Hippocampal theta rhythms from a computational perspective:
Code generation, mood regulation and navigation

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Abstract

In this paper three computer models are summarized discussing different functions of the cortico-hippocampal system. Mood regulation, rhythm and code generation and navigation are integrated into a coherent conceptual framework around the concepts of structural hierarchy and circular causality. First, a model of spatio-temporal code generation is reviewed in which the hippocampal population theta rhythm plays an important role. Next, generation and pharmacological modulation of this rhythm is examined using a computer model of multiple cell populations forming a feedback loop within the hippocampus and between the septum and the hippocampus. Last, an abstract, but biologically motivated model of navigation is described which achieves a near optimal mode of navigation by composing hierarchical levels of the cortico-hippocampal system. The connections among the different hierarchical structures of the cortico-hippocampal organization and their functional roles are discussed.

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1. Introduction

Cortico-hippocampal loops might be considered as the structural basis of a circular causal chain, where information can be stored, circulated, recalled and even created. More precisely, it was argued (Lavenex and Amaral, 2000) that the flow of information within the neocortical-hippocampal loop has a hierarchical structure: perirhinal and parahippocampal circuits, entorhinal cortex and the hippocampal formation implements the first, second and third level of integration, respectively. The cortical structures are connected to the medial temporal lobe generally by reciprocal connections. Since the higher level processing has a feedback to the first, neocortical level, we might assume that the anatomical structure implement information processing based on circular causality. Circular causality was analyzed to establish self-organized neural patterns related to intentional behavior (Freeman, 1999).

It is generally agreed that the hippocampal formation prepares information for long-term storage. Also, it has an important role in neurological diseases. Alzheimer’s disease, epilepsy and ischemia are associated with learning and memory impairment, and are accompanied by selective neuronal death or characteristic changes in the hippocampal circuitry. Recent studies have also indicated that the hippocampal formation is affected in human depression as well as in animal models of depression (McNaughton and Gray, 2000; Sapolsky, 2000) and anxiety (Gray et al., 2000). The integration of anatomical, physiological, neurochemical, pharmacological and behavioral data using computational methods provide a coherent picture about the structure-function relationship of the hippocampal circuitry and offer a working therapeutic strategy for controlling disorders.

Two main, normally occurring, global hippocampal states are known: the rhythmic slow activity, called the theta rhythm with the associated gamma oscillation, and the irregular sharp waves with the associated high frequency (ripple) oscillation. A pathological brain state, associated with epileptic seizures is also known to occur in the hippocampus (Érdi and Szalisznyó, 2002).

Based on experimental observations in rats, theta oscillation in the hippocampal formation is commonly regarded as the physiological basis of memory formation (Buzsáki, 2002).
Although most of our information on hippocampal oscillatory activity is derived from electrophysiological recordings in anesthetized and non-anesthetized rodents, recent findings also indicate a similar oscillatory activity in the hippocampal formation of the human brain (Bodizs et al., 2004; Jensen and Tesche, 2002; Kahana et al., 2001). In general, theta oscillation in the hippocampal system has been linked to mnemonic processes (Jensen and Tesche, 2002; Lisman and Idiart, 1995; Raghavachari et al., 2001), and the power of theta oscillation seems to correlate with the anxiety level (Fontani et al., 1997; Green and Arduini, 1954; McNaughton and Gray, 2000; Yamamoto, 1998).

2. Structural hierarchies, theta rhythm, hippocampal function

In this paper we integrate several research projects our research group has been involved in. It is interesting to see that structures at different levels of the hierarchical organization have been involved.

First, the role of the interplay between the interaction of the somatic and dendritic compartments of a pyramidal cell and the external theta excitation in the (double-) code generation of spatial information is discussed (Huhn et al., 2005; Lengyel et al., 2004). While our first study used integrate-and-fire model framework, the second adopted compartmental modeling technique.

