Assignment 2: Problem 4

STATS215: Statistical Models in Biology · Stanford University · Winter 2020

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Background

Connectomics (https://en.wikipedia.org/wiki/Connectomics) is an exciting field that is generating enormous amounts of information about how neurons in the brain are wired to one another. For example, the HHMI Janelia Research Campus and Google recently released an amazing map of connectivity in the fly brain. See their press release (https://www.janelia.org/news/unveiling-the-biggest-and-most-detailed-map-of-the-fly-brain-yet) for more information.

We will set our sights on a smaller dataset: the connectome of *C. elegans*, a small worm, and the first organism to have a fully mapped connectome. Recently, Cook et al (2018) (https://www.nature.com/articles/s41586-019-1352-7) released an updated version of this synaptic connecivity. The data is available at https://wormwiring.org (https://wormwiring.org/).

Let's put the Poisson matrix factorization model (PMF) to use on some neural connectivity data. You will implement the variational inference algorithm derived in Problem 3 and use it to find latent factors of variation in the connectivity between the ~300 neurons in the hermaphrodite *C. elegans* nervous system.

Instructions

Complete the code cells that say `# <<<Your code here>>>` and run the notebook. Once complete, print a .pdf version of the notebook and save the .ipynb file. Submit both along with your written assignment on Canvas.

References

Cook, S. J., Jarrell, T. A., Brittin, C. A., Wang, Y., Bloniarz, A. E., Yakovlev, M. A., ... & Bülow, H. E. (2019). Whole-animal connectomes of both Caenorhabditis elegans sexes. Nature, 571(7763), 63-71.

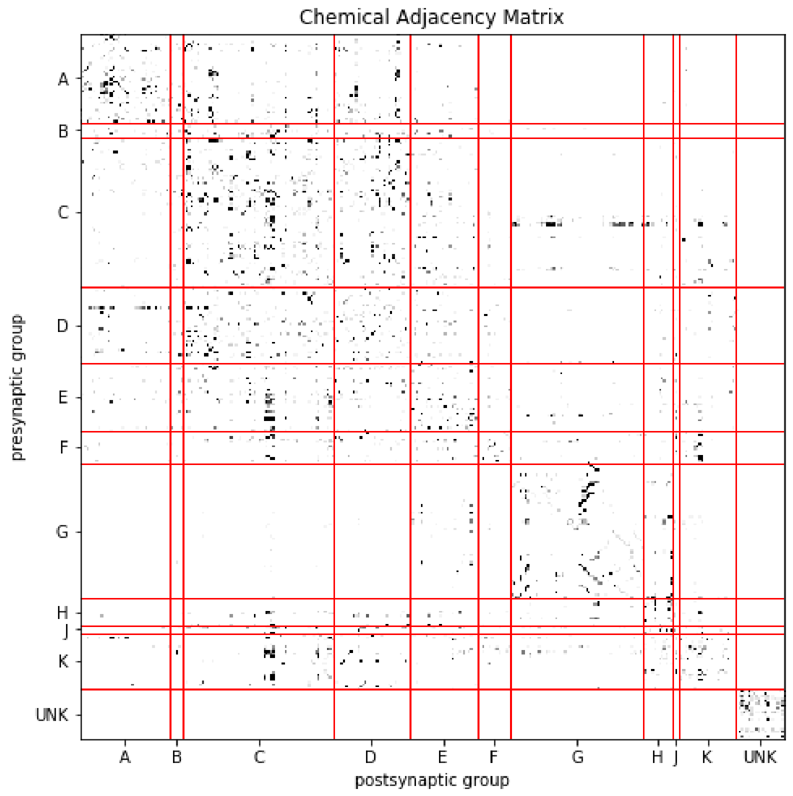
In [0]:
```
import os
import copy
import numpy as np
import numpy.random as npr
import matplotlib.pyplot as plt
from scipy.special import digamma, logsumexp
import pandas as pd
from tqdm.auto import tqdm, trange
```

