over-under-splitting-analysis

May 11, 2020

[1]:
```python
import sys
import matplotlib.pyplot as plt
import seaborn as sns
from scipy import sparse
from scipy import stats
from sklearn.metrics.pairwise import euclidean_distances
import collections
import itertools
import re
import fbpca
import datetime
import json

# in-house generated scripts
from __init__ import *
from __init__plot import *
import general_utils
import knn_utils
```

[2]:
```python
# smooth-within modality
def smooth_in_modality(counts_matrix, norm_counts_matrix, k, ka, npc=100,␣
↪sigma=1.0, p=0.1, drop_npc=0):
    """Smooth a data matrix

    Arguments:
        - counts_matrix (pandas dataframe, feature by cell)
        - norm_counts_matrix (pandas dataframe, feature by cell) log10(CPM+1)
        - k (number of nearest neighbors)
    Return:
        - smoothed cells_matrix (pandas dataframe)
        - markov affinity matrix
    """
    import fbpca
    import knn_utils

    assert counts_matrix.shape[1] == norm_counts_matrix.shape[1]
    c = norm_counts_matrix.columns.values
    N = len(c)

    # reduce dimension fast version
    U, s, Vt = fbpca.pca(norm_counts_matrix.T.values, k=npc)
    pcs = U.dot(np.diag(s))
    if drop_npc != 0:
        pcs = pcs[:, drop_npc:]

    # get k nearest neighbor distances fast version
    inds, dists = knn_utils.gen_knn_annoy(pcs, k, form='list',
                                            metric='euclidean', n_trees=10,␣
↪search_k=-1, verbose=True,
                                            include_distances=True)

    # remove itself
    dists = dists[:, 1:]
    inds = inds[:, 1:]

    # normalize by ka's distance
    dists = (dists/(dists[:, ka].reshape(-1, 1)))

    # gaussian kernel
    adjs = np.exp(-((dists**2)/(sigma**2)))

    # construct a sparse matrix
    cols = np.ravel(inds)
    rows = np.repeat(np.arange(N), k-1) # remove itself
    vals = np.ravel(adjs)
    A = sparse.csr_matrix((vals, (rows, cols)), shape=(N, N))

    # Symmetrize A (union of connection)
    A = A + A.T

    # normalization fast (A is now a weight matrix excluding itself)
    degrees = A.sum(axis=1)
    A = sparse.diags(1.0/np.ravel(degrees)).dot(A)

    # include itself
    eye = sparse.identity(N)
    A = p*eye + (1-p)*A

    # smooth fast (future?)
    counts_matrix_smoothed = pd.DataFrame((A.dot(counts_matrix.T)).T,
                                    columns=counts_matrix.columns,␣
↪index=counts_matrix.index)
    return counts_matrix_smoothed, A
```

0.0.1 Basic setup

[3]:
```
timestamp = datetime.datetime.now().date()
name = 'mctseq_over_under_split_{}'.format(timestamp)
output_figures = './results/figures/{}_{{}}.{{}}'.format(name)

DATA_DIR = './data'
sys.path.insert(0, DATA_DIR)
from __init__datasets import *

mods_selected = [
    'human_frontal_rna',
    'human_frontal_mch',
    ]
mod_i, mod_j = 'human_frontal_rna', 'human_frontal_mch'
```

0.0.2 Load data

- metadata
- feature matrix (gene-by-cell; genes are pre-selected highly correlated genes between modalities)

[4]:
```
np.random.seed(0)
```

[5]:
```
# within modality smoothing parameters
ps = {'mc': 0.9,
      'rna': 0.7,
     }
drop_npcs = {
    'mc': 0,
    'rna': 0,
    }
```

[6]:
```
# load cell level metedata
meta_f = os.path.join(DATA_DIR, '{0}_metadata.tsv')
metas = collections.OrderedDict()

for mod in mods_selected:
    metas[mod] = pd.read_csv(meta_f.format(mod), sep="\t").reset_index().
 ↪set_index(settings[mod].cell_col)
    print(metas[mod].iloc[:1, :2], len(metas[mod]))

# load palette and meta settings
cluster_col_major = 'ClusterAnno'
cluster_col_sub = 'SubClusterAnno'
```

```
f = './palette/modality_palette.json'
mod_colors = json.load(open(f), object_pairs_hook=collections.OrderedDict)
mod_colors['human_frontal_mch'] = mod_colors['mCH']
mod_colors[settings['human_frontal_mch'].name] = mod_colors['mCH']
mod_colors['human_frontal_rna'] = mod_colors['RNA']
mod_colors[settings['human_frontal_rna'].name] = mod_colors['RNA']

f = './palette/sub_cluster_palette.json'
subtype_colors = json.load(open(f), object_pairs_hook=collections.OrderedDict)
subtype_ranks = collections.OrderedDict({key: i for i, (key, val) in␣
 ↪enumerate(subtype_colors.items())})

f = './palette/major_cluster_palette.json'
majortype_colors = json.load(open(f), object_pairs_hook=collections.OrderedDict)
majortype_ranks = collections.OrderedDict({key: i for i, (key, val) in␣
 ↪enumerate(majortype_colors.items())})

for mod in mods_selected:
    metas[mod]['majortype_rank'] = metas[mod][cluster_col_major].apply(lambda x:
 ↪ majortype_ranks[x])
    metas[mod]['subtype_rank'] = metas[mod][cluster_col_sub].apply(lambda x:␣
 ↪subtype_ranks[x])


# major sub lookup and sub major lookup
major_clsts = np.sort(metas[mod_i][cluster_col_major].unique())
sub_clsts = np.sort(metas[mod_i][cluster_col_sub].unique())

major_sub_lookup = collections.OrderedDict({clst: [] for clst in major_clsts})
for clst in sub_clsts:
    prefix = '_'.join(clst.split('_')[:-1])
    major_sub_lookup[prefix].append(clst)
sub_major_lookup = collections.OrderedDict({clst: '_'.join(clst.split('_')[:
 ↪-1]) for clst in sub_clsts})
```

```
                                   index  Technology
sample
UMB5577_1_UMB5577_2_A10_AD001_rna      0  snmCT-NOMe 3898
                                   index  Technology
sample
UMB5577_1_UMB5577_2_A10_AD001_mch      0  snmCT-NOMe 3898
```

[7]:
```
# load feature matrices
hvftrs_f = os.path.join(DATA_DIR, '{0}_hvfeatures.{1}')
hvftrs_gene = os.path.join(DATA_DIR, '{0}_hvfeatures.gene')
hvftrs_cell = os.path.join(DATA_DIR, '{0}_hvfeatures.cell')
```

```
gxc_hvftrs = collections.OrderedDict()
for mod in mods_selected:
    print(mod)
    ti = time.time()

    if settings[mod].mod_category == 'mc':
        f_mat = hvftrs_f.format(mod, 'tsv')
        gxc_hvftrs[mod] = pd.read_csv(f_mat, sep='\t', header=0, index_col=0)

        # subsample
        gxc_hvftrs[mod] = gxc_hvftrs[mod][metas[mod].index.values]

        print(gxc_hvftrs[mod].shape, time.time()-ti)
        assert np.all(gxc_hvftrs[mod].columns.values == metas[mod].index.values)␣
↪# make sure cell name is in the sanme order as metas (important if save knn␣
↪mat)
        continue

    f_mat = hvftrs_f.format(mod, 'npz')
    f_gene = hvftrs_gene.format(mod)
    f_cell = hvftrs_cell.format(mod)

    _mat = sparse.load_npz(f_mat)
    _gene = pd.read_csv(f_gene, sep='\t', header=None).iloc[:, 0].values
    _cell = pd.read_csv(f_cell, sep='\t', header=None).iloc[:, 0].values

    gxc_hvftrs[mod] = GC_matrix(_gene, _cell, _mat)
    assert np.all(gxc_hvftrs[mod].cell == metas[mod].index.values) # make sure␣
↪cell name is in the sanme order as metas (important if save knn mat)
    print(gxc_hvftrs[mod].data.shape, time.time()-ti)
```

```
human_frontal_rna
(5107, 3898) 1.7448735237121582
human_frontal_mch
(5107, 3898) 7.480077028274536
```

[8]:
```
# GENE by CELL
smoothed_features = collections.OrderedDict()
for mod in mods_selected:
    print(mod)
    ti = time.time()

    if settings[mod].mod_category == 'mc':
        _df = gxc_hvftrs[mod]
    else:
        _mat = gxc_hvftrs[mod].data.todense()
        _df = pd.DataFrame(_mat,
                              index=gxc_hvftrs[mod].gene,
                              columns=gxc_hvftrs[mod].cell,
                              )

    mat_smoothed, mat_knn = smooth_in_modality(_df, _df, k=30, ka=5, npc=50,
                                               p=ps[settings[mod].mod_category],
                                               drop_npc=drop_npcs[settings[mod].
 ↪mod_category])
    smoothed_features[mod] = mat_smoothed
    print(smoothed_features[mod].shape)
    print(time.time() - ti)
```

```
human_frontal_rna
Time used to build kNN map 0.08980154991149902
Time used to get kNN 0.15803098678588867
(5107, 3898)
3.6637139320373535
human_frontal_mch
Time used to build kNN map 0.08808565139770508
Time used to get kNN 0.16025257110595703
(5107, 3898)
1.9735016822814941
```

0.0.3 Load integrated cell embedding

[9]:
```
f = './data/integrated_clustering_and_embedding.tsv'
df_info = pd.read_csv(f, sep="\t", index_col='sample')
df_info = df_info.rename({
                          'tsne_x': 'tsne_x_joint',
                          'tsne_y': 'tsne_y_joint',
                         }, axis=1)
df_info['modality_name'] = df_info['modality'].apply(lambda mod: settings[mod].
 ↪name)

# add cluster, annot info
for mod in mods_selected:
    _cells = metas[mod].index.values
    df_info.loc[_cells, 'cluster'] = metas[mod].loc[_cells, settings[mod].
 ↪cluster_col]
    df_info.loc[_cells, 'annot'] = metas[mod].loc[_cells, settings[mod].
 ↪annot_col]
    df_info.loc[_cells, 'sub_cluster'] = metas[mod].loc[_cells, settings[mod].
 ↪cluster_col_sub]
    df_info.loc[_cells, 'sub_annot'] = metas[mod].loc[_cells, settings[mod].
 ↪annot_col_sub]
```

```
print(df_info.shape)
df_info.head()
```

```
(7796, 10)
```

