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BioSystems 55 (2000) 15–22

BioSystems

www.elsevier.com/locate/biosystems

Coding efficiency and information rates in transmembrane signaling

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Abstract

A variety of cell types responds to hormonal stimuli by repetitive spikes in the intracellular concentration of calcium ($[Ca^{2+}]_i$) which have been demonstrated to encode information in their frequency, amplitude, and duration. These $[Ca^{2+}]_i$-spike trains are able to specifically regulate distinct cellular functions. Using a mathematical model for receptor-controlled $[Ca^{2+}]_i$ oscillations in hepatocytes we investigate the encoding of fluctuating hormonal signals in $[Ca^{2+}]_i$-spike trains. The transmembrane information transfer is quantified by using an information-theoretic reverse-engineering approach which allows to reconstruct the dynamic hormonal stimulus from the $[Ca^{2+}]_i$-spike trains. This approach allows to estimate the accuracy of coding as well as the rate of transmembrane information transfer. We found that up to 87% of the dynamic stimulus information can be encoded in the $[Ca^{2+}]_i$-spike train at a maximum information transfer rate of 1.1 bit per $[Ca^{2+}]_i$-spike. These numerical results for humoral information transfer are in the same order as in a number of sensory neuronal systems despite several orders of magnitude different time scales of operation suggesting a universal principle of information processing in both biological systems.

Keywords: Intracellular calcium oscillations; Hepatocyte; Stimulus reconstruction; Information rate; Frequency coding; Temporal coding

1. Introduction

1.1. Humoral information transmission and processing

Biological information is transmitted over long distances by the nervous system and the endocrine system. In the nervous system information is represented in the temporal pattern of discrete action potentials (neural spike train Adrian, 1928). The endocrine system encodes information in the structural specificity of its signaling molecules transported to distant target cells via the blood stream (Gammeltoff and Kahn, 1995) as well as in the temporal profile of secretion (Brabant et al., 1992). In recent years it has been demonstrated

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0303-2647/00/$ - see front matter
PII: S0303-2647(99)00078-7

that most hormones and neurotransmitters are secreted in a burstlike or pulsatile manner rather than constantly (Brabant et al., 1992). By making use of the temporal structure of pulsatile hormone secretion the endocrine system is capable of specifically regulating distinct cellular functions as has been examplified for many functions from the system to the molecular level (Knobil, 1980; Weigle and Goodner, 1986; Shupnik, 1990).

The cellular response upon extracellular agonist stimulation is mediated by a number of different intracellular second messenger pathways (Bhalla and Iygenar, 1999). The Ca^{2+}–phosphoinositide (PI) signaling pathway plays a major role in transmembrane signal transmission (Berridge and Galione, 1988) or a number of cell types (Berridge and Galione, 1988; Berridge, 1993; Clapham, 1995). Upon binding to plasma membrane receptors hormones, growth factors and neurotransmitters initiate the activation of phospholipase C (PLC) and the subsequent formation of diacylglycerol (DAG) and inositol(1,4,5)-trisphosphate (InsP3) which triggers the generation of repetitive ($[Ca^{2+}]_i$)-spikes varying in frequency, amplitude, and duration depending on the strength and type of the extracellular agonist. The amplitude (AM) and frequency modulation (FM) of ($[Ca^{2+}]_i$)-spike trains has been reported to regulate distinct cellular processes differentially (Berridge, 1997). The FM mode of ($[Ca^{2+}]_i$)-signaling is used to control processes such as secretion (Rapp and Berridge, 1981), glycogen metabolism in hepatocytes (Woods et al., 1986; Schöfl et al., 1993) and differentiation in the neuronal system (Gu and Spitzer, 1995; Gomez and Spitzer, 1999), whereas it has been reported that the AM mode and duration of the ($[Ca^{2+}]_i$)-signal allows for differential gene activation (Dolmetsch et al., 1997).

