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Two-state stochastic models for memory in ion channels[1]

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KEY WORDS ion channels; statistical models; memory

AIM: To study quantitatively the memory existing in ion channels. **METHODS**: Stochastic processes were used to model 2 categories of memory (short-term and long-term) by persisting in the standpoint of two-state, instead of multiple states, but with different transition mechanism. **RESULTS**: A two-state Markov process with constant transition intensities well fitted the short-term memory and a two-state Markov process within a kind of random environment well fitted the long-term memory. Statistical procedures for parameter estimation were proposed and demonstrated with 2 real examples on the channels of PC12 cells. **CONCLUSION**: The memory in ion channels can be quantitatively modelled as stochastic process with 2 states.

The existence of memory in ion channels of some cells was reported with auto-correlation functions of patch clamp recordings as an intrinsic feature of the channels, stable in repetition, responsive to changes, and free from the problem of time omission[1]. Two stochastic models and relevant statistical procedures to interpret the short-term memory and long-term memory were proposed and demonstrated with examples in physiology and pharmacology.

1 Stochastic models for memory in ion channels

1.1 Definitions of short-term memory and long-term memory

If the sample auto-correlation function had a decreasing trend with the time span τ and approximately followed the pattern of negative exponential function

$$\rho(\tau)=\exp(-A\tau)$$

then the memory of the channel was categorized as a short-term memory.

If the decreasing speed of the sample auto-correlation function was slower than the pattern of exponential function and approximately followed the pattern of negative power function

$$\rho(\tau)=(B\tau+1)^{-c}$$

then the memory of the channel was categorized as a long-term memory[2].

1.2 A two-state Markov model and short-term memory

Markov model was suggested by many authors for the analysis of single channel recording[3] that the distribution of the duration of successive open-status and the duration of successive close-status were summarized as a routine procedure ignoring the series of signals itself and the series of channel's open-close status. In most cases the exponential type distribution was used to fit the distributions of durations satisfactively which corresponded to a two-state Markov model in theory.

Assume a Markov-process with 2 states, C (close) and O (open), of a single ion channel and 2 constants λ and μ corresponding to the transitions from C to O and from O to C, respectively (Fig 1).

$$C \underset{\mu}{\overset{\lambda}{\rightleftharpoons}} O$$

Fig 1. Two-state Markov model

Let $p_{ij}(t)=\Pr(\text{state j at time } t \mid \text{state i at time } 0)$, under the initial condition of $p_{00}(0)=p_{11}(0)=1$, $p_{10}(0)=p_{01}(0)=0$, we had

$$p_{00}(t)=\mu_0+\lambda_0 e^{-(\lambda+\mu)t},\ p_{01}(t)=\lambda_0(1-e^{-(\lambda+\mu)t}),$$
$$p_{10}(t)=\mu_0(1-e^{-(\lambda+\mu)t}),\ p_{11}(t)=\lambda_0+\mu_0 e^{-(\lambda+\mu)t}$$

where

$$\lambda_0=\lambda/(\lambda+\mu),\ \mu_0=\mu/(\lambda+\mu)$$

For any stochastic process $X(t)$ with value either 0 or 1, the population mean M and the population auto-correlation function $\rho(\tau)$ were defined as

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$$M=\lim_{T\to\infty}\frac{1}{T}\int_0^T \mathrm{E}\,[X(t)]dt$$

$$\rho(\tau)=\lim_{T\to\infty}\frac{1}{T}\int_0^T \mathrm{D}(t,\tau)\ dt/\lim_{T\to\infty}\frac{1}{T}\int_0^T \mathrm{D}(t,0)\ dt$$

where

$$\mathrm{D}(t,\tau)=\mathrm{E}[X(t+\tau)X(t)]-\mathrm{E}[X(t+\tau)]\mathrm{E}[X(t)]$$

Let $p_i(t)=pr(X(t)=i)$, $i=0, 1$, and $p_0(0)=p_0$, $p_1(0)=p_1$, $p_0+p_1=1$.

