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Estimation of possible selectivity and sensitivity of a cooperative system to low-intensive microwave radiation

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Abstract

A cooperative bistable chemical system is considered as a possible mechanism for sensitive and selective reception of low-intensive microwaves in bio-objects. The mechanism is realized in a two-level hierarchical manner with a threshold for signal channeling from the first level to the second one. At the first stage the microwave signal is perceived in a population of primary receptors represented as molecules of definite species. Each primary receptor has an active and a non-active conformation. The subpopulations of active and non-active receptors are in thermal equilibrium at physiological temperatures, and thermal fluctuations are taken into account. The microwaves are expected to shift the equilibrium to the more active receptors when acting at the non-active receptor fundamental frequency of mechanical oscillations. If the concentration of the active receptors is high enough, the whole bistable system switches from one stable state to another. Due to thermal fluctuations the switching has a probabilistic nature, and is characterized via a mean waiting time for first switching. The whole system sensitivity is estimated in terms of the waiting time shortening due to microwaves. At the level of primary receptors the sensitivity is described as a relative increment of active receptors. It is expected that the individual receptor oscillations are overdamped with a quality factor $Q = 1$. The sensitivity to a 1 GHz field with power density 1 mW/cm^2 is estimated. Sensitivity to this field at the level of the primary receptors is characterized by the factor $\sim 10^{-8}$, which is indistinguishable from thermal fluctuations at physiological temperatures. If the bistable system has maximum volume consistent with spatial homogeneity (the coherent volume), then its sensitivity is estimated as shortening of waiting time by a factor as high as $\exp(10^4)$. The system selectivity is also much better than that of the individual primary receptor, and may be expressed by an apparent quality factor $Q \approx 10^3$.

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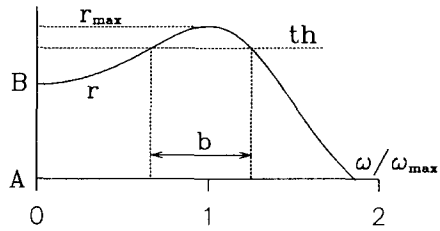


Fig. 1. The curve r represents response level of primary structure; th is the threshold for the channeling signal to the second structure; ω_{\max} is the frequency of maximal response. Selectivity is defined as $S = 1/b$. S tends to infinity when th approaches the maximal response, r_{\max} .

1. Introduction

In experimental investigations of microwaves acting on bio-objects it has been observed that under certain conditions the living object can produce a very sensitive response to a weak field [1]. The response is reported to be selective with respect to the field frequency, ω [2,3].

It is known that microwaves can influence biopolymer functioning [1], but sensitivity in a microwave frequency band would be very low. The reason is that oscillations of macromolecules in a specified band is subjected to high viscous friction [11,12] which prevents biopolymer from accumulating enough energy from microwave field even at its resonant frequency. The field intensity in some of above mentioned experiments was “non-thermal”, this means that the energy of molecular chaotic thermal oscillations well exceeds the energy accumulated from electromagnetic field applied. The question arises: How might whole organism sense a weak field which is jammed at the single macromolecule level by its thermal chaotic oscillations (thermal noise)?

It is natural to expect that mechanisms ensuring high-quality perception of signals in noisy background should be structurally similar both for the above example (microwave radiation) and for known sensory systems, such as hearing [13], olfaction [4], as well as for highly specific immune response [8]. The last examples have some features in common: they are hierarchical and of threshold-type. This means that after the primary structure has received the signal, it is sequentially processed in the structures of higher level, and it can be transmitted to the next structure if its intensity in the previous structure exceeds a definite threshold.

When any noise is absent a single structure with a threshold is able to ensure arbitrarily high sensitivity. We only need to adjust the threshold level low enough. A hierarchy of two structures is able to ensure arbitrarily high selectivity if the primary structure has a minimum selectivity.

We only need to adjust the second threshold level near the maximum of the primary structure response characteristic (Fig. 1).

When noise is present, the signal logging (excitation at higher levels of the signal processing pathway) becomes of a probabilistic nature: the logging takes place from time to time due to noise, even if the signal is absent at all. In the presence of a signal

the intervals between sequential loggings (or the mean waiting time, T) become shorter. How much shorter T becomes in response to signals of definite intensity depends on the system's sensitivity.

