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A New Mathematical Model in Mean Open Time Of Recombinant GABA Channels by using the Availability Of an R-Out-N System

S.Lakshmi* and P.Gomathi Sundari**
* Head and Associate Professor of Mathematics, K.N.Govt.Arts College for Women,Thanjavur -613005, TamilNadu, India.
** Assistant Professor of Mathematics, Rajah Serfoji Government College, Thanjavur-613005, TamilNadu, India.
E-mail: lakshmi291082@yahoo.co.in , gomathi.rsg@gmail.com

Abstract

We obtain the equilibrium of an solutions of an R-out-of-N system subject to random breakdown. These are M spares and a single repair, Who installs good spares into the system when breakdowns occurs and also repairs the failed items. For example, Single Channel Peak Current—In outside-out patches, the rapid application of high GABA concentrations [GABA] invariably induced overlapping single channel openings whose maximum peak current was reached within 20 ms of the application. The single channel peak current for each [GABA] (1, 10,100,and 1000 µM) was therefore determined as the peak amplitude of the current induced within the first 20 ms. Themeanpeak current was obtained by pooling data from three or more experiments. We have utilized these formulae in the application part for the variable GABA.In this paper we they to find out the time resolution of these rapid transitions from closed to open for both the 30-pS channels and 60-pS channels in the medical part.

Keywords: Pre-emptive, Random Breakdown, GABA

AMS Classification: 90GXX

1.Introduction

We consider a system of N identical components subject to random breakdown at rate λ per operational machine. The system is supposed to work provided at most K components are down ,i.e. if at least N-K components are operational (an (N-K) – out-of-N-system). We assume a fixed number of spares, M, are available. When a component fails it must be removed from the system , replaced by a good spare and repaired to good –as-new state to become part of the stock of good spares. This is done by a single service facility which gives per-emptive priority to the replacement activity. Thus,if breakdown occurs while a repair is in progress, the server immediately stops repairing and instead removes the faulty component and replaces it by a good spare, if one is a vailable; if no good spare is available the repair must be completed and then the repaired item may be installed into the system instead of the failed component. The installation and repair times are assumed to be random variables from distributions with probability densities $f_1(x)$ and $f_2(x)$ respectively, with corresponding hazards $\lambda_1(x)$, $\lambda_2(x)$, and survivor functions $R_1(x)$, $R_2(x)$. Thus for i =1,2 we have $f_i(x) = \lambda_i(x) R_i(x)$, where , $R_i(x) = \exp(-\int_0^x \lambda_i(u)du)$

The series system, K=0, was studied under both repeat and resume assumptions. We consider the general case 0 < K < N. We start by assuming at least one spare , M $\geqq$1, and later study the special case of no spares, M=0.

At any point in time the system may be considered to be in one of (K+2)(M+1) states in the particular case K=1, M=2. Let d be the total number of defective items (these may be in the system waiting to be replaced or held in stock waiting to be repaired) and let g be the number of good spares available. Then , g + d = M + k , so , d – k = M – g = r , say.

We choose to lable the states of the model by the pairs (k, r), through the above equations show that various other combinations are possible.

Example:

Consider a system consisting of n components such that the failure of the ith component occurs in accordance with a poisson process of intensity a_i. To find the reliability of the k-out of n system. Here T_i is exponential with mean $1/a_i$, and $R_i(t) = e^{-ait}$.

Suppose that a_i = a for all i. we have, R(t) = Pr (T> t)

$$= \sum_{r=k}^{n}\binom{n}{r} (e^{-ait})^r(1- e^{-ait})^{n-r}$$

$$E(T) = \int_0^\infty R(t)dt = \int_0^\infty \sum_{r=k}^{n}\binom{n}{r} (e^{-ait})^r(1- e^{-ait})^{n-r}dt$$

$$= \frac{1}{a}\sum_{r=k}^{n}\frac{n!}{r!(n-r)!}\frac{\Gamma(r)\Gamma(n-r+1))}{\Gamma(n+1)}$$

