Mapping white matter neurodegeneration in the human connectome: a network science study of hereditary diffuse leukoencephalopathy with spheroids
nodes represent GM regions and edges represent WM fibers connecting those regions

Integration of information in the brain has been characterized by the length and/or by the efficiency of shortest-paths

Search-information brings another dimensionality to shortest-paths, i.e. how hidden they are embedded in the rest of the network
T1 MRI

Grey matter segmentation
Cortical partition

diffusion weighted imaging, DSI, DTI
fibers detection
structural connectivity

fMRI, resting-state time-series
functional coupling

Hagmann et al. Plos Biol. 2008
structural connectivity (SC)

functional connectivity (FC)

fiber-tracts (model)

neural activity (model)
structural connectivity (SC)

neural activity (model)

fiber-tracts (model)

functional connectivity (FC)
structural connectivity (SC)
fiber-tracts (model)

functional connectivity (FC)
novel activity (model)
fiber-tracts (model)

structural connectivity (SC)

functional connectivity (FC)

neural activity (model)
log_{10}(\#fibers)

log_{10}(fiber-length)
Hereditary diffuse leukoencephalopathy with spheroids, (HDLS), is an autosomal dominant neurodegenerative disorder caused by mutations in the colony stimulating factor 1 receptor (CSF1R) gene.

It is characterized by white matter damage and axonal swelling (spheroids) leading to subcortical lesions visualized using MRI1.

Clinical symptoms include progressive motor problems and cognitive decline. Patients with HDLS can often be mistaken for other neurodegenerative diseases.

two siblings, HC (female, 48) and HDLS (male, 46)

HDLS mutation: three base deletion (TCT) in CSF1R
reliable
individual
connectomes
reliable individual connectomes

UCL MICROSTRUCTURE IMAGING GROUP

UCL Camino Diffusion MRI Toolkit

Camino is an open-source software toolkit for diffusion MRI processing. The toolkit implements standard techniques, such as diffusion tensor fitting, mapping fractional anisotropy and mean diffusivity, deterministic and probabilistic tractography. It also contains more specialized and cutting-edge techniques, such as Monte-Carlo diffusion simulation, multi-fibre and HARDI reconstruction techniques, multi-fibre PFCs, compartment models, and axon density and diameter estimation.

Camino has a modular design to enable construction of processing pipelines that include modules from other software packages. The toolkit is primarily designed for unix platforms and structured to enable simple scripting of processing pipelines for batch processing. Most users use linux, MacOS or a unix emulator like cygwin running under windows. However, the core code is written in Java and thus is simple to call from other platforms and programming environments, such as matlab running under unix or windows.

The microstructure imaging group at UCL lead development and maintenance of the toolkit. The PICeL group at the University of Pennsylvania also contribute heavily, as have Geoff Parker and colleagues at the University of Manchester. Many of the specialist modules arise from the research of the MIG and collaborating groups. However, the toolkit also includes implementations of many other techniques in the literature that we have found useful.

We hope you find Camino useful. We welcome any feedback, contributions or suggestions for additions to the toolkit.

Camino is distributed under the Artistic License 2.0. The full text of the license is here.

If you use Camino in your research, please include the appropriate citations from the Citations page.

http://cmic.cs.ucl.ac.uk/camino/index.php
how to model an individual connectome?

Contreras et al. (in prep.)
how to model an individual connectome?

tissue segmentation

Contreras et al. (in prep.)
how to model an individual connectome?

Contreras et al. (in prep.)
how to model an individual connectome?

Contreras et al. (in prep.)
how to model an individual connectome?

tissue segmentation

GM parcellation

multi-tensor modeling

WM fiber-tracts

Contreras et al. (in prep.)
how to model an individual connectome?

tissue segmentation

GM parcellation

multi-tensor modeling

structural connectivity (SC)

Contreras et al. (in prep.)
Hereditary diffuse leukoencephalopathy with spheroids

