Bioinformatics III

Second Assignment

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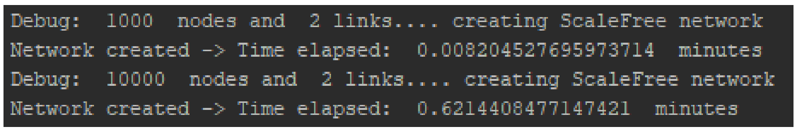
Exercise 2.1: The Scale-Free network

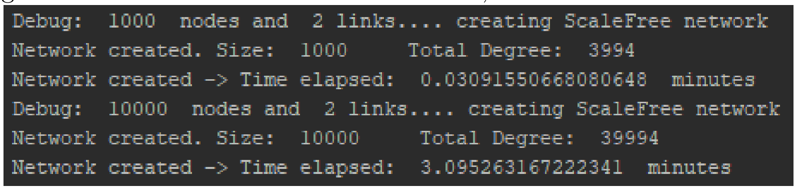
(a) *Implement the algorithm given in the lecture to set up a scale-free network according to the Barabási-Albert model (see Lecture 2, slide 8). Start from the first three connected nodes and add each new node with a given number of links. Connect the new links with increasing preference to nodes that have higher degrees. This ScaleFreeNetwork-class should again use the abstract network class that you wrote in the first assignment. To obtain a much faster implementation and full points, think of a method to map the probabilities to connect to nodes somehow instead of computing them from scratch in each iteration.*

Note: We first generated the probability distribution en each iteration and use the function *random.choices(pop, prob)* to select a node according to its probability (Method 1). After an intense reflection and the understanding of what what said during the tutorial, we tried a second option (Method 2) commented in the listing 1. The benchmark below (figure 2) shows that the first option seems more time-efficient.



```
Debug:  1000  nodes and  2 links.... creating ScaleFree network
Network created -> Time elapsed:  0.008204527695973714  minutes
Debug:  10000  nodes and  2 links.... creating ScaleFree network
Network created -> Time elapsed:  0.6214408477147421  minutes
```

Figure 1: Time of execution with method 1, with 1000 and 10'000 nodes



```
Debug:  1000  nodes and  2 links.... creating ScaleFree network
Network created. Size:  1000     Total Degree:  3994
Network created -> Time elapsed:  0.03091550668080648  minutes
Debug:  10000  nodes and  2 links.... creating ScaleFree network
Network created. Size:  10000     Total Degree:  39994
Network created -> Time elapsed:  3.095263167222341  minutes
```

Figure 2: Time of execution with method 2, with 1000 and 10'000 nodes

Implementation of the missing methods for the ScaleFreeNetwork-class. Listing 1 shows source code of ScaleFreeNetwork.py.

Listing 1: ScaleFreeNetwork.py

```
#Bioinformatics 3 : Wiebke Schmitt & Thibault Schowing
import random
from Node import Node
from AbstractNetwork import AbstractNetwork
class ScaleFreeNetwork(AbstractNetwork):
    """Scale-free network implementation of AbstractNetwork"""



    def __createNetwork__(self, amount_nodes, amount_links):
        """
        Create a network with an amount of n nodes, add m links per iteration
            step
        for n nodes:
            for m links:
                link node to other nodes
        """

        def symetricConnection(node1, node2):
            node1.addLinkTo(node2)
            node2.addLinkTo(node1)

        random.seed()
        print("Debug: ", amount_nodes, " nodes and ", amount_links, "links....
            creating ScaleFree network")

        # Initial m0 nodes connected to each other
        m0 = 3

        # Create Nodes
        for i in range(0, m0):
            self.appendNode(Node(i))

        # Connect Nodes to each other
        for i in range(0,amount_links):
            for j in range(i+1, m0):
                symetricConnection(self.getNode(i), self.getNode(j%3))


        # Method 1
        # In a first attempt we used the code below.


        def genProbList():
            prob_list = []
            sumkj = self.degreeSum()

            for key, node in self.nodes.items():
                ki = node.degree()
                prob_list.append(ki / sumkj)
            return prob_list


        # new nodes id (without the 3 initial nodes)
        for new_node_id in range(3, amount_nodes - 3):

            new_node = Node(new_node_id)
            self.appendNode(new_node)

            population = list(range(0, self.size()))

            # Generate probability list of existing nodes
            prob_list = genProbList()

            for i in range(amount_links):
                while(True):
                    # choose the neighbour according to its probability
                    chosen_neighbour = random.choices(population, weights=
                        prob_list, k = 1)[0]

                    # if it's a new link and it's not a self-connection
                    if not new_node.hasLinkTo(chosen_neighbour) and not
                        chosen_neighbour == new_node.id:

                        symetricConnection(new_node, self.getNode(
                            chosen_neighbour))
                        break


        # Method 2
        # In a second attempt, we used the code below
        # # the initial network contains 3x2 links
        # network_degree = 6

        # # next node ID
        # id = 3
        #
        # while id < amount_nodes:
        #     #print("debug: id", id)
        #     new_node = Node(id)
        #     self.appendNode(new_node)
        #
        #     # For each new node, reset the amount of links to 2 (in our case
            )
        #     remaining_links = amount_links
        #
        #     while remaining_links:
        #         #print("debug remaining linkl: ",remaining_links)
        #         # we randomly chose a node in the network
        #         rand_node = random.choice(self.nodes)
        #
        #         # The node must not be already connected or be == to
            new_node
        #         if(id != rand_node.id and not rand_node.hasLinkTo(new_node))
            :
        #             # The node probability according to its degree and the
            total network's degree
        #             node_prob = rand_node.degree() / network_degree
        #
        #             # Now we create a random number (uniform between [0,1[ )
        #             # If the probability of the node is bigger than the
            random probability, we can connect them
        #             random_prob = random.random()
        #             #print("debug node prob ", node_prob, "  random_prob  ",
             random_prob)
        #
        #             if(node_prob > random_prob):
        #                 rand_node.addLinkTo(new_node)
        #                 new_node.addLinkTo(rand_node)
        #
        #                 # Now we directly update the network's total degree
        #                 network_degree += 2
        #
        #                 #... and substract the number of link we need to
            create for the new node
        #                 remaining_links -= 1
        #
        #     # This node is done, it's time for the next one
        #     id += 1
        #
        # print("Network created. Size: ", len(self.nodes), "    Total Degree:
             ", network_degree)
```