$$= \frac{1}{a}\sum_{r=k}^{n}\frac{1}{r}$$

2.Solutions with at least one spare

In general, we shall need to consider the elapsed replacement time. $\tilde{x}_t$, or the elapsed repaire time, $\tilde{y}_t$, at time t as well as the currently occupied state ($\tilde{k}_t, \tilde{r}_t$), where the tilde indicates a random variable. It is possible to write down partial differential equations involving the probability distribution of these variables as a function t. However, we shall content ourselves with finding equilibrium solutions, which can be obtained by direct probabilistic arguments,t will, therefore, be omitted from the notation. Then most general quantity of interest is a probability density involving the lapsed installation time $\tilde{x}_t$:

$$p_{k,r}(x) = \lim_{\delta x\to 0} P((\tilde{k}_t=k) \cap (\tilde{r}_t=r) \cap (\tilde{x}_t \in(x, x+\delta x))) / \delta x, \quad 0 < k \leqq K+1,\ 0 \leqq r < M.$$

Down the rightmost diagonal repairs are in progress, because there are no good spares left to install, so

$$p_{k,m}(y) = \lim_{\delta y\to 0} P((\tilde{k}_t=k) \cap (\tilde{r}_t=M) \cap (\tilde{y}_t \in(y, y+\delta y))) / \delta y, \text{ for } 0 \leqq k \leqq K+1$$

This leaves us with one special state, (0,0), in which everything is good and so there is no installation and no repair in progress. Then we define

$$p_{0,0} = P((\tilde{k}_t = 0) \cap(\tilde{r}_t= 0)).$$

Along the bottom row of the state diagram the system is down, the system is up (available) in any other state.In order to develop equilibrium balancing equations, it is useful to define

$${}_bQ_n(x) = P(\text{b breakdowns out of n items over time interval x })$$

$$= \binom{n}{b}\exp(- (n- b) \lambda x))(1- \exp(- \lambda x))^b. \qquad \text{(Eq.1)}$$

This is simply a binomial probability with probability of failure given by the negative exponential distribution, as in a simple death process. If we take x in the above expression as a random variable with probability density f, then the probability of b failures out of n items over a random period will be denoted by

$${}_b(f AQ)_n= \int_0^\infty {}_bQ_n(x)\, f(x)dx$$

which, by expanding Equation (8), can be written as

$${}_b(f AQ)_n= \binom{n}{b} \sum_{i=0}^{b}\binom{b}{i} (-1)^I f^*((n-b+i) \lambda),$$

where , $f^*(s) = \int_0^\infty e^{-sx} f(x)dx$
is the Laplace transform of the density f.

In particular, the probability of no events is, ${}_0(f AQ)n = f^*(n \lambda)$.

Then the most general result on installation is

$$P_{k,r}(x) = \sum_{j=1}^{k} p_{j,r}(0)_{k-j}\, Q_{N-j}(x) R_1(x), \qquad 1 \leqq k \leqq K,\ \ 0 \leqq r \leqq M-1.$$

Thus the installation may have started at time x ago in state (j, r), with density $P_{j,r}(0)$, is still not complete (probability $R_1(x)$), and there have been k - j breakdowns out of the original N – j which were working when installation began. As breakdowns occur, the system slides down the rth diagonal. When the bottom row is reached no more failures can occur, because the system stops working, and so

$$P_{K+1,r}(x) = \sum_{j=1}^{k} p_{j,r}(0)\ (1 - \sum_{b=0}^{k-j} bQ_N\text{-}j(x)\ R_1(x) + P_{K+1,r}(0)R_1(x), \ \ 0 \leqq r \leqq M-1.$$

For the repairs down the rightmost diagonal we have

$$P_{k,M}(y) = \sum_{j=0}^{k} p_{j,M}(0)_{k-j}\ Q_{N-j}(y)\ R_2(y), \qquad 0 \leqq k \leqq K.$$

Notice that, in comparison to Equation (2.10), the summation starts at j=0 because, unlike installations, repairs can start in the top row. Again, k= K+1 is special:

$$P_{K+1,M}(y) = \sum_{j=0}^{k} p_{\ j,M}\ (0)(1 - \sum_{b=0}^{k-j}{}_{b}Q_N\text{-}j(y)\ R_2\ (y).$$

