Dynamics and Evolution of Single Cell Cognition

David C. Krakauer.
Santa Fe Institute
<table>
<thead>
<tr>
<th></th>
<th>Connectivity</th>
<th>Density</th>
<th>Dynamics</th>
<th>Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system</td>
<td>Physical &amp; Chemical</td>
<td>High</td>
<td>Variable time Constants</td>
<td>By Connection</td>
</tr>
<tr>
<td>Cell</td>
<td>Chemical</td>
<td>Sparse</td>
<td>Generally Rapid</td>
<td>By sequence</td>
</tr>
</tbody>
</table>
Genomic and Cellular Cognition

- **Distributed Coding:** Reading frame compression (*empirical e.g.*)

- **Elementary Logic:** Switches & Base Systems (*theory e.g.*)

- **Memory:** Enzymatic feedback circuits (*theory e.g.*)

- **Feature detection:** Signal transduction and frequency filtering (*theory e.g.*)

- **Robustness:** Population level redundancy (*theory e.g.*)
Coding & Compression

Localization of Function

A syntactic specialization for Broca’s area

David Embick*, Alec Marantz*, Yasushi Miyashita†, Wayne O’Neil†, and Kuniyoshi L. Sakai‡

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Communicated by Morris Halie, Massachusetts Institute of Technology, Cambridge, MA, March 7, 2000 (received for review February 15, 2000)
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Communicated by Morris Halie, Massachusetts Institute of Technology, Cambridge, MA, March 7, 2000 (received for review February 15, 2000)

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 9687–9692, September 1996
Genetics

Sexual orientation in Drosophila is altered by the satori mutation in the sex-determination gene fruitless that encodes a zinc finger protein with a BTB domain

(homosexual courtship/muscle of Lawrence/transformer/mating behavior)

HIROKI ITO, KAZUKO FUJITANI, KAZUE USUI, KEIKO SHIMIZU-NISHIKAWA*, SHOJI TANAKA, and Daisuke Yamamoto†

Yamamoto Behavior Genes Project, Exploratory Research for Advanced Technology (ERATO), Research Development Corporation of Japan, and Mitsubishi Kasei Institute of Life Sciences, 11 Minamioooya, Machida, Tokyo 194, Japan

Communicated by Susumu Ohno, Beckman Research Institutes of the City of Hope, Duarte, CA, May 29, 1996 (received for review April 10, 1996)
protein

----------
gene
Inheritance
# The Genetic Code

<table>
<thead>
<tr>
<th>First letter</th>
<th>Second letter</th>
<th>Amino Acid(s)</th>
<th>Third letter</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>UUC, UUA, UUG</td>
<td>Phe, Leu</td>
<td>UC, CA, CG</td>
</tr>
<tr>
<td></td>
<td>UUU</td>
<td>Leu</td>
<td>UG, GA</td>
</tr>
<tr>
<td>C</td>
<td>CUU, CUC, CUA, CUG</td>
<td>Leu, Pro</td>
<td>CG, GA, GG</td>
</tr>
<tr>
<td>A</td>
<td>AUU, AUC, AUA, AUG</td>
<td>Ile, Thr, Met</td>
<td>AG, GA, GG</td>
</tr>
<tr>
<td>G</td>
<td>GUU, GUC, GUA, GUG</td>
<td>Val, Ala, Val</td>
<td>GC, GA, GG</td>
</tr>
</tbody>
</table>

- **UUU** - Phe
- **UUC** - Phe
- **UUA** - Leu
- **UUG** - Leu
- **UCU** - Ser
- **UCC** - Ser
- **UCA** - Ser
- **UCG** - Ser
- **UAU** - Tyr
- **UAC** - Tyr
- **UAA** - Stop
- **UAG** - Stop
- **UAG** - Stop
- **UGU** - Cys
- **UGC** - Cys
- **UGA** - Stop
- **UGG** - Stop
- **UGG** - Trp

