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H2 control and Robustic Design for Acetyl Choline Channel Receptor States Transitions at Neuro Muscular Junction.

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We proposed an H2 control and system design method for analyzing multi states Acetylcholine channel transition in the synaptic transmission of the central nervous system. The acetyl choline-receptor binding processes consisted of one Ach -receptor complex, two Achs -receptor complex and Ach free receptor. Each of them have activated form or inactivated form. Ach was set as control input. For the H2 control, we induced the differential equations for the state variables and estimator of the system which were expressed by two Riccati equations. By solving the differential equations linked by the Riccati equation, the transient changes in the concentration of the Ach-receptor complexes were computed numerically. The present investigation will be available for Ach -receptor channel function of the central nervous system.

H2 control and design, Robustness, Acetly choline, Channel receptor. State transition. Riccati.

神経筋接合部におけるアセチルコリン受容体チャンネルのH2制御

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神経系のシナプス間隙伝達物質の１つであるアセチルコリンAchが特異的に結合するチャンネルの過渡的特性とH２制御機能を解析した。Ach受容体チャンネルの開閉を６つの状態モデルすなわちAch 分子が１こ、または２こ結合してチャンネルが開いている状態と閉じている状態、および Achが結合していない状態での開閉を６個の状態方程式で記述した。制御入力としてはAchを設定した。これに対してH２制御設計をおこなった。制御と観測の２つの方程式群はリカッチ方程式で連結した。質量保存則を用いて合計１０個の微分方程式を数値計算で解いた。 Ach 分子が１こ、または２こ結合した受容体分子の過渡的変動を計算することが可能であった。 本研究は中枢神経系伝達物質の受容体結合過程の制御特性を評価すううえで有用である。

中枢神経系. アセチルコリン. チャンネル. 受容体. Ｈ２ 制御. リッカチ方程式

1.Introduction.

Neural information transmission is achieved by the interaction between transmitter molecules and Acetyl choline is the typical transmitter for neuro muscular junction. The Acetyl choline-receptor complex has six states depending on the number of Acetyl choline molecules and states of the channel. There are lots of agonists and antagonists that compete with the receptors. These molecules are regarded as noises to disturb the signal transmission. In the present work, we apply H2 control theory for signal transmission across the neuro muscular junctional membrane disturbed by the agonist and antagonist.

2. Physiological Background.

The mechanisms for the Ach channel kinetics that have been confirmed are summarized as

1. Binding two agonist molecules opens channel (Katz 1958, Dionne 1978).
2. Non liganded (Jackson 1984, 1986) and mono liganded agonists can open the channel (Dionne 1978 , Jackson 1986, Sine 1990).
3. Affinity of the first ligand binding is different from the second ligand binding(Sine 1990, Jackson 1988).
4. Binding and gating are distinct (Blount and Merlie 1989) and multi states (Jackson 1988, Sine 1990).
5. The length of channel opening durations and closing durations have some stochastic correlations (Colquhoun and Sakmann 1985, Jackson 1988).

We explain briefly above findings as fundamentals for the modeling of multi states Ach channel gating. We did not, however take the desensitization (Jackson 1988, Sine 1990) and influence of extra cellular Calcium ion (Sine 1990) into modeling to avoid the complexity.

2-1. Structural findings.

Muscle cell nicotinic ACh receptor is composed of five homologous amphipathic helix subunits namely α β δ and either γ or ε (Guy 1984). They conform barrel like holes perforating the membrane with several different open conformations. The agonist binding sites lie at the α-γ or α-ε and α-δ subunit interfaces (Blount and Merlie 1989. Pedersen Cohen 1990). This fact suggests that a subunit pair constitutes a distinct gating domain.

2-2. Shut and open states.

Three exponential terms of the probability density function could well approximate the shut period histograms of gating currents (Colquhoun 1985, Jackson 1988 , Sine 1990). Biochemical studies (Dionne 1978, Karlin 1983) reported that there are two binding sites. Hence, there are three shut states corresponding to zero, one and two agonist bond states. Similar results have been reported for the open state (Colquhoun 1985, Jackson 1988).

The fraction of brief closures per mean open duration increased abruptly at the agonist concentration of 1 μM. (Jackson 1988). Beyond 1 μM, this fraction increased a little. Similar tendency was observed for the open states (Jackson 1988). More over, above 1 μM agonist concentration, long duration openings predominated while below 1 μM, short duration openings predominated. These support that there are distinct two different levels of Ach binding for channel closing and opening, one state which still has an empty site to catch Ach and another state which has been saturated (Jackson 1988, Sine 1990). For channel opening, mono liganded gating leads to short period openings while bi-liganded gating induces long period openings (Jackson 1988, Sine 1990).

Spontaneous opening and closing of the Ach channel without ligand binding have been reported (Jackson 1984, 1988). These components also depended heavily on the agonist concentration (Sine 1990).

2-3. Interrelations among different channel gating states.

Statistical correlation analysis among the open periods (Colquhoun and Sakmann 1985) revealed positive correlations between successive open states such that long open periods follow long open durations. The brief closures during an open period appeared at a constant frequency and associated with long period openings (Colquhoun 1985, Jackson 1986 and Sine 1986). The transition to the double liganded open state arises from the double liganded closed state but rarely from the mono liganded open state nor mono-liganded closed state (Colquhoun 1985). The possibility is low where the transitions from one closed state to two different open states such as to mono liganded open state and to bi-liganded open state (Colquhoun 1985). This observation is consistent to the ordinal assumption of the stochastic process in which the probability of simultaneous occurring of two events is negligible during sufficiently short time period Δt.