Second, the interaction among the networks of the hippocampus and the medial septum in generating and controlling the theta rhythm will be discussed. The effects of positive and negative allosteric modulators of the benzodiazepine binding site of the GABAA receptors were studied by multi-compartmental modeling technique, and results (Hajós et al., 2004) showed that impairment/improvement of the inhibitory mechanisms play a role in mood regulation (see also Freund and Freund, (2003)) in connection with population oscillations.

Third, the cortico-hippocampal loop, and its role in navigation using a lumped model framework elaborated by Freeman, (1975) and Kozma and Freeman, (2003), see also Kozma et al., (2003) and Kozma et al., (2004) will be reviewed. The model, which contains sampling of the environment by theta rhythm, was able to show place field generation and navigation.

3. Somato-dendritic interaction: the role of theta modulation in code generation

It is one of the central dogmas of neurobiology that information in nervous system is embedded in spike trains. However, it is still a question which parameters of a spike train codes for attributes of external stimuli. There are two fundamentally different ways of neural coding: rate and temporal coding. Rate coding implies that firing frequency, while temporal coding means that timing of spikes conveys information. The so called place cells of the rodent hippocampus are delicate subjects for investigation of neural coding since both frequency (Fig. 1A, C) and timing of their spikes related to the local theta field potential oscillation (Fig. 1A, B) correlate with the position of the animal. Each place cell fires only when the animal is in a specific portion of the environment called the place field of the cell. Firing frequency increases until the middle and decreases in the second part of the place field so it is a unimodal function of the environment the cell. Firing frequency increases until the middle and decreases in the second part of the place field so it is a unimodal function of the environment the cell. Firing frequency increases until the middle and decreases in the second part of the place field so it is a unimodal function of the environment the cell. Firing frequency increases until the middle and decreases in the second part of the place field so it is a unimodal function of the environment the cell. Firing frequency increases until the middle and decreases in the second part of the place field so it is a unimodal function of the environment the cell. Firing frequency increases until the middle and decreases in the second part of the place field so it is a unimodal function of the environment the cell. Firing frequency increases until the middle and decreases in the second part of the place field so it is a unimodal function of the environment the cell. Firing frequency increases until the middle and decreases in the second part of the place field so it is a unimodal function of the environment the cell.
In response to tonic stimulation (constant injected current) the frequency of this oscillation was a continuously increasing function of the stimulation strength (Fig. 2). In response to an oscillatory stimulation (sinusoid injected current) dendritic dynamics changed fundamentally. We kept the frequency and AC component (amplitude) of the sinusoid current at a fixed value and varied the DC component (average value of the current). Depending on the value of the DC component dendrite was in different dynamical states: when the value of DC component was relatively low dendrite was forced to oscillate with the frequency of the stimulating current independently of the exact value of the DC component (Fig. 2, regime I.). However when DC component exceeded a given value (Fig. 2, arrowhead) frequency of dendritic membrane potential oscillation became dependent on DC component and the f–I curve became overlapping with that recorded in response to tonic stimulation (Fig. 2, regime II.).

In our two compartmental model both soma and dendrite received an oscillatory input of theta frequency. Input currents were in antiphase and the DC component of dendritic input depended on the position of the animal (all the other parameters of the currents were kept constant). Outside the place field value of DC component was low so the dendritic membrane potential oscillation became dependent on DC component and the f–I curve became overlapping with that recorded in response to tonic stimulation (Fig. 2, regime I.). However when DC component exceeded a given value (Fig. 2, arrowhead) frequency of dendritic membrane potential oscillation became dependent on DC component and the f–I curve became overlapping with that recorded in response to tonic stimulation (Fig. 2, regime II.).

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to be adjusted infinitely precisely) which is essential in our model in order not to have spikes outside the place field. However, in case of a theta-modulated periodic input DC component of the current may vary without changing the frequency of dendritic oscillation (Fig. 2, regime I.). This way theta oscillation provides resistance for the mechanism against noisy inputs.

- **Theta rhythm as somatic input.** Rate code was based on that the cell fired at different somatic membrane potential values in the subsequent theta cycles (Fig. 3). Oscillation of membrane potential was necessary for this, which was provided by the theta modulation of somatic input.

