt} = J(t)f_1^* - k_{F_1}F_1^*, \tag{39}$$

where $J(t) = 1$ at the time of the nerve impulse and 0 at other times. They then solved the equation numerically in order to evaluate their model. Using the strategy outlined above for writing a recurrence relation, one can readily derive a closed-form solution to their model. Since f_1^* is switched on and off, a sequence of recurrence equations can be written describing the pulse-to-pulse behavior of F_1^*. Let b_n be the degree of facilitation before the nth pulse and a_n be the degree of facilitation after the nth pulse. Then

$$b_n = a_{n-1}e^{-k_{F_1}t_r}, \tag{40}$$

$$a_n = b_n + f_1^*. \tag{41}$$

Thus,

$$b_n = b_{n-1}e^{-k_{F_1}t_r} + f_1^*e^{-k_{F_1}t_r}. \tag{42}$$

After many pulses, a steady state is reached such that $b_n = b_{n-1}$ and

$$b_{ss} = \frac{f_1^*}{e^{k_{F_1}t_r} - 1} \tag{43}$$

so that the solution can be written as

$$b_n = b_{ss} + (b_0 - b_{ss})e^{-k_{F_1}t_r n}. \tag{44}$$

In this case, with variable frequency stimulation, one expects plots of λ vs t_r and b_{ss} vs $1/(e^{k_{F_1}t_r} - 1)$ to have zero intercepts, thus providing an additional consistency check between model and data.

In summary, some periodically stimulated biological processes can be described as piecewise exponential processes. The pulse-to-pulse behavior is described by simple constant coefficient recurrence relations that lead to closed-form analytic solutions. These solutions provide insight into designing appropriate stimulus protocols, testing the consistency between model and data, and providing procedures for parameter estimation. Furthermore, these results establish a parallel between the continuous behavior associated with single-value driving functions (traditional dose–response models) and the discrete behavior associated with switched-value driving functions. Most important, results from appropriately designed stimulus protocols can be used to uniquely identify process parameters, and data analysis can take advantage of several consistency checks that are mandated by the underlying model.

Acknowledgements

We wish to thank Dr Joe Arena for providing the cibenzoline data and Joanna Smaltz for editorial assistance. Research was supported in part by grants HL32994 and RR01693 from

the National Institutes of Health and by contract 4414804 from the Office of Naval Research.

Résumé

La réponse de certains processus biologiques est dépendante de la fréquence de stimulation. Avec les processus d'ordre un, la réponse est exponentielle jusqu'à un équilibre déterminé par la valeur de la fonction de commande. Quand on regarde le stimulus ou la fonction de commande comme une bascule entre des valeurs constantes, la réponse résultante est exponentielle par morceaux. Avec une excitation périodique, on montre que la courbe d'un point fixé dans le temps relativement au temps d'initiation de chaque stimulus, est exponentielle avec un taux et un état d'équilibre qui sont linéairement dépendants des taux et des équilibres associés à chaque composante exponentielle. Cette linéarité peut être utilisée, et conduit à une procédure simple d'estimation des taux dépendants des états apparents.

References

Coronado, R., Latorre, R., and Mautner, H. G. (1984). Single potassium channels with delayed rectifier behavior from lobster axon membranes. *Biophysical Journal* **45,** 289–299.

Courtney, K. R. (1975). Mechanism of frequency-dependent inhibition of sodium currents in frog myelinated nerve by the lidocaine derivative GEA968. *Journal of Pharmacology and Experimental Therapeutics* **195,** 225–236.

Grant, A. O., Starmer, C. F., and Strauss, H. C. (1983). Unitary sodium channels in isolated cardiac myocytes of rabbit. *Circulation Research* **53,** 823–829.

Magleby, K. L. (1973). The effect of repetitive stimulation on facilitation of transmitter release at the frog neuromuscular junction. *Journal of Physiology* **234,** 327–352.

Magleby, K. L. and Zengel, J. E. (1982). A quantitative description of stimulation-induced changes in transmitter release at the frog neuromuscular junction. *Journal of General Physiology* **80,** 613–638.

McCarren, M. and Alger, B. E. (1985). Use-dependent depression of IPSP's in rat hippocampal pyramidal cells *in vivo*. *Journal of Neurophysiology* **53,** 557–571.

McLean, M. J. and MacDonald, R. L. (1986). Sodium valproate, not ethosuximide, produces use- and voltage-dependent limitation of high frequency repetitive firing of action potentials of mouse central neurons in cell culture. *Journal of Pharmacology and Experimental Therapeutics* **237,** 1001–1011.

Pinsker, H., Kupperman, I., Castellucci, V., and Kandel, E. (1970). Habituation and dishabituation of the gill-withdrawal reflex in Aplysia. *Science* **167,** 1740–1742.

Rankin, C. H. and Carew, T. J. (1987). Development of learning and memory in Aplysia. II. Habituation and dishabituation. *Journal of Neuroscience* **7,** 133–143.

Smith, S. A. (1987). Progress on LTP at hippocampal synapses: A post-synaptic CA^{2+} trigger for memory storage. *Trends in Neuroscience* **10,** 142–144.

Snead, O. C. and Hosey, L. C. (1985). Exacerbation of seizures in children by carbamazepine. *New England Journal of Medicine* **313,** 916–920.

Starmer, C. F. (1986). Theoretical characterization of ion channel blockade: Ligand binding to periodically accessible receptors. *Journal of Theoretical Biology* **119,** 235–249.

Strichartz, G. R. (1973). The inhibition of sodium currents in myelinated nerve by quaternary derivatives of lidocaine. *Journal of General Physiology* **62,** 37–57.

Received January 1987; *revised July and November* 1987.