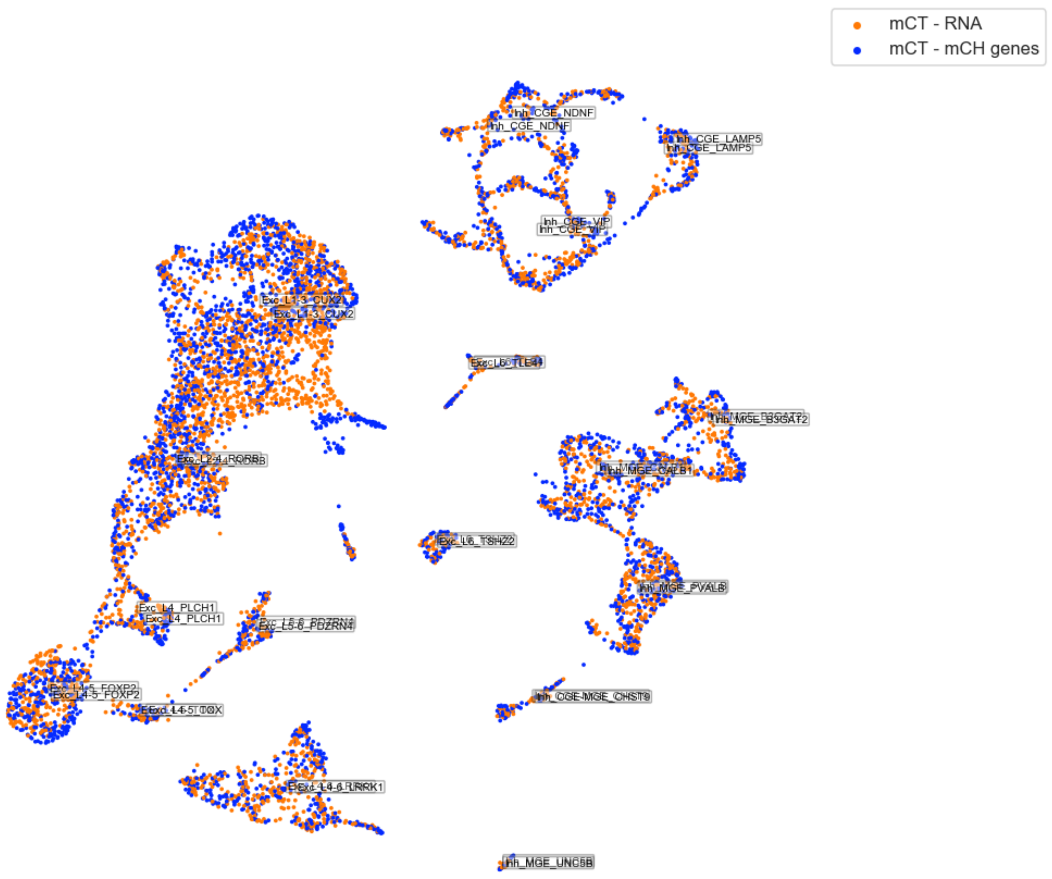
```
[9]:                                        modality  cluster_joint_r0.3  \
sample
UMB5577_1_UMB5577_2_A10_AD001_rna  human_frontal_rna                   2
UMB5577_1_UMB5577_2_A10_AD002_rna  human_frontal_rna                   1
UMB5577_1_UMB5577_2_A10_AD004_rna  human_frontal_rna                   7
UMB5577_1_UMB5577_2_A10_AD006_rna  human_frontal_rna                   8
UMB5577_1_UMB5577_2_A10_AD007_rna  human_frontal_rna                  12

                                   cluster_joint_r4  tsne_x_joint  \
sample
UMB5577_1_UMB5577_2_A10_AD001_rna                 2     -7.315885
UMB5577_1_UMB5577_2_A10_AD002_rna                 8     -3.863784
UMB5577_1_UMB5577_2_A10_AD004_rna                 6     12.818132
UMB5577_1_UMB5577_2_A10_AD006_rna                24     14.620861
UMB5577_1_UMB5577_2_A10_AD007_rna                16     -5.217489

                                   tsne_y_joint modality_name  \
sample
UMB5577_1_UMB5577_2_A10_AD001_rna      0.850225     mCT - RNA
UMB5577_1_UMB5577_2_A10_AD002_rna      8.486494     mCT - RNA
UMB5577_1_UMB5577_2_A10_AD004_rna     -5.993275     mCT - RNA
UMB5577_1_UMB5577_2_A10_AD006_rna      1.303185     mCT - RNA
UMB5577_1_UMB5577_2_A10_AD007_rna     -8.968289     mCT - RNA

                                          cluster            annot  \
sample
UMB5577_1_UMB5577_2_A10_AD001_rna    Exc_L2-4_RORB    Exc_L2-4_RORB
UMB5577_1_UMB5577_2_A10_AD002_rna    Exc_L1-3_CUX2    Exc_L1-3_CUX2
UMB5577_1_UMB5577_2_A10_AD004_rna    Inh_MGE_PVALB    Inh_MGE_PVALB
UMB5577_1_UMB5577_2_A10_AD006_rna   Inh_MGE_B3GAT2   Inh_MGE_B3GAT2
UMB5577_1_UMB5577_2_A10_AD007_rna  Exc_L5-6_PDZRN4  Exc_L5-6_PDZRN4

                                              sub_cluster  \
sample
UMB5577_1_UMB5577_2_A10_AD001_rna         Exc_L2-4_RORB_-
UMB5577_1_UMB5577_2_A10_AD002_rna  Exc_L1-3_CUX2_SLC35F3
UMB5577_1_UMB5577_2_A10_AD004_rna    Inh_MGE_PVALB_DISC1
UMB5577_1_UMB5577_2_A10_AD006_rna    Inh_MGE_B3GAT2_AOAH
UMB5577_1_UMB5577_2_A10_AD007_rna   Exc_L5-6_PDZRN4_RGS6

                                                sub_annot
sample
```

```
UMB5577_1_UMB5577_2_A10_AD001_rna        Exc_L2-4_RORB_-
UMB5577_1_UMB5577_2_A10_AD002_rna  Exc_L1-3_CUX2_SLC35F3
UMB5577_1_UMB5577_2_A10_AD004_rna     Inh_MGE_PVALB_DISC1
UMB5577_1_UMB5577_2_A10_AD006_rna     Inh_MGE_B3GAT2_AOAH
UMB5577_1_UMB5577_2_A10_AD007_rna    Exc_L5-6_PDZRN4_RGS6
```

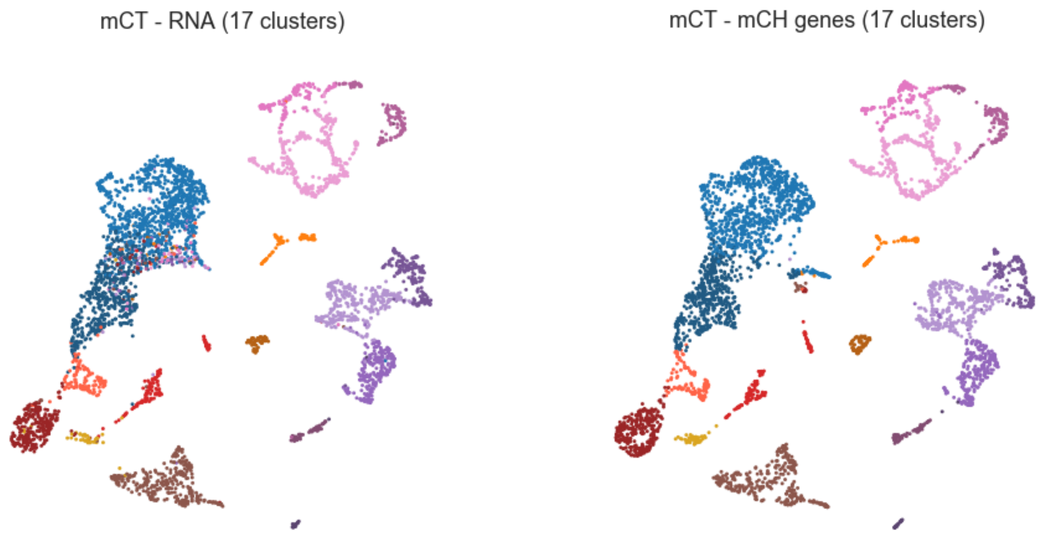
[10]:
```
centroids = {}
_x = (df_info[['tsne_x_joint', 'tsne_y_joint', 'annot', 'modality']]
             .groupby(['modality', 'annot']).median())
for mod in mods_selected:
    centroids[mod] = _x.loc[mod, :]
```

0.0.4 Plot cell embeddings colored by modality and clusterings

[11]:
```
# plot joint embedding colored by modality

fig, ax = plt.subplots(1, 1, figsize=(16*1,16*1))
tx, ty, tc = 'tsne_x_joint', 'tsne_y_joint', 'modality_name'
legend_kws = {'bbox_to_anchor': (1, 1), 'loc': 'upper left'}
general_utils.plot_tsne_labels_ax(df_info, ax, tx, ty, tc,
                                  legend_kws=legend_kws,
                                  legend_size=30,
                                  rasterized=True,
                                  kw_colors=mod_colors,
                                  s=5,
                                 )
ax.set_aspect('equal')
ax.set_title('')
ax.axis('off')

# add labels
for mod in mods_selected:
    for clst, centroid in centroids[mod].iterrows():
        facecolor='white'
        ax.text(centroid.values[0],
                centroid.values[1],
                clst,
                color='black',
                bbox=dict(facecolor=facecolor, alpha=0.3, edgecolor='black',␣
 ↪boxstyle='round,pad=0.1'),
                fontsize=10,
               )

fig.savefig(output_figures.format(2, 'pdf'), bbox_inches='tight', dpi=300)
plt.show()
```