Repetitive $[Ca^{2+}]_i$-spikes have been studied experimentally and theoretically mostly under constant hormonal stimulation. However, it has been demonstrated that almost all hormones are secreted in an episodic or pulsatile manner (Brabant et al., 1992; van Cauter and Turek, 1995). It has been examplified in single liver cells that periodic square-wave pulses of phenylephrine (an α–adrenoreceptor agonist) are mapped into distinct patterns of $[Ca^{2+}]_i$ spike trains and that the amplitude of $[Ca^{2+}]_i$-spikes is modulated by the frequency of the hormonal pulses (Schöfl et al., 1993). Based on this study, a mathematical model for receptor–controlled $[Ca^{2+}]_i$-oscillations was adapted (Chay et al., 1995) which had been numerically studied only under constant agonist stimulation (Cuthbertson and Chay, 1991). Transmembrane signal transfer has been studied experimentally (Schöfl et al., 1993) and numerically (Chay et al., 1995) using periodic stimuli only, whereas secretory pulses and the resulting hormonal fluctuations in the blood stream and tissue are usually not equally spaced (Brabant et al., 1992; Prank et al., 1996).

Here, transmembrane signaling was investigated numerically using a model for receptor-controlled $[Ca^{2+}]_i$-oscillations in hepatocytes (Chay et al., 1995). The stimuli consisted of bandlimited Gaussian white noise as a first approximation to physiological and pathophysiological pattern of hormonal fluctuations in the blood stream. The objective of this study was to quantify the flow of information from time-varying extracellular hormonal stimuli across the cell membrane into $[Ca^{2+}]_i$-spike trains.

1.2. Quantifying information transfer in neuronal systems

A number of experimental and numerical studies on the quantification of information transfer in sensory neuronal systems has been performed in recent years (Rieke et al., 1995; Bialek et al., 1991; Gabbiani et al., 1996; Gabbiani and Koch, 1996; Theunissen et al., 1996; Rieke et al., 1997). In these studies the question of coding of information in the timing of individual spikes temporal coding has recently received renewed attention. This temporal information of action potentials is neglected when only the mean firing rate (mean rate coding) is used as the relevant parameter to characterize the neuronal response. The idea behind temporal coding is that spike timing plays an important role in encoding various aspects of the stimulus as has been demonstrated in a number of different sensory neuronal systems (Bialek et al., 1991; Eskandar et al., 1992; Singer and Gray,

1995; deCharms and Merzenich, 1996; Gabbiani et al., 1996; Laurent, 1996; Wehr and Laurent, 1996; Wessel et al., 1996; Lisman, 1997). Using temporal coding allows for significantly increasing the information capacity of neural spike trains (de Ruyter van Steveninck et al., 1997).

2. Methods

2.1. Receptor-controlled model for $[Ca^{2+}]_i$ oscillations

In this study we used the model proposed by Chay et al. (1995) which assumes that the receptor–controlled $[Ca^{2+}]_i$ spikes are caused by the increase of activated guanosine-5′-triphosphate-(GTP) binding proteins (g–GTP) which in combination with positive feedback processes and cooperative effects activates phospholipase C (PLC). Activated PLC converts phosphatidylinositol-(4,5)bisphosphate ($PtdIP_2$) into diacylgylcerol (DAG) and inositol (1,4,5)-trisphosphate (IP_3) which triggers the release of Ca^{2+} from the endoplasmic reticulum (ER) by binding to the specialized tetrameric IP_3 receptor in the ER membrane. The level of cytosolic Ca^{2+} drops fast as Ca^{2+} is pumped back into the ER. The model comprises the simulation of phospholipase C (PLC), diacylgylcerol (DAG), and Gα–GTP time series to generate $[Ca^{2+}]_i$-spike trains.

Each $[Ca^{2+}]_i$ spike train, $x(t)$, was simulated for 240 000 s on a Sun SPARCstation 20 using source code written in MATLAB (MathWorks Inc., Natick, MA). The system of differential equations was integrated using a modified Rosenbrock formula stiff solver (variable integration time step). The stimulus, $s(t) + s_{mean}$, which corresponds to k_g in the Chay et al. model, was generated by low-pass filtering uncorrelated zero-mean, unit variance Gaussian white noise, and then resealing this signal to the interval $[0\ s^{-1}; 0.03\ s^{-1}]$. The average value of k_g is $s_{mean} = 0.015\ s^{-1}$. Filtering was performed in the frequency domain, by setting Fourier coefficients above the desired cut-off frequency, f_c, of the stimulus, $s(t)$, to zero. The cut-off frequency f_c ranged from 3 to 100 mHz. Short time traces of the simulation of the model are displayed in Fig. 1.