Download the data

In [0]:
```
# Download the edge list
if not os.path.exists("herm_full_edgelist.csv"):
    !wget https://wormwiring.org/series/data/herm_full/herm_full_edgelist.csv

# Read in the connectivity data, given as a list of synapses
data = pd.read_csv("herm_full_edgelist.csv",
                   names=["pre", "post", "weight", "type"],
                   header=0)

# Neurons start with capital letters.  There should be 302 total, but this
# heuristic filter leaves us with 300.  That's close enough for our purposes.
neurons = filter(lambda name: name[0].isupper(), np.unique(data["pre"]))
neurons = [name.strip() for name in neurons]
neurons = np.array(list(neurons))
num_neurons = len(neurons)
print("Found {} neurons in the data.".format(num_neurons))

# Construct the weighted chemical adjacency matrix
W = np.zeros((num_neurons, num_neurons), dtype=int)
for idx, row in data.iterrows():
    i = np.where(neurons == row["pre"].strip())[0]
    j = np.where(neurons == row["post"].strip())[0]
    if row["type"] == "chemical":
        # These are directed connections
        W[i, j] = int(row["weight"])
    else:
        # Note that there are also undirected electrical synapses
        # (i.e. gap junctions), and synapses between neurons and muscle cells.
        # We will not consider them here.
        pass

# Download information about neuron types from wormatlas.
if not os.path.exists("NeuronType.xls"):
    !wget https://www.wormatlas.org/images/NeuronType.xls
type_data = pd.read_excel("NeuronType.xls")

# Extract the neuron ganglion designation and use it as a proxy for cell type.
neuron_types = []
for name in neurons:
    match = type_data[type_data["Neuron"] == name]
    if len(match) > 0:
        neuron_types.append(match.iloc[0][" AY Ganglion Designation"])
    else:
        neuron_types.append("UNK")
neuron_types = np.array(neuron_types)

# Permute cells by type
perm = np.argsort(neuron_types)
neuron_types = neuron_types[perm]
neurons = neurons[perm]
W = W[np.ix_(perm, perm)]

# Find boundaries between groups
bounds = np.where(neuron_types[1:] != neuron_types[:-1])[0] + 1
midpoints = (np.concatenate(([0], bounds)) + np.concatenate((bounds, [num_neurons]))) / 2
type_names = np.unique(neuron_types)
```

```
Found 300 neurons in the data.
```

```
In [0]: def plot_adjacency_matrix(W, ax=None, vmax=10, cmap="Greys"):
            # Plot the weighted adjacency matrix.
            # Truncate the weights at 10 to highlight
            # lower weight synapses.
            if ax is not None:
                plt.sca(ax)
            else:
                plt.figure(figsize=(8, 8))

            plt.imshow(W, cmap=cmap, vmax=vmax)
            for b in bounds:
                plt.plot([0, num_neurons], [b, b], '-r', lw=1)
                plt.plot([b, b], [0, num_neurons], '-r', lw=1)

            plt.xticks(midpoints, type_names)
            plt.yticks(midpoints, type_names)
            plt.xlim(0, num_neurons)
            plt.ylim(num_neurons, 0)
            plt.ylabel("presynaptic group")
            plt.xlabel("postsynaptic group")
            plt.title("Chemical Adjacency Matrix")

        plot_adjacency_matrix(W)
```



Find the indices with spikes. Make sure you understand these arrays because you will need them for the updates!

In [0]:
```
# The adjacency matrix is super sparse.
# Pull out just the indicies of the non-zero entries (i.e. the synapses).
i_vals, j_vals = np.where(W)
y_vals = W[i_vals, j_vals]
num_synapses = len(y_vals)
print("Found {} synapses".format(num_synapses))
print('y_vals has shape: ', y_vals.shape)
print('W original shape: ', W.shape)
print(i_vals)
```

```
Found 3638 synapses
y_vals has shape:  (3638,)
W original shape:  (300, 300)
[  0   0   0 ... 299 299 299]
```

Implement the mean field variational inference algorithm for the PMF model

In problem 3 you derived the mean field coordinate ascent updates for the Poisson matrix factorization algorithm. There were three types of variational factors,

$$\begin{aligned} q(\bar{y}_{mn}) &= \mathrm{Mult}(\pi_{mn}) && \text{for } \{(m,n) \colon y_{mn} > 0\}, \\ q(u_{mk}) &= \mathrm{Gamma}(a_{mk}, b_{mk}) && \text{for } m = 1, \dots, N \text{ and } k = 1, \dots, K, \\ q(v_{nk}) &= \mathrm{Gamma}(a_{nk}, b_{nk}) && \text{for } n = 1, \dots, N \text{ and } k = 1, \dots, K, \end{aligned}$$

where K is a hyperparameter specifying the number of components.