Possible sources of noise may be external or internal. External noise can be averaged out if many identical receptors are used for primary reception of signals. This strategy seems to be used in triggering the cytotoxic T-lymphocyte, and in smell perception. In the immune system, the triggering of T-lymphocytes may happen if about 40 000 of its surface receptors are bound with corresponding antigens on the surface of the attacked cell [8]. For olfaction, it is now believed that a lot of identical primary receptors are excited in response to a definite odorant [10]. With external noise averaged out, the only factor limiting the informational quality of the system with a threshold is its internal noise.

A system with a threshold is necessarily non-linear. In a non-linear system the exact numerical values of the parameters are decisive. In our case these parameters are the external and internal noise levels, the signal level and the threshold height. In order to obtain, based on a model with a threshold, reasonable limits of the sensitivity to microwaves and other weak factors, we cannot establish the levels voluntarily. It is necessary, instead, to derive such a model in which these levels arise naturally, as its inherent features. One such model, a cooperative chemical system, has been considered in a general situation [18]. We formulate here the conclusions of the cited paper in a refined form, and use them for the estimation of possible sensitivity to microwaves.

2. Bistable cooperative system

We consider as a model the following set of chemical reactions:



Here X , A , B , C denote molecules of different species. C^* and C^{\sim} denote active and non-active states of the same molecule C . The concentrations of A , B , and C are kept constant (the reactor is open). Positive cooperativity is realized via the upper process in (1), and negative cooperativity is due to the lower process. Due to cooperativity, the system (1)–(3) is bistable in a wide range of concentrations and rate constants. Namely, two different concentrations of X , $[X]_3$ and $[X]_1$ are possible as its stable

state ($[X]_1 < [X]_3$), and definite thresholds must be overcome to switch between the states. Reaction (3) is the input for microwaves which shift the equilibrium to more C^* acting on the fundamental frequency of the molecule C^* . The set of reactions (1), (2) with the concentration of C^* kept constant is known as the Schlögl model [14].

3. Coherent volume

The schemes (1)–(3) describe the processes that take place in any point of the reactor. But these schemes are insufficient to describe the situation in the reactor volume as a whole. The schemes themselves are unable, e.g., to answer whether the concentrations are uniform over the reactor volume V . In the large volume V , separate domains with two different stable concentrations $[X]_1$ and $[X]_3$ are possible. The boundaries between the domains may be moving or not. In a realistic situation, when mixing is necessarily present, the fragmentation of V into domains with altering stable concentrations, $[X]_1$ and $[X]_3$, cannot be arbitrarily fine. The size of the minimum domain able to survive for a macroscopic² time is determined in the competition between the mixing rate and the rates of processes (1), (2) that maintain the stable concentrations. Indeed, the small domain will be stirred before a single elementary act from (1), (2) takes place. The characteristic size L of minimal heterogeneity, which the mechanism (1), (2) is able to maintain under the given mixing rate, is the coherence length. Another way to define L is as follows: In small reactors the simultaneous coexistence of different stable concentrations is impossible. The maximum among such reactors is named the maximum coherent reactor, and its volume the maximum coherent volume. Its characteristic size is also L . In some cases intensive mechanical stirring is used to guarantee spatial homogeneity [5], and L can be as high as 10^{-2} – 10^{-1} m. If mixing is due to thermal diffusion only, the coherent volume size is estimated by the following inequality:

$$\frac{kL^2}{2D_X} \leq 1, \quad (4)$$

where D_X is the diffusion coefficient of the X -type molecules, and k is the rate of the fastest process in (1), (2). Considering X -molecules as spheres of radius r in a viscous solvent with viscosity η at temperature T , we have from (4)

$$L \approx (k_B T / (3\pi\eta r k))^{1/2}. \quad (5)$$

If c denotes the volume concentration of the C -type molecules, then for the total number N of C -type molecules in the coherent volume we have from (5)

$$N \approx \frac{c(k_B T / (3\pi))^{1.5}}{r^{1.5} r_1^3 \eta^{1.5} k^{1.5}}, \quad (6)$$

where r_1 is the radius of the C -type molecules. To obtain possible numerical values of N we need to specify the numerical values in the r.h.s. of (6). Let $r = r_1 = 5 \text{ \AA}$,

² By macroscopic we mean the time interval necessary to realize the slowest elementary process in (1), (2).