In a second step we choose a fixed cut-off frequency of 10 mHz and varied the maximum stimulus amplitude between 0.015 and 0.060 s^{-1} to investigate the impact of increasing mean Ca^{2+}-spike frequency on the coding performance.

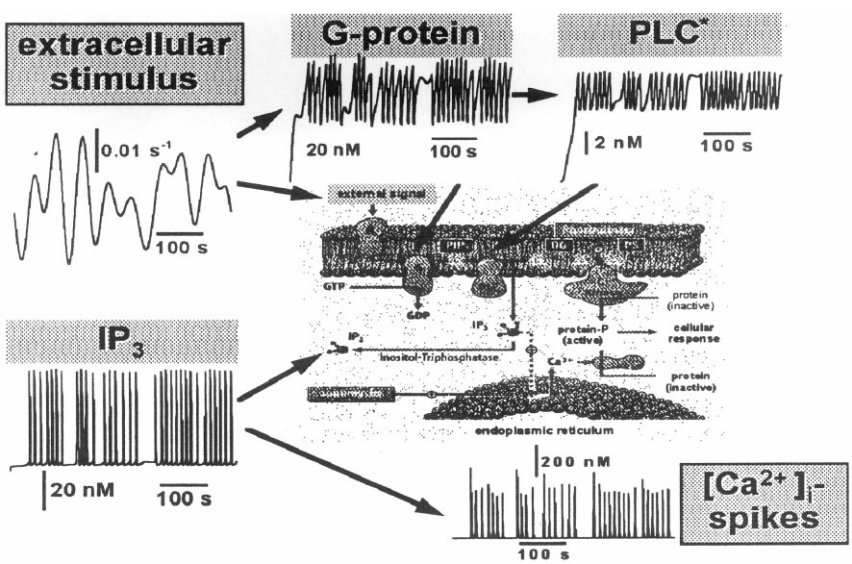

Fig. 1. Simulation of a $[Ca^{2+}]_i$-spike train and coupled intracellular second messenger in a single hepatocyte using the model of Chay et al. (1995).

2.2. Stimulus reconstruction from $[Ca^{2+}]_i$-spike trains

Methods from stochastic estimation theory (Wiener, 1949; Poor, 1994) allow to compute a temporal filter in $h(t)$ that, when convolved with a spike train in response to the stimulus, $s(t)$ will produce an estimate $s_{est}(t)$ of the stimulus $s(t)$. By using such a reverse engineering approach part of he temporal dynamics of the stimulus can be reconstructed from the spike train and the rate and accuracy of information transmission can be estimated (Bialek et al., 1991; Rieke et al., 1993).

The information encoded in $[Ca^{2+}]_i$ spike trains about time-varying hormonal stimuli was estimated using the following stimulus reconstruction algorithm (Bialek et al., 1991; Gabbiani and Koch, 1996; Gabbiani, 1996).

Let

$$x(t) = \sum_i \delta(t - t_i) - x_0 \tag{1}$$

be the $[Ca^{2+}]_i$ spike train with the mean value, x_0, subtracted. In Eq. (1) the denote t_i's the occurrence times of Ca^{2+} spikes in response to the Gaussian stimulus, $s(t)$. A linear estimate, $s_{est}(t)$, of the stimulus, $s(t)$, given the spike train, is calculated by convolving the $[Ca^{2+}]_i$ spike train with a filter, $h(t)$:

$$s_{est}(t) = \int_0^T dt' h(t - t') x(t') \tag{2}$$

The filter, $h(t)$, is to be chosen in such a way as to minimize the mean square error, ϵ^2, between the stimulus and estimate

$$\epsilon^2 = \frac{1}{T} \int_0^T dt [s(t) - s_{est}(t)]^2 \tag{3}$$

where the integration is over the duration of the simulation ($T = 240\,000$ s). Solving for the filter $h(t)$ leads to

