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Evaluation of noise filtering function of biological ion Channel by H infinity control theory.

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H infinity control principle was introduced to characterize the noise minimizing control of the Calcium ion selective channels on biological cellular membrane. The modeling was based on the structural changes of the four identical subunits and voltage sensitive cylindrical polypeptide in the subunits.

Key words: Calcium ion selective channel, Allosteric model, H infinity control

1.INTRODUCTION AND MECHANISM.

Calcium ions play essential roles in maintaining the physiological cellular functions[1],[2]. Calcium ions in the extra cellular space pass through specific pores on the biological cellular membranes. We call these pores, gating channels. The channel consists of four identical subunits (Fig.1a) each of which is composed of six membrane perforating cylindrical polypeptides. They are named as S1 to S6. (Fig.1b, Fig.1c). Those molecules operate as gates for channel opening and closing. Among these, S4 has a lot of charges on its surface and acts as a voltage sensor to a change in the potential gap across membrane (Fig.1d). A change of electric distribution on its surface evokes translocation from the resting position to the activated position within the subunit. As a result, such geometric displacement of the S4 triggers positional changes of all other Sn molecules in the subunit. Those secondary changes extends to an entire channel molecules. Since there are four S4s in one channel molecule, the Calcium channel has multiple phase transitions for channel opening and closing. Such channeling action depends on the amount of S4 molecules that are taking the specific locations within the subunit. These molecular structural change is called Allosteric change[3]. The essential function of the channel is to eliminate noises so as to elevate the S/N ratio for effective bio signal transmission. The noise controlling principle, however is still unknown by experimental approach. The present paper introduces the H infinity control [4] to evaluate the noise minimizing control of the calcium ion selective channel.

2.BASIC MOLUCULAR STRUCTURE.

Fig.2 is a transition map for activating positional changes of S4 molecules (denoted by +) in open states. A set of four circles expresses one channel molecule. Arrows indicate the conformational transition pathways. -denotes the inactive positioned S4. On expresses an open state with n active positioned S4. In the transition from O0 to O1 state, either of the four S4 molecules can take an activating position. Hence there are four possible conformations of O1 state (denoted by O1a, O1b,O1c,O1d). In each of these four O1 subclasses, three S4 molecules still do not take their activating locations. Hence each O1 subclass can take three possible transitions to achieve an O2 state with different rate constants. The rate constants for O2a and for O2d must be different. Because two activated S4 in O2a have taken parallel arrangement while those in O2d have taken diagonal arrangement.

Each of O2 subclasses has two inactive positioned S4s. Thus, each O2 state has two transitions to achieve an O3 state. For simplicity, we represent the open states of O1a to O1d by O1, O2a to O2f by O2, O3a, O3b,O3c and O3d by O3.

3. KINRTIC PARAMETERS.

3-1. ACTIVATING POSITIONING OF S4.

We set kc(1/msec) as an intrinsic elementary rate constant for activating positioning of one S4 within the subunit. For example, the transition from O0 to any of the O1 subset can be expressed by 4kc. The transition from any of the O1 subset to any of the O2 subset by 3kc. The transition from any of the O2 subset to any of the O3 subset by 2kc.

kc is an exponential function of a voltage gap across the membrane[2],[3], we set

$$kc=A\exp(V/Vs),\quad k\text{-}c=B\exp(-V/Vs) \text{-----(1)}$$

A and B are constants at 0 mV [3]

A= 0.26/msec, B=0.38/msec -------(2)

Vs=26 mV, V=20 mV ----(3)

kc has to be modified for the cooperative transitions among the open states due to the Allosteric property.

3-2.CONCERTED CHANNEL OPENING AND CLOSING.

A transition between open and closed structures occurs at one time in a concerted. This means that structures of all the subunits change altogether. This reform is facilitated as the number of activating positioned S4 increases. Rate constant kL (1/msec) of the concerted transition is independent of voltage[4]. When all the S4s took the activating positions (O4 and C4), the opening rate is measured [3] to

kL=12/msec, k-L=6/msec -----(4)

3-3. ELEMENTARY RATE CONSTANTS BY ALLOSTERIC PROPERTIES.