Since

$$p_0(t)=p_0p_{00}(t)+p_1p_{10}(t)$$
$$p_1(t)=p_0p_{01}(t)+p_1p_{11}(t)$$

we had $M=\lambda/(\lambda+\mu)$

and

$$\mathrm{D}(t,\tau)=p_1(t+\tau)p_{11}(t)-p_1(t)p_1(t+\tau)=p_1(t)p_0(t)e^{-(\lambda+\mu)\tau}$$

hence $\rho(\tau)=e^{-(\lambda+\mu)\tau}$

The latter showed that the short-term memory could be regared as a property of a two-state Markov process.

1.3 A Markov process with frail intensities and long-term memory

For long-term memory, λ and μ in Fig 1 were assumed as frail variables, independently influenced by a random environment and following gamma distributions $\Gamma(\alpha_1,\beta^{-1})$ and $\Gamma(\alpha_2,\beta^{-1})$, respectively.

Define the mean and auto-correlation function of the process with a random environment as

$$M=\mathrm{E}_{\lambda,\mu}[M(\lambda,\mu)]$$

and

$$\rho(\tau)=\mathrm{E}_{\lambda,\mu}[\rho(\tau|\lambda,\mu)]$$

where $M(\lambda,\mu)=\lambda/(\lambda+\mu)$, $\rho(\tau|\lambda,\mu)=\exp[-(\lambda+\mu)\tau]$, and $\mathrm{E}_{\lambda,\mu}[\cdot]$ referred to the expectation with respect to the distributions of λ and μ. Then (see Appendix)

$$M=\mathrm{E}_{\lambda,\mu}[\frac{\lambda}{\lambda+\mu}]=\frac{\alpha_1}{\alpha_1+\alpha_2}$$

and

$$\rho(\tau)=(\beta\tau+1)^{-(\alpha_1+\alpha_2)}$$

The latter showed that the long-term memory could be regarded as a property of a two-state Markov-process with gamma distributed frail transition intensities.

2 Estimation of parameters

2.1 Short-term memory

Denote the patch clamp recording with $x(t)$, $t=0,1,\ldots,n$ as a sample path of the Markov process. The sample auto-correlation was calculated:

$$r(k)=\sum_{i=0}^{n-k}[x(i)-\bar{x}_{k1}]\,[x(i+k)-\bar{x}_{k2}]\Big/\{\sum_{i=0}^{n-k}[x(i)-\bar{x}_{k1}]^2\cdot\sum_{i=0}^{n-k}[x(i+k)-\bar{x}_{k2}]^2\}^{1/2}$$

where

$$\bar{x}_{k1}=\sum_{i=0}^{n-k}x(i)/(n-k+1)$$
$$\bar{x}_{k2}=\sum_{i=0}^{n-k}x(i+k)/(n-k+1)$$

$r(k)$ can be fitted with $\rho(\tau)=e^{-A\tau}$ through a nonlinear regression approach to get a least squares estimate of $A=\lambda+\mu$ and its variance, denoted with $\hat{A}$ and $\mathrm{var}(\hat{A})$, respectively. Since

$$M=\lambda/(\lambda+\mu),\ \lambda=AM,\ \mu=A(1-M).$$

The sample mean of the signals was calculated:

$$\hat{M}=\sum_{i=0}^{n}x(i)/(n+1)$$

and its variance was estimated:

$$\mathrm{Var}(\hat{M})=\sum_{i=0}^{n}[x(i)-\hat{M}]^2/n$$

Then the estimates of λ and μ and their variances were given respectively by

$$\hat{\lambda}=\hat{A}\hat{M},\ \hat{\mu}=\hat{A}(1-\hat{M})$$

and

$$\mathrm{Var}(\hat{\lambda})\approx\hat{A}^2\mathrm{Var}(\hat{M})+\hat{M}^2\mathrm{Var}(\hat{A})$$
$$\mathrm{Var}(\hat{\mu})\approx\hat{A}^2\mathrm{Var}(\hat{M})+(1-\hat{M})^2\mathrm{Var}(\hat{A})$$

where the independency between $\hat{M}$ and $\hat{A}$ has been proved (see Appendix).

The confidence intervals of λ and μ were approximately

$$\lambda:\ \hat{\lambda}\pm Z_{\alpha/2}(\mathrm{Var}(\hat{\lambda}))^{1/2}$$
$$\mu:\ \hat{\mu}\pm Z_{\alpha/2}(\mathrm{Var}(\hat{\mu}))^{1/2}$$

where $Z_{\alpha/2}$ was the critical value of the standard normal distribution corresponding to the total of two tails equal to α.