Note that it is impossible to start a repair in state (K+1, M) so that $P_{K+1,M}(0) = 0$
Along the top row the repairs in progress satisfy

$$p_{o,r}(y) = p_{o,r}(0)\ \exp(-N\lambda y)\ R_2(y) = p_{o,r}(0)_0 Q_N(y)R_2(y), \qquad 1 \leqq r \leqq M.$$

Finally, by equating the rates of transition out of and into the special state (0,0) we have

$$N\lambda p_{0,0} = \int_0^\infty p_{0,1}(y)\ \lambda_2\ (y)dy = p_{o,1}\ (0)_0\ \ (f_2\ AQ)_N = p_{o,1}\ (0)\ f_2{*}\ (N\lambda)$$

Thus the solution depends on the initial densities $p_{k,r}(0)$ which give the rates at which installations or repairs being in the various states. These may be found by solving the following set of boundary equations governing the transitions between the states. In these equations we need to use the result that, using integration by parts,

$$\int_0^\infty e^{-sx} R\ (x)\ dx = (1 - f^*(s))/s$$

The effect of different shape distributions for the times taken to install and to repair items. In both cases we take gamma densities of the form

$$f(t) = (\alpha/\mu)^{\alpha}\ t^{\ \alpha-1}\exp(-\ \alpha t/\mu)/\Gamma(\alpha)\ , \quad t>0$$

For this distribution μ is the mean and α the shape parameter : included in this family is the exponential distribution, α = 1, and the constant distribution, α→x. From these results we see that the availability is not very sensitive to the form of the density, especially the installation time distribution which has a small mean, increasing a little as the shape parameter increases and, therefore, the variability decreases. There is some difference when the repair time distribution is j-shaped, $\alpha_2 <1$, but these is very little change when α_2 excceeds 1. The effect of the shape of the repair time distribution decreases as M increases but increases, slightly, as K increases.

3.Applications

Inhibitory signals in human brains are mediated primarily by γ-aminobutyric acid typeA ($GABA_A$)[2] receptors. These ligandgated ion channels are composed of multimembrane-spanning subunits that assemble into pentamers and function by gating a pore selective for chloride ions. The targeting and organization of $GABA_A$ receptors at specific membrane locations are critical for their normal function. For example, $GABA_A$ receptors are clustered at inhibitory synapses but are also found both clustered and nonclustered at other sites on the neuronal cell surface (3). These synaptic and nonsynaptic (extrasynaptic) sites reflect $GABA_A$ receptor involvement in both phasic and tonic signaling, respectively. The functional behavior of native $GABA_A$ receptors is complex. Much of the receptor's functional complexity has been attributed to its extensive structural heterogeneity as indicated by the 19 different genes identified to date (α1–6, β1–3, γ1–3, δ, ρ1–3, ℰ, θ, and π).

4. Mathematical Model for Experimental Procedures

Analysis of Currents—All single channel currents were analyzed using in-house software, CHANNEL 2. Statistical analyses were performed using Excel (Microsoft). To compare sample means, paired or unpaired, a twotailed *t* test, not assuming equal variance, was used.A critical value of $p<0.05$ was used to define statistical significance.

Single Channel Analysis—All single channel recordings were performed at a holding potential of - 60 mV using the outsideout patch clamp technique. Before analysis, the recordings were filtered at 2 kHz using the program CHANNEL 2, unless specified (*e.g.* mean open times). Single channel current amplitudes were measured directly and were only accepted as valid events if their open duration was at least 0.3 ms (*i.e.* 3 times the sampling rate). Amplitude histograms were then constructed using more than 500 openings in which the bin widths were 0.06 pA, and these were subsequently fitted to the sum of Gaussian components (Equation 2) using least-squares minimization. The number of Gaussian components required to fit the histogram was determined by the criteria set out by (4). The Gaussian function (*g(I)*) used to fit an amplitude frequency histogram was as follows.

$$g(I) = A_1 e^{-0.5} \left(\frac{I-m_1}{s_1}\right)^2 + A_2 e^{-0.5} \left(\frac{I-m_2}{s_2}\right)^2 + \ldots\ldots + A_n e^{-0.5} \left(\frac{I-m_n}{s_n}\right)^2 \qquad \text{(Eq. 2)}$$

Single Channel Peak Current—In outside-out patches, the rapid application of high GABA concentrations ([GABA]) invariably induced overlapping single channel openings whose maximum peak current was reached within 20 ms of the application. The single channel peak current for each [GABA] (1, 10, 100, and 1000 μM) was therefore determined as the peak amplitude of the current induced within the first 20 ms. Themeanpeak current was obtained by pooling data from three or more experiments.