In practice, the algorithm proceeds by updating the parameters associated with these distributions one at a time, holding the others fixed.

Initialization

This block of code initializes hyperparameters and defines some helper functions for initialization and computing expectations.

In [0]:
```
# Specify the hyperparameters
alpha0 = 1.0
beta0 = 1.0
hypers = dict(alpha0=alpha0, beta0=beta0)

def initialize_variational_params(K):
    """
    Initialize the parameters of the variational inference algorithm.
    Use random initializations to break symmetries that could otherwise
    lead to poor local optima.
    """
    # Parameters of q(\bar{y})
    pi = npr.dirichlet(np.ones(K), size=(num_synapses,))
    # Parameters of q(u)
    a_u = 10 * npr.rand(num_neurons, K)
    b_u = np.ones((num_neurons, K))
    # Parameters of q(u)
    a_v = 10 * npr.rand(num_neurons, K)
    b_v = np.ones((num_neurons, K))
    return dict(pi=pi, a_u=a_u, b_u=b_u, a_v=a_v, b_v=b_v)


def multinomial_expectations(y, pi):
    """
    Helper function to compute E[x] where x ~ Mult(y, pi).
    Assume y.shape == (N,) and pi.shape == (N, K)
    """
    return y[:, None] * pi

def gamma_expectations(a, b):
    """
    Helper function to compute E[x] and E[log x] for x ~ Ga(a, b).
    """
    return a / b, digamma(a) - np.log(b)
```

Implementation

This is skeleton code for running mean field VI. Implement the updates where it says `<<< Your code here >>>` .

```
In [0]: def run_mean_field_vi(num_factors, hypers, num_iters=300, print_intvl=10):
            """
            Run the mean field variational inference algorithm to approximate
            the posterior of a Poisson matrix factorization model with K factors.
            """
            def _update_q_ybar(params):
                """
                Update pi based on the expected sufficient statistics of q(u) and q(v).
                """
                E_u, E_logu = gamma_expectations(params["a_u"], params["b_u"])
                E_v, E_logv = gamma_expectations(params["a_v"], params["b_v"])

                NUM_NEURONS, NUM_FACTORS = E_u.shape
                NUM_SYNAPSES = i_vals.shape[0]
                # print('In q(ybar) update:')
                # print('E_u shape: %s, E_v shape: %s' %(E_u.shape, E_v.shape))

                # <<< Your code here >>>
                # We expect log_pi.shape = (3638,10) = (NUM_SYNAPSES x NUM_FACTORS)
                # E_u and E_v each have size (300,10)  = (NUM_NEURONS x NUM_FACTORS)
                log_pi = np.zeros((NUM_SYNAPSES, NUM_FACTORS))

                for k in range(NUM_FACTORS):
                  for s_idx, (i, j) in enumerate(zip(i_vals, j_vals)):
                    log_pi[s_idx,k] = E_logu[i,k] + E_logv[j,k]

                #log_pi = temp[i_vals, j_vals]
                # print('log_pi.shape: %s' %(log_pi.shape,))
                pi = np.exp(log_pi - logsumexp(log_pi, axis=1, keepdims=True))
                return pi

            def _update_q_u(params):
                """
                Update a_u and b_u based on the expected sufficient statistics
                of q(ybar) and q(v).
                """
                E_ybar = multinomial_expectations(y_vals, params["pi"])
                E_v, E_logv = gamma_expectations(params["a_v"], params["b_v"])

                # print('In q(u) update:')
                # print('E_ybar shape: %s, E_v shape: %s' %(E_ybar.shape, E_v.shape))

                # Update the parameters
                a_u = np.zeros((num_neurons, num_factors))
                b_u = np.zeros((num_neurons, num_factors))

                for m in range(num_neurons): # For each presynaptic neuron m
                    # <<< Your code here >>>

                    # Find all the synapses where m was the presynaptic neuron
                    s_idx = np.where(i_vals == m)[0]

                    a_u[m] = hypers['alpha0'] + np.sum(E_ybar[s_idx], axis=0)
                    b_u[m] = hypers['beta0']  + np.sum(E_v[j_vals[s_idx]],axis=0)
                return a_u, b_u

            def _update_q_v(params):
                """
                Update a_v and b_v based on the expected sufficient statistics
                of q(ybar) and q(u).
                """
                E_ybar = multinomial_expectations(y_vals, params["pi"])
                E_u, E_logu = gamma_expectations(params["a_u"], params["b_u"])

                # Update the parameters
                a_v = np.zeros((num_neurons, num_factors))
                b_v = np.zeros((num_neurons, num_factors))
                for n in range(num_neurons): # For each post-synaptic neuron n
                    # <<< Your code here >>>
                    # Find all the synapses where n was the post-synaptic neuron
                    s_idx = np.where(j_vals == n)[0]

                    # Debug log: confirmed that a_v[n,k]'s are different from each other
                    a_v[n] = hypers['alpha0'] + np.sum(E_ybar[s_idx], axis=0)
                    b_v[n] = hypers['beta0']  + np.sum(E_u[i_vals[s_idx]],axis=0)
                return a_v, b_v

            # Initialize the epectations
            params = initialize_variational_params(num_factors)

            # Run the mean field coordinate ascent algorithm
            for itr in trange(num_iters):
                # Save the old parameters
                old_params = copy.deepcopy(params)

                # Update the parameters
                params["pi"] = _update_q_ybar(params)
                params["a_u"], params["b_u"] = _update_q_u(params)
                params["a_v"], params["b_v"] = _update_q_v(params)

                # Check parameter convergence in l2
                dparams = dict()
                for k in old_params.keys():
                    dparams[k] = np.mean((params[k] - old_params[k])**2)

                if itr % print_intvl == 0:
                    progress = "Iter {}: ".format(itr)
                    for k, v in dparams.items():
                        progress += "d{} : {:.3f}\t".format(k, v)
                    print(progress)

            return params
```