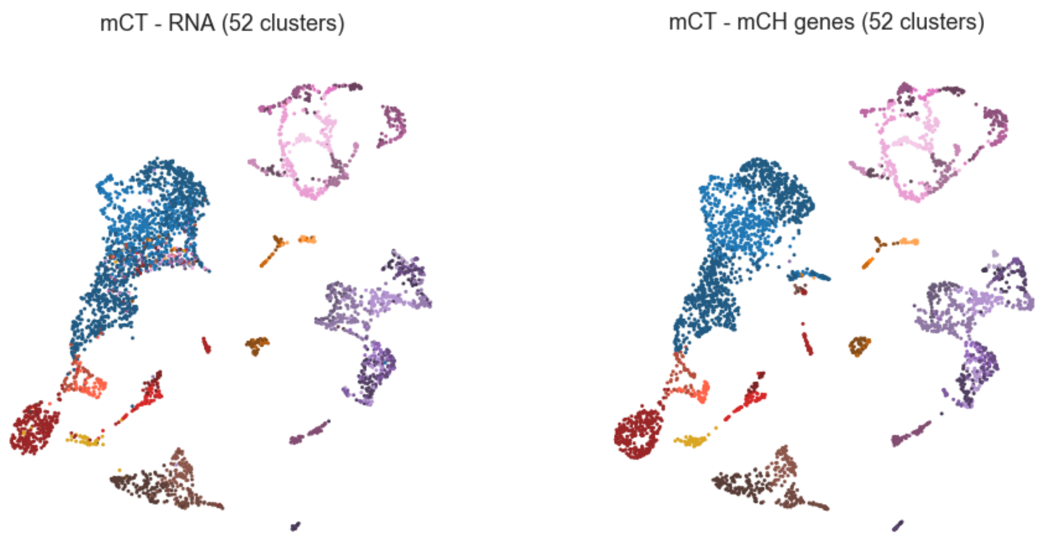


[12]:
```
# plot joint embedding colored by major clusters
n = len(mods_selected)
nx = 2
ny = int((n+nx-1)/nx)
fig, axs = plt.subplots(ny, nx, figsize=(8*nx,8*ny))
axs = axs.flatten()
tx, ty, tc = 'tsne_x_joint', 'tsne_y_joint', 'annot'

for ax, mod in zip(axs, mods_selected):
    general_utils.plot_tsne_labels_ax(df_info[df_info['modality']==mod], ax,␣
 ↪tx, ty, tc,
                                       legend_mode=-1,
                                       rasterized=True,
                                       kw_colors=majortype_colors,
                                       s=2,
                                      )
    ax.set_title('{} ({} clusters)'.format(settings[mod].name, len(df_info.
 ↪loc[df_info['modality']==mod, tc].unique())))
    ax.set_aspect('equal')
    ax.axis('off')
for ax in axs[n:]:
    ax.axis('off')


fig.savefig(output_figures.format('3-major', 'pdf'), bbox_inches='tight',␣
 ↪dpi=300)
plt.show()
```



[13]:

```
# plot joint embedding colored by sub-clusters
n = len(mods_selected)
nx = 2
ny = int((n+nx-1)/nx)
fig, axs = plt.subplots(ny, nx, figsize=(8*nx,8*ny))
axs = axs.flatten()
tx, ty, tc = 'tsne_x_joint', 'tsne_y_joint', 'sub_annot'

for ax, mod in zip(axs, mods_selected):
    general_utils.plot_tsne_labels_ax(df_info[df_info['modality']==mod], ax,␣
 ↪tx, ty, tc,
                                      legend_mode=-1,
                                      rasterized=True,
                                      kw_colors=subtype_colors,
                                      s=2,
                                        )
    ax.set_title('{} ({} clusters)'.format(settings[mod].name, len(df_info.
↪loc[df_info['modality']==mod, tc].unique())))
    ax.set_aspect('equal')
    ax.axis('off')
for ax in axs[n:]:
    ax.axis('off')


fig.savefig(output_figures.format('3-sub', 'pdf'), bbox_inches='tight', dpi=300)
plt.show()
```



0.0.5 Over- and under-splitting analysis

```
[14]: def get_self_radius(distances, axis=1):
          """Get self-radius from a distance matrix (with row and col in the same order)
          Args:
              - distance - 2d matrix
              - axis 1 - row self-radius (for each row, its pair ranking in col)
          return:
              -
          """
          return np.diag(pd.DataFrame(distances).rank(axis=axis))

      def reduce_dim_cca(X, Y, k):
```

```
    """Reduce dim
    Args:
        - X  cell by features
        - Y
        features needs to be matched between X and Y
    Return:
        - U   cell by features
        - V (Vt.T)
    """
    X = np.array(X)
    Y = np.array(Y)
    U, s, Vt = fbpca.pca(X.dot(Y.T), k=k)
    return U, Vt.T

def shuffle_matrix(X, metadata, groupby_col):
    """Shuffle X according to groups in metadata
    Args:
        - X: dataframe cell by gene
        - metadata: dataframe cell by groups
    Return:
        - X_shuffled: dataframe cell by gene
    """
    # begin gene by cell
    X = X.T # gene by cell

    cells_all = []
    shuffled_data_all = []
    for clst, df_sub in metadata.groupby(groupby_col):
        cells_sub = df_sub.index.values
        cells_all += cells_sub.tolist()

        shuffled_data_tmp = []
        for i, gene_row in enumerate(X[cells_sub].values):
            gene_row_shuffled = np.random.permutation(gene_row)
            shuffled_data_tmp.append(gene_row_shuffled)
        shuffled_data_tmp = np.array(shuffled_data_tmp)
        shuffled_data_all.append(shuffled_data_tmp)

    shuffled_data_all = np.hstack(shuffled_data_all)
    X_shuffled = pd.DataFrame(shuffled_data_all, index=X.index,␣
 ↪columns=cells_all)[metadata.index.values]
    ## end gene by cell

    X_shuffled = X_shuffled.T # cell by gene
    return X_shuffled

def shuffle_celllabels(X):
    """Shuffle X (rwos)
    Args:
        - X: dataframe cell by gene
        - metadata: dataframe cell by groups
    Return:
        - X_shuffled: dataframe cell by gene
    """
    X_shuffled = pd.DataFrame(np.random.permutation(X.values),
                              index=X.index,
                              columns=X.columns,
                             )
    return X_shuffled
```

[15]:
```
class DatasetPair:
    def __init__(self, mod_i, mod_j, mat_i, mat_j, direct_i, direct_j,):
        """mat_i and mat_j are cell by gene matricies
        """
        assert np.all(mat_i.columns.values == mat_j.columns.values)
        self.genes = mat_i.columns.values
        self.cells_i = mat_i.index.values
        self.cells_j = mat_j.index.values

        self.mod_i = mod_i
        self.mod_j = mod_j
        self.mat_i = mat_i
        self.mat_j = mat_j
        self.direct_i = direct_i
        self.direct_j = direct_j

    def _normalize(self):
        """Generate zscored (by gene) feature matrix and flip sign for DNA␣
↪methylation
        add:
         - self.mat_norm_i
         - self.mat_norm_j
        """
        self.mat_norm_i = self.mat_i.apply(general_utils.zscore, axis=1)*self.
↪direct_i
        self.mat_norm_j = self.mat_j.apply(general_utils.zscore, axis=1)*self.
↪direct_j

    def _coembed(self, k=20):
        """Embed cells from the 2 datasets (zscored) into a low dimentional␣
↪(k=20) CCA space
        add:
         - self.mat_cca_i
         - self.mat_cca_j
        """
        self.mat_cca_i, self.mat_cca_j = reduce_dim_cca(self.mat_norm_i, self.
↪mat_norm_j, k=k)

    def _cross_mod_knn(self, knn_max):
        """Get k-nearest-neighbors (up to knn_max) of each cell from the other␣
↪dataset
        add:
         - self.knn_ji_grand: for each cell in j get kNN in i
         - self.knn_ij_grand: for each cell in i get kNN in j
        """
        # knn
        self.knn_ji_grand = knn_utils.gen_knn_annoy_train_test(
                                                            self.mat_cca_i, #␣
↪look for nearest neighbors in i
                                                            self.mat_cca_j, #␣
↪for each row in j
                                                             knn_max,
                                                           form='list', # adj␣
↪matrix
                                                             verbose=False,
                                                             ).astype(int)
        self.knn_ij_grand = knn_utils.gen_knn_annoy_train_test(
                                                            self.mat_cca_j, #␣
↪look for nearest neighbors in j
                                                            self.mat_cca_i, #␣
↪for each row in i
                                                             knn_max,
                                                           form='list', # adj␣
↪matrix
                                                             verbose=False,
                                                             ).astype(int)

    def _cross_mod_distance(self):
        """Get cross modality distance matrix
        add:
         - self.distances: (num_cells_i, num_cells_j)
        """
        # distances
        self.distances = euclidean_distances(self.mat_cca_i, self.mat_cca_j)

    def _self_radius(self):
        """Get the self-radius for each cell
        add:
         - self.rankings_i: rankings for each cell in i
         - self.rankings_j: rankings for each cell in j
        """
        # self-radius
        self.rankings_i = get_self_radius(self.distances, axis=1) # for each i,␣
 ↪its pair ranking in j
        self.rankings_j = get_self_radius(self.distances, axis=0) # for each j,␣
 ↪its pair ranking in i

    def compute_cross_mod_metrics(self, knn_max):
        """Compute all cross modality related metrics
        """
        self._normalize()
        self._coembed()
        self._cross_mod_knn(knn_max)
        self._cross_mod_distance()
        self._self_radius()
```

[16]:
```
knn_max = 1000

mat_ii = smoothed_features[mod_i].T
mat_jj = smoothed_features[mod_j].T
direct_i = settings[mod_i].mod_direction
direct_j = settings[mod_j].mod_direction
```

[17]:
```
# original data
orig_data_pair = DatasetPair(mod_i, mod_j, mat_ii, mat_jj, direct_i, direct_j)
orig_data_pair.compute_cross_mod_metrics(knn_max)
```