Single Channel Mean Open Time—Unfiltered segments of typical single channel data were used for analysis only if simultaneous openings were rare or accounted for less than 1% of the total number of channel openings sampled. Using a program available in CHANNEL 2, the single channel amplitudes and their corresponding open duration can be measured automatically,after an "open" and "closed" threshold has been set. To determine the open time of single channel events that were ≤ 40 pS, the open and closed thresholds were set at half the amplitude of the smallest single channel conductance, typically 20 pS; hence, the threshold was set at 10 pS. At a holding potential of - 60 mV, this threshold was set at 0.6 pA. Using the same criteria to determine the open time of single channel events that had conductances greater than 40 pS, the open and closed thresholds were set at 1.2 pA. In single channel recordings that exhibited both high and low single channel conductance events, the open times of these channel events were sampled twice. The first round was to collect the open times of the low conducting channels (≤ 40 pS), and the second was for the high conducting channels (>40 pS). This procedure was done because it was found that a number of the high conducting channels had brief closures (it was considered a closed event when the channel closed more than half the amplitude of that channel opening). These closures, however, did not cross the "lower" closed threshold set at 0.6 pA and was therefore deemed to be a single open event by the analysis program. Under these conditions, the mean open time of the higher conducting channels was biased toward longer times.

Probability of Simultaneous, Independent Channel Openings— To determine whether high conductance channels could be due to the random simultaneous openings of independent channels, the probability of observing rapid transitions between the closed level and Imax(maximumsingle channel current) were calculated. We calculated whether the 60-pS conductances were due to the simultaneous openings of two 30-pS independent channel openings, because the 30-pS channels account for more than 50% of all opening events. Furthermore, the low frequencies of the 20- and 40-pS channels make their random participation in generating a 60-pS channel less likely.

The probability of *n* independent channels opening simultaneously can be examined by a binomial distribution.

$$\Pr(s) = [n! / s!(n - s)!]\, p_o^2\, (1 - p_o)^{n-s}$$

The probability that two channels open simultaneously ($s = 2$) thus becomes the following.

$$\Pr(s = 2) = n! / [2!(n - 2)!]\, P_o^{\,2}(1 - p_o)^{n-2} = [n(n - 1) / 2]\, p_o^2(1 - p_o)^{n-2}$$

Since $(1 - p_o)^{n-2} < 1$, then

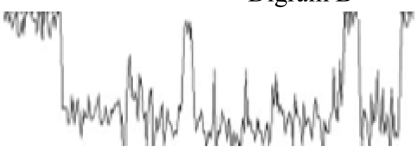
$$\Pr(s = 2) < [n(n-1)/2]p_o^2$$

Since $n^2 - n < n^2$, then the following is true

$$\Pr(s = 2) < (np_o)^2/2$$

Digram A

Digram B



Digram. **Single channel opening transitions.** These single channel traces are from a patch (P2) co-expressing αβγ receptors and GABARAP that displayed 60-pS channel openings more than 50% of the time. 30 s of channel activity from an outside-out patch activated by 100 µM GABA. On an expanded time scale, transitions to the 30- and 60-pS open states are depicted in *A* and *B*, respectively, illustrating that the fast transitions to each conductance occur within 400µs. Recordings were filtered at 5 kHz and sampled at a frequency of 10 kHz (hence, each data point represents 100µ s). Membrane potential was -60 mV.
From our single channel recordings, np_o can be calculated as follows.