Execution

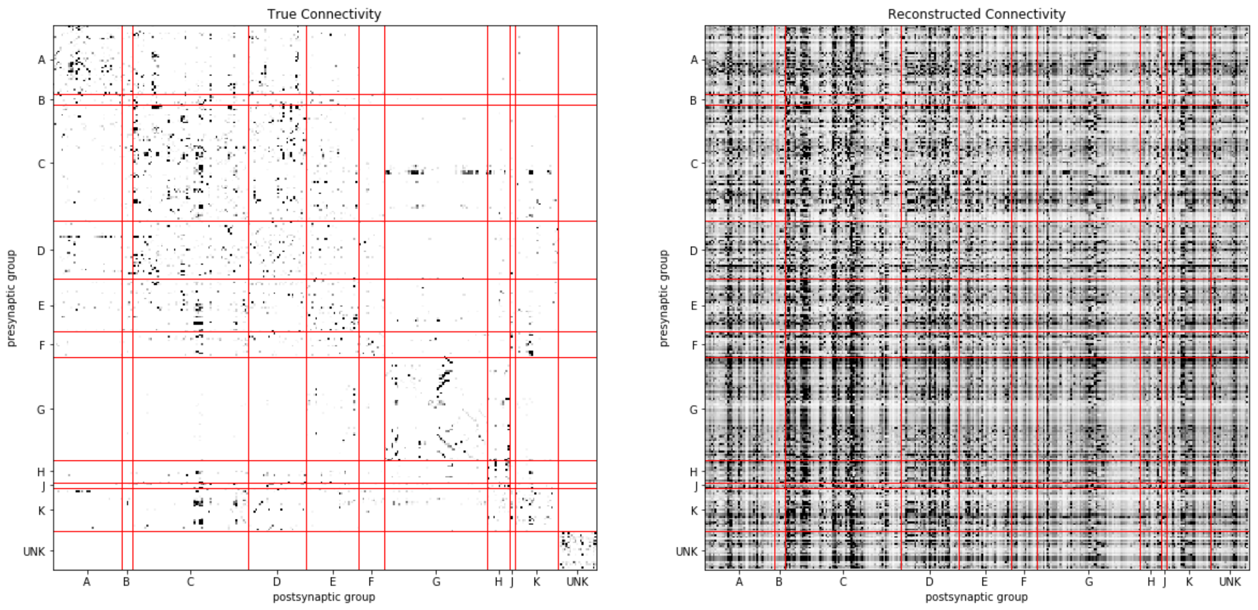
In [0]:
```
# Run the mean field coordinate ascent algorithm
num_factors = 10
params = run_mean_field_vi(num_factors, hypers)

# Extract the posterior expectations with the fitted approx. posterior
E_u, _ = gamma_expectations(params["a_u"], params["b_u"])
E_v, _ = gamma_expectations(params["a_v"], params["b_v"])

# Use the posterior mean as our reconstruction
E_W = np.dot(E_u, E_v.T)
```

```
Iter 0: dpi : 0.017     da_u : 67.026    db_u : 5490.675 da_v : 132.307    db_v : 3.962
Iter 10: dpi : 0.000    da_u : 0.537     db_u : 0.825    da_v : 0.867    db_v : 0.199
Iter 20: dpi : 0.000    da_u : 0.126     db_u : 0.040    da_v : 0.273    db_v : 0.020
Iter 30: dpi : 0.000    da_u : 0.061     db_u : 0.014    da_v : 0.122    db_v : 0.007
Iter 40: dpi : 0.000    da_u : 0.048     db_u : 0.006    da_v : 0.121    db_v : 0.004
Iter 50: dpi : 0.000    da_u : 0.021     db_u : 0.004    da_v : 0.079    db_v : 0.002
Iter 60: dpi : 0.000    da_u : 0.009     db_u : 0.002    da_v : 0.039    db_v : 0.001
Iter 70: dpi : 0.000    da_u : 0.008     db_u : 0.001    da_v : 0.022    db_v : 0.001
Iter 80: dpi : 0.000    da_u : 0.006     db_u : 0.001    da_v : 0.015    db_v : 0.000
Iter 90: dpi : 0.000    da_u : 0.006     db_u : 0.001    da_v : 0.013    db_v : 0.001
Iter 100: dpi : 0.000   da_u : 0.004     db_u : 0.001    da_v : 0.008    db_v : 0.000
Iter 110: dpi : 0.000   da_u : 0.003     db_u : 0.000    da_v : 0.007    db_v : 0.000