2.2 Long-term memory

The sample mean $\hat{M}$ and sample correlation $r(k)$ as the estimates of M and $\rho(k)$ were calculated:

$$\frac{\hat{\alpha}_1}{\hat{\alpha}_1+\hat{\alpha}_2}=\hat{M},\ (\hat{\beta}k+1)^{-(\hat{\alpha}_1+\hat{\alpha}_2)}\approx r(k)$$

The procedure of estimation of parameters was suggested:

2.2.1 Fit the sample auto-correlation function $r(k)$ with the model of negative power function $(B\tau+1)^{-c}$ through a nonlinear regression and obtain the estimates $\hat{B}=\hat{\beta}$, $\hat{c}=\hat{\alpha}_1+\hat{\alpha}_2$ and their variances.

2.2.2 Obtain the estimates $\hat{\alpha}_1$ and $\hat{\alpha}_2$, and their variances:

$$\hat{\alpha}_1=\hat{M}\hat{c},\ \hat{\alpha}_2=(1-\hat{M})\hat{c}$$
$$\mathrm{Var}(\hat{\alpha}_1)\approx\hat{M}^2\mathrm{Var}(\hat{c})+\hat{c}^2\mathrm{Var}(\hat{M})$$
$$\mathrm{Var}(\hat{\alpha}_2)\approx(1-\hat{M})^2\mathrm{Var}(\hat{c})+\hat{c}^2\mathrm{Var}(\hat{M})$$

where the independency between $\hat{M}$ and $\hat{c}$ was proved in Appendix.

2.2.3 Obtain the estimates of the expectations and variances of λ and μ.

$$\hat{E}(\lambda)=\hat{\alpha}_1\hat{\beta},\ \hat{E}(\mu)=\hat{\alpha}_2\hat{\beta}$$

$$\hat{Var}(\lambda)=\hat{\alpha}_1\hat{\beta}^2,\ \hat{Var}(\mu)=\hat{\alpha}_2\hat{\beta}^2$$

The variances of $\hat{E}(\lambda)$, $\hat{E}(\mu)$, $\hat{Var}(\lambda)$, and $\hat{Var}(\mu)$ could be approximately estimated with the covariance between $\hat{\beta}$ and $\hat{c}$ given by the previous nonlinear regression for $r(k)$.

3 Examples

3.1 Short-term memory

A patch-clamp recording of PC12 with NGF added and pipette voltage $V_p=40$ mV was shown in Fig 2A[5]. Its auto-correlation function, histograms of open-time and close-time were given in Fig 2 B—D. The pattern of memory was subject to short-term one. The λ and μ in the model for short-term memory were estimated through the above procedure.

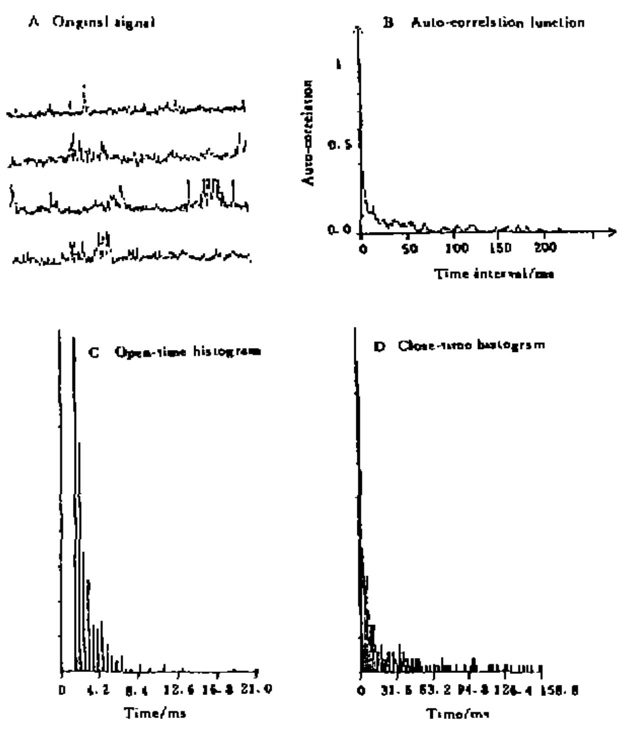

Fig 2. Patch-clamp recording of PC12 with NGF added and related functions, pipette voltage = 40 mV.