$T = 310$ K, $c = 0.01$. To specify the numerical value for k , we should bear in mind that it is known experimentally that chemical reactions offer a very large range for possible rate constants. For example, one oscillating chemical reaction described in Ref. [5] (Ch. 8) has rate constants for different stages of its three-molecular processes varying between 2.1×10^{-10} – 8.0×10^9 $M^{-2} s^{-1}$. We take for k the value $1 s^{-1}$, which is in the range of known rates for protein functioning [9,16]. Finally, Eqs. (5), (6) give for water at $20^\circ C$ ($\eta = 0.001$ Pa·s) $L = 3 \times 10^{-5}$ m, $N = 2 \times 10^{12}$; and for lipid membrane at $37^\circ C$ ($\eta = 0.1$ Pa·s) $L = 3 \times 10^{-6}$ m, $N = 2 \times 10^9$.

4. Assumptions

The system (1)–(3) is too complicated to be analyzed without simplification. We make two assumptions, in order to be able to obtain final conclusions in an exact mathematical form.

4.1. Relative rates of reactions

We suppose that the fastest processes in (1)–(3) are those represented in (3). This allows applying the slaving principle [7] for the evolution of $[C^*]$. It is convenient to claim even more: The influence of the processes in (2) on $[C^*]$ is negligible small, as compared with the processes in (3). Consequently, $[C^*]$ becomes constant:

$$[C^*] = \frac{\kappa_2}{\gamma} [C], \quad (7)$$

where $\gamma = \kappa_1 + \kappa_2$.

As a result of the assumption made, the time dependence of $[X]$ is described by a single equation³ of the following form:

$$\frac{d[X]}{dt} = F([X]), \quad (8)$$

where $F(x) = -k_1^- x^3 + k_1^+ [A] x^2 - k_2^- [B] x + k_2^+ [C^*]$.

4.2. Relative intensities of noise

Each process in (1)–(3) has a stochastic nature, and is a source of noise in Eq. (8). We assume that the most noisy processes are those in (3). This is satisfied if, e.g., the total number of C^* -type molecules in V exceeds the others by far:

$$[C^*]V \gg [X]V$$

³Note that the exact dynamical system describing (1)–(3) is two-dimensional. Eq. (8) is one-dimensional, but together with (7) it becomes two-dimensional as well. The phase portraits of the two systems are topologically equivalent.

The noise due to the processes (1), (2) will be neglected, as compared with (3). The noise mentioned above leads to an additional term in Eq. (8). This term has the following form:

$$k_2^+ C^* \frac{n(t)}{N^*}, \quad (9)$$

where $N^* = [C^*]V$, and $n(t)$ is the birth–death stochastic process due to (3). The spectral function of $n(t)$ is as follows (see Appendix A):

$$S(\omega) = N \frac{\kappa_1 \kappa_2}{\pi} \frac{1}{\gamma(\gamma^2 + \omega^2)}. \quad (10)$$

Based on the assumption (4.1) we may conclude that the fast harmonics in (10) will not be able to influence slow processes (1), (2). If so, we may consider white noise instead of (9), provided the white noise spectral density is equal to $S(0)$. Namely, instead of (9) we consider the noise

$$\left(\frac{2k_2^{+2} [C^*]^2 \kappa_1}{N^* \gamma^2} \right)^{1/2} \xi(t), \quad (11)$$

where $\langle \xi(t) \xi(t + \tau) \rangle = \delta(\tau)$. Finally, Eq. (8) with white noise (11) leads to the Fokker–Planck equation:

$$\frac{\partial P(x, t)}{\partial t} = \frac{\partial (U'(x) P(x, t))}{\partial x} + D \frac{\partial^2 P(x, t)}{\partial x^2}, \quad (12)$$

where $x = [X]$, $P(x, t)$ is the probability density to find $[X] = x$ at moment t ,

$$U(x) = - \int^x F(y) dy, \quad D = \frac{k_2^{+2} c^{*2} \kappa_1}{N^* \gamma^2}, \quad c^* = [C^*].$$