Iter 120: dpi : 0.000   da_u : 0.002     db_u : 0.000    da_v : 0.006    db_v : 0.000
Iter 130: dpi : 0.000   da_u : 0.001     db_u : 0.000    da_v : 0.002    db_v : 0.000
Iter 140: dpi : 0.000   da_u : 0.001     db_u : 0.000    da_v : 0.001    db_v : 0.000
Iter 150: dpi : 0.000   da_u : 0.001     db_u : 0.000    da_v : 0.001    db_v : 0.000
Iter 160: dpi : 0.000   da_u : 0.001     db_u : 0.000    da_v : 0.001    db_v : 0.000
Iter 170: dpi : 0.000   da_u : 0.001     db_u : 0.000    da_v : 0.002    db_v : 0.000
Iter 180: dpi : 0.000   da_u : 0.001     db_u : 0.000    da_v : 0.001    db_v : 0.000
Iter 190: dpi : 0.000   da_u : 0.001     db_u : 0.000    da_v : 0.001    db_v : 0.000
Iter 200: dpi : 0.000   da_u : 0.000     db_u : 0.000    da_v : 0.001    db_v : 0.000
Iter 210: dpi : 0.000   da_u : 0.000     db_u : 0.000    da_v : 0.000    db_v : 0.000
Iter 220: dpi : 0.000   da_u : 0.000     db_u : 0.000    da_v : 0.000    db_v : 0.000
Iter 230: dpi : 0.000   da_u : 0.001     db_u : 0.000    da_v : 0.001    db_v : 0.000
Iter 240: dpi : 0.000   da_u : 0.003     db_u : 0.000    da_v : 0.002    db_v : 0.000
Iter 250: dpi : 0.000   da_u : 0.002     db_u : 0.000    da_v : 0.001    db_v : 0.000
Iter 260: dpi : 0.000   da_u : 0.001     db_u : 0.000    da_v : 0.001    db_v : 0.000
Iter 270: dpi : 0.000   da_u : 0.001     db_u : 0.000    da_v : 0.001    db_v : 0.000
Iter 280: dpi : 0.000   da_u : 0.000     db_u : 0.000    da_v : 0.000    db_v : 0.000
Iter 290: dpi : 0.000   da_u : 0.000     db_u : 0.000    da_v : 0.000    db_v : 0.000
```