2-4. Difference in the first and the second ligand binding and dissociation.

Kinetic differences between the mono ligand binding and bi ligand binding have been verified by biochemically (Karlin 1967, 1983) ,pharmacologically (Sine and Taylor 1981) and physiologically (Jackson 1988, Sine 1990, Auerbach 1993). Although both of these binding rates are diffusion -limited (Sine and Steinbach 1987, Sine 1990, Auerbach 1993), Ach binds to its two sites with 300 fold (Sine 1990) to 1000 fold different affinity (Jackson 1988) .The first ligand binds tightly but opening the channel weakly. The second ligand binds less tightly than the first one but accelerates the rate of channel opening by the factor 2500 (Jackson 1986).

For dissociation of the ligand, the dissociation rate of Ach from a mono-liganded complex was 350 to 1000 fold lower than the rate from a bi-liganded complex (Sine 1990). More over, the dissociation constants of the first and the second ligand from the receptor sites differ when the channel is open (four fold) and closed (1000 fold) (Jackson 1986).

Fig 1

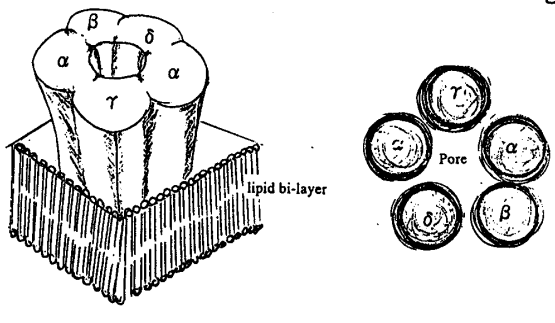
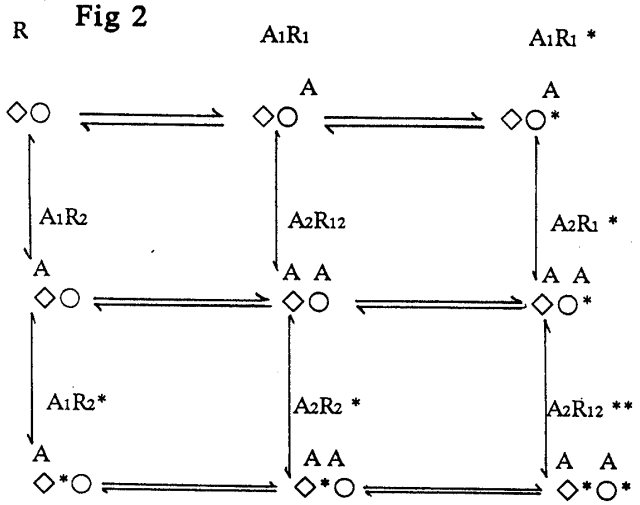


Fig 2



where * denotes activated state, subscript for R denotes the subunit of Ach receptor. Subscript for A indicates the number of agonist molecule.

3. Modeling and simplification.

Fig 2 and table 1 are the most detailed picture of multi states Ach channel proposed by Auerbach (1993). This schema discriminates two subunits for Ach binding. Incorporating all of these possible states requires an extensive matrix computation for H2 control. Hence, we assumed (but see discussion) the functional equivalency of the two subunits.

1. Inactive two mono-liganded states A_1R_1 and A_1R_2 are associated to AR.
2. Mono-liganded partially activated states A_1R_1* and A_1R_2* are condensed to AR*.
3. Bi-liganded partially activated states A_2R_1* and A_2R_2* are summarized to A_2R*.

These simplifications are practical because it is difficult to discriminate the rate constants between A_1R_1 and A_1R_2, between A_1R_1* and A_1R_2*, between A_2R_1* and A_2R_2*

4. When two agonists have bound on the receptor subunits, the resting subunits are immediately and simultaneously activated (Unwin 1993, 1995). This can be interpreted as the allosteric nature (Monod et 1965). We omit the intermediate partially activated states. This means ignoring sub-conductance state or partial closed and open states (Colquhoun 1985).
5. Once doubly liganded, the channel opens rapidly at a rate of at least 25000/s which is diffusion limited rate (Rohrbough & Kidokoro 1990, Land and Salepeta 1981, Colquhounn & Sakmann 1985, Sine 1990, Auerbach 1993). Thus we can approximate the A_2R* by the bi-liganded open state A_2O. Thus, we approximate

$$A_2R^* \fallingdotseq A_2R^{**} = \text{open state.}$$

Fig 3 is the most reliable and approved picture (Colquhoun 1985, Jackson 1988) to which we apply H2 control. In summary the present model bases on the allosteric transition and functional equivalency between the two subunits.

4. Mathematical description of multiple states Ach channel.

4-1. State equations.