[18]:
```
# shuffled genes within major subtypes
mat_i_shuffled = shuffle_matrix(mat_ii, metas[mod_i], cluster_col_major)
mat_j_shuffled = shuffle_matrix(mat_jj, metas[mod_j], cluster_col_major)
shuffled_by_majortype_data_pair = DatasetPair(mod_i, mod_j, mat_i_shuffled,␣
 ↪mat_j_shuffled, direct_i, direct_j)
shuffled_by_majortype_data_pair.compute_cross_mod_metrics(knn_max)

# shuffled genes within subtypes
mat_i_shuffled = shuffle_matrix(mat_ii, metas[mod_i], cluster_col_sub)
mat_j_shuffled = shuffle_matrix(mat_jj, metas[mod_j], cluster_col_sub)
shuffled_by_subtype_data_pair = DatasetPair(mod_i, mod_j, mat_i_shuffled,␣
 ↪mat_j_shuffled, direct_i, direct_j)
shuffled_by_subtype_data_pair.compute_cross_mod_metrics(knn_max)

# shuffle3: shuffle cell cluster labels
mat_i_shuffled = shuffle_celllabels(mat_ii)
mat_j_shuffled = shuffle_celllabels(mat_jj)
shuffledCelllabel_data_pair = DatasetPair(mod_i, mod_j, mat_i_shuffled,␣
 ↪mat_j_shuffled, direct_i, direct_j)
```

```
shuffledCelllabel_data_pair.compute_cross_mod_metrics(knn_max)
```

Plot the cumulative distributions of self-radius for different clusters and shuffled clusters

[19]:
```
def compute_area(x, y, xstart, xend, bins=100):
    """
    """
    bins = 100
    width = (xend - xstart)/bins
    xeval = np.linspace(xstart, xend, bins)
    yeval = np.interp(xeval, x, y)
    area = np.trapz(yeval, x=xeval, dx=width)
    return area

def gather_self_radius_info(choose_mod, metadata, cluster_col, data_pairs):
    """
    input:
        choose_mod is a string 'mod_i' or mod_j'
        metadata is a dataframe indexed by cell_id
                    and contains a column cluster_col indicating the cluster␣
↪assignment of each cell
        data_pairs are a dictionary of the DatasetPair object
        assuming all data pairs have the same genes and cells (2 pairs)
    output:
        cell_level_info - dataframe with cell, cluster, cluster_size,␣
↪self_radius for the choose_mod of each data pair
        cluster_level_info - dataframe with cluster level stats

    """
    assert choose_mod in ['mod_i', 'mod_j']

    cells = metadata.index.values
    cluster_lookup = metadata[cluster_col].values
    cluster_size_lookup = metadata.groupby(cluster_col).size()

    cell_level_info = pd.DataFrame()
    cell_level_info['clst_id'] = cluster_lookup
    cell_level_info['n_clst_size'] = cluster_size_lookup.loc[cluster_lookup].
↪values

    for datapair_type, datapair in data_pairs.items():
        if choose_mod == 'mod_i':
            assert np.all(cells == datapair.cells_i)
            self_radius = datapair.rankings_i
        elif choose_mod == 'mod_j':
            assert np.all(cells == datapair.cells_j)
            self_radius = datapair.rankings_j
        else:
            raise ValueError('choose from mod_i and mod_j')
        cell_level_info['n_self_radius_{}'.format(datapair_type)] = self_radius.
↪astype(int)

    cluster_level_info = []
    for clst_id, df_sub in cell_level_info.groupby('clst_id'):
        clst_size = df_sub['n_clst_size'].iloc[0]
        cluster_level_info_1row = {
            'clst_id': clst_id,
            'cluster_size': clst_size,
            }
        for datapair_type in data_pairs.keys():
            xcol = 'n_self_radius_{}'.format(datapair_type)
            ## scores
            # num
            num = (df_sub[xcol] < clst_size).sum() # y(1)
            frac = num/clst_size
            # calculate area
            x = df_sub[xcol].sort_values().values/clst_size # self_radius
            y = np.arange(len(x))/len(x)
            area = compute_area(x, y, 0, 1, bins=100)
            # calculate half rate
            xhalf = np.interp(0.5*frac, y, x)
            # calculate slope at y(0.25)
            x_eval = 0.25
            slope25 = np.interp(x_eval, x, y)/x_eval
            x_eval = 0.5
            slope50 = np.interp(x_eval, x, y)/x_eval

            cluster_level_info_1row['num1_'+datapair_type] = num
            cluster_level_info_1row['frac1_'+datapair_type] = frac
            cluster_level_info_1row['area1_'+datapair_type] = area
            cluster_level_info_1row['xhalf_'+datapair_type] = xhalf
            cluster_level_info_1row['slope25_'+datapair_type] = slope25
            cluster_level_info_1row['slope50_'+datapair_type] = slope50

        cluster_level_info.append(cluster_level_info_1row)
    cluster_level_info = pd.DataFrame(cluster_level_info)

    return cell_level_info, cluster_level_info
```

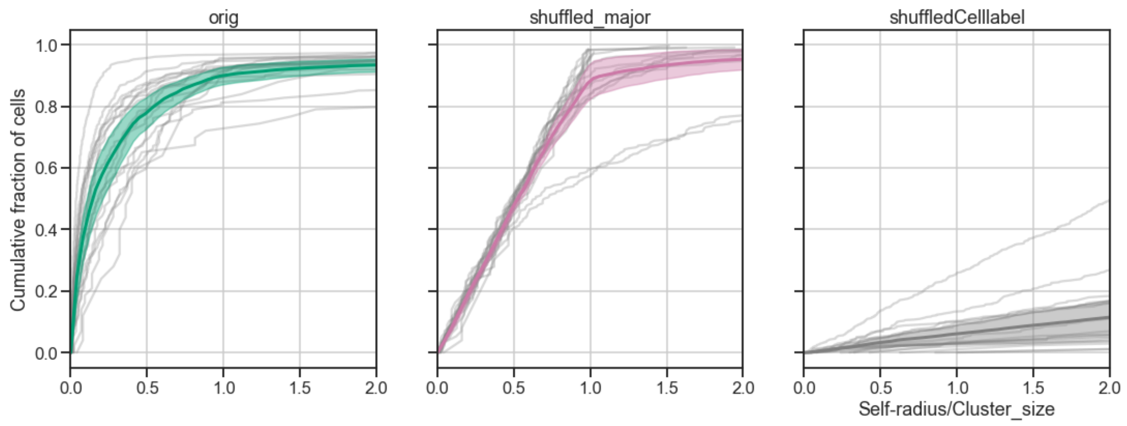
[20]:
```
def plot_self_radius(cell_level_info, colors, output=''):
    """
    clst_id, n_clst_size, n_self_radius_$datapair_type1, ...
    """
```

```
cols = cell_level_info.filter(regex='^n_self_radius_', axis=1).columns.values
ncols = len(cols)
nclsts = len(cell_level_info['clst_id'].unique())
assert len(colors) == ncols

fig, axs = plt.subplots(1, ncols, figsize=(6*ncols,6), sharex=True,␣
↪sharey=True)
xlim = 2
xbins = np.linspace(0, xlim, 50)
ybins_agg = {}
for i, (clst_id, df_sub) in enumerate(cell_level_info.groupby('clst_id')):
    clst_size = df_sub['n_clst_size'].iloc[0]
    for xcol, ax in zip(cols, axs):
        if i == 0:
            ybins_agg[xcol] = []

        x = df_sub[xcol].sort_values().values/clst_size
        y = np.arange(len(x))/len(x)
        ax.plot(x, y, label=clst_id, color='grey', alpha=0.3, zorder=1)

        ybins = np.interp(xbins, x, y)
        ybins_agg[xcol].append(ybins)

    ax.set_xlabel("Self-radius/Cluster_size")

ybins_mean = {}
ybins_err = {}
for xcol, ax, color in zip(cols, axs, colors):
    ybins_agg[xcol] = np.array(ybins_agg[xcol])
    ybins_mean = ybins_agg[xcol].mean(axis=0)
    ybins_err = 1.96*ybins_agg[xcol].std(axis=0)/np.sqrt(nclsts)

    ax.plot(xbins, ybins_mean, color=color, zorder=2, linewidth=3)
    ax.fill_between(xbins,
                    ybins_mean-ybins_err,
                    ybins_mean+ybins_err,
                    color=color, alpha=0.4, zorder=2)
    ax.set_title(xcol[len('n_self_radius_'):])
ax.set_xlim([0, xlim])
axs[0].set_ylabel(r"Cumulative fraction of cells")

if output:
    fig.savefig(output, bbox_inches='tight')
plt.show()
```

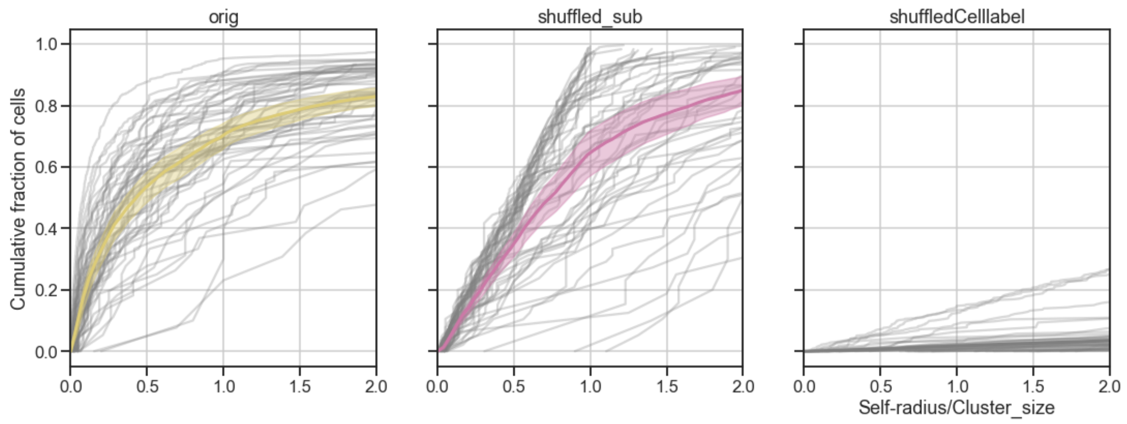
```
def plot_self_radius_mean(ax, cell_level_info, colors, xcols, xcol_names,␣
↪output=''):
    """
    """
    assert len(xcols) == len(xcol_names)

    nclsts = len(cell_level_info['clst_id'].unique())
    xlim = 2
    xbins = np.linspace(0, xlim, 50)
    ybins_agg = {}

    x = [0, 1, 2]
    y = [0, 1, 1]
    ax.plot(x, y, '--',
            color='k',
            label='Ideal cluster'
           )

    for i, (clst_id, df_sub) in enumerate(cell_level_info.groupby('clst_id')):
        clst_size = df_sub['n_clst_size'].iloc[0]
        for xcol, xcol_name in zip(xcols, xcol_names):
            if i == 0:
                ybins_agg[xcol] = []

            x = df_sub[xcol].sort_values().values/clst_size
            y = np.arange(len(x))/len(x)
            ybins = np.interp(xbins, x, y)
            ybins_agg[xcol].append(ybins)

    ybins_mean = {}
    ybins_err = {}
    for xcol, xcol_name, color in zip(xcols, xcol_names, colors):
        ybins_agg[xcol] = np.array(ybins_agg[xcol])
        ybins_mean = ybins_agg[xcol].mean(axis=0)
        ybins_err = 1.96*ybins_agg[xcol].std(axis=0)/np.sqrt(nclsts)

        ax.plot(xbins, ybins_mean, color=color, zorder=2, linewidth=3,␣
↪label=xcol_name)
        ax.fill_between(xbins,
                        ybins_mean-ybins_err,
                        ybins_mean+ybins_err,
                        color=color, alpha=0.4, zorder=2)

    ax.set_xlim([0, xlim])
    ax.set_xlabel("Self-radius/Cluster_size")
    ax.set_ylabel(r"$P(\leq$ Self-radius/Cluster_size$)$")
    ax.legend()
    return
```