Contreras et al. (in prep.)
HC (<FA> progression) $R^2 = 0.67$

$V_2 = 0.82V_1 + 0.08$

HDLS (<FA> progression) $R^2 = 0.56$

$V_2 = 0.75V_1 + 0.09$
shortest-paths on networks

adjacency matrix

$$\begin{bmatrix}
A & B & C & D & E & F \\
A & 0 & 0.1 & 0 & 0 & 0 & 0 \\
B & 0.1 & 0 & 0.5 & 0 & 0 & 0 \\
C & 0 & 0.5 & 0 & 0.1 & 0.7 & 0 \\
D & 0 & 0 & 0.1 & 0 & 0.1 & 0 \\
E & 0 & 0 & 0.7 & 0.1 & 0 & 0.8 \\
F & 0 & 0 & 0 & 0 & 0.8 & 0
\end{bmatrix}$$

shortest-path distance (SPD)

$$\begin{bmatrix}
A & B & C & D & E & F \\
A & - & 10 & 12 & 22 & 13.4 & 14.7 \\
B & 10 & - & 2 & 12 & 3.4 & 4.7 \\
C & 12 & 2 & - & 10 & 1.4 & 2.7 \\
D & 22 & 12 & 10 & - & 11.3 & \\
E & 13.4 & 3.4 & 1.4 & 10 & - & 1.3 \\
F & 14.7 & 4.7 & 2.7 & 11.3 & 1.3 & -
\end{bmatrix}$$

shortest-path #edges (SPE)

$$\begin{bmatrix}
A & B & C & D & E & F \\
A & - & 1 & 2 & 3 & 3 & 4 \\
B & 1 & - & 1 & 2 & 2 & 3 \\
C & 2 & 1 & - & 1 & 1 & 2 \\
D & 3 & 2 & 1 & - & 1 & 2 \\
E & 3 & 2 & 1 & 1 & - & 1 \\
F & 4 & 3 & 2 & 2 & 1 & -
\end{bmatrix}$$

$$\text{SP}(A,B) = \{A,B,C,E,F\}$$
Shortest-path # Edges (SPE)
Shortest-path # Distance (SPD)

Brain regions ranked by integration impairment

Contreras et al. (in prep.)
Brain regions ranked by integration impairment:
- superior frontal (L,R)
- caudal middle frontal (R)
- precentral (L,R)
- inferior parietal (R)
- insula (R)
- paracentral (L)
Segregation: organization in communities

Main segregation changes

Contreras et al. (in prep.)
Segregation: organization in communities

Main segregation changes

- HDLS patient a more segregated structural organization
- Module 2 disruption involves bilateral portions of insula, superior frontal area, caudate and pre/paracentral areas
Information theoretical approaches to brain connectivity
Information theoretical approaches to brain connectivity
(making sense on network measurements, what they represent, and what the assumptions are when using them)
Information theoretical approaches to brain connectivity
(making sense on network measurements, what they represent, and what the assumptions are when using them)
Information theoretical approaches to brain connectivity

(making sense on network measurements, what they represent, and what the assumptions are when using them)
will be studied further elsewhere [14]. The random walk is also interesting since it could be a mechanism of transport and search on networks [15, 16, 17]. Those processes would be optimal if one follows the shortest path between two nodes under considerations. Among all paths connecting two nodes, the shortest path is given by the one with the smallest number of links [18]. However the shortest path can be found only after global connectivity is known at each node, which is improbable in practice.

will be studied further elsewhere [14]. The random walk is also interesting since it could be a mechanism of transport and search on networks [15, 16, 17]. Those processes would be optimal if one follows the shortest path between two nodes under considerations. Among all paths connecting two nodes, the shortest path is given by the one with the smallest number of links [18]. However the shortest path can be found only after global connectivity is known at each node, which is improbable in practice.
Navigability of complex networks

Marián Boguñá\textsuperscript{1*}, Dmitri Krioukov\textsuperscript{2} and K. C. Claffy\textsuperscript{2}

Routing information through networks is a universal phenomenon in both natural and man-made complex systems. When each node has full knowledge of the global network connectivity, finding short communication paths is merely a matter of distributed computation. However, in many real networks, nodes communicate efficiently even without such global intelligence. Here, we show that the peculiar structural characteristics of many complex networks support efficient communication without global knowledge. We also describe a general mechanism that explains this connection between network structure and function.

M. Boguñá et al. Nature Physics 2009
1. Head west on W 16th St toward Senate Blvd
2. Take the 1st right onto Senate Blvd
3. Turn left onto W 21st St
4. Take the ramp onto I-65 S
5. Keep left to stay on I-65 S
7. Keep right at the fork, follow signs for Interstate 465 W/Interstate 74 W and merge onto I-465 W/I-74
8. Take exit 4 for Indiana 37 S/Harding St
9. Turn left onto IN-37 S/S Harding St Continue to follow IN-37 S
10. Take the Walnut St N exit toward College Ave
11. Merge onto N State Road 37 Business/N Walnut St Continue to follow N Walnut St
12. Continue onto N College Ave
13. Turn left onto W 10th St
   Destination will be on the left
1. Head west on W 16th St toward Senate Blvd
2. Take the 1st right onto Senate Blvd
3. Turn left onto W 21st St
4. Take the ramp onto I-65 S
5. Keep left to stay on I-65 S
6. Take exit 86 for IN-46 toward Columbus/Nashville/Bloomington
7. Turn right onto IN-46 W/Jonathan Moore Pike
8. Turn left onto IN-46 W/Van Buren St
9. Turn right to stay on IN-46 W
10. Turn left onto E 10th St