The sample auto-correlation function $r(k)$ was fitted with function $\exp(-A\tau)$ through a nonlinear regression with statistical package (Gauss method in SAS[6]).

$$\hat{A}=\hat{\lambda}+\hat{\mu}=0.5795,$$

$$Std(\hat{A})=0.02140,$$

$$Var(\hat{A})=4.5803\times10^{-4}$$

and the coefficient of determinant $R^2=0.78$.

By the software P-Clamp[4], the mean and the variance of $\hat{M}$ were obtained,

$$\hat{M}=2.8310\times10^{-3},$$

$$Var(\hat{M})=1.4533\times10^{-7}$$

The estimates $\hat{\lambda}$ and $\hat{\mu}$, and their variances were estimated,

$$\hat{\lambda}=\hat{A}\hat{M}=1.6406\times10^{-3}$$

$$\hat{\mu}=\hat{A}(1-\hat{M})=0.5779$$

$$Var(\hat{\lambda})\approx\hat{A}^2Var(\hat{M})+\hat{M}^2Var(\hat{A})=5.2470\times10^{-8}$$

$$Std(\hat{\lambda})=2.2906\times10^{-4}$$

$$Var(\hat{\mu})\approx\hat{A}^2Var(\hat{M})+(1-\hat{M})^2Var(\hat{A})=4.5549\times10^{-4}$$

$$Std(\hat{\mu})=2.1342\times10^{-2}$$

The 95 % confidence intervals of λ and μ were obtained,

$$\lambda:\ (1.1916\times10^{-3},\ 2.0896\times10^{-3})$$

$$\mu:\ (0.5360,\ 0.6196)$$

3.2 Long-term memory

A patch-clamp recording of PC12 cell with NGF added and pipette voltage $V_p=-50$ mV was shown in Fig 3 A[5]. Its auto-correlation function, histograms of open-time and close-time were given in Fig 3 B—D. A long-term memory existed.

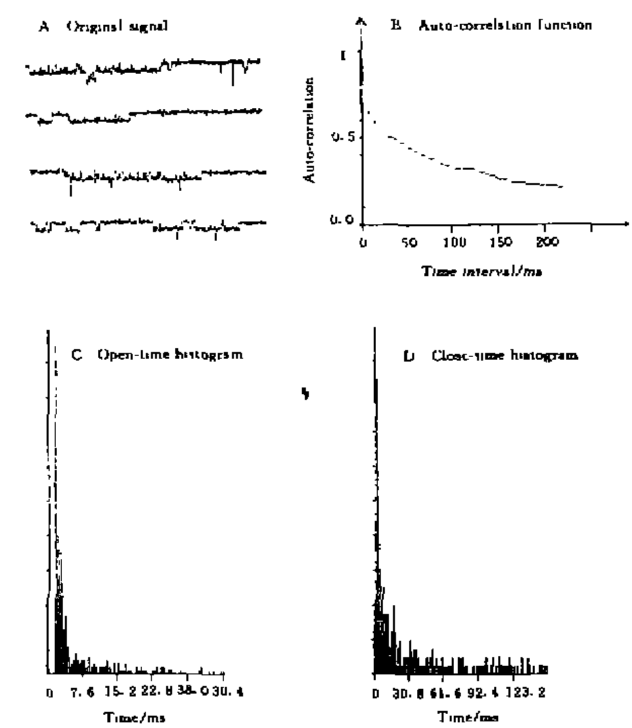

Fig 3. Patch-clamp recording of PC12 with NGF added and related functions, pipette voltage = −50 mV.

The α_1, α_2 and β in the model for long-term memory were estimated through the above procedure.

The sample auto-correlation function $r(k)$ was fitted with function $(B\tau+1)^{-1}$ through a nonlinear regression (with statistical package SAS[6]) to obtain the coefficient of determinant $R^2=0.986$ and the estimates.

