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Oscillatory ongoing activity gives rise to state-dependent input processing in neuronal networks in vitro

Oliver Weihberger, Samora Okujeni, Ulrich Egert

The neocortex receives massive sensory input, processes this information and generates output commands of astonishing precision and reliability. Although individual neurons fire reproducibly to natural stimuli, the responses of cortical networks to repeated sensory stimuli vary considerably. Our goal is to understand how neuronal networks respond to incoming stimuli, which interactions arise and how these influence their responses. We aim for predictable input/output relationships in user-defined interaction with neuronal networks.

Dissociated cortical cell cultures from neonatal Wistar rats were prepared on microelectrode arrays. Multi-site recording and electrical stimulation enabled to study spatio-temporal response characteristics. Ongoing activity consisted of oscillatory network-wide bursting, called network bursts. Superbursting periods of three- to fourfold increased global firing rate and concomitant increase in network burst rate and length developed in some networks. Single-pulse electrical stimulation elicited precise and reliable early components (≤ 25 ms post-stimulus) followed by seemingly stochastic firing of variable duration during delayed components (≥ 50 ms poststimulus). Our main result is that the timing of stimulation with respect to ongoing activity modulated reliability, length and delay of induced responses. Response length increased with the delay of the stimulus to the preceding burst, while response delays concomitantly decreased exponentially. We identified a relation between recovery time constant and spontaneous burst length. Stimulus efficacy was maximal and responses were longest during superbursts. Responses were shortest or stimulation even failed to elicit spikes directly after superbursts. Network-state dependent response dynamics hampered the identification of input/output relations and a defined interaction with networks. We show that phase-coupled stimulation during a pre-defined network-state consequently increased response reliability and reproducibility.

The modulation of stimulus/response relations by ongoing activity gives rise to state-dependent processing of external inputs. Short-term synaptic depression induced by synchronous bursting may underlie this state-dependency. Activity-dependent recovery time constants support recent ideas of history-dependent time constants and the absence of fixed, pre-determined values. Phase-coupled input in relation to ongoing activity can significantly increase predictability of responses and help to identify the processing capabilities in neuronal networks in vitro.

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Differential stimulation of neurogenesis and gliogenesis in relation to the spread of epileptiform activity in a mouse model for mesial temporal lobe epilepsy

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Epileptiform activity (EA) has been shown to trigger an increase in neurogenesis in the subgranular zone (SGZ) of adult animals which leads to a substantial restructuring of the hippocampal network. On the other hand, granule cell dispersion (GCD), as it occurs in mesial temporal lobe epilepsy (MTLE), is accompanied by the loss of neurogenesis and is likely caused by the displacement of adult neurons in patients and in the intrahippocampal kainate model (KA) in mice (Heinrich et al., 2006, J Neurosci 26(17); Fahrner et al., 2007, Exp. Neurol 203.; Mueller et al., 2009, Exp. Neurol 216(2)). To clarify this apparent discrepancy, we used the intrahippocampal KA model for MTLE in mice and investigated the relationship between the spread of status epilepticus and recurrent EA, the extent of GCD and changes in neurogenesis. To address these questions we recorded status epilepticus and recurrent EA with electrodes implanted into the dentate gyrus at several positions along the septo-temporal axis in the ipsilateral and contralateral hippocampus of KA-injected mice. In parallel, bromodeoxyuridin (BrdU) injections were used to display cell proliferation along this axis in combination with immunocytochemistry for doublecortin (DCX) to label newly generated neurons and for GFAP and Iba1 to label astrocytes and microglia.

We show that status epilepticus occurred at all recorded positions in the ipsilateral and contralateral hippocampus. During the following four weeks EA was not limited to the area of strongest GCD, but it spread within the hippocampus. Highest power in the fast ripple range (200-500 Hz) at 0.8 mm distance from the injection site indicated higher epileptogenicity in this region than at the injection site. Regarding the cellular level, we found that GCD was spatially correlated with the loss of neurogenesis but increased gliogenesis surrounding the injection site. In contrast, at distance from the injection site, a decline in GCD coincided with the recovery of neurogenesis. Counting of BrdU-positive cells and DCX immunolabeling even revealed a substantially increased neurogenesis in the SGZ of the distal ipsilateral and of the entire contralateral hippocampus. Therefore, the propagation of activity during status epilepticus and/or recurrent EA within the hippocampus stimulated neurogenesis in the SGZ of intrahippocampally KA-injected mice. In contrast, GCD and the disturbance of neurogenesis close to the injection site were not correlated with strongest EA and hence they seem to have additional underlying mechanisms despite EA.