Analyze the results

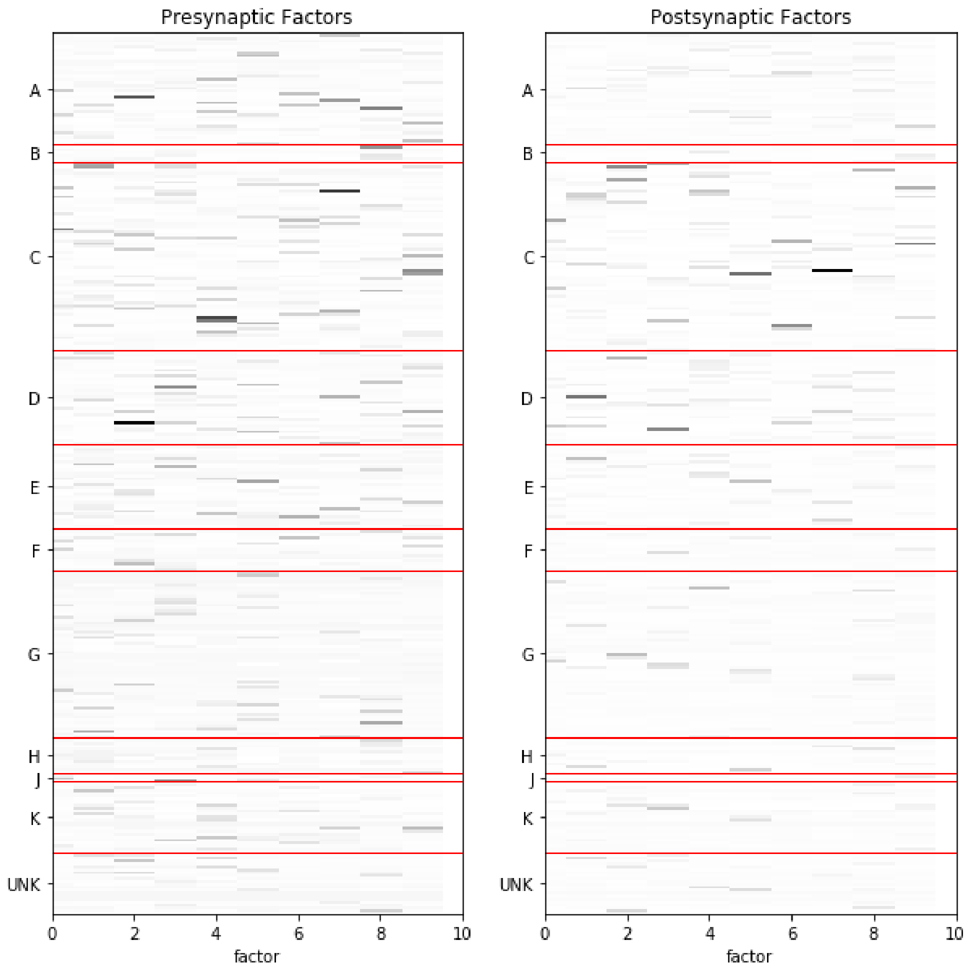
In [0]:
```python
# Plot the true and reconstructed matrices.
fig, axs = plt.subplots(1, 2, figsize=(20, 10))
plot_adjacency_matrix(W, ax=axs[0])
axs[0].set_title("True Connectivity")
plot_adjacency_matrix(E_W, ax=axs[1])
axs[1].set_title("Reconstructed Connectivity")
```