The temporal changes in the amount of these six channel gating states per unit membrane area are expressed as followings on the basis of mass action law.

$$\partial [R]/\partial t = \alpha_0 [R^*] + k_{-1} [AR] - (\beta_0 + 2 k_1 [Ach]) R$$

$$\partial [AR]/\partial t = 2 k_1 [Ach] [R] + \alpha_1 [AR] + 2 k_{-2} [A_2C] - (k_{-1} + \beta_1 + k_2 [Ach]) [AR] \quad \text{------(2)}$$

$$\partial [A_2R]/\partial t = k_2 [Ach] [AR] + \alpha_2 [A_2R^*] - (2 k_{-2} + \beta_2)[A_2R] \quad \text{----------(3)}$$

$$\partial [A_2R^*]/\partial t = \beta_2 [A_2R] + k_2^* [Ach] [AR^*] - (\alpha_2 + 2 k_{-2}^*)[A_2R^*] \quad \text{----------(4)}$$

$$\partial [AR^*]/\partial t = 2 k_{-2}^* [A_2R^*] + \beta_1 [AR] + 2 k_1^* [Ach] [R^*] - (k_2^* [Ach] + \alpha_1 + k_{-1}^*) [AR^*] \quad \text{---(5)}$$

$$\partial [R^*]/\partial t = \beta_0 [R] + k_{-1}^* [AR^*] - (\alpha_0 + 2 k_1^* [Ach]) [R^*] \quad \text{----------(6)}$$

where [ ] denotes the amount of Ach-channel state per unit membrane area. βn is opening rate, αn is closing rate and kn is rate constant. The conservation law holds

$$\Sigma \{ [R] + [R^*] + [AR^*] + [A_2R^*] + [AR] + [A_2R] \} = Et \quad \text{----------(7)}$$

where Et is the total amount of all of these channel states per unit membrane area. Substituting

$$[R] = Et - \Sigma \{ [R^*] + [AR^*] + [A_2R^*] + [AR] + [A_2R] \} \quad \text{----------(8)}$$

reduces above six equations to five ones. Setting

$$x_1 = [R^*],\ x_2 = [AR^*],\ x_3 = [A_2R^*],\ x_4 = [A_2R] \text{ and } x_5 = [AR] \quad \text{--------(9)}$$

The matrix form of the above state equations disturbed by noise w is

$$\partial \mathbf{x}/\partial t = A\mathbf{x} + B_1 \mathbf{w} + B_2 \mathbf{u}^\wedge \quad \text{--------(10)}$$

where $\mathbf{x}$ is the state vector.

4-2. Input $\mathbf{u}^\wedge$ and noises w.

Many statistical analysis with varying agonist concentration reported that the short period open probability increased linearly as agonist concentration and constancy of long period open probability beyond a critical agonist concentration (Colquhoun 1985, Jackson 1988, Sine 1990). We interpreted that Ach controls the channel opening period because bi liganded channel state evokes longer open duration than the mono-liganded one does (Jackson 1988, Sine 1990). Moreover, Ach binding converts the thermodynamically unstable channel state to be stable open state, an internally stabilizing effect. Therefore we regard [Ach] as a control input and set by a matrix form $\mathbf{u}^\wedge$ weighted by rate constants such that,

$$u_1 = -2 k_1^* [Ach],\quad u_2 = k_2^* [Ach],\quad u_3 = k_2 [Ach]$$
$$u_4 = -2 k_1 [Ach] \quad \text{------(11)}$$

$\mathbf{w}$ is the disturbance vector. We interpret agonist and antagonist that compete the receptor sites with Ach as noises to disturbe the effective Ach binding on the gating channel.

$\mathbf{y}$ is the measured out put vector disturbed by the noises

$$\mathbf{y} = C_2 \mathbf{x} + D_{21} \mathbf{w} \quad \text{--------(12)}$$

z is the regulated out put vector for evaluation, an estimating vector.

$$z = C_1 x + D_{12} u^{\wedge} \quad \text{----(13)}$$

The matrix forms of B_1, B_2, C_1 C_2, D_{12} and D_{21} are given in the table 2. The actual form of estimating vector z is given in Table 3.

Associating these, the system analyzed in the present investigation is expressed by the standard generalized block diagram (Fig 4). G is the generalized plant with two sets of inputs, exogenous ones w including disturbances and control inputs u. G has two sets of out puts, the measured outputs y and regulated ones z. K is the controller to be designed. The realization of the transfer matrix G is (Zhou 1998)

$$G = \left[\begin{array}{ccc} A & B_1 & B_2 \\ C_1 & D_{11} & D_{12} \\ C_2 & D_{21} & D_{22} \end{array}\right] = \left[\begin{array}{cc} G_{11}(s) & G_{12}(s) \\ G_{21}(s) & G_{22}(s) \end{array}\right]$$

We set $D_{11} = D_{22} = 0$ for applying H2 control (Sanche-Pena 1998).

4-3. Mathematical processes for H2 control

The performance of normal physiological Ach channel gating under agonist and antagonist can be understood as to elucidate the undistrubed out put originated purely from Ach binding and to minimize the influence on the output by the noises. In the mathematical expression, this can be interpreted as the magnitude of closed loop transfer function from the disturbance to the regulated out put is minimized. Then, the present problem for minimizing control of noises on the Ach channel gating process is formalized to (Zhou 1998)

" To find a proper real rational controller K that stabilizes G internally and minimizes the 2 norm of the transfer matrix from noise w to regulated out put z II Tzw II2. "

P norm of the function x is defined as (see also APPENDIX 0)

$$\| x \|_p = \left(\sum_{i=1}^{n} | x_i |^p \right)^{1/p} \quad \text{--------(16)}$$

where vector $x \in \mathbb{C}^n$, and $\mathbb{C}^n$ is an n dimensional vector space over the complex field.

The exact form of the minimized 2 norm of the transfer function Tzw is (Zhou 1998)

$$\min \| T_{zw} \| = \mathrm{trace}(B_1^* X B_1) + \mathrm{trace}(R_1 F_2 Y F_2^*)$$

where $F_2 = -R^{-1} (B_2^* X + D_{12}^* C_1)$, $R = D_{12}^* D_{12}$

We set following assumptions for the rpesent H2 problem (Sanchez-Pena 1998).