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Visual evoked activity in V1 of anesthetized rats: From gratings to natural scenes

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In the primary visual cortex, earlier studies have shown that spiking activity dynamics are strongly influenced by the level of complexity of visual stimuli. In particular, it has been shown that spiking activity becomes sparser and more reliable under natural-like conditions compared to the classical use of simplified artificial stimuli (e.g. gratings).

In the present study, we investigated the properties of single cells in different layers and the dynamics of visual evoked network activity in the primary visual cortex of anesthetized rats. We chose to study rat V1 because recent studies showed that the response of these neurons are surprisingly well tuned, with cells responding to a highly specific set of stimulus parameters and having receptive field organization characterized by complex center-surround interactions. Such findings indicate that the responses of these neurons are as specialized, in many ways, as those of highly visual animals (cat, primate).

We used layered extracellular recording techniques combined with different types of visual stimulations. Technically, we recorded network activity using a 3 x 4 array of extracellular electrodes. It is a major aim of this study to reveal how stimulus complexity is reflected in the spatio-temporal patterns of sensory evoked activity, and how dynamical properties of the network change according to it. Thus, the visual stimulation paradigms we used are characterized by different levels of complexity, ranging from simple full-field bright flashes and drifting gratings to moving natural scenes and dense noise. For the natural-like condition, we animated a static picture with a realistic eye movement model. The model was built according to the features of the saccadic behaviour of the rat described in the literature and included fixations, saccades, micro-saccades and drifts. Note, however, that it differed from real natural conditions, in which the occulomotor system is involved.

Consistent with previous studies, our results showed that V1 neurons are indeed well tuned to the features of artificial stimuli, such as orientation, spatial and temporal frequency of moving gratings. Under natural-like conditions, we observed that activity dynamics changed, becoming sparser and more reliable as previously described in cats and monkeys. In particular, we observed strong and transient increases in firing rate related either to fixation onset or to the artificial saccades themselves, as well as an increase in the trial by trial reliability of neuronal activity within these epochs. Acknowledgments: We want to thank Yves Frégnac and colleagues for their help with implementing the visual stimulation paradigms.

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Effects of visuomotor rotation learning on backward movements support localized directional learning with transfer to new locations

Eva-Maria Neitzel, Carsten Mehring, Simone Cardoso de Oliveira

Previous studies using center-out-and back tasks have suggested that visuomotor rotations are learned locally for the trained target directions, and that directional learning can be transferred to new locations in workspace. This suggestion implies two predictions concerning backward movements returning from a training target.

1. If directional learning is indeed local, then backward movements from a given target should not be affected by learning the forward movement to the same target, since forward and backward movements are per definition in different directions.

2. If directional learning can indeed be transferred to new locations, then learning of forward movements to a given target should be transferred to backward movements from the opposite target, since in that case, movement directions are the same.

This study tests these predictions in a center-out-and-back task. Although backward movements are by default part of the task in center-out-and-back paradigms, they to our knowledge have not yet been analyzed separately. In order to allow for a separate analysis of forward and backward movements, we required subjects to stop briefly at the target.

In our task, subjects learned a visuomotor rotation of 60 deg in forward movements. During backward movements to the origin, learning was prevented by switching off visual feedback after the target was hit. We quantified the performance in forward and backward movements by measuring initial movement errors. In the first experiment, two targets were used, positioned 60 deg apart, thus involving backward movements in directions at least 120 deg away from trained directions. In the second experiment, the two training targets were positioned 180 deg apart, thus involving backward movements in exactly the same directions that were trained during forward movements, albeit at different workspace locations. In accordance with the two predictions, we found transfer of learning to backward movements in the second, but not in the first experiment. Our findings clearly support the notion of localized direction learning in visuomotor rotations that can be transferred to new locations.

In addition, however, we found a new phenomenon. Even in the very first transformation trial, and in all experiments, initial movement errors in backward movements were lower than in forward movements. We hypothesize that this is caused by integration of visual and proprioceptive inputs.