3-3-1. For the concerted transition, kL has to be timed by a power function f^n where n is the number of active positioned S4 and f is a non dimensional Allosteric parameter. Since the rate of channel opening depends on the number of activating positioned S4 [1,3], the rate kL of transition from C4 to O4 is the fastest. Thus for the concerted transition from C2 to O2, f^2 has to be multiplied on kL Because two S4s in two subunits have to behave at one time to open the channel.

3-3-2. For the cooperative transitions among the open states, kc has to be timed by the factor f^n. This is because that the cooperative activating positioning of the S4 is stronger in open states than in closed states [1,2,3]. The residual inactive S4s in other subunits are facilitated to take the activating positions.

We set for simplicity, the rate of transition from O1 to O2 accompanied by activating positioning of two S4 as $3kc/f^2$. Factor 3 indicates that one of the three inactive S4 takes the active position. Factor 2 on the exponent indicates that two S4 have to take the active positions simultaneously. Hence, we set

$4kc/f$, $3kc/f^2$, $2kc/f^3$ and $1kc/f^4$. -------(5)

We set [3] f=1/75 as a standard value based on simulations for experimental data [2,3].

4. SIGNIFICANCE AS A BIOLOGICAL INSPIRED MATERIAL.

The present modeling will be available for creating a new channel systems in relation to solid state devices and material. The Allosteric properties, coordinated and concerted structural changes, will give a new insight for producing the biological inspired material. In the biological Allosteric systems, only a small local molecular structural change acts as a trigger signal. The coordinated structural change extends to an entire part of the channel molecule with significant amplification. As the structural change proceeds in time and space domain, the rate of structural change is markedly accelerated and finally the state changes most rapidly. This will save the energy needed for molecular reform. The concerted change will save the time required for molecular structural changes. The Allosteric system might be so organized as the time minimum, the shortest time manipulation in order to react to the changes in external environmental conditions. Such control strategy might be also available for evaluating the high speed signal transmission system in electronic devices and materials. Both of these properties are inherent in the biological Allosteric channels and will be understood as a time evolutional system. Hence, these properties will be available for creating the biological inspired new devices and materials.

5. SYSTEM EQUATION.

The instantaneous changes in amounts per unit membrane are of the channel species can be expressed

$$dC0/dt = -(k1+ k2 +k3 + k4 + L0)C0 + k-1C1a + k-2C1b + k-3C1c + k-4C1d + L-0O0 + p1U1 \quad ----(6)$$

and similar sets for Cn and for open states. With the conservation law, we have a vector state equation for the present system as

$$\partial x(t)/\partial t = A x + B1 w + B2 U \quad ----(7)$$

6. H INFIBITY NORM AND ITS BIOLOGICAL SIGNIFICANCE.

The functions of the Calcium ion channel are preserved in the physiological state even under disturbances. There must be any noise filtering control principle against the disturbances. The Ca channel must be so organized to operate even under the worst disturbance noises or must be ready to the worst situation of the signal transmission. Since there is no perfect noise filter, it is inevitable to eliminate all the noises completely. Rather than this might be to minimize the influence of the invaded unavoidable noise on the signal transfer loop of the channel system. Such strategy links to the H infinity control. The present problem for minimizing control of noises on the Ca channel gating process is formalized by the ordinal H infinite control as [4]"Given a finite value γ , synthesize an internally stabilizing proper controller K(s) such that the closed- loop transfer matrix from noise w to output z, Tzw satisfies the H infinite norm

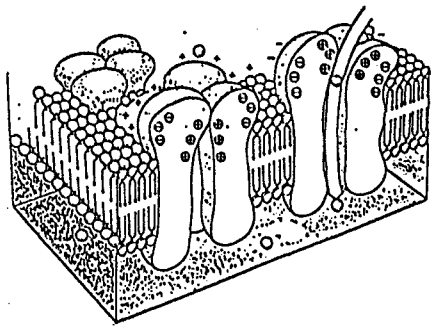


Fig. 1-a. Channel molecules on bio membrane.

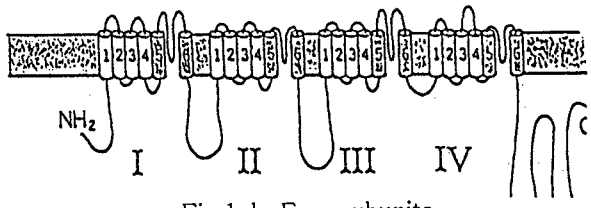


Fig.1-b. Four subunits.