1]. (A, B_2) is stabilizable and (C_2, A) is detectable.

2]. (A,B_1) is stabilizable and (C_1, A) is detectable.

3]. $C_1^* D_{12} = 0$ and $B_1 D_{21}^* = 0$: * denotes complex conjugate transposed matrix.

4]. D_{12} has full column rank with $D_{12}^* D_{12} = I$ and D_{21} has full row rank with $D_{21} D_{21}^* = I$.

Assumption 1 is necessary for the system to be stabilizable via output feed back (see discuaaion). Assumptions 1 and 2 together guarantee that the control and filtering Riccati equations associated with the H2 problem admit positive semi definite stabilizing solutions. Assumption 3 is the orthogonality property. Assumption 4 are the rank assumptions which guarantee the H2 problem is non singular. The conditions of $D_{12}^* D_{12} = I$ and $D_{21} D_{21}^* = I$ are normalizing assumptions.

4-4. Riccati equation.

Solving the H2 problem, we set following two Riccati equations (Sanchez-Pena 1998)

$$X A + A^T X - X B_2^T B_2 X + C_1^T C_1 = 0 \quad \text{---------(17)}$$

$$Y A + A^T Y - Y C_2^T C_2 Y + B_1^T B_1 = 0 \quad \text{---------(18)}$$

Superscript ^{T} indicates transposition. X , Y are symmetric matrixes. These equations are associated to the following two Hamiltonian matrices H2 and J2 that characterizes the system,

$$H_2 = \left[\begin{array}{cc} A & -B_2 B_2^* \\ -C_1^* C_1 & -A^* \end{array}\right], \quad J_2 = \left[\begin{array}{cc} A^* & -C_2^* C_2 \\ -B_1 B_1^* & -A \end{array}\right] \quad \text{-(19,20)}$$

The mathematical processes for inducing these Riccati equations (17,18) in relation to the Hamiltonians are given in APPENDIX 2 as an extension of the present problem to the H infinite problem.

Under the assumptions 2 and 3, these matrices H_2, J_2 belong to the Riccati domain, $H_2, J_2 \in \mathrm{dom}(RIC)$. This in turn implies that the two Riccati equations (17, 18) have unique positive definite solutions $X = \mathrm{Ric}(H2) \geqq 0$ and $Y = \mathrm{Ric}(J2) \geqq 0$ which are stabilizing. (The definition of function of Ric(H) is given in the APPENDIX I).

4-5. Estimator.

When the system states are available for feed back, the system closed- loop poles can be assigned through a constant feedback using **the exact state as it is** such that u = F x. In the Ach channel gating system, however, the system states are not always perfectly accessible. Because the Ach channel gating system has six different states which are determined by the probabilistic transitions. Hence, it is impossible to catch an exact entire state of Ach channel gating system. All that are measured are only the out put y and input u. Thus, the estimation of the system states from given outputs y and inputs u is necessary. This requires an observer system for estimating the channel states instead of direct examination of the channel states . This process is achieved by setting the differential equations for the estimator x^.

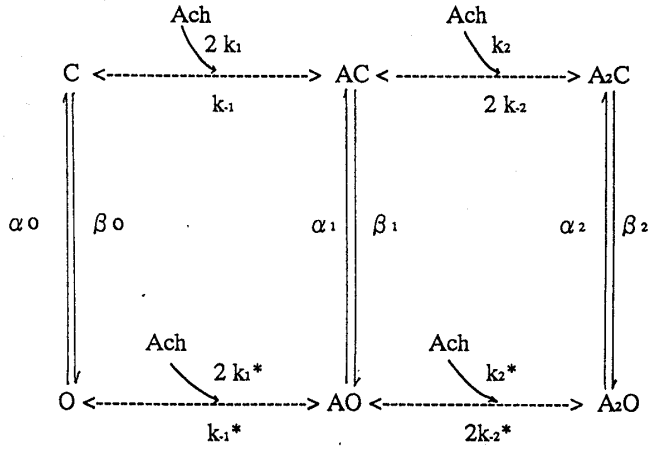
The optimal control input $u^{\wedge}$ is then, given by (Sanchez-Pena 1998)

$$u^{\wedge} = F x^{\wedge} = - B_2^T X x^{\wedge} \quad \text{---------(21)}$$

This describes that the control input for the system derives from the oberver based estimator. $u^{\wedge}$ is determined uniquely by the solutions of the two Riccati equations. The differential equation for the estimated state $x^{\wedge}$ from the observer is

$$\partial x^{\wedge} / \partial t = A x^{\wedge} + B_2 u^{\wedge} + Y C_2^T (y - C_2 x^{\wedge}) \quad \text{---------(22)}$$

Fig3.Multiple states Ach channel



4-6. Computational forms,

$\mathbf{u}^\wedge$ can be calculated to the form $= f(X x^\wedge)$ as a function of products of X and $x^\wedge$. Substituting this to equation (10), we get

$$\partial \mathbf{x}/\partial t = A\mathbf{x} + B_2 \mathbf{u}^\wedge = g(x, Xx^\wedge) \quad \text{---------(23)}$$

For the estimated state (the equation 22), substituting the equation (21) to (22),

$$\partial \mathbf{x}^\wedge/\partial t = h(x^\wedge, X x^\wedge, Y y, Y x^\wedge)$$

Substituting the equation (12) to the equation (22) eliminates y from the above equation ,

$$\partial \mathbf{x}^\wedge/\partial t = J(x^\wedge, X x^\wedge, Yx, Y x^\wedge) \quad \text{---------(24)}$$

Since X and Y are determined uniquely by the two Riccati equations 17, 18, we have two sets of differential equations for the state x and estimator $x^\wedge$ which coefficients (X, Y) were restricted by the Riccati equations. We have solved these four sets of equations under the assumptions 1] to 4] by computational approach with MATLAB. The solutions of X, Y were canceled automatically when they do not satisfy those assumptions.