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Learning and generalization of visuomotor rotations in three dimensions

Dmitry Kobak, Stephan Waldert, Ad Aertsen, Carsten Mehring

Visuomotor rotations are frequently used as a tool to investigate motor learning. Such transformations in two dimensions depend only on a single parameter, namely on the angle of rotation. We investigated visuomotor rotations in three dimensions, where each rotation is specified not only by an angle of rotation, but also by two angles defining the direction of the rotation axis. Subjects had to make center-out movements in 3D using a robotic arm to track their hand movements, while a head-mounted display was used to present a 3D visual environment. First, we showed that there is some generalization over the workspace: learned rotations are partially transferred to a novel target in a way that is consistent with the assumption that subjects learned the true axis of rotation. This indicates that 3D rotations are learned globally and that the motor system correctly identifies the true axis of rotation (which is common for all targets), instead of learning target-specific rotation axes. Second, we compared rotations around different axes. Here, three different groups of subjects were exposed to visuomotor rotations of 40° around three different axes: horizontal, vertical and the diagonal between them. Learning curves of the initial directional error and the cumulative error showed no difference between these three axes. In addition to the calculation of the learning curves, we also estimated the parameters of the internal model of rotation (characterized by two angles defining the rotation axis plus the angle of rotation around this axis) that the subjects used during learning. The evolution of these values across learning trials was computed based on the performance errors briefly after movement onset (representing feed-forward control) and on the errors near the end of the movement (representing a mixture of feed-forward and feed-back control). The results show that the axis of a novel rotation was learned much faster than the angle of rotation, especially in the case of feed-back control. The evolution of the feed-forward internal model was more variable across subjects but showed the same trend. Consistent with the learning curves of the initial directional error and the cumulative error, no dependence of these learning curves on the axis of rotation was found. Taken together, these results indicate that learning of 3D visuomotor rotations might be independent of the rotation axis, which is learned globally and faster than the rotation angle.

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Non-linear decoding of movement velocity from the human electrocorticogram (ECoG)

Tomislav Milekovic, Tobias Pistohl, Tonio Ball, Andreas Schulze-Bonhage, Ad Aertsen, Carsten Mehring

Brain-machine interfaces (BMIs) enable subjects to control external devices like computers, robotic arms or prostheses directly by their brain activity. To this end BMIs decode the movement intention of the subject from its neuronal activity and send respective control signals to the external effector. Recently, linear decoding algorithms have been used successfully to decode movements from neuronal activity measured directly from the surface of the human brain (Electrocorticogram, ECoG). Here we investigate whether ECoG signals exhibit non-linear tuning to movement velocity and whether the accuracy of movement prediction can be improved by using non-linear decoding algorithms.
To this end, we recorded ECoG signals from patients undergoing pre-neurosurgical epilepsy diagnosis, while they performed arm movements in the horizontal plane. Using local linear regression we analyzed the tuning of the low-pass filtered ECoG signal to movement velocity and found that many ECoG channels exhibit 2D tuning functions which significantly deviate from linear velocity tuning. By means of a non-linear extension of the Kalman filter (the unscented Kalman filter) we decoded continuous velocity trajectories from the ECoG signals using the computed non-linear tuning functions. Thereby, the mean squared error (MSE) between predicted and real trajectories was substantially reduced in comparison to linear decoding by means of a Kalman filter. Moreover, by using neural activity not only at one time point before the movement but at multiple time points the MSE could be further reduced. In summary, our results suggest that non-linear decoding algorithms can improve the performance of human ECoG BMIs.

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Co-adaptivity during learning to control a myoelectric interface

Xiang Liao, Jörg Fischer, Tomislav Milekovic, Jörn Rickert, Ad Aertsen, Carsten Mehring

Human-machine interfaces, like myoelectric prostheses and brain-machine interfaces, profit from the adaptivity of the user and from the adaptivity of the machine. While combining these two adaptive mechanisms seems highly attractive at first sight, this approach also carries the danger that the two adaptive mechanisms might work against each other. Here, we investigate whether an adaptive decoding algorithm can improve the learning and the final performance of a myoelectrically controlled computer cursor.

Subjects had to learn to control a computer cursor in two-dimensions by using the electromyographic (EMG) activity of 6 different hand and arm muscles. First, subjects were exposed to 160 trials of centre-out movements and, afterwards, to 160 trials of target-pursuit movements. Four different conditions were investigated: (Ia) 'intuitive' translation of muscle activity to cursor movements with static decoding, (Ib) 'intuitive' control with adaptive decoding, (IIa) 'non-intuitive' translation of muscle activity to cursor movements with static decoding, (IIb) 'non-intuitive' control with adaptive decoding. Each condition was investigated with a separate group of subjects.