4. Septohippocampal theta rhythm: its role in mood regulation

Theta frequency oscillation of the septo-hippocampal system has been considered as a prominent activity associated with cognitive function and affective processes. As the hippocampus is part of the Papez circuitry (Papez, 1937) responsible for emotions, involvement of the hippocampus in mood regulation and related pathological disorders seems plausible. Indeed, the hippocampus was found to be in connection with stress and anxiety (Freund and Freund, 2003; McNaughton and Gray, 2000; Yamamoto, 1998). It is well documented that anxiolytics and hypnotics reduce amplitude of septo-hippocampal oscillatory theta activity, which contributes to their therapeutic effect but causes unwanted side effects, e.g. cognitive impairment as well (Lees et al., 2004; Maubach et al., 2004).

In a joint pharmacological and computational work (Hajós et al., 2004) effects of the injection of the positive and negative GABA\_A allosteric modulators diazepam and FG-7142, respectively, were studied. To elaborate on the mode of action of these pharmacological agents a biologically realistic computer model of the septo-hippocampal system was built.

The **skeleton network** model (Fig. 4) of the hippocampal CA1 region and the septal GABAergic cells consisted of five cell populations. The hippocampal CA1 pyramidal cell model was a multicompartmental model modified from Varona et al., (2000) and supplemented with hyperpolarization activated current $I_h$ based on Magee and Magee, (1998). Besides $I_h$, the cell model contained sodium ($I_{Na}$), delayed rectifier potassium ($I_{K}$), A-type potassium ($I_{KA}$), muscarinic potassium ($I_{KM}$), C-type potassium ($I_{KC}$), low threshold calcium ($I_{Ca}$) and calcium concentration dependent potassium ($I_{K(AHP)}$) currents. Active and leakage currents were described using the Hodgkin–Huxley formalism (Hodgkin and Huxley, 1952) with parameter intervals described in details on the online supplementary page: http://geza.kzoo.edu/theta/theta.html.

Fig. 4. Skeleton network of the septo-hippocampal system used to model rhythm generation and control by pharmacological means. The model consists of four cell populations: pyramidal cells of the hippocampal CA1 region (CA1p), stratum oriens interneurons ($I_{O-LM}$), basket interneurons ($I_b$) and septal GABAergic cells ($I_{Sept}$). The single cell models are described by Hodgkin – Huxley-like currents. Pyramidal cells have 256 compartments, other cells due to their electrotonic compactness are represented by a single compartment. Solid lines represent explicitly modeled synaptic connections, light gray lines denote GABAergic, dark gray lines denote glutamatergic innervation. Effect of other areas are described as depolarizing current sources (dashed line). Synapses where GABAergic connections were modified are marked by black arrowhead.
In the hippocampal CA1 region basket neurons and two types of horizontal neurons were taken into account. Basket neurons formed the fast spiking neuron population of the pyramidal layer, containing $I_{Na}$ and $I_K$ currents. These model neurons were previously used (Orbán et al., 2001; Wang et al., 1996) to account for the population of fast, regularly spiking neurons.

The two types of horizontal neurons represented those interneuron populations whose somata resided at the oriens/alveus border (Wang, 2002). These neurons were described by the same set of equations as their observed physiological properties are similar and contained sodium, potassium, high-threshold calcium and hyperpolarization-activated currents (Maccaferri and McBain, 1996). The basket and O-LM neurons were able to generate repetitive action potentials autonomously, and O-LM neurons showed adaptation and low-frequency autonomous firing in the theta band.

Medial septal GABAergic neurons were single-compartment models previously described in (Wang, 2002). This cell type evokes action potentials repeatedly in clusters. Between any two clusters the cell exhibits subthreshold oscillation but no action potentials due to a slowly inactivating potassium current, which was added to this model neuron besides the Hodgkin–Huxley type sodium and potassium currents.