[21]:
```
data_pairs = collections.OrderedDict({
    'orig': orig_data_pair,
    'shuffled_major': shuffled_by_majortype_data_pair,
    'shuffled_sub': shuffled_by_subtype_data_pair,
    'shuffledCelllabel': shuffledCelllabel_data_pair,
})

palette_cluster_types = {
    "orig_major": "#009E73",
    "orig_sub": "#DDCC77",

    "shuffled_major": "#CC79A7",
    "shuffled_sub": "#CC79A7",

    "shuffledCelllabel_major": "C7",
    "shuffledCelllabel_sub": "C7",
}

choose_mod = 'mod_j'
```

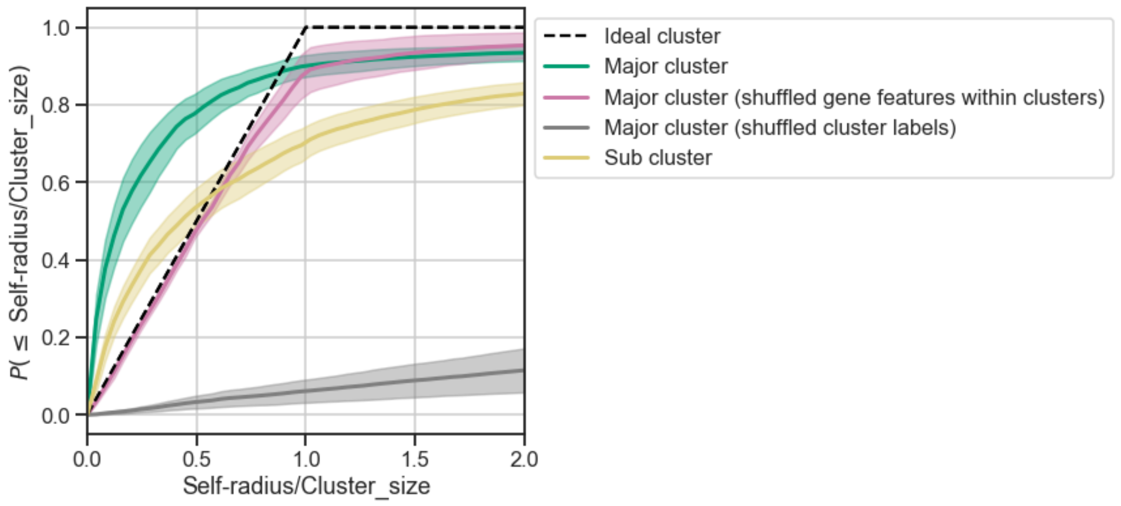
[22]:
```
selected_data_pairs = collections.OrderedDict({
    key: data_pairs[key] for key in ['orig', 'shuffled_major',␣
 ↪'shuffledCelllabel']
})
colors = [
    palette_cluster_types['orig_major'],
    palette_cluster_types['shuffled_major'],
    palette_cluster_types['shuffledCelllabel_major'],
]

cell_level_info_major, cluster_level_info_major = gather_self_radius_info(
                            choose_mod, metas[mod_j], cluster_col_major,
                            selected_data_pairs,
                            )
plot_self_radius(cell_level_info_major, colors,
                output=output_figures.
 ↪format('plot_self_radius_cdf_groupby_majortypes', 'pdf'))
```



```
[23]: selected_data_pairs = collections.OrderedDict({
          key: data_pairs[key] for key in ['orig', 'shuffled_sub', 'shuffledCelllabel']
      })
      colors = [
          palette_cluster_types['orig_sub'],
          palette_cluster_types['shuffled_sub'],
          palette_cluster_types['shuffledCelllabel_sub'],
      ]

      cell_level_info_sub, cluster_level_info_sub = gather_self_radius_info(
                                  choose_mod, metas[mod_j], cluster_col_sub,
                                  selected_data_pairs,
                                  )
      plot_self_radius(cell_level_info_sub, colors,
                       output=output_figures.
       ↪format('plot_self_radius_cdf_groupby_subtypes', 'pdf'))
```



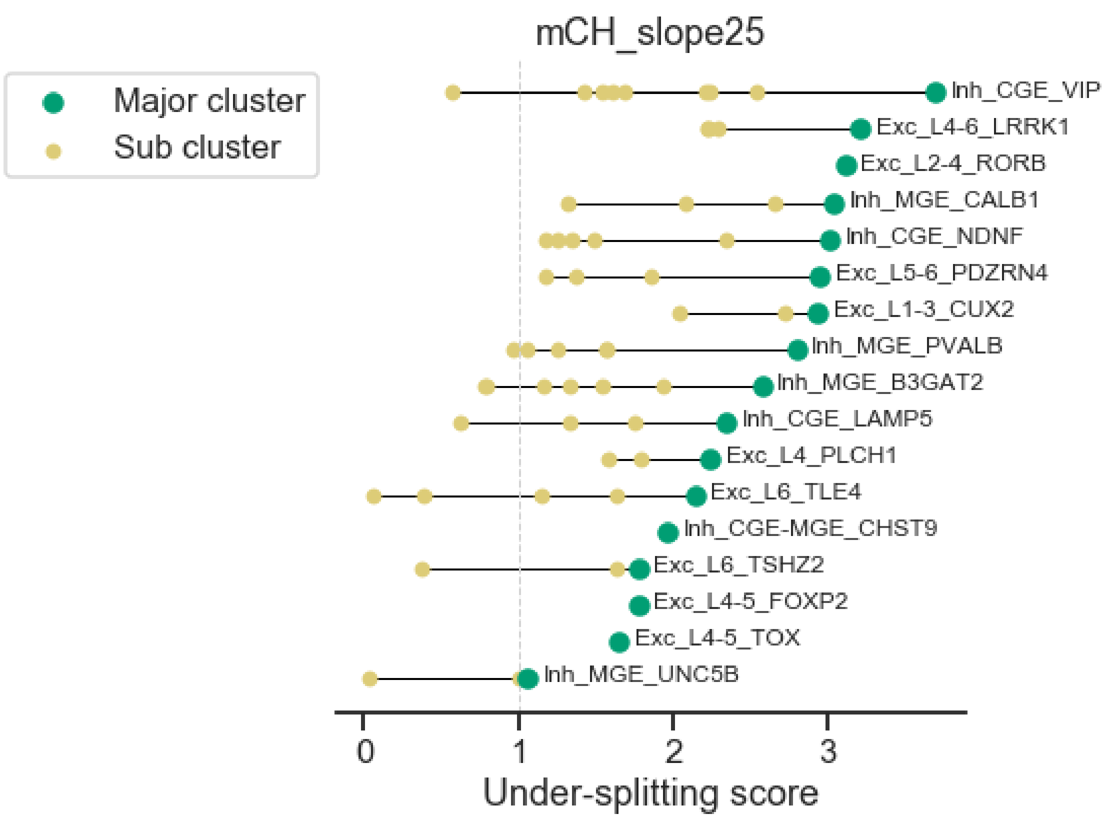
[24]:
```
# summarize mean only
output = output_figures.format('plot_self_radius_cdf_mean_summary', 'pdf')

# plot
fig, ax = plt.subplots(1, 1, figsize=(6,6))

# plot grouped by major
xcols = [
    'n_self_radius_' + datapair_type
    for datapair_type in ['orig', 'shuffled_major', 'shuffledCelllabel']
]
xcol_names = [
    'Major cluster',
    'Major cluster (shuffled gene features within clusters)',
    'Major cluster (shuffled cluster labels)',
    ]
colors = [
    palette_cluster_types['orig_major'],
    palette_cluster_types['shuffled_major'],
    palette_cluster_types['shuffledCelllabel_major'],
]
plot_self_radius_mean(ax, cell_level_info_major, colors, xcols, xcol_names)

# plot grouped by sub
xcols = [
    'n_self_radius_' + datapair_type
    for datapair_type in ['orig']
]
xcol_names = [
    'Sub cluster',
    ]
colors = [
    palette_cluster_types['orig_sub'],
]
plot_self_radius_mean(ax, cell_level_info_sub, colors, xcols, xcol_names)
# remove duplicated legend
general_utils.nondup_legends(bbox_to_anchor=(1,1))
# save
fig.savefig(output, bbox_inches='tight')
plt.show()
```