$$h(t) = \int_{-fc}^{fc} df \frac{S_{sx}(-f)}{S_{xx}(f)} e^{-i2\pi ft} \tag{4}$$

In this equation, f_c is the cut-off frequency of the stimulus, $S_{sx}(f)$ represents the Fourier transform of the cross-correlation between the stimulus and the spike train and $S_{xx}(f)$ the Fourier transform of the autocorrelation function of the $[Ca^{2+}]_i$ spike train. We define the cross-correlation between the stimulus, $s(t)$, and the spike train, $x(t)$, as

$$R_{sx}(\tau) = \frac{1}{T} \int_0^T dt\, s(t) x(t + \tau) \tag{5}$$

and the autocorrelation function of the $[Ca^{2+}]_i$ spike train, $x(t)$, as

$$R_{xx}(\tau) = \frac{1}{T} \int_0^T dt\, x(t) x(t + \tau) \tag{6}$$

The filter, $h(t)$, computed from Eq. (4) is not causal in general in the sense that $h(t) \neq 0$ for $t > 0$, i.e. the occurrence of a spike can be used to predict the future temporal dynamics of the stimulus (this is of course only possible because of correlations in the stimulus and because of the response properties of the simulated cell). Causality is usually implemented by introducing a time delay into the reconstructions (Bialek et al., 1991) or by applying a causal Wiener–Kolmogorov filter (Poor, 1994). If no correlations exist between the stimulus, $s(t)$, and the spike train, $x(t)$, (i.e. $S_{xx}(f) = 0$ for all frequencies f) the best linear estimate of the stimulus, $s(t)$, is equal to the mean value, $\langle s(t) \rangle = 0$. The maximal mean square error computed from Eq. (3) is then equal to the variance of the stimulus, $\epsilon^2 = \sigma_s^2$. Once the best linear estimate, $s_{est}(t)$, is found, the 'noise' contaminating the reconstructions is defined as the difference between the estimated stimulus, $s_{est}(t)$, and the stimulus, $s(t)$,

$$n(t) = s_{est}(t) - s(t). \tag{7}$$

The mean square error in the reconstructions (Gabbiani and Koch, 1996) is then given by

$$\epsilon^2 = \int_{-fc}^{fc} df \frac{S_{ss}(f)}{\mathrm{SNR}(f)'} \tag{8}$$

where the signal-to-noise-ratio is defined as

$$\mathrm{SNR}(f) = \frac{S_{ss}(f)}{S_{nn}(f)} \geq 1 \tag{9}$$

In this equation S_{nn}(f) and $S_{ss}(f)$ are the power spectra of the noise and the stimulus, respectively. Thus the signal-to-noise-ratio, SNR(f), is a measure of the amount of signal power present at a

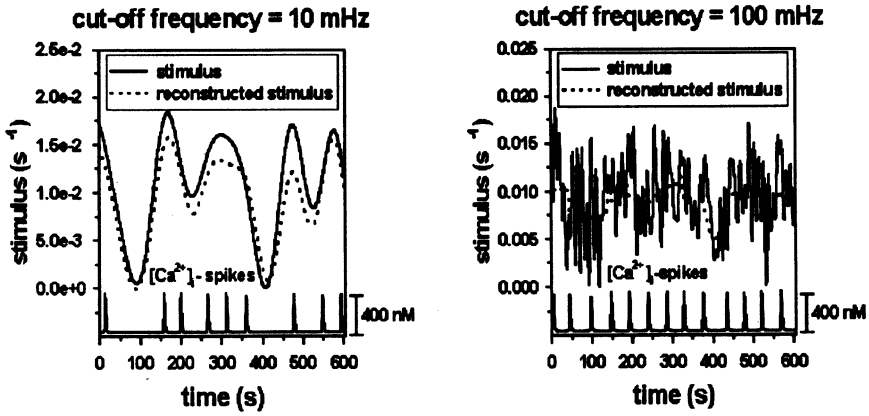

Fig. 2. Stimulus reconstruction from the $[Ca^{2+}]_i$-spike train.

given frequency relative to the noise contaminating the reconstructions. In the extreme case where the spike train is completely unrelated to the signal, $SNR(f) = 1$ for all frequencies, otherwise $SNR(f) > 1$.