Connections within and among cell populations were created faithfully following the hippocampal structure. The main excitatory input to horizontal neurons is provided by the pyramidal cells via AMPA mediated synapses (Lacaille et al., 1987). Synapses of the septally projecting horizontal cells (Jinno et al., 2002) and synapses of the O-LM cell population innervating distal apical dendrites of pyramidal cells (Lacaille et al., 1990) are of the GABA$_A$ type. O-LM neurons also innervate parvalbumin containing basket neurons (Katona et al., 1999). Basket neurons innervate pyramidal cells at their

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**Fig. 5.** Emergent rhythm observed in the firing rate of all four simulated cell populations. Firing histograms were calculated by binning firings of all cells of one of the four populations (pyr – pyramidal cells, i(b) – basket cells, i(O-LM) – alveus/oriens interneurons, MS-GABA – septal GABAergic cells) into discrete bins. Resulting graph shows the total activity of the respective population.
somatic region and other basket neurons (Freund et al., 1996) as well. Septal GABAergic cells innervate other septal GABAergic cells and hippocampal interneurons (Freund et al., 1988; Varga et al., 2002) (Fig. 4). The model experiment gave explanation for the possible mechanism of intrahippocampal theta generation, and served as a framework to investigate modulatory effects.

An explanation of intrahippocampal theta oscillation generation—based on this model—includes (i) signal propagation in the pyramidal cell→O-ML cell→basket cell→pyramidal cell feed-back loop, (ii) synchronization of neural activity via the recurrent, inhibitory GABA A connections between basket and basket neurons, (iii) synchronization of pyramidal cell firing due to rebound action potential generation. Theta frequency modulation of firing rate was found in all five cell populations as shown on Fig. 5. Synchronization of neural activity on the population level was further confirmed by the power spectrum of the synthetic EEG (Fig. 6, dark line).

Neurotransmission at GABA A receptors were modulated by means of pharmacological tools: the actions of the GABA A receptor positive allosteric modulator diazepam and inverse agonist/negative allosteric modulator FG-7142 were evaluated on the septohippocampal activity in vivo. Systemic administration of diazepam inhibited, whereas FG-7142 enhanced theta oscillation of MS/DB neurons and hippocampal EEG theta activity.

In our mathematical model the synaptic current represented the chloride current assigned to the GABA receptor complex. The description of the synaptic channel also followed the formalism of the conductance-based compartmental technique:

\[ F(V_{\text{pre}}) = \frac{1}{1 + \exp\left(\frac{V_{\text{pre}} - \Theta_{\text{syn}}}{k}\right)} \]

with \( I_{\text{syn}} \) being the synaptic current, \( g_{\text{syn}} \) the maximal synaptic conductance, \( s \) the gating variable of the synaptic channel, \( E_{\text{syn}} \) the synaptic reversal potential, \( F(\cdot) \) is an activation function, \( \alpha \) and \( \beta \) rate functions describing opening and closing of the gate of the synaptic channel, \( \Theta_{\text{syn}} \) is a threshold. We modeled the effect of negative/positive allosteric modulators by decreasing/increasing the maximal conductance (\( g_{\text{syn}} \)) of GABA A synapses.

Simulations of drug action revealed that increasing the synaptic conductance induced a shift from theta-periodic to non theta-periodic behavior in a number of septal GABAergic neurons. This observation shows that the level of perturbation arising from inhibitory postsynaptic potentials of different GABA neurons is a crucial factor contributing to theta-periodic characteristics of neuronal activity (Fig. 6). It was also found that different GABAergic connections in the hippocampus have different roles in synchronizing neuron populations. Thus, we showed that strength of interconnections between basket neurons had a great influence on the septo-hippocampal activity. Similarly, simultaneous modulation of connections between septal and septal neurons together with the modulation of synaptic transmission between basket and basket neurons also induced strong septo-hippocampal activity. In contrast, selective modulation of GABA A connection between septal and septal neurons alone failed to alter theta activity of the septo-hippocampal system, although it had a clear effect on activity of individual septal neurons.

