

understanding the full life cycle of bacterial chromosomes.

#### References

1. Postow, L., Hardy, C.D., Arsuaga, J., and Cozzarelli, N.R. (2004). Topological domain structure of the *Escherichia coli* chromosome. *Genes Dev.* 18, 1766–1779.
2. Espeli, O., Mercier, R., and Boccard, F. (2008). DNA dynamics vary according to macrodomain topography in the *E. coli* chromosome. *Mol. Microbiol.* 68, 1418–1427.
3. Wang, X., Tang, O.W., Riley, E.P., and Rudner, D.Z. (2014). The SMC condensin complex is required for origin segregation in *Bacillus subtilis*. *Curr. Biol.* 24, 287–292.
4. Gruber, S., Veening, J.-W., Bach, J., Blettinger, M., Bramkamp, M., and Errington, J. (2014). Interlinked sister chromosomes arise in the absence of condensin during fast replication in *B. subtilis*. *Curr. Biol.* 24, 293–298.
5. Nasmyth, K., and Haering, C.H. (2009). Cohesin: its roles and mechanisms. *Annu. Rev. Genet.* 43, 525–558.
6. Britton, R.A., Lin, D.C., and Grossman, A.D. (1998). Characterization of a prokaryotic SMC protein involved in chromosome partitioning. *Genes Dev.* 12, 1254–1259.
7. Mascarenhas, J., Soppa, J., Strunnikov, A.V., and Graumann, P.L. (2002). Cell cycle-dependent localization of two novel prokaryotic chromosome segregation and condensation proteins in *Bacillus subtilis* that interact with SMC protein. *EMBO J.* 21, 3108–3118.
8. Sullivan, N., Marquis, K., and Rudner, D. (2009). Recruitment of SMC by ParB-parS organizes the origin region and promotes efficient chromosome segregation. *Cell* 137, 697–707.
9. Gruber, S., and Errington, J. (2009). Recruitment of condensin to replication origin regions by ParB/SpoOJ promotes chromosome segregation in *B. subtilis*. *Cell* 137, 685–696.
10. Cozzarelli, N.R., Cost, G.J., Nollmann, M., Viard, T., and Stray, J.E. (2006). Giant proteins that move DNA: bullies of the genomic playground. *Nat. Rev. Mol. Cell Biol.* 7, 580–588.
11. Danilova, O., Reyes-Lamothe, R., Pinskaya, M., Sherratt, D., and Possoz, C. (2007). MukB colocalizes with the *oriC* region and is required for organization of the two *Escherichia coli* chromosome arms into separate cell halves. *Mol. Microbiol.* 65, 1485–1492.
12. Vos, S.M., Stewart, N.K., Oakley, M.G., and Berger, J.M. (2013). Structural basis for the MukB-topoisomerase IV interaction and its functional implications *in vivo*. *EMBO J.* 32, 2950–2962.
13. Lee, P.S., and Grossman, A.D. (2006). The chromosome partitioning proteins Soj (ParA) and SpoOJ (ParB) contribute to accurate chromosome partitioning, separation of replicated sister origins, and regulation of replication initiation in *Bacillus subtilis*. *Mol. Microbiol.* 60, 853–869.
14. Jun, S., and Wright, A. (2010). Entropy as the driver of chromosome segregation. *Nat. Rev. Microbiol.* 8, 600–607.
15. Lesterlin, C., Pages, C., Dubarry, N., Dasgupta, S., and Cornet, F. (2008). Asymmetry of chromosome replicohores renders the DNA translocase activity of FtsK essential for cell division and cell shape maintenance in *Escherichia coli*. *PLoS Genet.* 4, e1000288.
16. Dubarry, N., Possoz, C., and Barre, F.-X. (2010). Multiple regions along the *Escherichia coli* FtsK protein are implicated in cell division. *Mol. Microbiol.* 78, 1088–1100.
17. Fiche, J., Cattoni, D., Diekmann, N., Mateos Langerak, J., Clerie, C., Royer, C.A., Margeat, E., Doan, T., and Nollmann, M. (2013). Recruitment, assembly and molecular architecture of the SpoIIIE DNA pump revealed by super-resolution microscopy. *PLoS Biol.* 11, e1001557.
18. Murray, H., and Errington, J. (2008). Dynamic control of the DNA replication initiation protein DnaA by Soj/ParA. *Cell* 135, 74–84.
19. Marko, J. (2009). Linking topology of tethered polymer rings with applications to chromosome segregation and estimation of the knotting length. *Phys. Rev. E* 79, 051905.
20. Vecchiarelli, A., Mizuuchi, K., and Funnell, B. (2012). Surfing biological surfaces: exploiting the nucleoid for partition and transport in bacteria. *Mol. Microbiol.* 86, 513–523.