Our preliminary results show: (1) Subjects from all groups were able to generalize from centreout movements to target-pursuit movements with only some re-learning necessary at the beginning of the target-pursuit block. (2) During 'intuitive' control, the adaptive decoding did not increase the learning speed, but slightly increased the final accuracy of control. (3) For 'nonintuitive' control, the adaptive decoding increased the learning speed and the final accuracy during both centre-out and target-pursuit.

In summary, our preliminary results indicate that for a myoelectric-controlled interface an adaptive decoding algorithm can help to improve the leaning speed and the final accuracy of control according to the level of difficulty of the task.

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Human ECoG gamma band activity evoked by natural auditory stimuli

Chloe Huetz, G. Schalk, A. Riacco, P. Brunner, Carsten Mehring

Understanding the role of auditory evoked gamma activity (GBA) is important for deciphering the neural code underlying the perception of natural stimuli. Several features of auditory evoked GBA such as amplitude, spatial or frequency range, phase-locking to stimulus onset, anatomical localization or functional lateralization have been investigated and related to relatively high cognitive functions such as attention, acoustic object representation, and memory. However, the relationship between GBA and features of the acoustic stimulus, such as amplitude or frequency modulation, remained unknown.

In this study, we investigated high GBA (60-200 Hz) evoked by several different natural acoustic stimuli. We recorded electrocorticographic (ECoG) activity from electrodes grids in five human subjects that were implanted with subdural electrodes over their temporal lobe to localize epileptic seizure foci. A set of 19 natural acoustic stimuli, belonging to different categories (speech, animal vocalizations, music, engine and natural environmental sounds) were presented to the subjects. Their task was to categorize the stimulus according to its category. First, we found that acoustic stimulation evoked a pronounced increase of GBA on several electrodes located over the temporal lobe on the left as well as on the right hemisphere for all patients. This was in accordance with previous findings (Crone et al., 2001, Clin Neurophysiol., Apr;112(4):565-82). We then selected these electrodes for further analyses. Second, we investigated which features of natural stimuli are encoded in the GBA. We computed the spectrogram of each stimulus as a function of time. For each of these spectrograms, we extracted the frequency of the amplitude modulations across frequency, also called the spectral modulation (expressed in cycles / kHz). We then determined the correlation between the time-course of each spectral modulation and the GBA of the selected electrodes. This analysis revealed that the GBA of the temporal lobe exhibits the strongest correlation with spectral modulations below approximately 10 cycles / kHz.

In the light of recent psychoacoustic findings (Elliott & Theunissen, 2009, PLoS Comput Biol., Mar;5(3)), which show that spectral modulations below 7 cycles / kHz are important for speech comprehension, these results suggest that GBA encodes acoustic features necessary for the comprehension of natural acoustic stimuli.

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Neuronal pathway formation in cortical networks depends on PKC regulated structural plasticity

Samora Okujeni, Nila Mönig, Steffen Kandler, Oliver Weihberger, Ulrich Egert

The cortical micro-circuitry is considerably shaped by activity-dependent metabolic processes in neurons that govern neuronal wiring in the course of development. Herein, the protein kinase C (PKC) takes a key-position cross-linking many biochemical pathways involved in structural regulation and targeting many cytoskeletal proteins directly. In a simplified scheme, activation of PKC via metabotropic glutamate receptor downstream signaling mobilizes cytoskeletal proteins, thereby promoting structural plasticity, since antagonistic pathways in turn promote cytoskeletal assembly and stabilization (Quinlan '96). Previous studies showed that inhibition of PKC activity in cerebellar slice cultures promotes dendritic outgrowth and arborization in Purkinje cells (Metzger '00) and that climbing fiber pruning is impaired in PKC deficient mice (Kano '95). Further in vitro data demonstrate the importance of PKC activity for the experience-dependent modulation of synaptic weights on the basis of AMPA receptor trafficking (Zheng '08). Not surprisingly, behavioral studies show that spatial learning crucially depends on PKC activity (Alvarez-Jaimes '04, Bonini '08).

It remains, however, largely unknown how differentially regulated PKC activity i.e. structural and synaptic plasticity during development results in particular network structures and dynamics. We investigate these dependencies in cortical cell cultures developing on micro-electrode arrays. These generic random networks display a self-regulated maturation process with similar phases as the developing cortex, during which we interfered with neuronal differentiation by chronically inhibiting PKC activity.