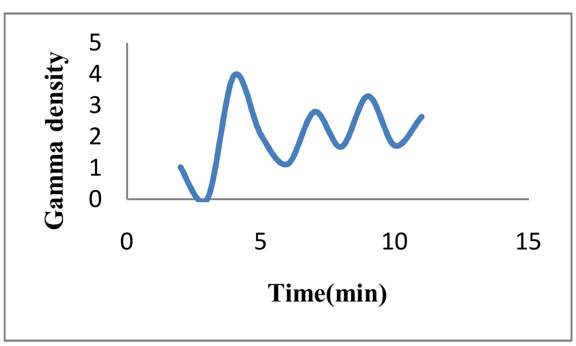
$$nP_o = (x_1 + 2x_2) / Tr$$

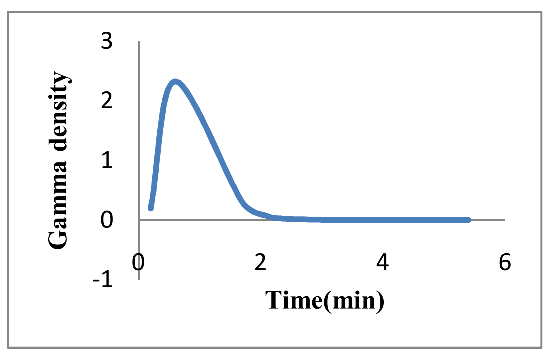
where x_1 is the number of 30-pS channel openings, x_2 is the number of 60-pS channel openings, and Tr is the number of rapid transition periods in that particular recording.

Single channels go from the closed state to an open state in a very short space of time. With our current sampling resolution, one point per 100µs (10 kHz), we have found that channels take less than four points to go from a closed state to an open state. Thus, this rapid transition from channel closed to channel open takes less than 400 µs and therefore is defined as our rapid transition period. In a 30-s recording, there are 75,000 rapid transition periods (Tr = 30s/400µs). A typical single channel recording is depicted in Digram from a cell coexpressing $GABA_A$ receptors and GABARAP. The digram illustrates the time resolution of these rapid transitions from closed to open for both the 30-pS channels (Dig.*A*) and the 60-pS channels (Dig.*B*), where each data point represents 100 µs.

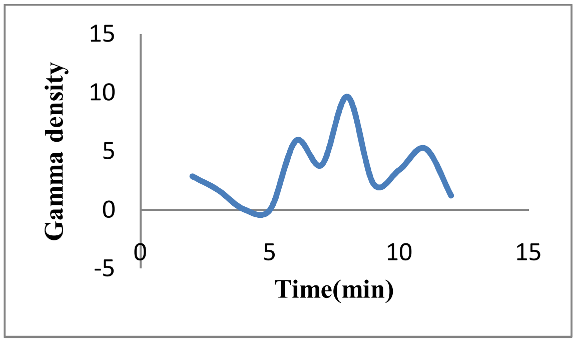
5. Results

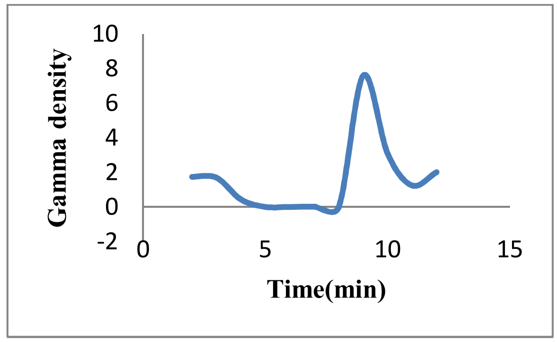
Digram A (i) α =5.5152 μ =0.204 **(ii)** α =5.5152 μ =0.897





Digram B (i) α =2.0881 μ =0.2158 **(ii)** α =1.9621 μ =0.4328





Conclusion

From these results we see that the availability is not very sensitive to the form of the density, especially the installation time distribution which has a small mean, increasing a little as the shape parameter increases and, therefore, the variability decreases. There is some difference when the repair time distribution is j-shaped. The effect of the shape of the repair time distribution decreases as M increases but increases, slightly, as K increases. The digram illustrates the time resolution of these rapid transitions from closed to open for both the 30-pS channels (Dig.*A*) and the 60-pS channels (Dig.*B*), where each data point represents 100 µs. This model is used for finding the concluding remark in the medical science for the variable GABA. The Gaussian function (g(I)) is used to fit the amplitude frequency.

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