The accuracy of the reconstruction and thus the information transmitted from the stimulus, $s(t)$, to the spike train, $x(t)$, is determined by the *coding fraction* defined as

$$\gamma = 1 - \frac{\epsilon}{\sigma} \tag{10}$$

where ϵ is the root-mean-square-error (rmse) between the actual stimulus, $s(t)$, and the estimated stimulus, $s_{est}(t)$, and σ is the standard deviation of the stimulus, $s(t)$ (Wessel et al., 1996). Thus the *coding fraction* represents the percentage of temporal stimulus fluctuations encoded, in units of the stimulus standard deviation. The *coding fraction* takes a maximum value of 1 when the stimulus is perfectly estimated ($\epsilon = 0$) and the minimum value of 0 if the stimulus estimation from the $[Ca^{2+}]_i$ spike train is at chance level ($\epsilon = \sigma$) (Gabbiani, 1996; Gabbiani and Koch, 1996). The accuracy of encoding in different simulations can be compared on the basis of the *coding fraction*. An alternative measure, the mutual information transmitted by the reconstructions, $s_{est}(t)$, about the stimulus, $s(t)$, can be used (Bialek et al., 1991; Rieke et al., 1993). For a Gaussian white noise stimulus, the ϵ — entropy or rate of distortion function is defined as

$$I_\epsilon = \frac{-f_c}{\log(2)} \log\left(\frac{\epsilon}{\sigma}\right) \quad \text{(in bit/s)} \tag{11}$$

and is a measure of the equivalent rate of information transmission (Shannon, 1963; Gabbiani, 1996). A lower bound for the rate of information transmitted per $[Ca^{2+}]_i$-spike is obtained by dividing I_ϵ by the mean $[Ca^{2+}]_i$-spike frequency, λ,

$$I_s = \frac{I_\epsilon}{\lambda} \quad \text{(in bit/spike)} \tag{12}$$

3. Results

Short segments of the stimuli, the corresponding reconstructed stimuli, and the $[Ca^{2+}]_i$ spike train are plotted in (Fig. 2). Irregular stimuli with high cut-off frequencies, resulted in poor estimates of the reconstructed stimulus with a *coding fraction* below 10%). Decreasing the cut-off frequency of the Gaussian stimulus to adjust it to the frequency band encoded in the $[Ca^{2+}]_i$-spike train resulted in a better reconstruction of the stimulus (Fig. 2). More than 70% of the stimulus were reconstructed (Fig. 3). In the following, the effect of the cut-off frequency, f_c on the coding performance was investigated by calculating the *coding faction*, γ, and the *information* transmitted per spike, I_s The cut-off frequency, f_c, was varied between 3 and 100 mHz. Increasing f_c led to a monotonic decrease of the *coding fraction*, whereas the information transmitted per spike (I_s)

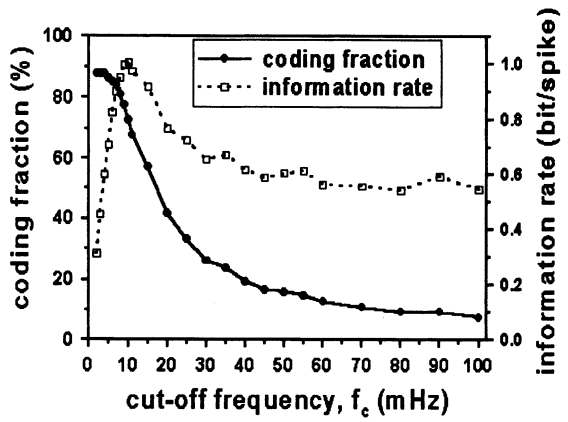

Fig. 3. Effect of the cut-off frequency, f_c, on the coding behavior.