1101 E 10th St
Bloomington, IN 47405

These directions are for planning purposes only. You may find that construction projects, traffic, weather, or other events may cause conditions to differ from the map results, and you should plan your route accordingly. You must obey all signs or notices regarding your route.
81mi, 10 decisions
left

right

intersection

path A

path B

intersection
path A, path B

left
intersection
right

\[ p(\text{choice}) = 0.5 \]
p(choice) = .5
p(path) = (.5)^d
p(choice) = 0.5
p(path) = (0.5)^d
search information: -log(0.5^d)
\[ p(\text{choice}) = 0.5 \]
\[ p(\text{path}) = (0.5)^{#d} \]

Search information: \(-\log(0.5^{#d})\)

<table>
<thead>
<tr>
<th></th>
<th>length</th>
<th>#d</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>path A</td>
<td>58 mi</td>
<td>13</td>
<td>9.01 bits</td>
</tr>
<tr>
<td>path B</td>
<td>81 mi</td>
<td>10</td>
<td>6.93 bits</td>
</tr>
</tbody>
</table>
p(choice) = 0.5
p(path) = (0.5)^d
search information: -\log(0.5^d)

<table>
<thead>
<tr>
<th></th>
<th>length</th>
<th>#d</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>path A</td>
<td>58 mi</td>
<td>13</td>
<td>9.01 bits</td>
</tr>
<tr>
<td>path B</td>
<td>81 mi</td>
<td>10</td>
<td>6.93 bits</td>
</tr>
</tbody>
</table>

path A is **shorter** than path B
<table>
<thead>
<tr>
<th></th>
<th>length</th>
<th>#d</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>path A</td>
<td>58 mi</td>
<td>13</td>
<td>9.01 bits</td>
</tr>
<tr>
<td>path B</td>
<td>81 mi</td>
<td>10</td>
<td>6.93 bits</td>
</tr>
</tbody>
</table>

$p(\text{choice}) = .5$
$p(\text{path}) = (.5)^d$

Search information: $-\log(.5^d)$

path A is **shorter** than path B
path A is more **hidden** than path B
Which hypotheses are we aiming to test?

shortest-path communication measures
A) search information (S)

B) log (S)

Goñi et al. PNAS 2014
Network randomization test

Goñi et al. PNAS 2014
network theory is a useful framework to better understand the human brain and how its connectivity gets affected by diseases.

communication model(s) based on SC can predict resting-state FC.

the way shortest-paths are embedded (hidden) in the network is a strong predictor of resting-state FC.

evidence of SC driving / shaping collective dynamics and fluctuations of neural activity during resting-state.

analytical, almost immediate computation.
the shortest-path ‘paradox’

Hagmann et al. Plos Biol. 2008
the shortest-path (the only one?)

Hagmann et al. Plos Biol. 2008
“all roads lead to Rome”
“all roads lead to Rome”
understanding the human connectome from an information theoretical perspective
“I promise you I’ll reach the destination. But I cannot really tell you which path I will take. Hopefully a good one among a set of possible ones.”
generalized k-search-information. Example A
generalized k-search-information. Example A

\[ \Pi = \{A, B, C, D\} \]
generalized k-search-information. Example A

\[ \Pi_1 = \{A, B, C, D\} \]

\[ \text{SI}(\Pi_1) = -\log\left(\frac{.7}{1.8} \cdot 1 \cdot \frac{.5}{1.1}\right) = 1.73 \text{ bits} \]
generalized k-search-information. Example A

\[ \Pi_1 = \{A, B, C, D\}\]

\[ SI(\Pi_1) = -\log(\frac{.7}{1.8} \cdot 1 \cdot \frac{.5}{1.1}) = 1.73 \text{ bits} \]

\[ \Pi_2 = \{A, E, C, D\}\]
generalized k-search-information. Example A

\[ \Pi_1 = \{A,B,C,D\} \]