Department of Single-Molecule Biophysics, Centre de Biochimie Structurale, CNRS UMR5048, INSERM U1054, Universit es Montpellier I et II, 29 rue de Navacelles, 34090 Montpellier, France.

\*E-mail: [marcelo.nollmann@cbs.cnrs.fr](mailto:marcelo.nollmann@cbs.cnrs.fr)

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## Spatial Mapping: Graded Precision of Entorhinal Head Direction Cells

Representation of head direction in medial entorhinal cortex shows a gradient of precision, from high directional precision dorsally to low ventrally; this parallels the gradient of spatial scale in place and grid cells, and suggests that the brain constructs spatial maps of varying resolution, perhaps to serve different requirements.

Kate Jeffery

The medial temporal cortex of the brain, which includes the hippocampus and associated structures, is well known to have a specialised role in spatial cognition. This navigation system collects together information about head direction, travel distance and context, in order to construct a representation of an individual's current location and heading [1]. This representation culminates in the focal firing patterns, or 'place fields', of the hippocampal place cells, which are sometimes thought of as a map which serves both to guide navigation and to store/retrieve memories. Early studies of place cells revealed a gradient of spatial scale, with small place fields in the dorsal-most regions of

hippocampus, and large fields ventrally [2,3]. More recently [4], the Moser lab discovered that an important cortical input to the place cells, the grid cells in dorso-medial entorhinal cortex (MEC), also shows spatial scaling. Grid cells produce multiple, often evenly-spaced firing fields arranged in a hexagonal close-packed array, with a characteristic orientation in a given environment, and a characteristic spacing for a given cell (or set of cells); they may provide an estimation of distance travelled — path integration — for place cells. Just as with place cells, grid spacing (scale) increases markedly from around 30 cm dorsally to some metres ventrally [5,6]. Now, as they report in this issue of *Current Biology* [7], the Moser lab has discovered that head direction cells

in this same region of MEC also show a gradient of precision, with a range of tuning curves dorsally but only the broader tuning curves ventrally.

Giocomo *et al.* [7] analysed large numbers of medial entorhinal neurons in both rats and mice for directional firing preference. As Sargolini *et al.* [8] have also reported previously, head direction cells were found throughout the MEC in layers III, V and VI (not layer II). In layer III (but not V/VI), the authors observed a clear gradient, or topography, of directional precision, with sharply tuned cells being found only dorsally. The gradation in tuning was observed to be continuous, unlike that for grid cells in which the increase in scale from dorsal to ventral occurs in stepped transitions that imply a modular organisation [9]. This large sample also confirmed the absence of clustering of directional firing; directional firing preferences were distributed evenly around the 360 degrees, even though grids — the presumed major recipient of head direction information — have six-fold rotational symmetry.

The finding of a continuous gradation of directional tuning raises questions about the network interactions

underlying the generation of head direction cell directional firing properties. Head direction cells are generally thought to comprise recurrently connected one-dimensional attractor networks [10] in which the cells have similar connectivities; tuning width gradations do not emerge naturally from such self-organising network models. In order to understand how such gradation could arise, it will be important to determine whether the more broadly tuned cells differ in intrinsic membrane properties or synaptic plasticity profiles, whether the difference in tuning is extrinsic and results from a difference in inputs, or whether the differently tuned cell types actually belong to different subnetworks, each of which is internally consistent, which are differentially distributed across the dorso-ventral extent of MEC.

What might be the adaptive advantage of spatial encoding gradients in the spatial system? It has been suggested that variably-sized place fields might allow the representation of different sized environments [2]; navigating around the house is different from navigating across town, or across the country, and might require maps of different scales. If scale were the relevant factor, however, then we might expect to see scaling relative to body size — large grids in adults and small in infants; large scales in rats and small in mice, and so on. In fact, grid scales so far seem fairly constant across developmental stages [11,12] and across species [13,14]. Also, the notion of scale does not apply in the head direction system in which there are always only 360 degrees of direction no matter how large the environment.

An alternative (albeit related) possibility, therefore, is that the relevant difference is one of resolution — small fields and tight directional tuning might be used where a high degree of precision is required, while large fields and coarse directional tuning might be used where the specifics of location/direction are less critical and the important processing concerns the environment as a whole (“this field is dangerous” versus “I buried my food here”). This association of environments with more generalised properties such as valence may explain why the ventral regions of the entorhinal-hippocampal system,

where the low-resolution maps are, are also the regions less intensely connected to sensory areas and more richly imbued with subcortical connections to emotional/motivational systems [15,16]. Being able to defocus the map means that information that is relevant across an environment can be efficiently associated with it using a smaller number of neurons.