4. Results.

1. Temporal changes in the amounts of Ach gating states under the H2 control.

Fig 5-a shows the temporal changes in the amounts of states, [O], [AO], [A2O], [AC] and [A2C] per unit membrane area during normalized unit time under the H2 control. [A2O] increased rapidly to fully open the channel and [AO] less rapidly. Rapid decrease in [A2C] indicates effective conversion of the inactivated state to activated state [A2O] when the Ach has operated. Fig 5-b compares the temporal changes of these species (denoted by H2) to non H2 control (denoted by -sd). Non H2 controlled [A2O] increased more rapidly than H2 controlled one. H2 controlled [AO] increased more rapidly than non H2 controlled one. H2 controlled [O] decreased more gradually than non H2 controlled [O]. Hence, rapid increase was reduced as in [A2O], gradual increase was accelerated as in [AO] and decrease was decelerated as in [O]. As a result, the total behavior of the system approached to an averaged state in which any excessive change of the species were averaged by the changes in the controversial directions.

5. Discussion.

5-1. H2 control.

5-1-a. Agonist and antagonist as Gaussian noises.

At the normal physiological state, Ach reasonable well achieves the role of transmitter across the synaptic cleft

Fig 5-a

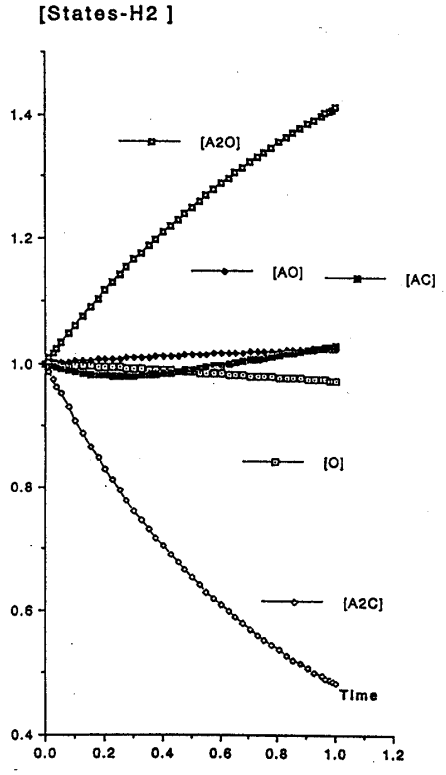


Fig 5-b

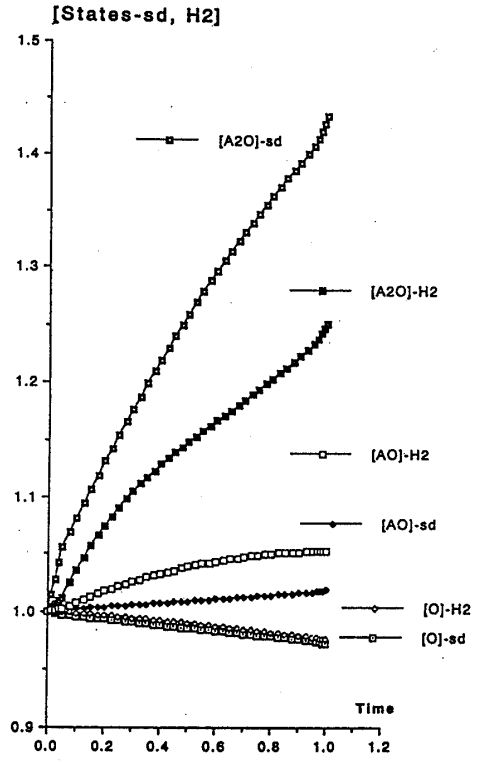


Table 4. Rate constants

1. Opening rate constants.

1-1. β_2 (Bi liganded channel opening rate)
25000/s (Auerbach 1993), (Colquhoun 1985),
45000/s. (Sine 1990)
31000/s (Colquhoun and Sakman 1985)
1700- 56000 /s.(Auerbach and Lingel 1987)
25000/s. (Land (1981))

1-2. β_1 (Mono liganded channel opening rate)
1100 /s (Jackson 1988) ,

1-3. β_0 (Vacant form channel opening rate : Spontaneous opening)
28000/s , $\beta / \beta_0 = 10^4$ (Jackson 1988)

2. Closing rate constants.

2-1. α_2 (Bi liganded closing rate)
15000/s (Sine 1990)
1320/s (Auerbach and Lingel 1987)

2-2. α_1(Mono liganded closing rate)
900 /s (Jackson 1988),
7800 /s(Kidokoro and Rohrbough (1990)
6520/s (Clquhoun and Sakmann 1985).

2-3. α_0 (Spontaneous closing rate)
5000/s (Jackson 1988).

3. β_2/α_2 : 5.3 (Sine 1990),
: 43 (Colquhoun and Sakmann 1985),
: 20 (Auerbach and Lingle 1987),
: 15 (Sine and Steinbacj 1986, 1987).