Out[0]:
```
Text(0.5, 1.0, 'Reconstructed Connectivity')
```

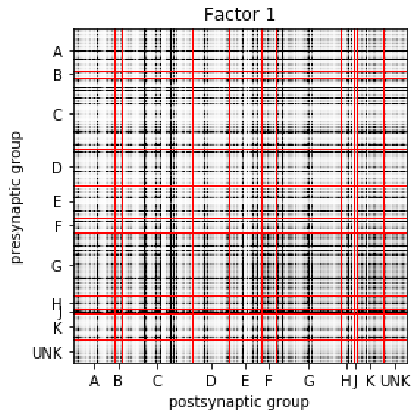


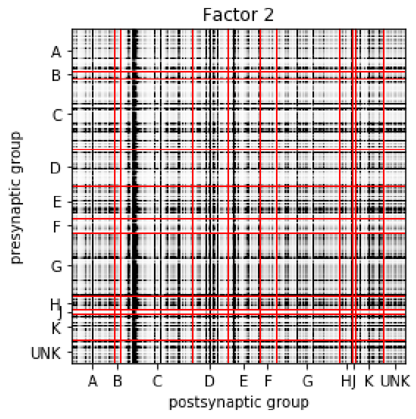
In [0]:
```
# Plot the neuron presynaptic (U) and postsynaptic (V) factors.
fig, axs = plt.subplots(1, 2, figsize=(10, 10))
axs[0].imshow(E_u, cmap="Greys", aspect="auto")
for b in bounds:
    axs[0].plot([0, num_factors], [b, b], '-r', lw=1)
axs[0].set_yticks(midpoints)
axs[0].set_yticklabels(type_names)
axs[0].set_ylim(num_neurons, 0)
axs[0].set_xlabel("factor")
axs[0].set_xlim(0, num_factors)
axs[0].set_title("Presynaptic Factors")

axs[1].imshow(E_v, cmap="Greys", aspect="auto")
for b in bounds:
    axs[1].plot([0, num_factors], [b, b], '-r', lw=1)
axs[1].set_yticks(midpoints)
axs[1].set_yticklabels(type_names)
axs[1].set_ylim(num_neurons, 0)
axs[1].set_xlabel("factor")
axs[1].set_xlim(0, num_factors)
axs[1].set_title("Postsynaptic Factors")
```

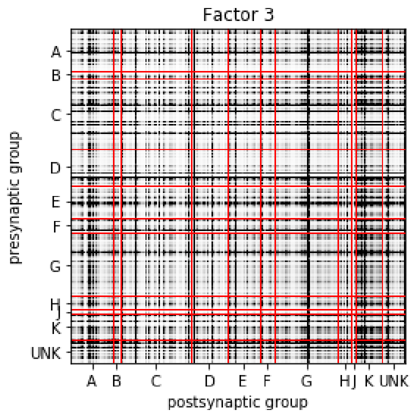
Out[0]:
```
Text(0.5, 1.0, 'Postsynaptic Factors')
```

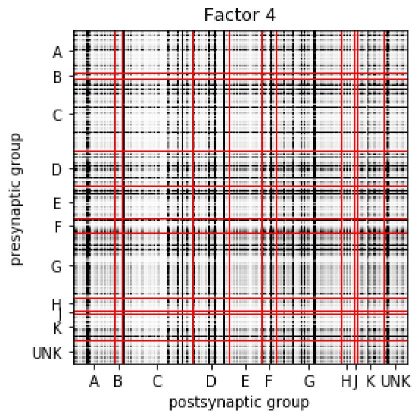


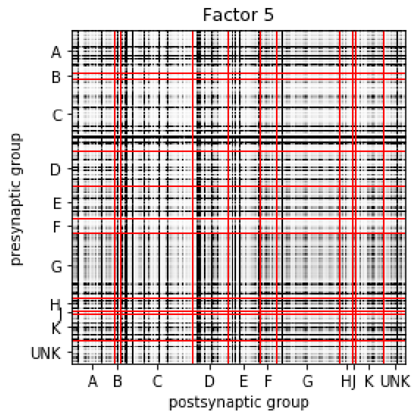
In [0]:
```
# Plot the additive contribution of each factor to the overall connectivity
ncols = 3
nrows = int(np.ceil(num_factors / ncols))

fig, axs = plt.subplots(nrows, ncols, figsize=(ncols * 4, nrows * 4))
for k in range(num_factors):
    row, col = k // ncols, k % ncols
    plot_adjacency_matrix(np.outer(E_u[:, k], E_v[:, k]), ax=axs[row, col], vmax=1)
    axs[row, col].set_title("Factor {}".format(k+1))

for k in range(num_factors, nrows * ncols):
    row, col = k // ncols, k % ncols
    axs[row, col].set_visible(False)

plt.tight_layout()
```