Plot cluster level metric of self-radius–undersplitting score

[25]:
```python
def plot_self_radius_cluster_level_metric(metric, baseline_level, datapair_type,
                              cluster_level_info_major, cluster_level_info_sub,
                              major_sub_lookup, color_major, color_sub, title='',␣
↪output=''):
    """Plot cluster level metric (compare between major and sub clusters) for a␣
↪given datapair type
    """
    nclsts = len(cluster_level_info_major)
    x = np.arange(nclsts)
   order = np.argsort(cluster_level_info_major[metric+'_'+datapair_type].values)
    xticks = cluster_level_info_major['clst_id'].values[order]
    y1 = cluster_level_info_major[metric+'_'+datapair_type].values[order]
    clsts = cluster_level_info_major['clst_id'].values[order]
    y2 = []
    y2_ticks = []
    for clst in clsts:
        _tmp = cluster_level_info_sub.set_index('clst_id').
↪loc[major_sub_lookup[clst], metric+'_'+datapair_type]
        y2.append(_tmp.values)
        y2_ticks.append([clst.split('_')[-1] for clst in _tmp.index.values])

    scale = np.max([1, nclsts/30])
    fig, ax = plt.subplots(1, 1, figsize=(8*1,6*scale))
    ax.scatter(y1, x, zorder=2, color=color_major, label='Major cluster')
    ax.axvline(baseline_level, linestyle='--', linewidth=1, color='lightgray',␣
↪zorder=1)
    for _x, _y1, _y2, _xtick, _ytick in zip(x, y1, y2, xticks, y2_ticks):
        miny = min([np.min(_y2), _y1])
        maxy = max([np.max(_y2), _y1])
        ax.plot([miny, maxy], [_x, _x], color='k', linewidth=1, zorder=0)
        ax.text(maxy+0.1, _x+0.1, _xtick, fontsize=12,
                ha='left', va='center',
               )
        ax.scatter(_y2, [_x]*len(_y2), zorder=1, label='Sub cluster',
                   s=40, color=color_sub, marker='o')

    ax.set_xlabel('Under-splitting score')
    ax.set_yticks([])
    general_utils.nondup_legends(ax, bbox_to_anchor=(0,1))
    ax.grid(False)
    sns.despine(ax=ax, left=True)
    ax.set_title(title)
    fig.tight_layout()

    if output:
        fig.savefig(output, bbox_inches='tight')
    plt.show()
```

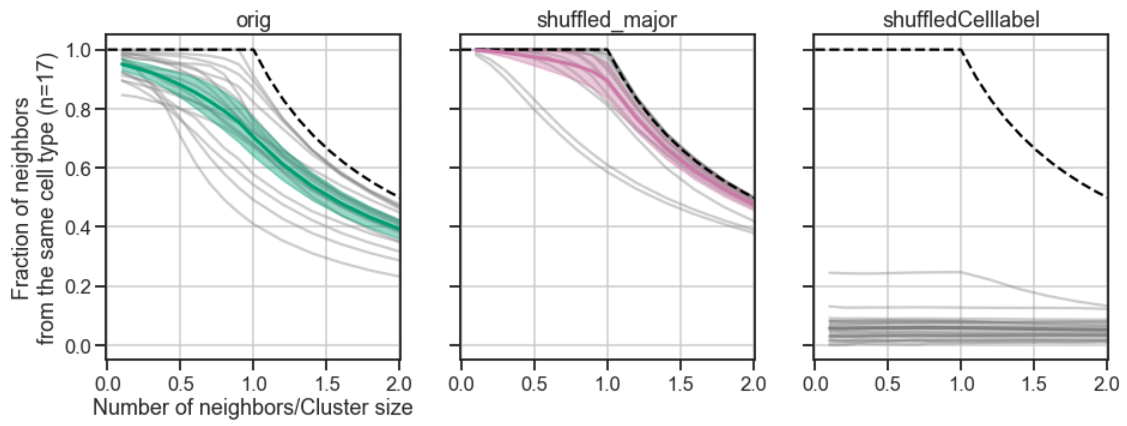
[26]:
```
metric = 'slope25'
baseline_level = 1
title = 'mCH_slope25'
datapair_type = 'orig'

color_major = palette_cluster_types['orig_major']
color_sub = palette_cluster_types['orig_sub']
plot_self_radius_cluster_level_metric(
    metric, baseline_level, datapair_type,
    cluster_level_info_major, cluster_level_info_sub,
    major_sub_lookup, color_major, color_sub,
    title=title,
    output=output_figures.format('plot_self_radius_cluster_level_major-{}'.
 ↪format(title), 'pdf')
    )
```



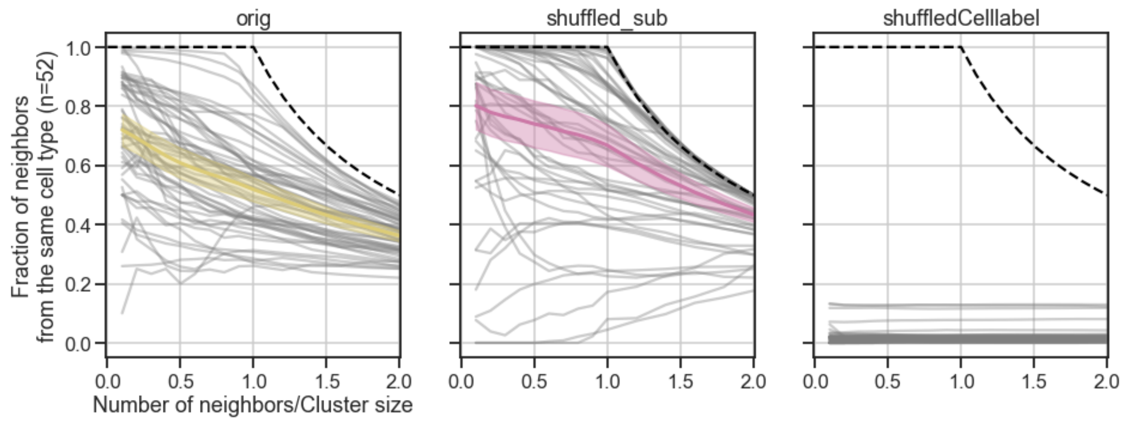
evaluate kNN–related to oversplitting score

[27]:
```
def gather_knn_info(choose_mod, metadata, cluster_col, data_pairs):
    """knn for each i
    """
    cluster_lookup = metadata[cluster_col].values
    cluster_size_lookup = metadata[[cluster_col]].groupby(cluster_col).size()
    nclsts = len(np.unique(cluster_lookup))
    ncells = len(cluster_lookup)
    frac_knn_clst_size = np.sort(np.unique(np.hstack([
                                                np.linspace(0, 1, 11),
                                                np.linspace(1, 4, 16),
                                               ])))[1:]
    knn_cluster_level_dist_alldatapairs = collections.OrderedDict({})
    for datapair_type, data_pair in data_pairs.items():
        # get knn_mat
        if choose_mod == 'mod_i':
            knn_mat = data_pair.knn_ij_grand
        elif choose_mod == 'mod_j':
            knn_mat = data_pair.knn_ji_grand
        else:
            raise ValueError('Choose from mod_i and mod_j')

        knn_cluster_level_dist = []
        for frac_knn in frac_knn_clst_size:
            knn_clsts = (frac_knn*cluster_size_lookup).astype(int)
            # evaluate i
            nagree_i = {}
            for row_idx in np.arange(ncells):
                row_clst = cluster_lookup[row_idx]
                if row_clst not in nagree_i.keys():
                    nagree_i[row_clst] = 0
                row_clst_size = cluster_size_lookup[row_clst]
                row = knn_mat[row_idx, :][:knn_clsts[row_clst]]
                nagree_i[row_clst] += (cluster_lookup[row] ==␣
↪cluster_lookup[row_idx]).astype(int).sum()/
↪(row_clst_size*knn_clsts[row_clst])
            knn_cluster_level_dist.append(nagree_i)

        knn_cluster_level_dist = pd.DataFrame(knn_cluster_level_dist,␣
↪index=frac_knn_clst_size)
        knn_cluster_level_dist.index.name = 'frac_knn_clst_size'
        # add it into the dictionary
        knn_cluster_level_dist_alldatapairs[datapair_type] =␣
↪knn_cluster_level_dist


    x = np.linspace(1, 4, 30)
    y = 1/x
    x = np.hstack([[0, 1], x])
    y = np.hstack([[1, 1], y])
    area_ref = compute_area(x, y, 0, 4)


    knn_cluster_level_stats_alldatapairs = collections.OrderedDict({})
    for datapair_type, data_pair in data_pairs.items():
        knn_cluster_level_stats = []
        knn_cluster_level_dist =␣
↪knn_cluster_level_dist_alldatapairs[datapair_type]
        for clst_id in knn_cluster_level_dist.columns:
            clst_size = cluster_size_lookup[clst_id]
            x = frac_knn_clst_size
            y = knn_cluster_level_dist[clst_id].values
            area = compute_area(x, y, 0, 4)/area_ref
            y1 = 1 - np.interp(1, x, y)
            knn_cluster_level_stats.append({
                'clst_id': clst_id,
                'clst_size': clst_size,
                'area': area,
                'y1': y1,
                })
        knn_cluster_level_stats = pd.DataFrame(knn_cluster_level_stats)
        knn_cluster_level_stats_alldatapairs[datapair_type] =␣
↪knn_cluster_level_stats

    return knn_cluster_level_dist_alldatapairs,␣
↪knn_cluster_level_stats_alldatapairs

def plot_knn_distribution(knn_cluster_level_dist_alldatapairs, metadata,␣
↪cluster_col, colors, output=''):
    """"""
    cluster_size_lookup = metadata[[cluster_col]].groupby(cluster_col).size()
    nclsts = len(cluster_size_lookup)
    ndatapairs = len(knn_cluster_level_dist_alldatapairs)

    fig, axs = plt.subplots(1, ndatapairs, figsize=(5*ndatapairs,5),␣
↪sharex=True, sharey=True)
    for i, (ax, datapair_type, color) in enumerate(zip(
                                            axs,␣
↪knn_cluster_level_dist_alldatapairs.keys(), colors)):
        knn_cluster_level_dist_alldatapair =␣
↪knn_cluster_level_dist_alldatapairs[datapair_type]
        frac_knn_clst_size = knn_cluster_level_dist_alldatapair.index.values
        x = np.linspace(1, 4, 30)
        y = 1/x
        x = np.hstack([[0, 1], x])
        y = np.hstack([[1, 1], y])
        ax.plot(x, y, '--',
                color='k',
               )

        ys = []
        for clst_id in knn_cluster_level_dist_alldatapair.columns:
            x = frac_knn_clst_size
            y = knn_cluster_level_dist_alldatapair[clst_id].values
            ax.plot(x, y, '-',
                    color='grey', alpha=0.4, zorder=1,
                   )
            ys.append(y)
        ys = np.array(ys)
        y_mean = ys.mean(axis=0)
        y_err = 1.96*ys.std(axis=0)/np.sqrt(nclsts)

        ax.plot(x, y_mean, color=color, zorder=2, linewidth=3)
        ax.fill_between(x,
                        y_mean-y_err,
                        y_mean+y_err,
                        color=color, alpha=0.4, zorder=2)
        ax.xaxis.set_major_locator(mtick.MaxNLocator(5))

        if i == 0:
            ax.set_xlabel('Number of neighbors/Cluster size')
            ax.set_ylabel('Fraction of neighbors\nfrom the same cell type␣
 ↪(n={})'.format(nclsts))
        else:
            ax.set_xlabel('')
            ax.set_ylabel('')

        ax.set_title(datapair_type)
        ax.set_xlim([-0.01, 2.01])

    if output:
        fig.savefig(output, bbox_inches='tight')
    plt.show()
    return
```