4-a. k_{+1} (Closed tansition)
6.0 10^7 /M/s (Sine 1990).
8.0 10^7 /M/s (Coluqhoun and Ogden 1988)
1.0 10^7 /M/s (Sine Steinbach 1987)
1.3 - 5.0 10^8 /M/s (Auerbach and Lingel 1987)

4-b. k_{+1}* (Open tansition)
1.5 10^{-3} /M/s (Jackson 1988).

5-a. k_{+2} (Closed transition)
1.0 10^8 /M/s (Sine 1990, Sine Steinbach 1987).
2.9 10^8 /M/s (Auerbach and Lingel 1987)
8.0 10^7 /M/s (Coluqhoun and Ogden 1988)

5-b. k_{+2}* (Open transition)
5.0 10^6 /M/s (Jackson 1988)
1.6 10^8 /M/s (Colquhoun 1985)

6-a. k_{-2} (closed transition)
40000- 70000/s .(Sine 1990).
16300/s (Colquhoun & Sakman 1985),
13000/s (Auerbach 1987), (Sine 1986)
1000/s (Sine Steinbacjh 1986)
28000/s - 30000 /s(Auerbach 1993).

6-b . k_{-2}* (Open transition)
8.5 10^{-3} /s (Jackson 1988).
9.6 10^{-3} /s (Colquhoun 1985).

7-a. k_{-1} (closed transition)
k_{-2} / 1000 (Sine 1990).
500/s (.Sine and Steinbach 1987)

7-b. k_{-1}* (Open transition)
0.0375 10^{-9} /s (Jackson 1988)

although there are lots of agonists and antagonists that compete the binding sites. But on average, Ach binding is well accomplished under these distrubances without severe deterioraiton. Hence, the agonist and antagonist can be regarded as an averaged zero Gaussian white noises. The agonists and antagonists can bind to the Ach binding sites at any channel state whether closed or opened (Coluqhoun 1985). Agonist acts by all or non fashion without provoking intemediate sub-conductance state. Hence, these actions can be regarded as channel non specific unit impulse input. The macroscopic accesses of the agonist and antagonist to Ach receptors are dominated by fluid dynamical and diffusion processes which are not molecular specific but non specific averaged processes. This treatment of agonist actions is consistent to the concept of H2 control about the disturbance noise. Controlling such situation by the closed loop transfer function can be achieved by the H2 control principle, namely to minimize the inflfuences of noises on the out puts (Sabchez 1998). The present analysis attend H2 rather than H infinite control because 2-norm concerns the disturbances with unit intensity white Gaussian processes while the infinite norm treates the disturbances with **unknown spectra**.

5-1-b. Internally stabilizing effects of Ach as a control input.

Without Ach, the channel states are considerably unsteady. The gating system can not transit to any stable open state. Under the existence of Ach, however, it can easily bind to the open state. Once Ach has bound, the molecular conformation of the Ach channel is converted to be stable. The thermodynamically fluctuation of the Ach channel state is then, driven to open the channel. The open state can persist to have sufficient gating currents. Hence, Ach has an internally stabilizing effects which is consistent to the internally stabilizign input controller of the H2 problem.

6. Conclusion.

We proposed a mathematical method to evaluate the performance of Ach that compete the channel receptor sites with agonists and antagonist while Ach internally stabilizes the channel state on the basis of H2 control theory.

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Then, H $\in$ dom(Ric) if (A,B) is stabilizable and

$$\begin{bmatrix} A - j\omega I & B \\ C & D \end{bmatrix} \quad \text{----------(A-12)}$$

has full-column rank for all ω. Furthermore, X = Ric(H) $\geqq$ 0 iff H $\in$ dom(Ric) and Ker(X) =0 if and only if ($D\perp^* C$, $A - B R^{-1} D^* C$) has no stable unobservable modes. Here

Ker(X) : kernel (or null) space of

$X. = \{ x \in \mathbb{F}^n : Ax = 0 \}$ ----------(A-13)

$D\perp$ is the orthogonal complement of D.

Comparing this form to **A15** makes one to understand that the present method can easily be extended to an H infinite problem.

For H∞ problem.

Step 1. Corollary (Zhou 1998) Let $\gamma > 0$,

$$G = \left[\begin{array}{c|c} A & B \\ \hline C & D \end{array}\right] \in RH_\infty \quad \text{-------(A-14)}$$

and

$$H = \begin{bmatrix} A + BR^{-1} D^* C & B R^{-1} B^* \\ - C^*(I + D R^{-1} D^*) C & -(A + BR^{-1} D^* C)^* \end{bmatrix} \text{--(A-15)}$$

where $R = \gamma^2 I - D^* D$

Then, the condition that the infinite norm of the function space G

$$\| G \|_\infty < \gamma \quad \text{----------(A-16)}$$

is equivalent to $\sigma(D) < \gamma$ where σ denotes the largest singular values of matrix D and there exists an X>0 such

$$X(A + BR^{-1} D^* C) + (A + BR^{-1} D^* C)^* X + X B R^{-1} B^* X + C^*(I + D R^{-1} D^*) C < 0 \text{ ----(A-17)}$$

By this corollary, there exists an

$$X^{\sim} = \begin{bmatrix} X_1 & X_{12} \\ X_{12}^* & X_2 \end{bmatrix} > 0 \quad \text{----------(A-18)}$$

such that

$$X^{\sim}(Ac + BcR^{-1} Dc^* Cc) + (Ac + Bc R^{-1} Dc^* Cc)^* X^{\sim} + X^{\sim} Bc R^{-1} Bc^* X^{\sim} + Cc^* R^{\sim -1} Cc < 0.$$

After much algebraic manipulation,we arrive to the following Lemma.