In summary, then, the current findings extend observations of dorso-ventral spatial gradients in the entorhinal-hippocampal system from linear to angular domains. These findings raise questions about both the cause and consequence of such gradients, and suggest that the brain makes a multiplicity of maps for a variety of settings.

#### References

1. Moser, E.I., Kropff, E., and Moser, M.B. (2008). Place cells, grid cells, and the brain's spatial representation system. *Annu. Rev. Neurosci.* 31, 69–89.
2. Jung, M.W., Wiener, S.I., and McNaughton, B.L. (1994). Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat. *J. Neurosci.* 14, 7347–7356.
3. Maurer, A.P., Vanhoads, S.R., Sutherland, G.R., Lipa, P., and McNaughton, B.L. (2005). Self-motion and the origin of differential spatial scaling along the septo-temporal axis of the hippocampus. *Hippocampus* 15, 841–852.
4. Hafting, T., Fyhn, M., Molden, S., Moser, M.B., and Moser, E.I. (2005). Microstructure of a spatial map in the entorhinal cortex. *Nature* 436, 801–806.
5. Brun, V.H., Solstad, T., Kjelstrup, K., Fyhn, M., Witter, M.P., Moser, E.I., and Moser, M.B. (2008). Progressive increase in grid scale from dorsal to ventral medial entorhinal cortex. *Hippocampus* 18, 1200–1212.
6. Kjelstrup, K.B., Solstad, T., Brun, V.H., Hafting, T., Leutgeb, S., Witter, M.P., Moser, E.I., and Moser, M.B. (2008). Finite scale

of spatial representation in the hippocampus. *Science* 321, 140–143.

7. Giocomo, L.M., Stensola, T., Bonnevie, T., Van Cauter, T., Moser, M.-B., and Moser, E.I. (2014). Topography of head direction cells in medial entorhinal cortex. *Curr. Biol.* 24, 252–262.
8. Sargolini, F., Fyhn, M., Hafting, T., McNaughton, B.L., Witter, M.P., Moser, M.B., and Moser, E.I. (2006). Conjunctive representation of position, direction, and velocity in entorhinal cortex. *Science* 312, 758–762.
9. Stensola, H., Stensola, T., Solstad, T., Froland, K., Moser, M.B., and Moser, E.I. (2012). The entorhinal grid map is discretized. *Nature* 492, 72–78.
10. Knierim, J.J., and Zhang, K. (2012). Attractor dynamics of spatially correlated neural activity in the limbic system. *Annu. Rev. Neurosci.* 35, 267–285.
11. Wills, T.J., Cacucci, F., Burgess, N., and O'Keefe, J. (2010). Development of the hippocampal cognitive map in preweanling rats. *Science* 328, 1573–1576.
12. Langston, R.F., Ainge, J.A., Couey, J.J., Canto, C.B., Bjerknes, T.L., Witter, M.P., Moser, E.I., and Moser, M.-B. (2010). Development of the spatial representation system in the rat. *Science* 328, 1576–1580.
13. Fyhn, M., Hafting, T., Witter, M.P., Moser, E.I., and Moser, M.B. (2008). Grid cells in mice. *Hippocampus* 18, 1230–1238.
14. Yartsev, M.M., Witter, M.P., and Ulanovsky, N. (2011). Grid cells without theta oscillations in the entorhinal cortex of bats. *Nature* 479, 103–107.
15. Risold, P.Y., and Swanson, L.W. (1996). Structural evidence for functional domains in the rat hippocampus. *Science* 272, 1484–1486.
16. Petrovich, G.D., Canteras, N.S., and Swanson, L.W. (2001). Combinatorial amygdalar inputs to hippocampal domains and hypothalamic behavior systems. *Brain Res. Brain Res. Rev.* 38, 247–289.

Institute of Behavioural Neuroscience,  
Department of Cognitive, Perceptual and  
Brain Sciences, Division of Psychology and  
Language Sciences, University College  
London, London WC1H 0AP, UK.  
E-mail: [k.jeffery@ucl.ac.uk](mailto:k.jeffery@ucl.ac.uk)

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## Pain: Novel Analgesics from Traditional Chinese Medicines

The search for analgesics with fewer side effects and less abuse potential has had limited success. A recent study identifies an analgesic alkaloid compound from *Corydalis yanhusuo*, a traditional Chinese medicinal herb that has a surprising mechanism of action.

Susan L. Ingram

Opioids are the gold standard for the treatment of severe acute and chronic pain, but they induce undesirable side effects and drug addiction in many patients. The search for efficacious pain relievers for both acute and

chronic pain that do not produce tolerance or dependence has been essentially futile, with few candidates that have been successful in clinical trials. Thus, identification of novel pain therapeutics has been the basis of research and design programs for drug companies for many years. The lack of