[28]:
```
choose_mod = 'mod_j'
selected_data_pairs = collections.OrderedDict({
    key: data_pairs[key] for key in ['orig', 'shuffled_major',␣
 ↪'shuffledCelllabel']
})
colors = [
    palette_cluster_types['orig_major'],
    palette_cluster_types['shuffled_major'],
    palette_cluster_types['shuffledCelllabel_major'],
]

knn_cluster_level_dist_alldatapairs_major,␣
 ↪knn_cluster_level_stats_alldatapairs_major = gather_knn_info(
                choose_mod, metas[mod_j], cluster_col_major,
                selected_data_pairs)
plot_knn_distribution(knn_cluster_level_dist_alldatapairs_major, metas[mod_j],␣
 ↪cluster_col_major, colors,
          output=output_figures.
 ↪format('plot_knn_distribution_groupby_majortypes'.format(title), 'pdf'))
```

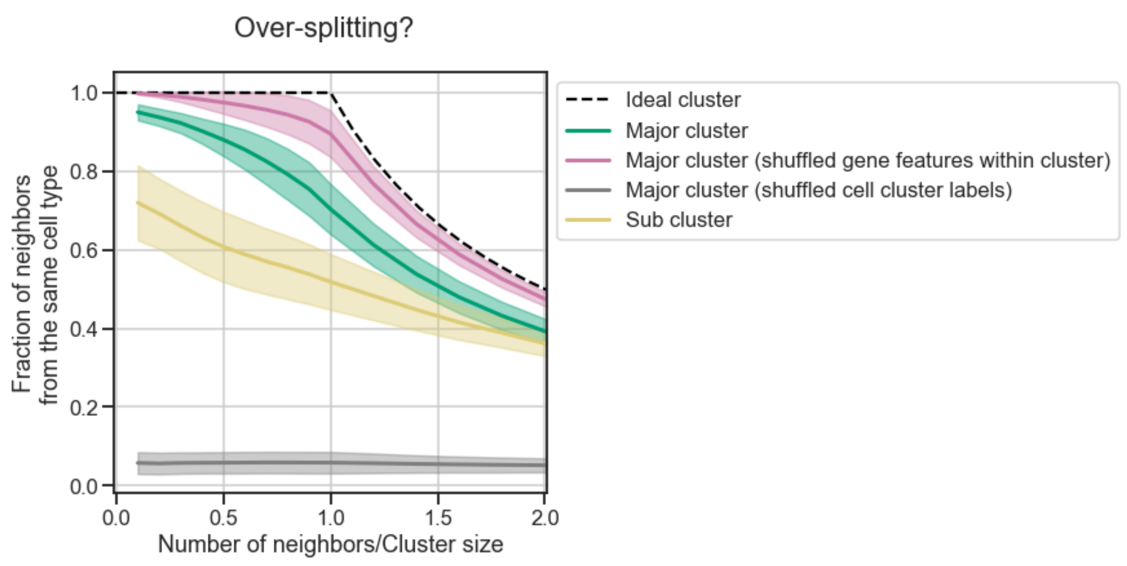


```
[29]: choose_mod = 'mod_j'
selected_data_pairs = collections.OrderedDict({
    key: data_pairs[key] for key in ['orig', 'shuffled_sub', 'shuffledCelllabel']
})
colors = [
    palette_cluster_types['orig_sub'],
    palette_cluster_types['shuffled_sub'],
    palette_cluster_types['shuffledCelllabel_sub'],
]

knn_cluster_level_dist_alldatapairs_sub,␣
 ↪knn_cluster_level_stats_alldatapairs_sub = gather_knn_info(
                 choose_mod, metas[mod_j], cluster_col_sub,
                 selected_data_pairs)
plot_knn_distribution(knn_cluster_level_dist_alldatapairs_sub, metas[mod_j],␣
 ↪cluster_col_sub, colors,
            output=output_figures.format('plot_knn_distribution_groupby_subtypes'.
 ↪format(title), 'pdf'))
```



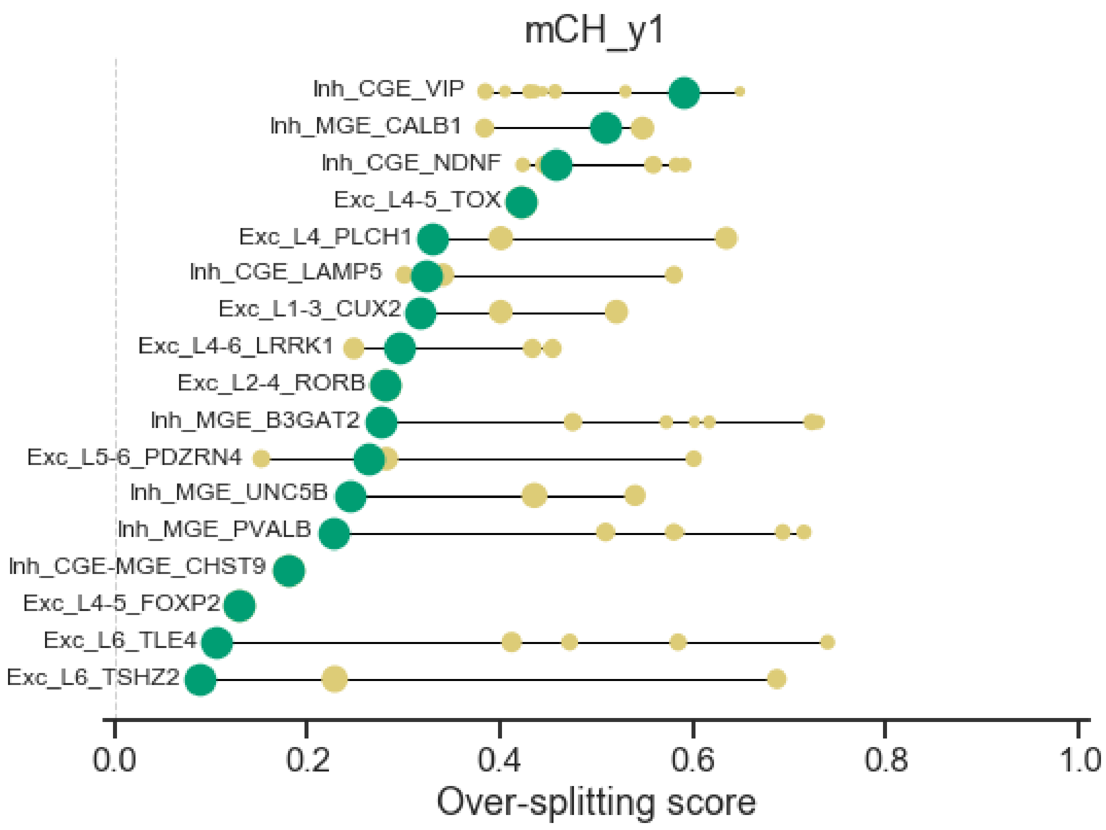
[30]:
```python
def plot_knn_distribution_mean(ax, metadata, cluster_col,
                            knn_cluster_level_dist_alldatapairs, colors, labels,
                              output=''):
    """
    """
    cluster_size_lookup = metadata[[cluster_col]].groupby(cluster_col).size()
    nclsts = len(cluster_size_lookup)
    ndatapairs = len(knn_cluster_level_dist_alldatapairs)

    x = np.linspace(1, 4, 30)
    y = 1/x
    x = np.hstack([[0, 1], x])
    y = np.hstack([[1, 1], y])
    ax.plot(x, y, '--',
            color='k',
            label='Ideal cluster'
           )

    for i, (datapair_type, color, label) in enumerate(zip(
                                knn_cluster_level_dist_alldatapairs.keys(),␣
 ↪colors, labels)):
        knn_cluster_level_dist =␣
 ↪knn_cluster_level_dist_alldatapairs[datapair_type]
        frac_knn_clst_size = knn_cluster_level_dist.index.values
        ys = []
        for clst_id in knn_cluster_level_dist.columns:
            x = frac_knn_clst_size
            y = knn_cluster_level_dist[clst_id].values
            ys.append(y)

        ys = np.array(ys)
        y_mean = ys.mean(axis=0)
        y_err = 1.96*ys.std(axis=0)/np.sqrt(nclsts)

        ax.plot(x, y_mean, color=color, zorder=2, linewidth=3, label=label)
        ax.fill_between(x,
                        y_mean-y_err,
                        y_mean+y_err,
                        color=color, alpha=0.4, zorder=2)
        ax.xaxis.set_major_locator(mtick.MaxNLocator(5))

        ax.set_xlabel('Number of neighbors/Cluster size')
        ax.set_ylabel('Fraction of neighbors\nfrom the same cell type'.
 ↪format(nclsts))
        ax.set_xlim([-0.01, 2.01])
    return
```

[31]:
```
output = output_figures.format('plot_knn_distribution_mean', 'pdf')

# 4 results
knn_cluster_level_dist_selected_datapairs = collections.OrderedDict({
    k: knn_cluster_level_dist_alldatapairs_major[k] for k in ['orig',␣
 ↪'shuffled_major', 'shuffledCelllabel']
})
knn_cluster_level_dist_selected_datapairs['orig_sub'] =␣
 ↪knn_cluster_level_dist_alldatapairs_sub['orig']

labels = [
    'Major cluster',
    'Major cluster (shuffled gene features within cluster)',
    'Major cluster (shuffled cell cluster labels)',
    'Sub cluster',
]
colors = [
    palette_cluster_types['orig_major'],
    palette_cluster_types['shuffled_major'],
    palette_cluster_types['shuffledCelllabel_major'],
    palette_cluster_types['orig_sub'],
]



fig, ax = plt.subplots(1, 1, figsize=(6*1,6))
plot_knn_distribution_mean(ax, metas[mod_j], cluster_col_major,
                           knn_cluster_level_dist_selected_datapairs, colors,␣
 ↪labels,
                           output=output)
general_utils.nondup_legends(ax, bbox_to_anchor=(1,1))
fig.suptitle('Over-splitting?')
if output:
    fig.savefig(output, bbox_inches='tight')
```