5. Response to external influences

Eq. (8) represents a dynamical system with two stable states. This implies, for the “potential” $U(x)$ above, that it has two minima: U_1 at $x = [X]_1$, and U_3 at $x = [X]_3$, separated with a maximum U_2 , corresponding to unstable state of rest at $x = [X]_2$ ($[X]_1 < [X]_2 < [X]_3$). If the system (12) is prepared in the state $[X]_1$, then it may switch to the state $[X]_3$ due to noise. This process is characterized by the mean waiting time for first switching $T_{1 \rightarrow 3}$ [6]. If some external influence changes the equilibrium in reaction (3) then $[C^*]$ changes, and so does $T_{1 \rightarrow 3}$. The following estimate has been obtained [18]:

$$\frac{T_{1 \rightarrow 3}(c^*)}{T_{1 \rightarrow 3}(c^* + \Delta c^*)} = \exp \left(\frac{3}{2} N^* \frac{\gamma}{k_2^+} \frac{\Delta c^*}{c^*} \right), \quad (13)$$

where Δc^* is the concentration increment due to the influence.

If the external influence is characterized with a parameter ω , and there exists a value ω_{\max} , which causes Δc^* to be maximal, then we may speak of system selectivity.

Let $\nu(\omega)$ denote the response characteristics of the C -type molecules:

$$\nu(\omega) = \frac{c^* + \Delta c^*(\omega)}{c^* + \Delta c^*(\omega_{\max})},$$

and $\mu(\omega)$ denote the response characteristic at the level of the whole bistable system:

$$\mu(\omega) = \frac{T_{1 \rightarrow 3}(c^* + \Delta c^*(\omega_{\max}))}{T_{1 \rightarrow 3}(c^* + \Delta c^*(\omega))}.$$

The following relation between $\mu(\omega)$ and $\nu(\omega)$ has been obtained [18]:

$$\mu(\omega) = (\nu(\omega))^P, \quad (14)$$

where $P = N^* \gamma / k_2^+$. If κ_1 and κ_2 are of the same order, as it was expected when deriving (13), then estimate of N in Section 3 is applicable to N^* also. If so, then we may conclude from (13) that a very small change in c^* is able to cause a pronounced response at the level of whole system. Also, it follows from (14) that a broad maximum in $\nu(\omega)$ can be transformed into a sharp maximum in $\mu(\omega)$, due to a cooperative mechanism. The latter is formulated in terms of the half-width:

$$\frac{B_i}{B_e} = \sqrt{P \cdot (1 - \nu_0)}, \quad (15)$$

where B_i and B_e are the $\nu(\omega)$ and $\mu(\omega)$ half-widths; ν_0 is the individual C -type molecule noise level:

$$\nu_0 = \frac{c^*}{c^* + \Delta c^*(\omega_{\max})}.$$

The effect is illustrated in Fig. 3.

6. Selectivity and sensitivity to microwaves

Suppose that the rate constants κ_1, κ_2 correspond to conformation switching in some conformational potential $E(q)$, where q is the reaction (3) coordinate (Fig. 2). In this case, in accordance with the Arrhenius formula we have

$$\kappa_i = A_i \exp(-E_i / (k_B T)), \quad i = 1, 2.$$

We consider small oscillations of $C \sim$ molecules in the vicinity of \bar{q} to be linear. Let the corresponding linear oscillator have a mass m , fundamental frequency ω_0 , and quality factor Q .