- **CUU** - Leu
- **CUC** - Leu
- **CUA** - Leu
- **CUG** - Leu
- **CCU** - Pro
- **CCC** - Pro
- **CCA** - Pro
- **CCG** - Pro
- **CAU** - His
- **CAC** - His
- **CAA** - His
- **CAG** - His
- **CGU** - Arg
- **CGC** - Arg
- **CGA** - Arg
- **CGG** - Arg
- **AUU** - Ile
- **AUC** - Ile
- **AUA** - Ile
- **AUG** - Met
- **ACU** - Thr
- **ACC** - Thr
- **ACA** - Thr
- **ACG** - Thr
- **AAA** - Lys
- **AAG** - Lys
- **AGU** - Ser
- **AGC** - Ser
- **AGA** - Ser
- **AGG** - Ser
- **GUU** - Val
- **GUC** - Val
- **GUA** - Val
- **GUG** - Val
- **GCU** - Ala
- **GCC** - Ala
- **GCA** - Ala
- **GCG** - Ala
- **GAU** - Asp
- **GAC** - Asp
- **GAA** - Asp
- **GAG** - Asp
- **GGU** - Gly
- **GGC** - Gly
- **GGA** - Gly
- **GGG** - Gly
Genomes Store Information
Genomes Store Information

Aligned genomes

ACGTC...T
ATGTG...T
ATCTG...A

1 2 3 4 5...!
Genomes Store Information

Aligned genomes

\[ H_i = - \sum_j p_j^{(i)} \log_4 p_j^{(i)} \]
Genomes Store Information

Aligned genomes

\[ H_i = - \sum_j p_j^{(i)} \log_4 p_j^{(i)} \]

\[ I_i = H_{max} - H_i \]
Genomes Store Information

Aligned genomes

\[ H_i = - \sum_j p_{j}^{(i)} \log_4 p_{j}^{(i)} \]

\[ I_i = H_{\text{max}} - H_i \]

Information in Population of genomes

\[ C = L - \sum_i H_i \]
Evolutionary Information Storage

Information Conserved

Information Lost
Evolutionary Information Storage

Information Conserved

$$s \geq \frac{\mu L}{N}$$

Information Lost
Evolutionary Information Storage

Information Conserved

\[ s \geq \frac{\mu L}{N} \]

Information Lost

\[ s < \frac{\mu L}{N} \]
Evolutionary Information Storage

Information Conserved

\[ s \geq \frac{\mu L}{N} \]

Information Lost

\[ s < \frac{\mu L}{N} \]
<table>
<thead>
<tr>
<th>Phase</th>
<th>Alignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>321321321321321321321321321321</td>
</tr>
<tr>
<td></td>
<td>321321321321321321321321321321</td>
</tr>
<tr>
<td></td>
<td>321321321321321321321321321321</td>
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<tr>
<td></td>
<td>321321321321321321321321321321</td>
</tr>
<tr>
<td>0</td>
<td>123123123123123123123123123123</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>123123123123123123123123123123</td>
</tr>
</tbody>
</table>

\[ F_0(123,123) \quad F_{-2}(123,321) \quad F_{2}(123,231) \]
ONTONEWHEEL

+2 spaces

ONTONEWHEEL

ONTONEWHEEL
Functional Sequence Space

\[ \begin{align*} &000 & 100 & 110 \\
&010 & 101 & 111 \end{align*} \]
Functional Sequence Space

![Diagram of a hypercube with labeled nodes: 000, 001, 010, 011, 100, 101, 110, 111. The diagram illustrates a sequence space with a perspective view and an arrow indicating a transformation or transition between nodes.](image-url)
Functional Sequence Space
Functional Sequence Space