Step 2. Lemma (Zhou 1998). There exists an r th - order admissible controller such that a infinite norm of the closed loop transfer function from the input noise w to out put z satisfies

$$\| Tzw \|_\infty < \gamma \quad \text{----------(A-19)}$$

when the following three conditions hold

1. There exists a $Y_1 > 0$ such that

$$AY_1 + Y_1 A^* + Y_1 C_1^* C_1 Y_1/\gamma^2 + B_1 B_1^* - \gamma^2 B_2 B_2^* < 0 \quad \text{---------- (A-20-a)}$$

2. There exists an $X_1 > 0$ such that

$$X_1 A + A^* X_1 + X_1 B_1 B_1^* X_1/\gamma^2 + C_1^* C_1 - \gamma^2 C_2^* C_2 < 0 \quad \text{---------- (A-20-b)}$$

3. Inequality condition or the rank condition

$$\begin{bmatrix} X_1/\gamma & I_n \\ I_n & Y_1/\gamma \end{bmatrix} \geqq 0 \quad \text{rank} \begin{bmatrix} X_1/\gamma & I_n \\ I_n & Y_1/\gamma \end{bmatrix} \ll n + r$$

where In is n $\times$n identity matrix.

Step 3. Theorem (Zhou 1998)

Let R $\geqq$0 and suppose (A,R) is controllable and there is an X = X* such that

$$Q(X) := XA + A^*X + XRX + Q < 0 \quad \text{-------(A-21)}$$

Then, there exists a solution $X_+ > X$ to the Riccati equation

$$X_+ A + A^* X_+ + X_+ R X_+ + Q = 0 \quad \text{----- (A-22)}$$

such that $A + R X_+$ is anti stable. In this theorem with step 2, by setting (Zhou 1998)

$R = B_1^* B_1 / \gamma^2$ and $Q = C_1^* C_1 - \gamma^2 C_2^* C_2$, we have ----- (A-23)

$$X A + A^* X + X B1^* B1 X/\gamma^2 + C1^* C1 - \gamma^2 C_2^* C_2 = 0 \quad \text{---------(A-24)}$$

By setting $R = C_1^* C_1/\gamma^2$ and $Q = B_1^* B_1 - \gamma^2 B_2^* B_2$

$$AY + YA^* + Y C1^* C1/\gamma^2 Y + B1^* B1 - \gamma^2 B_2^* B_2 = 0 \quad \text{---------(A-25)}$$

this is identical that

$$\| Tzw \|_\infty < \gamma \quad \text{-------(A-26)}$$

Hence we arrive the final lemma. By putting

$X_\infty = \gamma^2 Y^{-1}$, $Y_\infty = \gamma^2 X^{-1}$

Step 4. Lemma (Zhou 1998)

There exists an admissible controller such that II Tzw II $\infty < \gamma$ only if the following three conditions hold.

1. There exist a stabilizing solution $X_\infty > 0$ to

$$X_\infty A + A^* X_\infty + X_\infty (B_1^* B_1/\gamma^2 - B_2^* B_2) X_\infty + C_1^* C_1 = 0 \quad \text{---------(A-27-a)}$$

2. There exist a stabilizing solution $Y_\infty > 0$ to

$$A Y_\infty + Y_\infty A^* + Y_\infty (C_1^* C_1/\gamma^2 - C_2^* C_2) Y_\infty + B_1^* B_1 = 0 \quad \text{---------(A-27-b)}$$

3. Matrix inequality or the upper limit condition for the singular value.

$$\begin{bmatrix} \gamma Y^{-1}{}_\infty & I_n \\ I_n & \gamma X^{-1}{}_\infty \end{bmatrix} > 0 \quad \text{or} \quad \rho(X_\infty Y_\infty) < \gamma^2 \quad \text{---------(A-27-c)}$$

The last condition means that the singular value of the product of X_∞ and Y_∞ is smaller than the square of γ. The present problem can be easily be extended to H infinite problem by solving the system equations which coefficients (X_∞ Y_∞) are determined by the two Riccati equations (A27-a and A27- b) under the constraint of A 27-c.

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APPENDIX 0. Definition of the norm of functional space.

For stable Laplace transform matrices $G(s) \in C^{m \times n}$, $p = \min \{ m,n \}$, the H2 and the H∞ infinite norm in terms of the frequency- dependent singular values are

$$\| G \|_2 = [\int_{-\infty}^{\infty} \sum_{i=1}^{p} (\sigma_i(j\omega))^2 \, d\omega]^{1/2} \quad \text{----(A-1)}$$

$$\| G \|_\infty = \sup_{\omega} \sigma (G(j\omega)) \quad \text{: sup indicates the least upper bound} \quad \text{----------(A-2)}$$

σ_i is the singular values of a rank r matrix of $A \in C^{m \times n}$,. They are the non-negative square-roots of the eigen values of A* A ordered such that

$$\sigma_1 \geqq \sigma_2 \geqq \sigma_3 \geqq \sigma_i \geqq \geqq \geqq \sigma_p$$
$p = \min \{ m,n \}$ ----------(A-3)