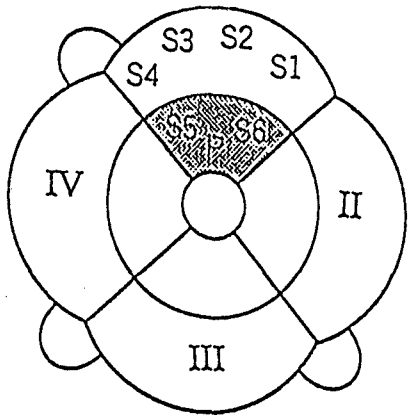
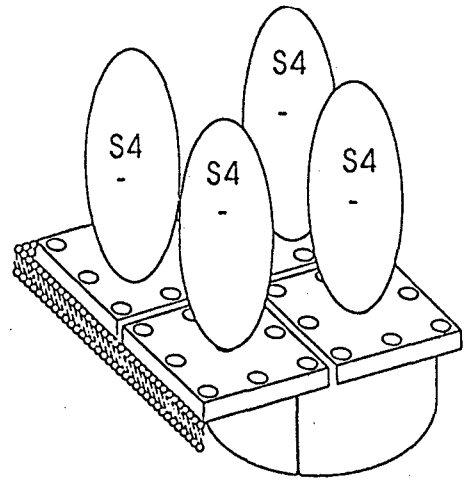


Fig.1-c. Top view of the channel molecule.



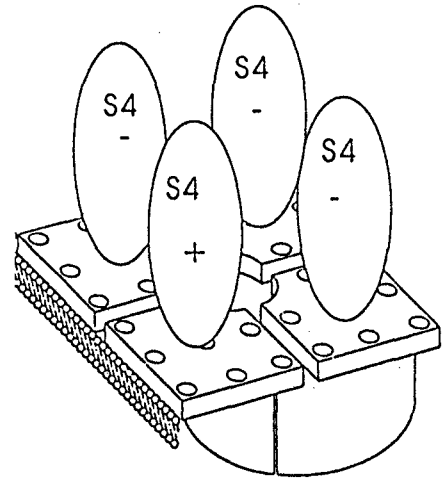


Fig.1-d. S4 voltage sensor molecule

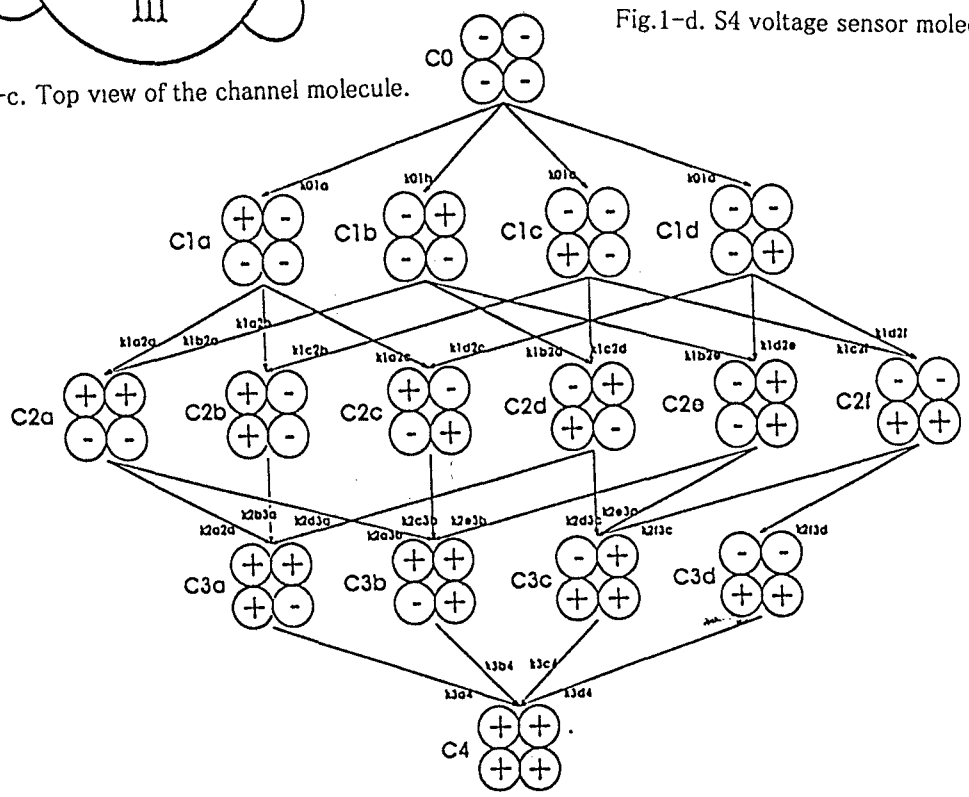


Fig.2 The state transition diagram.