\[ \text{SI}(\Pi_1) = -\log(0.7/1.8 \cdot 1 \cdot 0.5/1.1) = 1.73 \text{ bits} \]

\[ \Pi_2 = \{A,E,C,D\} \]

\[ \text{SI}(\Pi_2) = -\log(0.6/1.8 \cdot 0.6/1.1 \cdot 0.5/1.3) = 2.66 \text{ bits} \]
generalized k-search-information. Example A

\[ \Pi_1 = \{A, B, C, D\} \]
\[ SI(\Pi_1) = -\log(\frac{.7}{1.8} \cdot 1 \cdot \frac{.5}{1.1}) = 1.73 \text{ bits} \]

\[ \Pi_2 = \{A, E, C, D\} \]
\[ SI(\Pi_2) = -\log(\frac{.6}{1.8} \cdot \frac{.6}{1.1} \cdot \frac{.5}{1.3}) = 2.66 \text{ bits} \]

\[ \Pi_{12} = \{A, B, C, D\} \parallel \{A, E, C, D\} \]
generalized k-search-information. Example A

\[ \Pi_1 = \{A, B, C, D\} \]
\[ \text{SI}(\Pi_1) = -\log(0.7/1.8 \cdot 1 \cdot 0.5/1.1) = 1.73 \text{ bits} \]

\[ \Pi_2 = \{A, E, C, D\} \]
\[ \text{SI}(\Pi_2) = -\log(0.6/1.8 \cdot 0.6/1.1 \cdot 0.5/1.3) = 2.66 \text{ bits} \]

\[ \Pi_{12} = \{A, B, C, D\} \parallel \{A, E, C, D\} \]
\[ \text{SI}(\Pi_{12}) = -0.5 \cdot \log(1.3/1.8) - \log(1 \cdot 0.5/1.1)
\quad -0.5 \cdot \log(1.3/1.8) - \log(0.6/1.1 \cdot 0.5/1.3)
\quad = 1.5 \text{ bits} \]
generalized k-search-information. Example B
generalized k-search-information. Example B

\[ \Pi_1 = \{A, B, C, D\} \]
generalized k-search-information. Example B

\[ \Pi_1=\{A,B,C,D\} \quad \text{SI}(\Pi_1) = 2.85 \text{ bits} \]
generalized k-search-information. Example B

\[ \prod_1 = \{A, B, C, D\} \quad \text{SI}(\prod_1) = 2.85 \text{ bits} \]

\[ \prod_2 = \{A, E, C, D\} \]
generalized k-search-information. Example B

\[ \Pi_1 = \{A, B, C, D\} \quad \text{SI}(\Pi_1) = 2.85 \text{ bits} \]

\[ \Pi_2 = \{A, E, C, D\} \quad \text{SI}(\Pi_2) = 3.09 \text{ bits} \]
generalized k-search-information. Example B

\[ \Pi_1 = \{A, B, C, D\} \quad \text{SI}(\Pi_1) = 2.85 \text{ bits} \]
\[ \Pi_2 = \{A, E, C, D\} \quad \text{SI}(\Pi_2) = 3.09 \text{ bits} \]
\[ \Pi_3 = \{A, B, H, C, D\} \]
generalized k-search-information. Example B

\( \prod_1 = \{A, B, C, D\} \quad \text{SI}(\prod_1) = 2.85 \text{ bits} \\
\prod_2 = \{A, E, C, D\} \quad \text{SI}(\prod_2) = 3.09 \text{ bits} \\
\prod_3 = \{A, B, H, C, D\} \quad \text{SI}(\prod_3) = 3.04 \text{ bits} \)
generalized k-search-information. Example B

\[ \prod_1 = \{A, B, C, D\} \quad \text{SI}(\prod_1) = 2.85 \text{ bits} \]

\[ \prod_2 = \{A, E, C, D\} \quad \text{SI}(\prod_2) = 3.09 \text{ bits} \]

\[ \prod_3 = \{A, B, H, C, D\} \quad \text{SI}(\prod_3) = 3.04 \text{ bits} \]

\[ \prod_{12} = \{A, B, C, D\} \parallel \{A, E, C, D\} \]
generalized k-search-information. Example B

\[\Pi_1 = \{A, B, C, D\}\]
\[\Pi_2 = \{A, E, C, D\}\]
\[\Pi_3 = \{A, B, H, C, D\}\]

\[SI(\Pi_1) = 2.85 \text{ bits}\]
\[SI(\Pi_2) = 3.09 \text{ bits}\]
\[SI(\Pi_3) = 3.04 \text{ bits}\]

\[\Pi_{12} = \{A, B, C, D\} \parallel \{A, E, C, D\}\]
\[SI(\Pi_{12}) = 2.27 \text{ bits}\]
generalized k-search-information. Example B