$\hat{c}=\hat{\alpha}_1+\alpha_2=0.5019$, $\mathrm{Std}(\hat{c})=0.005885$

$\mathrm{Var}(\hat{c})=3.4676\times10^{-5}$

$\hat{\beta}=0.09496$, $\mathrm{Std}(\hat{\beta})=0.003303$

The software P-Clamp[4] was used to obtain the mean $\hat{M}$ and its variance,

$$\hat{M}=7.6982\times10^{-2}$$

$$\mathrm{Var}(\hat{M})=2.1590\times10^{-6}$$

The estimates $\hat{\alpha}_1$ and $\hat{\alpha}_2$, and their variances were estimated,

$\hat{\alpha}_1=\hat{c}\hat{M}=3.8637\times10^{-2}$

$\hat{\alpha}_2=\hat{c}(1-\hat{M})=0.46326$

$\mathrm{Var}(\hat{\alpha}_1)\approx\hat{M}^2\mathrm{Var}(\hat{c})+\hat{c}^2\mathrm{Var}(\hat{M})$

$=7.4936\times10^{-7}$

$\mathrm{Std}(\hat{\alpha}_1)=8.6566\times10^{-4}$

$\mathrm{Var}(\hat{\alpha}_2)\approx(1-\hat{M})^2\mathrm{Var}(\hat{c})+\hat{c}^2\mathrm{Var}(\hat{M})$

$=3.0086\times10^{-5}$

$\mathrm{Std}(\hat{\alpha}_2)=5.4851\times10^{-3}$

The 95 % confidence intervals of α_1, α_2 and β were obtained,

α_1: $(3.69401\times10^{-2}, 4.0334\times10^{-2})$

α_2: $(0.4525, 0.4740)$

β: $(0.08848, 0.10145)$

The estimates of the expectations and variances of λ and μ were obtained,

$$\hat{E}(\lambda)=\hat{\alpha}_1\hat{\beta}=3.6690\times10^{-3}$$

$$\hat{E}(\mu)=\hat{\alpha}_2\hat{\beta}=4.3991\times10^{-2}$$

$$\hat{V}\mathrm{ar}(\lambda)=\hat{\alpha}_1\hat{\beta}^2=3.4841\times10^{-4}$$

$$\hat{V}\mathrm{ar}(\mu)=\alpha_2\hat{\beta}^2=4.1774\times10^{-3}$$

DISCUSSION

From the expression of auto-correlation function related to the model for short-term memory, one could see that the parameter $A=\lambda+\mu$ was related to the speed of memory losing, that was, the parametrer A reflects the activity of the channel, a large value of A corresponded to frequently switching of the status, and hence the memory declined rapidly. From the expression of $\lambda=AM$ and $\mu=A(1-M)$, one also could see that the parameter A had an equal importance as the grand mean M. M was usually understood as the probability of opening, such that the transition intensities λ and μ were the partition of parameter A with probabilities M and $(1-M)$ respectively.

As for the meaning of parameters in the model for long-term memory, λ and μ were the transition intensities which were assumed frail, easily influenced by the random environment under the framework of gama distribution which was widely applicable due to its great diversity of shape, the expectations of λ and μ were equal to $\alpha_1\beta$ and $\alpha_2\beta$ respectively, and the coefficients of variation of λ and μ were independent of β. The speed of memory losing depended on the values of $\alpha_1+\alpha_2$ and β that a smaller (larger) $\alpha_1+\alpha_2$ and a smaller (larger) β implied a longer-term memory and lower (higher) average levels of λ and μ. The latter implies a less (more) frequent transition of states between close and open.

In the literature, being aware of the valuable meaning of parameters λ and μ, some authors tried to estimate them through the distribution of the durations of either opening or closing. However, constrained by the resolution of the patch clamp technique, the durations of successive opening (or closing) were unobservable, and hence the procedure based on the distribution of durations encountered the "omission problem"[7] inevitably, while the procedure based on the auto-correlation was free of such a problem in nature and the estimates of λ and μ might be better in stability and intuitive in the sense of memory losing.