![Diagram of Functional Sequence Space](image)
Logic & Stochastic Switches

Phosphorylation:
Modulation of Protein Function

Variable Binding Domain

Conserved Catalytic Domain
\[
\frac{d}{dt} \Pr(n) = \sum_{j=0}^{J-1} \left[ (I + n_j - \delta_{j,j+1})(n_j + 1)\Pr(n+1_j - 1_{j+1}) - (I + n_j)n_j \Pr(n) \\
+ (P + n_0 - \delta_{0,j})(n_{j+1} + 1)\Pr(n-1_j + 1_{j+1}) - (P + n_0)n_{j+1} \Pr(n) \right].
\]
\[ \frac{d}{dt} \Pr(n) = \sum_{j=0}^{J-1} \left[ (I + n_j - \delta_{j,j+1})(n_j + 1)\Pr(n+1_j - 1_j+1) - (I + n_j)n_j \Pr(n) \right] + (P + n_0 - \delta_{0,j})(n_{j+1} + 1)\Pr(n-1_j + 1_j+1) - (P + n_0)n_{j+1} \Pr(n) \]
states

tiers

s(1)

s(2)

s(n)
Tier 1
Tier 2
Tier 3
Tier n

Gene Layer

Depth(d)

Extent(e)
Depth(d)

Extent(e)

Tier 1

Tier 2

Tier 3

Tier n

Gene Layer
Kinase Lattice Logic

\[ I(222) > I(211) > I(122) > I(121) > I(112) > I(111) \]
Protein Memory
signal
quenching

signal
auto-catalysis
quenching

hypersensitivity

switch
1 level & 2 P-sites, various feedback entries
Persistent Protein Kinase Activation in the Maintenance Phase of Long-term Potentiation

(Received for publication, September 12, 1991)

Eric Klaun, Shu-Jen Chen, and J. David Sweatt
From the Division of Neuroscience, Baylor College of Medicine, Houston, Texas 77030

Long-term potentiation (LTP) of synaptic transmission in the hippocampus is a robust form of synaptic plasticity that may contribute to mammalian memory formation. A variety of pharmacological evidence suggests that persistent kinase activation contributes to the maintenance of LTP. To determine whether persistent activation of protein kinases was associated with the maintenance phase of LTP, protein kinase activity was measured in control and LTP samples using exogenous protein kinase substrates in an in vitro assay of homogenates of the CA1 region of rat hippocampal slices. After LTP, protein kinase activity was persistently increased, and the induction of this effect was blocked by the N-methyl-D-aspartate receptor antagonist DL-2-amino-5-phosphonovaleric acid. The increased protein kinase activity was found to be significantly attenuated by PKC (19–30), a selective peptide inhibitor of protein kinase C. Thus, LTP is associated with an N-methyl-D-aspartate receptor-mediated generation of a persistently activated form of protein kinase C. These data lend strong support to the model that persistent protein kinase activation contributes to the maintenance of LTP.

Presynaptic Protein Kinase Activity Supports Long-Term Potentiation at Synapses Between Individual Hippocampal Neurons

Paul Pavlidis, Johanna Montgomery, and Daniel V. Madison
Department of Molecular and Cellular Physiology, Stanford University School of Medicine, Stanford, California 94305-5345

Simultaneous microelectrode recording from two individual synaptically connected neurons enables the direct analysis of synaptic transmission and plasticity at a minimal synaptic connection. We have recorded from pairs of CA3 pyramidal neurons in organotypic hippocampal slices to examine the properties of long-term potentiation (LTP) at such minimal connections. LTP in minimal connections was found to be identical to the NMDA-dependent LTP expressed by CA3-CA1 synapses, demonstrating this system provides a good model for the study of the mechanisms of LTP expression. The LTP at minimal synaptic connections does not behave as a simple increase in transmitter release probability, because the amplitude of unitary EPSCs can increase several-fold, unlike what is observed when release probability is increased by raising extracellular calcium. Taking advantage of the relatively short axon connecting neighboring CA3 neurons, we found it feasible to introduce pharmacological agents to the interior of presynaptic terminals by injection into the presynaptic soma and have used this technique to investigate presynaptic effects on basal transmission and LTP. Presynaptic injection of nisoldipine reduced basal transmission, but LTP in these pairs was essentially normal. In contrast, presynaptic injection of H-7 significantly depressed LTP but not basal transmission, indicating a specific role of presynaptic protein kinases in LTP. These results demonstrate that pharmacological agents can be directly introduced into the presynaptic cell and that a purely presynaptic perturbation can alter this plasticity.