Future models of mood regulation should be extended by taking into account the control mechanisms of the serotonergic input originated from the midbrain raphe nuclei to the septohippocampal theta-generating network (Vertes et al., 1997).
5. Cortico-hippocampal circuit: navigation with the KIV model

K sets (presently from K0 up to KIV) represent a family of models of increasing complexity that describe various aspects of functioning of vertebrate brains (Freeman, 1975). The KIII model exhibits several higher level brain functions like robust pattern recognition, classification of stimuli and fast transition between global brain states represented by high dimensional aperiodic (chaotic) or lower dimensional (a local wing of the high dimensional attractor) dynamics. The next level of K sets is the KIV model, which incorporates and extends KIII models. The KIV model of the cortico-hippocampal system (Kozma et al., 2004) was designed to integrate sensory processing and decision-making.

A hippocampus-related navigating algorithm based on the combination of aperiodic dynamics and reinforcement learning and sensor sampling with theta rhythm was given (Kozma and Freeman, 2003), see also Kozma et al., (2003).

For decision making and navigation the KIV model uses both external and internal signals for its functioning: exteroceptive inputs like touch, vision and audition are processed by the cortical KIII unit (see leftmost part of Fig. 8); orientation signals, like gravity, electric fields, magnetic fields, rotational and translational accelerations are the external inputs of the KIII unit representing the hippocampal formation; signals from interoceptors, reporting about the internal state of the system and proprioception is processed by the midline forebrain.

The hippocampal formation (HF) unit is the main focus of cognitive mapping, which supports spatial navigation and spatio-temporal orientation. The KIII unit representing the HF receives input from orientation beacons via the dentate gyrus. The HF unit consists of the CA1, CA2 and CA3 subunits implemented as KII sets. CA3 combines various modalities of the input signal, which is further processed by CA1 and CA3. CA2 serves as a chaotic controller of the HF KIII.

Reinforcement learning is applied together with non-Hebbian habituation for category formation. Active reinforcement learning takes place in two situations. First, when sensory information conveys danger, harm or frustration negative reinforcement is applied. Second, positive reinforcement takes place when moving toward a desired target, moving away from danger, refueling or any kind of motion occurs. This learning is episodic, not continuous, long-term, and irreversible.

The hippocampal formation and cortex complete their functions by sampling the environment at theta rate. To achieve this periodicity, KIV relies on the septum to generate the theta frame rate as a gating function. According to this scheme, a pattern is shown to the system for a theta period followed by an other period of resting without input pattern. This kind of temporal framing is done in all sensory systems. Examples of this sampling are the saccadic movement in the visual system, sniffing in olfaction, and perhaps something similar in the cochlea.

To test our navigation algorithm a simple 2D multiple T-maze environment has been chosen. In this environment, the movement can take place along a grid. Consequently, at any instance, the robot can chose the next move from one of the four direct neighbors of the given grid point.

If the robot has properly learned the environment, it would navigate efficiently and find a reasonably optimal path to the goal based on the use of the internally formed cognitive map. Cortical learning highly improved the efficiency of the navigating algorithm as Fig. 7 shows it.

6. Conclusions

Generation, control and the multiple functional role of hippocampal theta rhythm could be conceptually integrated by taking into account the structural hierarchies of the hippocampus, see Fig. 8.

Theta rhythm has multiple role in the functioning of the cortico-hippocampal system, and in this paper we reviewed a few of them. The two main issues studied here are: (i) spatial coding and navigation, (ii) pharmacological modulation of theta rhythm. In the first problem two different approaches were used, and in the long run we hope to unify our detailed model on code generation with more integrated, more phenomenological navigating algorithms, such as the KIV.
models. As theta rhythm has functional roles at different level of structural hierarchy, a multi-scale model might be a conceptual framework to integrating the different levels.