Applying new morphometrics, we found significantly increased arborization and extent of dendrites as well as increased synapse density, indicating increased connectivity in these networks. Reduced neuronal clustering further suggests impaired cell migration. The resulting increased topological homogeneity was accompanied by reduced complexity in the emerging network oscillations. Pronounced and, moreover, developmentally conserved wave-like neuronal recruitment patterns in network-wide bursting events further indicate a homogeneous connectivity lacking distinct neuronal pathways.

We conclude that PKC activity is essential for the continuous reorganization of network structure and dynamics in developing cortical cell cultures. This supports the idea that the embedding of functional pathways in the cortex depends on the coordinated regulation of structural plasticity by PKC.

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Spatiotemporal features of rank order coding in generic neuronal networks

Steffen Kandler, Samora Okujeni, Sebastian Reinartz, Ulrich Egert

Neuronal communication relies on the precisely timed spiking of individual neurons (Fellous et al., 2004). Recent reports demonstrated that temporal patterns of neuronal activity are used by, e.g., somatosensory areas for coding of stimulus information (Ikegaya et al., 2008; Foffani et al., 2009). Furthermore, a synchronization of activity facilitates a robust propagation of information across neuronal ensembles (Diesmann et al., 1999; Thorpe et al., 2001; Ikegaya et al., 2004). So far, it is unclear in how far patterns of activity arise in dependence on structural features of the underlying neuronal circuitry, although there is evidence for specific connection motifs facilitating signal integration within the cortex (Kampa et al., 2007). It is, however, the complexity of native networks that makes studies on a network level laborious, but also very simple generic neuronal networks show distinctive patterns of activity, governed by the onsets of individual neurons and carrying information of stimulus properties (Shahaf et al., 2008). To understand how such onset-based activation sequences are related to network connectivity in neuronal network cultures, we investigated spontaneous bursting with extracellular microelectrode arrays and dual intracellular patch-clamp electrodes. We focused on the local connectivity and embedding of individual neurons into network burst onset sequences and how these propagate across the networks.

Based on the patch-clamp recordings, we identified pairwise connections at up to 300µm distance. We identified excitatory (E) and inhibitory (I) projections as unidirectional (UD) or bidirectional (BD) connections. Of 102 pairs, 29% were connected and 71% were unconnected. Of these connections, 13% were UD-E, 3% UD-I, 10% BD-EE, 2% BD-II, and 1% BD-EI. In addition to a propagation of activity characterized by the spreading to neighboring recordings sites alone, we observed a regime characterized by the onset rank of neuron groups on distant sites. Herein, we observed motifs initiated by the activity of a small group of neurons that reliably preceded the global network activation after network burst onset. In 54 networks, burst activity started on one of 14±5% of all active recording sites. Individual neurons followed these rank sequences rather than local neighborhood firing.

We conclude, that a heterogeneous connectivity, i.e. long-range or polysynaptic connections linking distant parts of the networks, is the basis of the recruitment motifs observed within generic network cultures and facilitates burst propagation across the networks.

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Neural coding of arm movement direction under different behavioral contexts

Jörn Rickert, G. Schalk, P. Brunner, A. Ritaccio, Carsten Mehring

Abstract: A Brain-Computer Interface (BCI) provides a non-muscular communication channel to severely disabled or able-bodied people. A common BCI approach uses signals that correspond to kinematic parameters of hand or arm movements. These kinematic parameters are decoded and translated into device commands, such as the movement of a prosthesis. The stability of the neural representation of these parameters across different behavioral contexts is an important question, as it defines the extent to which the decoder of the BCI could generalize from one context (i.e. the training context) to other contexts. Such generalization capability is likely an important requirement of clinically relevant BCI-systems.

Here, we examined the stability of the neural representation of arm movement direction, when the movements are carried out under different behavioral contexts. We recorded electrocorticographic (ECoG) activity from up to 64 electrodes in six human subjects that were implanted with subdural electrodes to localize epileptic seizure foci. The subjects' task was to move a joystick left or right in a self-paced manner. This task was carried out repetitively under five different conditions, following each other sequentially: (1) baseline, in which the subject sat upright in bed, still and fixating; (2) talking, where the subject engaged in a conversation with the experimenter; (3) different body-position, where the subject lied in bed; (4) watching TV, where the patient sat upright in bed and was asked to pay attention to a short movie; and (5) simultaneous engagement of the other arm, where the subject was rotating a deck of cards in his/her other hand. Offline data analysis were performed to find out how accurate the joystickmovements can be decoded (computer classification accuracy about arm movement direction) across the five contexts.