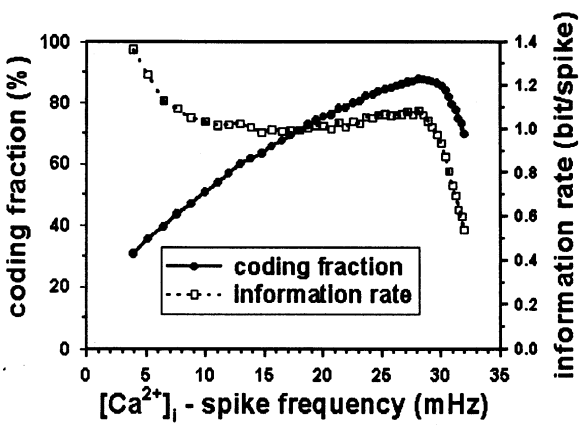

Fig. 4. Effect of the spike frequency on the coding behavior.

Table 1
Rates of information transfer

System information rate	Information rate (bit/spike)	Information rate (bit/s)
Retinal ganglion cell (rabbit)	3.6	360
Auditory neuron (frog)	1.1 … 3.5	40 … 270
Visual neuron (fly)	~3	64
Electroreceptor (electric fish)	0.8 … 1.5	100 … 200
Cereal system (cricket)	~1	10 … 80
Endocrine model system	~1	0.03

kept constant for cut-off frequencies larger than approximately 30 mHz (Fig. 3).

To study the effect of the mean $[Ca^{2+}]_i$-spike frequency on the coding behavior, a cut-off frequency of 10 mHz was chosen, which has been demonstrated to yield good reconstructions of the stimulus. The coding fraction and the information transmitted per spike showed a maximum of $\gamma = 0.87$ and $I_s = 1.1$ *bit/spike*, respectively at a value for the $[Ca^{2+}]_i$-spike frequency of 27 mHz (Fig. 4). The information rate per spike is thus of the same order as in a number of sensory neuronal systems (Table 1).

4. Discussion

The issue of coding in the temporal structure (*temporal code*) and *frequency code* of neural spike trains has received a lot of attention in the last couple of years (see for an overview ref. Rieke et al., 1997). However, this issue has not yet been studied in humoral information transfer. Within the framework of information theory reverse-engineering methods for stimulus reconstruction have been used to quantify information transmission from sensory neuronal stimuli to neural spike trains (Bialek et al., 1991; Gabbiani et al., 1996; Gabbiani and Koch, 1996; Wessel et al., 1996; Rieke et al., 1997). In the endocrine system the effect of pulse frequency (*mean rate coding*) and amplitude on the regulation of intracellular signaling as well as cellular function and structure has been studied experimentally (Shupnik, 1990; Haisenleder et al., 1992; Schöfl et al., 1993) as well as numerically (Chay et al., 1995). However, to date experimental as well as numerical studies exploring the issue of (*temporal coding*) on the regulation of intracellular signaling and target cell function and structure are lacking.

This study is a first approach to quantify the transmembrane information transfer in dynamic endocrine systems from the secretory signal to the intracellular effect in the target cell, examplified for the Ca^{2+}-hosphoinositide (PI) signaling pathway in a model system (Chay et al., 1995). An information-theoretic stimulus reconstruction method (Bialek et al., 1991; Gabbiani and Koch,

1996; Gabbiani, 1996) was used to estimate the dynamic hormonal stimulus signal from the corresponding $[Ca^{2+}]_i$-spike train. The coding performance of transmembrane information transfer was determined by two different measures: the *coding fraction* and the rate of information transmitted per $[Ca^{2+}]_i$ spike. The quality of the reconstruction of the stimulus in the time domain can be compared directly by estimating the *coding fraction* whereas the information transmitted per spike on the other hand reports the effective information transmission in a given frequency band. However this measure does not directly compare the actual and the reconstructed stimulus. Thus, it is possible to find a relatively high values for the information rate, I_s, although the quality of the reconstruction indicated by the *coding fraction* is poor (Fig. 3). More regular stimuli generated with lower cut-off frequencies, result in $[Ca^{2+}]_i$-spike trains which are able to convey significantly more information about the dynamics of the stimulus at a similar rate of information transmission, I_s. Thus, the information which the $[Ca^{2+}]_i$-spike train conveys about the stimulus remains relatively constant over a broad range of stimuli whereas the quality of the stimulus reconstruction strongly depends on the dynamics of the time-varying stimulus. It would be challenging to test these numerical results experimentally by using time-varying hormonal stimuli whose bandwidth is matched to the encoding mechanism of the transmembrane signaling system.