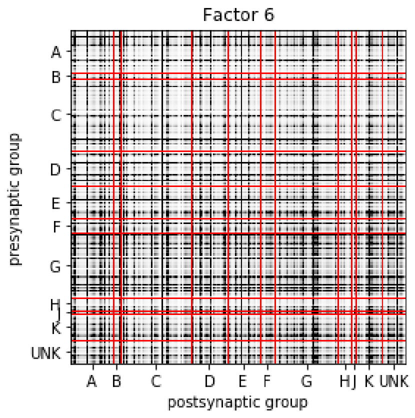

Factor 1
presynaptic group
A B C D E F G H J K UNK
postsynaptic group
A B C D E F G HJ K UNK

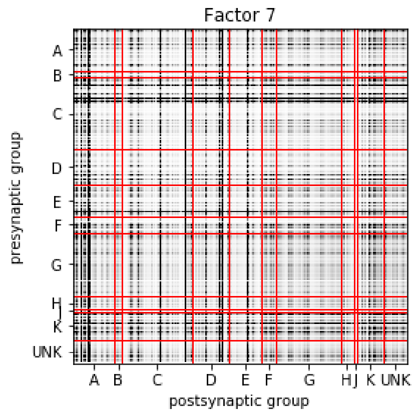

Factor 2
presynaptic group
A B C D E F G H J K UNK
postsynaptic group
A B C D E F G HJ K UNK

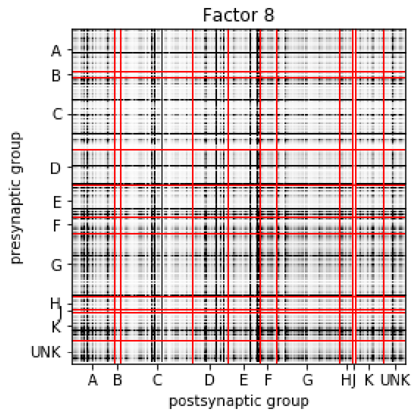

Factor 3
presynaptic group
A B C D E F G H J K UNK
postsynaptic group
A B C D E F G HJ K UNK

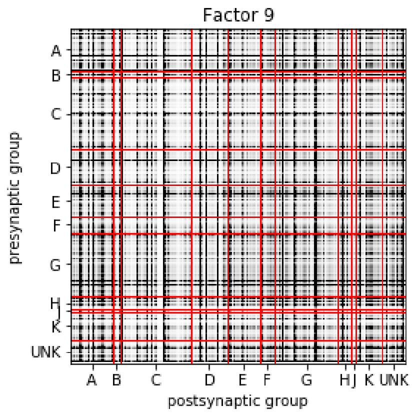

Factor 4
presynaptic group
A B C D E F G H J K UNK
postsynaptic group
A B C D E F G HJ K UNK

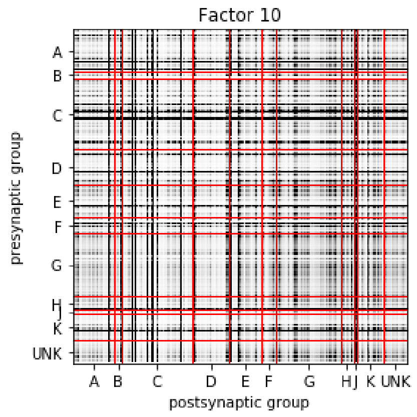

Factor 5
presynaptic group
A B C D E F G H J K UNK
postsynaptic group
A B C D E F G HJ K UNK


Factor 6
presynaptic group
A B C D E F G H J K UNK
postsynaptic group
A B C D E F G HJ K UNK


Factor 7
presynaptic group
A B C D E F G H J K UNK
postsynaptic group
A B C D E F G HJ K UNK


Factor 8
presynaptic group
A B C D E F G H J K UNK
postsynaptic group
A B C D E F G HJ K UNK


Factor 9
presynaptic group
A B C D E F G H J K UNK
postsynaptic group
A B C D E F G HJ K UNK


Factor 10
presynaptic group
A B C D E F G H J K UNK
postsynaptic group
A B C D E F G HJ K UNK

```
In [0]:
```