Its coupling with microwaves is due to the charge e . We treat the oscillations in the microwave frequency band as classic ones. Namely, the differential equation describing the oscillator dynamics reads as usual

$$m \frac{d^2 q}{dt^2} + \Lambda \frac{dq}{dt} + kq = f_0 \sin(\omega t),$$

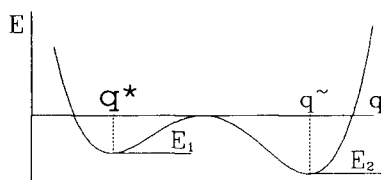


Fig. 2. Potential energy vs. reaction coordinate for reaction (3).

where $f_0 = e\mathcal{E}$, and \mathcal{E} is the amplitude of the electric field stress in the microwave. For this oscillator we have, as usual, $\omega_0 = \sqrt{k/m}$, $Q = \sqrt{km}/\Lambda$, $\omega_{\max} = \omega_0 \sqrt{(1 - 1/(2Q^2))}$,

$$\Delta E(\omega) = \frac{kf_0^2}{2m} / ((\omega_0^2 - \omega^2)^2 + (\omega_0\omega/Q)^2).$$

If the microwaves have frequency ω_{\max} corresponding to maximum coupling, then the maximum energy the oscillator is able to accumulate from the field is given by the following expression:

$$\Delta E = ZQ^4 / (Q^2 - 0.25), \quad (16)$$

where I is the surface power density of microwaves, and $Z = (378\Omega)e^2 / (m\omega_0^2)$ is the factor characterizing the coupling between the oscillator and the field.

If ΔE is small, it can be treated as a decrement of the activation energy E_2 . As a result, the rate constant and concentration are changed:

$$\kappa_2 \rightarrow \kappa_2 \exp(\Delta E / (k_B T)), \quad c^* \rightarrow c^* + \Delta c^*.$$

Up to first order in $\Delta E / (k_B T)$ we have

$$\Delta c^* / c^* \approx 2\Delta E / (3k_B T). \quad (17)$$

For numerical evaluation we consider the oscillator mass $m = 200$ a.u.m.; the charge $e = 3e$; the fundamental frequency $\omega_0 / (2\pi) = 1$ GHz, the quality factor $Q = 1$, the field intensity $I = 1$ mW/cm² and the temperature $T = 310$ K. For the values specified we have from (16), (17)

$$\Delta E \approx 2.6 \times 10^{-28} \text{ J}, \quad \frac{\Delta E}{k_B T} \approx 6 \times 10^{-8}, \quad (18)$$

$$\Delta c^* / c^* \approx 4 \times 10^{-8}. \quad (19)$$

It follows from the latter evaluations that at the level of *C*-type molecules the microwaves influence is negligible small. At the same time, we have from Eq. (13) for phospholipid membranes:

$$\frac{T_{1 \rightarrow 3}(I = 0)}{T_{1 \rightarrow 3}(I = 1 \text{ mW/cm}^2)} \sim \exp(10^4). \quad (20)$$

We supposed here that the assumption in Subsection 4.1 is realized in the form $\gamma/k_2^+ \geq 10^3$.

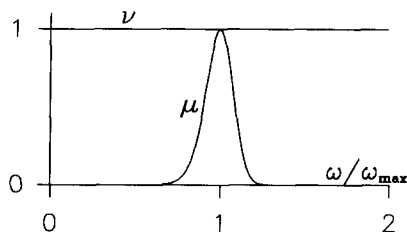


Fig. 3. The individual molecule (ν) and cooperative (μ) response characteristics. The curves are calculated with parameter values given in Section 6. The exponent P in Eq. (14) has been chosen to be equal to 10^{10} in accordance with estimates of Section 3 and the assumption in Subsection 4.1. The ν graph looks like a straight line due to its very smooth course. The curve r in Fig. 1 represents this ν if we assume $A = 0.999999955$, $B = 0.999999985$.

The huge reduction of the waiting time expressed in (20) means that the following situation is possible: Without microwaves the state $[X]_1$ is preserved as long as desired, but weak microwaves cause immediate switching to $[X]_3$.

The selectivity of the response can be evaluated based on (15), where

$$1 - \nu_0 = \frac{2}{3} \Delta E(\omega_{\max}) / (k_B T)$$

up to first order in $\Delta E / (k_B T)$. It follows from Eqs. (15), (18) that selectivity at the level of a cooperative system can be characterized by a quality factor $Q \approx 10^3$. The situation is illustrated in Fig. 3.