A number of papers addressed the problem of generation and control of hippocampal rhythms using abstract (Borisyuk et al., 1999; Denham and Borisyuk, 2000) or more biophysical models (Rotstein et al., 2005; Tiesinga et al., 2001; Traub et al., 1992). The models presented in Tiesinga et al., (2001); Traub et al., (1992) studies effects of carbachol on the in vitro population activity of hippocampal pyramidal cells via modifying model parameters. The computer models offered in these papers include a population of pyramidal cells and interneurons with necessary active currents and synapses to account for phenomena in hippocampal slice preparations. In (Rotstein et al., 2005) the interaction of inhibitory cell populations producing slowly and rapidly decaying postsynaptic potentials generate coherent theta rhythm. This model explains how theta-frequency population oscillation can emerge in a CA1 slice preparation when all ionotropic receptors are blocked.

When the problem of interaction of the — probably putative—in vivo hippocampal pacemaker with other brain regions arises, several new difficulties arise, and simplified assumptions should be made. In (Borisyuk et al., 1999) authors simplify the description of cells using the phase oscillator model (Hoppensteadt and Hoppensteadt, 1997) and of the Wilson—Cowan model (Wilson and Cowan, 1972). They were able to simulate effects of phase deviation of the septal and entorhinal phasic inputs distributed along the septotemporal axis. Similarly, in (Denham and Borisyuk, 2000) the use of the amplitude model (Wilson and Cowan, 1972) enables the authors to study the septo-hippocampal feedback circuit and shed light on modulatory effects of ascending brainstem inputs to the septum.
In previous works (Kiss et al., 2001; Orbán et al., 2001) we extended the inhibitory network model of Wang et al., (1996) with phasic input representing the entorhinal innervation of the CA3 region. Simulation results showed that the phase dispersion of this phasic input can entrain the network of interneurons oscillating in the gamma frequency band to modulate its population activity in theta frequency. In the original work (Hajoés et al., 2004) reviewed in this paper the septohippocampal interaction is studied. Experimental evidence suggests (King et al., 1998; Petsche et al., 1962; Stewart and Fox, 1989; Vinogradova, 1995) that the septal input might play some role in the generation or control of the hippocampal theta oscillation. The inclusion of the septal area in our model enabled us to study the interaction of the complicated intrahippocampal pacemaker and the septum composed of either periodically or non-periodically firing cells and make predictions to the role distinct GABAergic connections play in in vivo theta generation. In the light of recent experimental results (Borhegyi et al., 2004), however, to faithfully describe properties of the septum, a more detailed model will be necessary.

We also believe that a more effective modeling tool to evaluate the pharmacological effects of the different modulators, or even to give help for offering new putative molecules for drug discovery, the inclusion of more detailed kinetic studies of GABA receptor modulation is indispensable. Jones and Westbrook, (1995) established a model for describing the rapid desensitization of the GABA_A receptors. More specific kinetic models should be studied to describe the effects of the different (full and partial) agonists and antagonists.

Recently it became clear that α subunits of GABA_A receptors exhibit a remarkable functional specificity. Genetic manipulations helped to show that α1 subunits are responsible for mediating sedative effects, while α2 subunit mediates anxiolytic effects (Rudolph et al., 2004). Preliminary experimental data and modeling studies for the effects of the preferential GABA_A α1 and an α2 positive allosteric modulator, zolpidem and L-838, 417 for the septo-hippocampal theta activity have been reported (Ujfalussy et al., 2005).

Many functional aspects of theta rhythm, however, have been neglected here. E.g. recently it was suggested (Hasselmo et al., 2002) that theta rhythm might allow rapid transitions between encoding and retrieval. The computational theories on the functional significance of theta rhythms have been reviewed recently (Lengyel and Lengyel, 2005). Theta rhythms (not necessarily related to hippocampus) play a role in pattern recognition, storing and recalling oscillatory patterns, sequence learning, navigation.

A more general theory of hippocampal theta rhythms is, however, still missing. We incline to believe that the cortico-hippocampal loop might be an anatomical substrate (among others) of implementing circular causality in neural systems. Whether or not neural circular causality is anything to do with the self-organizing patterns in the nervous system is beyond the scope of this paper.

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