Key words: long-term potentiation; presynaptic; protein kinase; hippocampus; electrophysiology; synaptic transmission
Feature Detection

Reproductive Cycles

- High Frequency: α
- Medium Frequency: LH β
- Low Frequency: FSH β
\[ \dot{b} = h'(a(t)) - pb \equiv f'(t) - pb, \quad (9) \]

\[ \dot{c} = \begin{cases} 
   kb(t - \sigma) - c', & a = 0, \\
   -c', & a = a_0. 
\end{cases} \quad (10) \]

The activation of B only ensues in the presence of A, whereas the production of C only ensues in the presence of activated B. The choice of a piecewise function in our analysis reflects the total inhibition of the expression of C during the activation of A. Integrating eqn (9), analogously to the integration of eqn (1) to derive eqns (3) and (4), yields

\[ b(n\tau) = \frac{e^{-pt}}{1 - e^{-pt}} \int_0^\tau f(t)e^{pt} \, dt \quad \text{for } n \text{ large,} \quad (11) \]

\[ b(n\tau + t_1) = e^{-pt_1} \left[ b(n\tau) + \int_0^{t_1} f(t)e^{pt} \, dt \right] \quad (12) \]

for \( t_1 \in [0, \tau] \).
Signal Transduction

- Fast Activation
- Fast Inhibition
- Slow Production
- Slow Decay

Gene Expression

Extracellular Input
Robustness Issues:
Dichotomous approaches for Cells and Brains

Low \( s \) value

![Graph showing survival rate (\( w \)) decreasing with increasing \( i \)-mutations for low \( s \) values.]

High \( s \) value

![Graph showing survival rate (\( w \)) decreasing with increasing \( i \)-mutations for high \( s \) values.]

More Robust Components \( \rightarrow \) More Fragile Components

Survival rate

\[
\frac{dz}{dt} = \sum_{i=0}^{L} z_i w_i Q_{ki}
\]

Competitiveness

\[
w_i = \frac{(1 - s)^i}{\sum_{j=0}^{L} (1 - s)^j}
\]
Low $s$ value favored at small $N$

Low $C = \frac{L}{\sum_i^L H_i}$

High $s$ value favored at high $N$

High $C = \frac{L}{\sum_i^L H_i}$
Low $s$ value favored at small $N$

Low $C = \frac{L}{\sum_i^L H_i}$

High $s$ value favored at high $N$

High $C = \frac{L}{\sum_i^L H_i}$
Low \( s \) value favored at small \( N \)

\[
\text{Small } N \quad \text{Low } C = \frac{L}{\sum_{i}^{L} H_i}
\]

High \( s \) value favored at high \( N \)

\[
\text{Large } N \quad \text{High } C = \frac{L}{\sum_{i}^{L} H_i}
\]
Pair-wise invasability plots

Large $N$

mutant $s'$

wildtype $s$

Small $N$

mutant $s'$

wildtype $s$
Pair-wise invasability plots

Large $N$

Small $N$

wildtype $s$

mutant $s'$

wildtype $s$

mutant $s'$
Pair-wise invasability plots

Large $N$

Small $N$

wildtype $s$

mutant $s'$

wildtype $s$

mutant $s'$
From Cells to Brains
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- Individual cells can only respond to stimuli of comparable space and time dimensions to their receptors - hence multi-cells required for larger features.
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- Long lived cells force the emergence of cell-population memory etc.
Select Bibliography

www.santafe.edu/~krakauer