Preliminary results indicate two findings: First, the motor cortical representation of the movement was similarly accurate in all five conditions. Second, the motor cortical representation was sufficiently stable to allow the decoding of movement direction also when the decoder was trained in one of the other conditions. The features encoding the arm movement thus remained at least partially constant when the subjects were engaged in different additional activities or changed their positions.

This capacity of the motor cortex, to produce a movement representation of sufficient stability across different behavioral contexts, suggests that a BCI decoder might in some cases be able to generalize from one training condition to other conditions which are likely to occur in real life applications.

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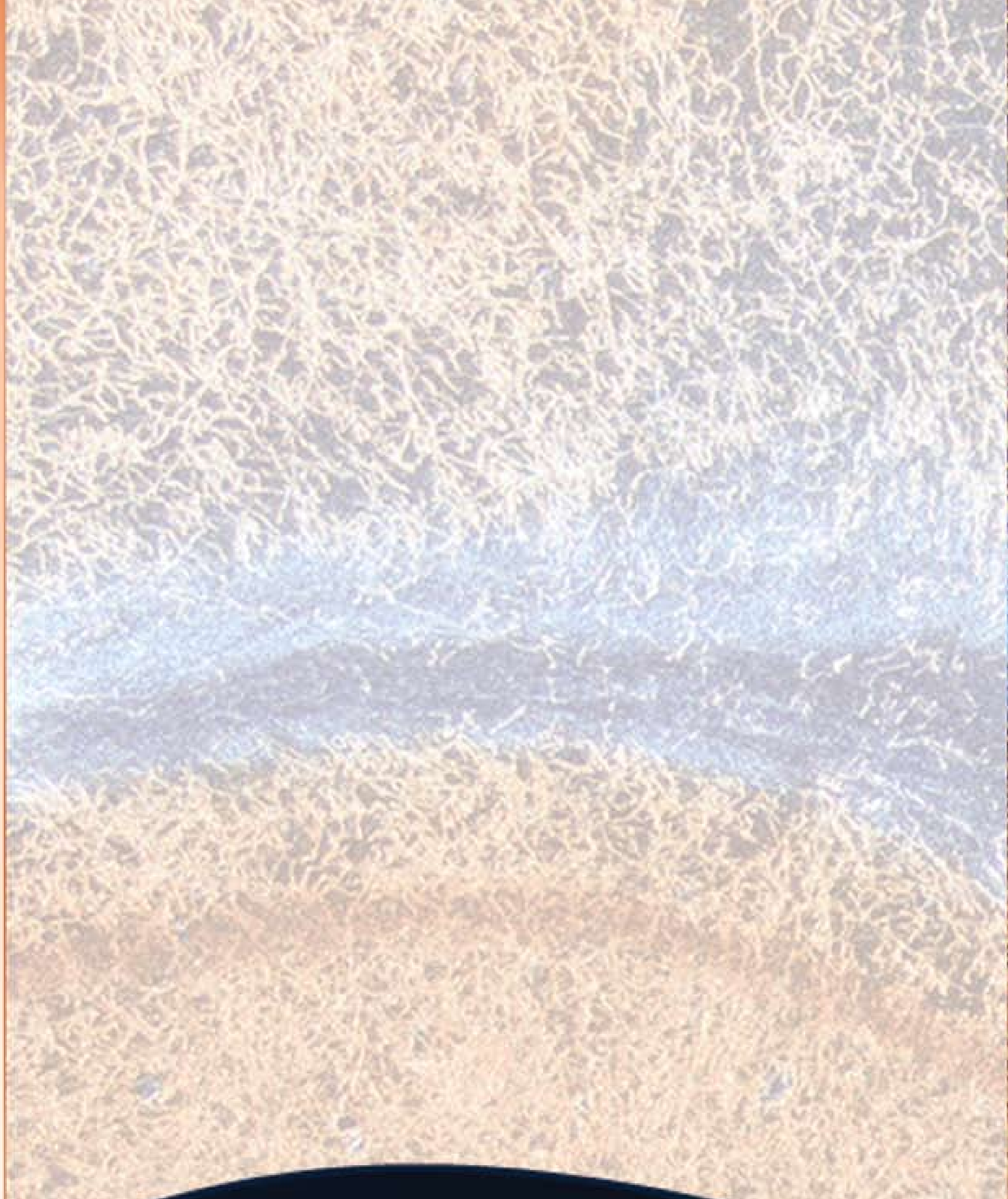

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