Many authors had found that a homogeneous two state Markov model did not always well fit the patch clamp signals. One of the straightforward extensions was to increase the number of states such that multiple close states and multiple open states were assumed and it immediately met with the problem of identifiability among close states and among open states and the problem of explanation for the biological background in addition to the problem of time interval omission[5].

The alternative way of thinking adopted here was to stick on two and only two states while the mechanism of state transition was influenced by the random environment which could be explained by the randomly switching of conformation of the channel protein[9] so that the model for long-term memory might be thought as a two-state stochastic process but nonhomogeneous in time. However, if one regarded the protean changes of the channel protein as the changes of state itself, then the above model might also be thought as an infinity-state model (fractal) in nature, and only the properties on average could be observed and understood.

There was no critical cutoff point between short-term memory and long-term memory. Actually, since when $B \to 0$ and $cB \to A$ one had $(B\tau+1)^{-c} \to \exp(-A\tau)$, such that when B was small and cB was not too small, the negative power function would have little difference in comparison with a negative exponential function. In practice, the negative exponential function and negative power function might beused to fit the same auto-correlation function simultaneously and the better fit one could be accepted as the pattern of memory.

The phenomenon of long-term memory had been observed empirically by many scientists in other fields and it had also gained increasing attention with the term "long-range dependence" in statistics. Beran (1992)[2] gave a definition that a stationary process X_t was said to exhibit long-range dependence if the correlations $\rho_k = \mathrm{corr}(X_t, X_{t+k})$ decayed approximately like $|k|^{2H-2}$, $H \in (0.5, 1)$ as $|k| \to \infty$. As the long-term memory in ion channels could be well fitted with a pattern of $(B\tau+1)^{-c}$ and the value of c was often taken between 0 and 1 in practice, one might see that the long-term memory in ion channels bore suprising analogy with those happen to other fields such as geophysics, hydrology, astronomics, agriculture, chemistry and environment science, where several authors had also discussed possible physical reasons for the occurrence of long-term memory and derived physical models justified in their specific contexts. Some of these might also be useful as reference, but the model suggested in this paper was specifically for explanation of the long-term memory in ion channels. Particularly, the change of memory pattern or the change of parameters in the models might be used as new indicators of response to certain stimulus in studies of physiology, pharmacology and others.

APPENDIX

1 Proof for the independency between $r(k)$ and $\hat{M}$.

The denominator of $r(k)$ was independent of $\hat{M}$. Denote the numerator of $r(k)$ proportional to $X'AX$ and $\|A\| = \max_{0<i<n} \sum_{j=1}^{n} |a_{ij}|$, where $X = (x_1, x_2, \cdots, x_n)'$, a_{ij} was coefficent of the term $x_i x_j$, then $\|A\| = (k-1)/(n-k+1)$. Since $\hat{M} \to \mu$ w. p. 1 as $n \to \infty$ and $\|X\|$ had a bound, $\|X'AX\,\hat{M}\| \to 0$ w. p. 1 as $n \to \infty$, ie. $X'AX$ and $\hat{M}$ were independent with probability 1. Hence $r(k)$ and $\hat{M}$ were indenpendent with probability 1.

2 Proof for $\mathrm{E}[\frac{\lambda}{\lambda+\mu}] = \frac{\alpha_1}{\alpha_1+\alpha_2}$

Since the density functions of λ and μ were $\Gamma(\alpha_1, \beta^{-1})$ and $\Gamma(\alpha_2, \beta^{-1})$ respectively , and assumed independent each other, the density function of μ/λ was

$$\frac{\Gamma(\alpha_1+\alpha_2)}{\Gamma(\alpha_1)\,\Gamma(\alpha_2)}\,(1+z)^{-(\alpha_1+\alpha_2)} z^{\alpha_2-1},\ z \geqslant 0$$

hence that of $1+\mu/\lambda = (\lambda+\mu)/\lambda$ was

$$\frac{\Gamma(\alpha_1+\alpha_2)}{\Gamma(\alpha_1)\,\Gamma(\alpha_2)}\, z^{-(\alpha_1+\alpha_2)}(z-1)^{\alpha_2-1},\ z \geqslant 1$$

and that of $\lambda/(\lambda+\mu)$ was

$$\frac{\Gamma(\alpha_1+\alpha_2)}{\Gamma(\alpha_1)\,\Gamma(\alpha_2)}\, x^{\alpha_1-1}(1-x)^{(\alpha_2-1)},\ 0 \leqslant x \leqslant 1$$

which was Beta(α_1, α_2). Therefore,

$$\mathrm{E}[\frac{\lambda}{\lambda+\mu}] = \frac{\alpha_1}{\alpha_1+\alpha_2}.$$