[32]:
```
def plot_knn_cluster_level_metric(metric, baseline_level,
                          knn_cluster_level_stats_major, knn_cluster_level_stats_sub,
                            major_sub_lookup, metadata,
                            cluster_col_major, cluster_col_sub,
                            color_major, color_sub,
                            title='', output=''):
    """
    """
    dot_size = 200
    cluster_size_lookup_major = metadata[[cluster_col_major]].
↪groupby(cluster_col_major).size()
    cluster_size_lookup_sub = metadata[[cluster_col_sub]].
↪groupby(cluster_col_sub).size()

    nclsts = len(knn_cluster_level_stats_major)
    x = np.arange(nclsts)
    order = np.argsort(knn_cluster_level_stats_major[metric].values) #[::-1]
    xticks = knn_cluster_level_stats_major['clst_id'].values[order]
    y1 = knn_cluster_level_stats_major[metric].values[order]
    clsts = knn_cluster_level_stats_major['clst_id'].values[order]
    y2 = []
    y2_ticks = []
    y2_size = []
    for clst in clsts:
        _tmp = knn_cluster_level_stats_sub.set_index('clst_id').
↪loc[major_sub_lookup[clst], metric]
        y2.append(_tmp.values)
        y2_ticks.append([clst.split('_')[-1] for clst in _tmp.index.values])
        y2_size.append(cluster_size_lookup_sub[_tmp.index.values])

    scale = np.max([1, nclsts/30])
    fig, ax = plt.subplots(1, 1, figsize=(8*1,6*scale))
    ax.axvline(baseline_level, linestyle='--', linewidth=1, color='lightgray',␣
↪zorder=1)
    ax.scatter(y1, x, zorder=2, s=dot_size, color=color_major, label='Major␣
↪cluster')
    for _x, _y1, _y2, _xtick, _ytick, _y2_size in zip(x, y1, y2, xticks,␣
↪y2_ticks, y2_size):
        miny = min([np.min(_y2), _y1])
        maxy = max([np.max(_y2), _y1])
        ax.plot([miny, maxy], [_x, _x], color='k', linewidth=1, zorder=0)
        ax.text(miny-0.02, _x+0.1, _xtick, fontsize=12,
                ha='right', va='center',
               )
        ax.scatter(_y2, [_x]*len(_y2), s=dot_size*_y2_size/np.sum(_y2_size),
                   zorder=1, label='Sub cluster',
                   color=color_sub, marker='o')

    ax.set_xlabel('Over-splitting score')
    ax.set_yticks([])
    ax.grid(False)
    ax.set_xlim([-0.01, 1.01])
    sns.despine(ax=ax, left=True)
    ax.set_title(title)
    fig.tight_layout()

    if output:
        fig.savefig(output, bbox_inches='tight')
    plt.show()
```

[33]:
```
metric = 'y1'
title = 'mCH_{}'.format(metric)

color_major = palette_cluster_types['orig_major']
color_sub = palette_cluster_types['orig_sub']
baseline_level = 0

plot_knn_cluster_level_metric(
                    metric, baseline_level,
                    knn_cluster_level_stats_alldatapairs_major['orig'],
                    knn_cluster_level_stats_alldatapairs_sub['orig'],
                    major_sub_lookup, metas[mod_j],
                    cluster_col_major, cluster_col_sub,
                    color_major, color_sub,
                    title=title,
                    output=output_figures.
↪format('plot_oversplit_cluster_level_{}'.format(title), 'pdf'))
```



0.0.6 Combining both metrics

[34]:
```
combined_metrics = []
metric_undersplit = 'slope25'
metric_oversplit = 'y1'

for datapair_type in ['orig', 'shuffled_major', 'shuffledCelllabel']:
    _df = cluster_level_info_major[
        ['clst_id', 'cluster_size', metric_undersplit+'_'+datapair_type]
        ].rename(columns={metric_undersplit+'_'+datapair_type:␣
↪metric_undersplit})

    _df2 = knn_cluster_level_stats_alldatapairs_major[datapair_type][
        ['clst_id', metric_oversplit]
    ]
    _df = pd.merge(_df, _df2, on='clst_id')
    if datapair_type.endswith('_major'):
        _df['cluster_type'] = datapair_type
    else:
        _df['cluster_type'] = datapair_type + '_major'
    combined_metrics.append(_df)

for datapair_type in ['orig', 'shuffled_sub', 'shuffledCelllabel']:
    _df = cluster_level_info_sub[
        ['clst_id', 'cluster_size', metric_undersplit+'_'+datapair_type]
        ].rename(columns={metric_undersplit+'_'+datapair_type:␣
↪metric_undersplit})

    _df2 = knn_cluster_level_stats_alldatapairs_sub[datapair_type][
        ['clst_id', metric_oversplit]
    ]
    _df = pd.merge(_df, _df2, on='clst_id')
    if datapair_type.endswith('_sub'):
        _df['cluster_type'] = datapair_type
    else:
        _df['cluster_type'] = datapair_type + '_sub'
    combined_metrics.append(_df)

combined_metrics = pd.concat(combined_metrics)
print(combined_metrics.shape)
combined_metrics.head()
```

```
(207, 5)
```

[34]:

```
          clst_id  cluster_size   slope25        y1 cluster_type
0   Exc_L1-3_CUX2           928  2.935345  0.317507   orig_major
1   Exc_L2-4_RORB           512  3.109375  0.281193   orig_major
2  Exc_L4-5_FOXP2           280  1.771429  0.129579   orig_major
3    Exc_L4-5_TOX            43  1.651163  0.421850   orig_major
4  Exc_L4-6_LRRK1           312  3.205128  0.295190   orig_major
```

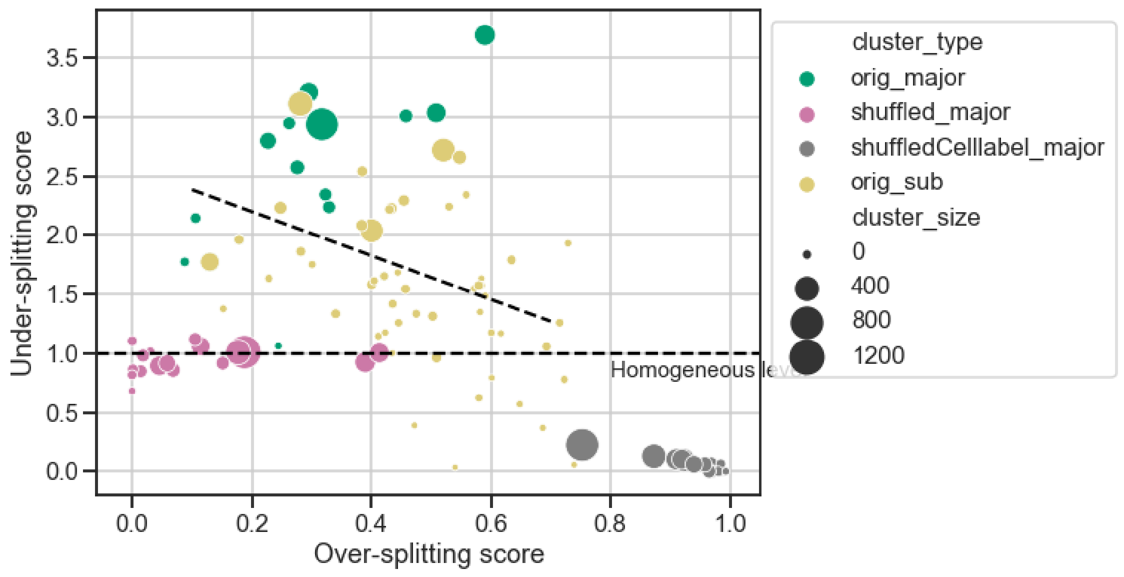
[35]:

```
# save combined metrics
combined_metrics.head()
f = './results/combined_metrics_{}.tsv'.format(name)
combined_metrics.to_csv(f)
```

[36]:

```
output = output_figures.format('plot_scatter_combined_metrics', 'pdf')
plot_types = ['orig_major', 'orig_sub', 'shuffledCelllabel_major',␣
↪'shuffled_major']
scale=0.8

fig, ax = plt.subplots(1, 1, figsize=(8*1,6))
sns.scatterplot(x=metric_oversplit, y=metric_undersplit,
                hue='cluster_type',
                size='cluster_size',
                sizes=(20,500),
#                 size_norm=(0, 1000),
                palette=palette_cluster_types,
                data=combined_metrics[combined_metrics['cluster_type'].
 ↪isin(plot_types)],
                ax=ax)
ax.axhline(1, linestyle='--', color='black')
ax.text(0.8, 0.8, 'Homogeneous level', fontsize=15)

x = combined_metrics[combined_metrics['cluster_type'].isin(['orig_major',␣
 ↪'orig_sub'])]
_x = x[metric_oversplit]
_y = x[metric_undersplit]
k, b, r, p, stderr = stats.linregress(_x, _y)
print(k, b, r, p)
_x = np.linspace(0.1, 0.7, 10)
_y = k*_x + b
ax.plot(_x, _y, linestyle='--', color='k')

ax.set_xlabel('Over-splitting score')
ax.set_ylabel('Under-splitting score')
# ax.set_xlim([-0.02, 1.02])
# ax.set_ylim([-0.02, 1.02])
ax.legend(bbox_to_anchor=(1,1),)
fig.savefig(output, bbox_inches='tight')
plt.show()
```

```
-1.8520831682593943 2.566115875484746 -0.3948105828698815 0.000787577406678902
```


Under-splitting score
Over-splitting score
Homogeneous level
cluster_type
orig_major
shuffled_major
shuffledCelllabel_major
orig_sub
cluster_size