However, it remains an open question to determine whether the information of time-varying hormonal stimuli that can be encoded in $[Ca^{2+}]_i$-spike trains is actually used by target cells. In this context, it would be particularly interesting to correlate the quantitative measures of the coding performance with measures of the cellular response such as protein phosphorylation, secretion, and gene expression. Approaches to quantify the information flow for transmembrane signaling may be used in other parts of cellular information transmission systems and may be extended to intercellular information transfer.

Acknowledgements

This work was supported by DFG under grants Pr 333/12–1 and Br 915/4–4.

References

Adrian, E.D., 1928. The Basis of Sensation. New York, Norton.

Berridge, M.J., Galione, A., 1988. Cytosolic calcium oscillators. FASEB J. 2, 3074–3082.

Berridge, M.J., 1993. Inositol trisphosphate and calcium signalling. Nature 361, 315–325.

Berridge, M.J., 1997. The AM and FM of calcium signalling. Nature 386, 759–760.

Bhalla, U.S., Iygenar, R., 1999. Emergent properties of networks of biological signaling pathways. Science 283, 381–387.

Bialek, W., Rieke, F., de Ruyter van Steveninck, R.R., Warland, D., 1991. Reading a neural code. Science 252, 1854–1857.

Brabant, G., Prank, K., Schofl, C., 1992. Pulsatile patterns in hormone secretion. Trends Endocrinol. Metab. 3, 183–190.

Chay, T.R., Lee, Y.S., Fan, Y.S.T., 1995. Appearance of phase-locked Wenckebach-like rhythms, devil's staircase and universality in intracellular calcium spikes in non-excitable cell models. J. Theor. Biol. 174, 21–44.

Clapham, D.E., 1995. Calcium signaling. Cell 80, 259–268.

Cuthbertson, K.S.R., Chay, T.R., 1991. Modelling receptor-controlled intracellular calcium oscillators. Cell Calcium 12, 97–109.

de Ruyter van Steveninck, R.R., Lewen, G.D., Strong, S.P., Koberle, R., Bialek, W., 1997. Reproducibility and variability in neural spike trains. Science 275, 1805–1808.

deCharms, R.C., Merzenich, M.M., 1996. Primary cortical representation of sounds by the coordination of action-potential timing. Nature 381, 610–613.

Dolmetsch, R.E., Lewis, R.S., Goodnow, C.C., Healy, J.I., 1997. Differential activation of transcription factors induced by Ca^{2+} response amplitude and duration. Nature 386, 855–858.

Eskandar, E.N., Richmond, B.J., Optican, L.M., 1992. Role of inferior temporal neurons in visual memory. I. Temporal encoding of information about visual images, recalled images, and behavioral context. J. Neurophysiol. 68, 1277–1295.

Gabbiani, F., Koch, C., 1996. Coding of time-varying signals in spike trains of integrate-and-fire neurons with random threshold. Neural Comput. 8, 44–66.

Gabbiani, F., Metzuer, W., Wessel, R., Koch, C., 1996. From stimulus encoding to feature extraction in weakly electric fish. Nature 384, 564567.

Gabbiani, F., 1996. Coding of time-varying signals in spike trains of linear and half-wave rectifying neurons. Network Comp. Neural Syst. 7, 61–85.

Gammeltoff, S., Kahn, R., 1995. In: DeGroot, L.J. (Ed.), Endocrinology. W.B. Saunders Company, Philadelphia, pp. 17–56.

Gomez, T.M., Spitzer, N.C., 1999. In vivo regulation of axon extension and pathfinding by growth-cone calcium transients. Nature 397, 350–355.

Gu, X., Spitzer, N.C., 1995. Distinct aspects of neuronal differentiation encoded by frequency of spontaneous Ca^{2+} transients. Nature 375, 784787.