3 Proof for $\rho(\tau) = (\beta\tau+1)^{-(\alpha_1+\alpha_2)}$

Since λ and μ followed $\Gamma(\alpha_1, \beta^{-1})$ and $\Gamma(\alpha_2, \beta^{-1})$ respectively and independent each other,

$$\rho(\tau) = \mathrm{E}_{\lambda,\mu}[\rho(\tau|\lambda,\mu)] = \mathrm{E}_{\lambda,\mu}[e^{-(\lambda+\mu)\tau}] =$$

$$\int_0^\infty \int_0^\infty e^{-(x+y)\tau} \frac{1}{\Gamma(\alpha_1)\beta^{\alpha_1}} x^{\alpha_1-1} e^{-x/\beta} \frac{1}{\Gamma(\alpha_2)\beta^{\alpha_2}} y^{\alpha_2-1} e^{-y/\beta} \mathrm{d}x\mathrm{d}y$$

$$= (\beta\tau+1)^{-(\alpha_1+\alpha_2)}$$

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离子通道记忆的二状态随机模型[1]

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关键词 离子通道；统计学模型；记忆

目的：定量研究存在于通道中的记忆并提供有关统计方法以应用于生物医学研究. **方法**：利用随机过程分别建立短期和长期两类记忆的模型，坚持两状态而不是多状态，只是转移机制不同. **结果**：恒定转移强度的二状态马氏过程较好地拟合短期记忆的情形，处于一类随机环境中的二状态马氏过程较好地拟合长期记忆的情形；提出了参数估计的方法并以 PC12 细胞通道作为示例. **结论**：离子通道中的记忆可以用仅含两个状态的随机过程定量地建立模型.

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(—)-Stepholidine *vs* 12-chloroscoulerine enantiomers on firing activity of substantia nigral dopamine neurons[1]

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KEY WORDS stepholidine; 12-chloroscoulerine; electrophysiology; dopamine receptors; reserpine; substantia nigra; apomorphine; benzazepines

AIM: To compare the potencies between (—)-stepholidine ((—)-SPD) and 12-chloroscoulerine (CSL) enantiomers on firing of substantia nigra (SN) dopamine (DA) neurons. **METHODS**: Extracellular single unit recordings in paralyzed rats. **RESULTS**: In rats, (—)-SPD, (—)-, (±)-, and (+)-CSL attenuated iv apomorphine (Apo, 10 $\mu g \cdot kg^{-1}$)-induced inhibition on firing of DA cell, and their ED_{50} values were 15.1 (11.9—19.4), 7.8 (7.0—8.7), 12.6 (2.0—17.9) $\mu g \cdot kg^{-1}$, and 2.9 (2.6—3.3) $mg \cdot kg^{-1}$, respectively. Thus, (—)-CSL was 1 time more potent than (—)-SPD and 371 times more potent than (+)-CSL on D_2 receptors. In reserpinized rats, (—)-SPD, (—)-, (±)-, and (+)-CSL blocked the inhibition caused by iv 4 $mg \cdot kg^{-1}$ SKF-38393, with ED_{50} values of 0.53 (0.51—0.55), 0.51 (0.43—0.60), 1.2 (0.7—2.0), and 5.9 (4.9—7.1) $mg \cdot kg^{-1}$, respectively. The potency of (—)-CSL was similar to that of (—)-SPD on D_1 receptors and 11 times higher than that of (+)-CSL. **CONCLUSION**: CSL enantiomers are D_1/D_2 mixed antagonists as (—)-SPD. (—)-CSL is the most, while (+)-CSL is the least, potent one among them.

Dopamine (DA) receptors have been divided into D_1 and D_2 subtypes[1]. Autoreceptors, a special subpopulation of D_2 receptors, concentrate on presynaptic terminals and soma-dendrites of DA neurons in substantia nigra pars compacta

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