7. Conclusions and discussion

A possible mechanism for the reliable perception of weak signals in the presence of noise has been considered. The main features of the mechanism proposed are: (1) hierarchy; (2) threshold; (3) coherence. Features (1) and (2) are typical for known sensory systems [17]. The coherence is widely discussed in connection with the functioning of realistic neural networks, see e.g. [15]. In the model (1)–(3) the hierarchy is represented by two levels of signal perception: the first level is realized via a C -type molecule subsystem able to change concentration $[C^*]$ under the signal action. The second level is realized via the cooperatively coupled X -type molecules, able to switch between two stable concentrations $[X]_{1,3}$. The signal channeling from the first level to the second one is due to reaction (2), and a certain threshold must be overcome to cause the switching.

The coherence in this context means that the switching between two stable concentrations is only possible in the entire volume simultaneously. Whether the coherence is present depends on the system size, the effectiveness of mixing, and the rates of the processes maintaining stable concentrations $[X]_{1,3}$. In this sense the concept of coherent volume (Section 3) seems to be a significant characteristic of a non-linear system, combining together its intensive and extensive properties.

All consideration is made for the model system (1)–(3). But it is general enough, because any bistable system after suitable choosing of coordinates may be described by equation with cubic polynomial similar to Eq. (8). On the other hand, neglecting of noise generated in the processes (1) and (2) yields a simplification in the mathematical treatment.

The considered mechanism of the primary perception of microwaves—the shift of the chemical equilibrium—is the most obvious one. Unfortunately, exact experimentally tested systems of type (1)–(3) are not described. On the other hand, it will not be easy to establish experimentally the above hypothetical two-level mechanism of perception. Indeed, the microwave effect at the first level is very small (see Eq. (19)), and will be neglected. At the same time, the effect at the level of X -type molecules is clear (see Eq. (20)), but it will be difficult to explain how the effect may appear if X -type molecules themselves do not perceive microwaves. The situation is similar to cases of extrasensory perception, when the fact of communication is acknowledged, while it is difficult to find a communication channel.

Appendix A

Let $P(n, t|n, 0)$ denote conditional probability to find $N^* = n$ at moment t if $N^* = n'$ at moment 0. The master equation for (3) is as follows:

$$\begin{aligned} \frac{dP(n, t|n, 0)}{dt} = & -(\kappa_1 n + \kappa_2(N - n))P(n, t|n, 0) \\ & + \kappa_1(n + 1)P(n + 1, t|n, 0) \\ & + \kappa_2(N - n + 1)P(n - 1, t|n, 0), \quad 0 \leq n \leq N, \end{aligned} \quad (\text{A.1})$$

where $N = [C]V$ is the number of C -type molecules. Instead of the system (A.1) let us consider the equation for the generating function $G(s, t)$:

$$\begin{aligned} G(s, t) &= \sum_{0 \leq n \leq N} s^n P(n, t|n, 0), \\ \frac{\partial G(s, t)}{\partial t} &= (\kappa_1 + (\kappa_2 - \kappa_1)s - \kappa_2 s^2) \frac{\partial G(s, t)}{\partial s} + \kappa_2 N(s - 1)G(s, t) \end{aligned} \quad (\text{A.2})$$

with initial and boundary conditions:

$$G(s, 0) = s^{n'}, \quad G(1, t) = 1. \quad (\text{A.3})$$

Solving the system (A.2), (A.3) we have

$$G(s, t) = \left(\frac{1 + q e^{-\gamma t}(s - 1)/(s + q)}{1 + e^{-\gamma t}(s - 1)/(s + q)} \right)^{n'} \left(\frac{s + q - e^{-\gamma t}(s - 1)}{1 + q} \right)^N,$$

where $q = \kappa_1/\kappa_2$. The stationary generating function has the form $G(s) = [(s + q)/(1 + q)]^N$. This allows us to calculate the stationary correlation function

$$c(t) \equiv \langle (n(t) - \langle n \rangle)(n(0) - \langle n \rangle) \rangle = \frac{\kappa_1 \kappa_2}{\gamma^2} N e^{-\gamma|t|},$$

and the noise spectral function

$$S(\omega) = N \frac{\kappa_1 \kappa_2}{\pi} \frac{1}{\gamma(\gamma^2 + \omega^2)}.$$

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