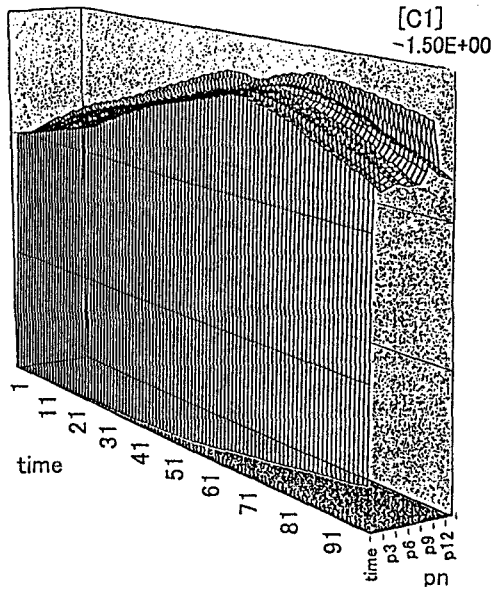


Fig.3-a.Temporal changes inC1

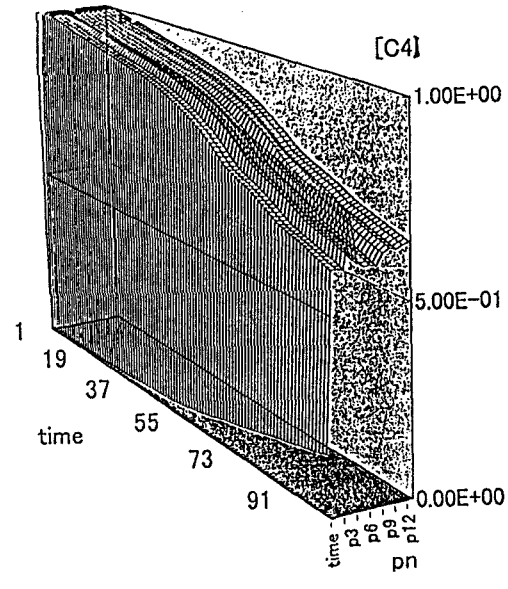


Fig.3-b. Temporal changes inC4

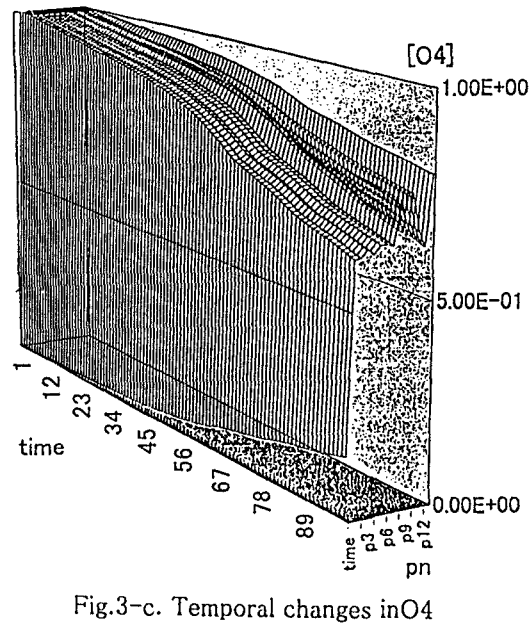


Fig.3-c. Temporal changes inO4

$$\| T_{zw} \|_\infty < \gamma . \text{“} \qquad \text{-----(14)}$$

7. COMPUTED RESULTS AND CONCLUSION.

Fig.3-a,Fig.3-b and Fig.3-c shows the influence of changes in weighting parameters pn of the control inputs on the temporal changes in C1,C4 and O4 states. As the weighting coefficients of the system has been changed for 10 times, the temporal changes in species were significantly influenced.

The present work will be available for evaluating the noise filtering function of the artificial membrane which essential properties can be inspired by the biological Alosteric nature.

8. REFERENCES.

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