Haisenleder, D.J., Ortolano, G.A., Dalkin, A.C., Yasin, M., Marshall, J., 1992. Differential actions of thyrotropin (TSH)-releasing hormone pulses in the expression of prolactin and TSH subunit messenger ribonucleic acid in rat pituitary cells in vitro. Endocrinology 130, 2917–2923.

Knobil, E., 1980. The neuroendocrine control of the menstrual cycle. Recent Prog. Horm. Res. 36, 53–88.

Laurent, G., 1996. Dynamical representation of odors by oscillating and evolving neural assemblies. Trends Neurosci. 19, 489–496.

Lisman, J.E., 1997. Bursts as a unit of neural information: making unreliable synapses reliable. Trends Neurosci. 20, 38–43.

Poor, H.V., 1994. An Introduction to Signal Detection and Estimation. Springer-Verlag, New York.

Prank, K., Kloppstech, M., Nowlan, S.J., Sejnowski, T.J., Brabant, G., 1996. Random episodic release of growth hormone in humans. Phys. Rev. Lett. 77, 1909–1911.

Rapp, P.E., Berridge, M.J., 1981. The control of transepithelial potential oscillations in the salivary gland of *Calliphora erythrocephala*. J. Exp. Biol. 93, 119–132.

Rieke, F., Bodnar, D.A., Bialek, W., 1995. Naturalistic stimuli increase the rate and efficiency of information transmission by primary auditory afferents. Proc. R. Soc. Lond. B. Biol. Sci. 262, 259–265.

Rieke, F., Warland, D., Bialek, W., 1993. Coding efficiency and information rates in sensory neurons. Europhys. Lett. 22, 151–156.

Rieke, F., Warland, D., de Ruyter van Steveninck, R.R., Bialek, W. (Eds.), 1997. Spikes: Exploring the Neural Code. MIT Press, Cambridge, MA.

Schöfl, C., Brabant, G., Hesch, R.D., von zur Muhlen, A., Cobbold, P.H., Cuthbertson, K.S., 1993. Temporal patterns of alpha 1-receptor stimulation regulate amplitude and frequency of calcium transients. Am. J. Physiol. 265, C1030–C1036.

Shannon, C.E., 1963. In: Shannnon, C.E., Weaver, W. (Eds.), The Mathematical Theory of Communication. Illinois University Press, Urbana, IL.

Shupnik, M.A., 1990. Effects of gonadotropin-releasing hormone on rat gonadotropin gene transcription in vitro: requirement for pulsatile administration for luteinizing hormone-beta gene stimulation. Mol. Endocrinol. 4, 1444–1450.

Singer, W., Gray, C.M., 1995. Visual feature integration and the temporal correlation hypothesis. Ann. Rev. Neurosci. 18, 555–586.

Theunissen, F., Roddey, J.C., Stufflebeam, S., Clague, H., Miller, J.P., 1996. Information theoretic analysis of dynamical encoding by four identified primary sensory interneurons in the cricket cereal system. J. Neurophysiol. 75, 1345–1364.

van Cauter, E., Turek, F.W., 1995. In: DeGroot, L.J. (Ed.), Endocrinology. W.B. Saunders Company, Philadelphia, pp. 2487–2548.

Wehr, M., Laurent, G., 1996. Odour encoding by temporal sequences of firing in oscillating neural assemblies. Nature 384, 162–166.

Weigle, D.S., Goodner, C.J., 1986. Evidence that the physiological pulse frequency of glucagon secretion optimizes glucose production by perifused rat hepatocytes. Endocrinology 118, 1606–1613.

Wessel, R., Koch, C., Gabbiani, F., 1996. Coding of time-varying electric field amplitude modulations in a wave-type electric fish. J. Neurophysiol. 75, 2280–2293.

Wiener, N., 1949. Extrapolation, Interpolation and Smoothing of Stationary Time Series. John Wiley & Sons, New York.

Woods, N.M., Cuthbertson, K.S., Cobbold, P.H., 1986. Repetitive transient rises in cytoplasmic free calcium in hormone-stimulated hepatocytes. Nature 319, 600–602.