APPENDIX 1. Definitions for the Riccati operator.(Zhou 1998)

dom(Ric) X is uniquely determined by Hamiltonian matrix H (H $\rightarrow$X is a function denoted by Ric). The domain of Ric denoted by dom(Ric) is taken to be consisted of Hamiltonian matrices H with two properties: 1). H has no eigen values on the imaginary axis (the stability property) and 2). the two sub spaces

$$\chi_-(H) \text{ and } \mathrm{Im} [\, 0 \quad I \,]^T \quad \text{---------(A-4)}$$

are complementary (the complementarity property). $\chi_-(H)$ is the stable n-dimensional invariant spectral sub space of H which corresponds to eigen values of H in Re s < 0 (Hamiltonian matrix H has no eigen values on the imaginary axis and having n eigen values in open left half plane). Im A is the image or range of matrix A

$$\mathrm{Im}\, A := \{ y \in \mathbb{F}^m : y = Ax, x \in \mathbb{F}^m \} \quad \text{----------(A-5)}$$

Let qi, i=1,2,,---n denote the columns of a matrix $Q \in \mathbb{F}^{m \times n}$: Then

$$\mathrm{Im}\, Q = \mathrm{span} \{q_1, q_2, q_3, \text{---}, q_n \}$$
$$= \{ q = \alpha_1 q_1 + \alpha_2 q_2 + \alpha_3 q_3 \text{---} + \alpha_n q_n : \alpha_n \in \mathbb{F} \} \quad \text{----------(A-6)}$$

where $\mathbb{F}$ is either $\mathbb{R}$ (the real scalar field) or $\mathbb{C}$ (the complex scalar field) and $\mathbb{F}^n$is the n dimensional vector field over $\mathbb{F}$. The solution of the Riccati equation characterized by the Hamiltonian matrices is called stabilizing solution and expressed by X = Ric (H).

APPENDIX 2. H∞ control.

Step 0. Staring from H2 problem, the assumptions 2, 3 and 4 in the Method can be relaxed to (Sanchez-Pena 1998).

1. (A, B_2) is stabilizable and (C_2, A) is detectable.
2. $\begin{bmatrix} A - j\omega I & B_2 \\ C_1 & D_{12} \end{bmatrix}$ has full column rank for all ω.
3. $\begin{bmatrix} A - j\omega I & B_1 \\ C_2 & D_{21} \end{bmatrix}$ has full row rank for all ω.

4. D_{12} full column rank and D_{21} full row rank which is equal to $R = D_{12}^* D_{12} > 0$ and $S = D_{21} D_{21}^* > 0$.

The second condition indicates that $G_{12}(s)$ (equation 15) does not have zero on the imaginary axis. The third condition indicates that $G_{21}(s)$ (equation 15) does not have zero on the imaginary axis. The second and the third assumptions together with the first one guarantee that the two Hamiltonian matrices associated with the present H2 problem belong to the Riccati functional domain, dom(Ric) (see APPENDIX 1). By the theory of stabilizing solution and Riccati operator (see following **supplement**), the Hamiltonian matrix for state X (X=Ric(H2)) is (Sanchez-Pena 1998) (Zhou 1998).

$$H_2 = \begin{bmatrix} A - B_2 R^{-1} D_{12}^* C_1 & -B_2 R^{-1} B_2^* \\ -C_1^* (I - D_{12} R^{-1} D_{12}^*) C_1 & -(A - B_2 R^{-1} D_{12}^* C_1)^* \end{bmatrix} \quad \text{---(7)}$$

Similarly, the first and the third assumptions are necessary and sufficient for $J_2 \in$ dom(Ric), the specified Hamiltonian matrix for observer Y (Y=Ric(J2)) is (Sanchez-Pena 1998)

$$J_2 = \begin{bmatrix} (A - B_1 D_{21}^* S^{-1} C_2)^* & -C_2^* S^{-1} C_2 \\ -B_1 (I - D_{21}^* S^{-1} D_{21}) B_1^* & -(A - B_1 D_{21}^* S^{-1} C_2) \end{bmatrix} \quad \text{---------(A-8)}$$

where $R = D_{12}^* D_{12} > 0$, $S = D_{21} D_{21}^* > 0$. Using the normalizing conditions

$$D_{12}^* D_{12} = D_{21} D_{21}^* = I, \quad \text{---(A-9)}$$

By the solutions X and Y of the two Riccati equations which are uniquely determined by above two Hamiltonians, the observer can be expressed

$$K_2(s) = \left[\begin{array}{c|c} A + B_2 F_2 + L_2 C_2 & L_2 \\ \hline -F_2 & 0 \end{array}\right] \quad \text{-------(A-10)}$$

where $F_2 = - R^{-1} (B_2^* X_2 + D_{12}^* C_1)$,
$L_2 = - (Y_2 C_2^* + B_1 D_{21}^*) S^{-1}$
This expression is an observer based - system. B_1 and D_{21} corresponds to the system noise and observed noise in the Kalman filter system.

 # Supplement (Zhou 1998)

Suppose D has full column rank and denote $R = D^* D > 0$. Let H have the form for the system described by G(s) in Fig 4.

$$H = \begin{bmatrix} A & 0 \\ -C^* C & -A^* \end{bmatrix} - \begin{bmatrix} B \\ -C^* D \end{bmatrix} R^{-1} \begin{bmatrix} D^* C & B^* \end{bmatrix}$$

$$= \begin{bmatrix} A - B R^{-1} D^* C & -B R^{-1} B^* \\ -C^* (I - D R^{-1} D^*) C & -(A - B R^{-1} D^* C)^* \end{bmatrix} \text{-(A-11)}$$