$\prod_1 = \{A, B, C, D\}$  \hspace{1cm}  SI($\prod_1$) = 2.85 bits

$\prod_2 = \{A, E, C, D\}$  \hspace{1cm}  SI($\prod_2$) = 3.09 bits

$\prod_3 = \{A, B, H, C, D\}$  \hspace{1cm}  SI($\prod_3$) = 3.04 bits

$\prod_{12} = \{A, B, C, D\} \parallel \{A, E, C, D\}$  \hspace{1cm}  SI($\prod_{12}$) = 2.27 bits

$\prod_{123} = \{A, B, C, D\} \parallel \{A, E, C, D\} \parallel \{A, B, H, C, D\}$
generalized k-search-information. Example B

\[\prod_1 = \{A, B, C, D\}\]
\[\text{SI}(\prod_1) = 2.85 \text{ bits}\]

\[\prod_2 = \{A, E, C, D\}\]
\[\text{SI}(\prod_2) = 3.09 \text{ bits}\]

\[\prod_3 = \{A, B, H, C, D\}\]
\[\text{SI}(\prod_3) = 3.04 \text{ bits}\]

\[\prod_{12} = \{A, B, C, D\} \parallel \{A, E, C, D\}\]
\[\text{SI}(\prod_{12}) = 2.27 \text{ bits}\]

\[\prod_{123} = \{A, B, C, D\} \parallel \{A, E, C, D\} \parallel \{A, B, H, C, D\}\]
\[\text{SI}(\prod_{123}) = 1.97 \text{ bits}\]
Framework that permits to introduce the concept of information along the first k-shortest-paths within a system

It represents a generalization on integration of information (by allowing local segregation).

It permits to evaluate how a system may operate under different amounts of information.

Challenging questions:

- Is resting-state ‘parsimonious’ with respect to k-search-information?
- Are task-specific FCs related to particular k-shortest-paths?
- Are there k-values for which SI is particularly affected in neurodegeneration?
What are the network features and parcellation resolution that better characterize WM disruption in neurodegeneration?

- Mapping episodic memory into connectome neurodegeneration
- Impaired relationship between SC and FC in neurodegeneration
- Approaches based on multiplex networks
neurodegeneration: a disconnection syndrome in **“the” human connectome?**

<table>
<thead>
<tr>
<th>article</th>
<th>diagnostics</th>
<th># subjects</th>
<th>#regions</th>
<th>parcellation</th>
<th>subcortical</th>
<th>definition of weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daianu et al. 2013</td>
<td>HC,eMCI,lMCI,AD</td>
<td>111</td>
<td>68</td>
<td>Freesurfer</td>
<td>no</td>
<td>relative #fibers</td>
</tr>
<tr>
<td>Reijmer et al. 2013</td>
<td>HC,eAD</td>
<td>30</td>
<td>90</td>
<td>AAL</td>
<td>yes</td>
<td>relative #fibers</td>
</tr>
<tr>
<td>Bai et al. 2012</td>
<td>HC,aMCI,RGD</td>
<td>103</td>
<td>90</td>
<td>AAL</td>
<td>yes</td>
<td>#fibers</td>
</tr>
<tr>
<td>Lo et al. 2010</td>
<td>HC,AD</td>
<td>55</td>
<td>78</td>
<td>AAL</td>
<td>no</td>
<td>#fibers * FA</td>
</tr>
</tbody>
</table>
Evidence of white matter disruption in MCI

Reduced FA in parahippocampal WM (bilateral)
Increased RD in parahippocampal WM (right hemisphere)
interpretations on fractional anisotropy along fibers
interpretations on fractional anisotropy along fibers
interpretations on fractional anisotropy along fibers
Evidence of white matter disruption in MCI

Reduced FA in parahippocampal WM (bilateral)
Increased RD in parahippocampal WM (right hemisphere)

Wang et al. (2012)
Evidence of white matter disruption in MCI

Reduced FA in parahippocampal WM (bilateral)
Increased RD in parahippocampal WM (right hemisphere)
Evidence of white matter disruption in MCI

Reduced FA in parahippocampal WM (bilateral)
Increased RD in parahippocampal WM (right hemisphere)
thank you for your attention