(b) *Determine the degree distributions for scale-free networks of 10 000 and 100 000 nodes (each with two new links per iteration), respectively, and plot them with double logarithmic axes. A new pre-implemented method in Tools.py will help you with that. What are the differences? Next, compare one of the distributions to the degree distribution of an equally sized random network (play around with the plot-scaling). What are the major differences?*

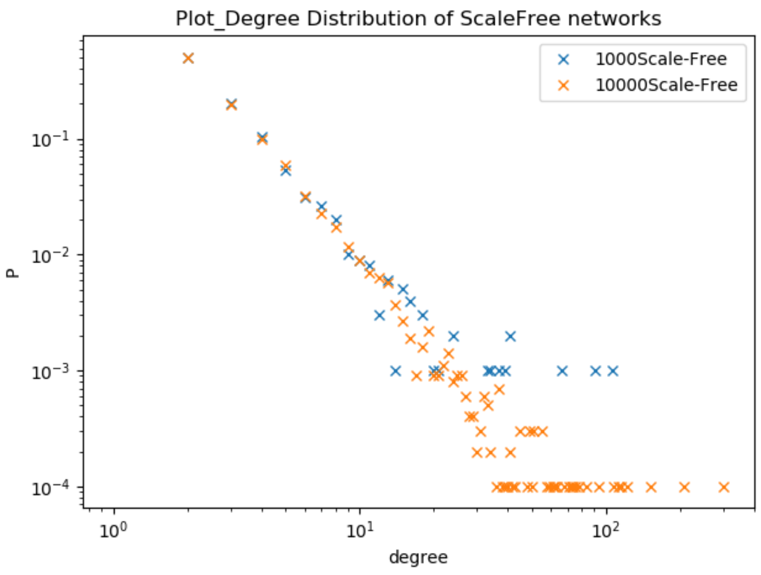


Figure 3: Two scale-free network, one with 10000 nodes and one with 100000 nodes.

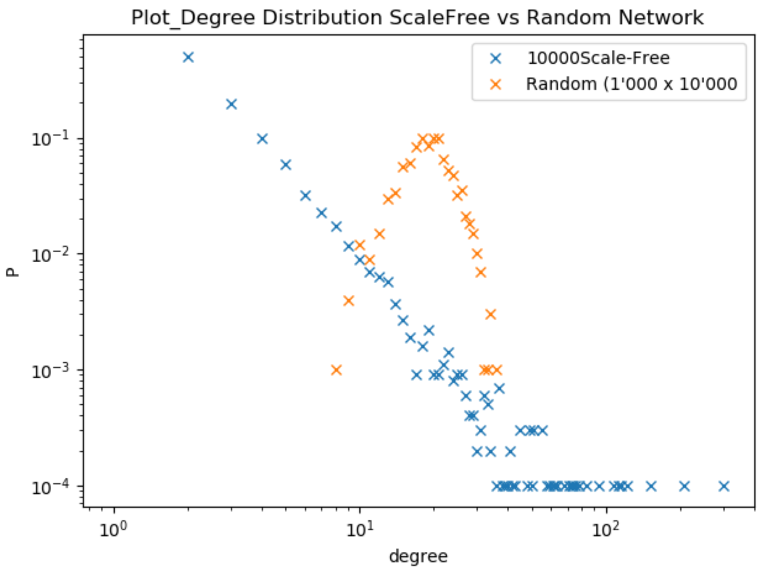


Figure 4: We can observe that the Scale-Free distribution follow a power-law style, as it is almost a straight line when plotted with log-log axes. On the other hand, the random network is more Poisson distributed as seen in Assignment 1.

Listing 2: ScaleFreeTest.py

```
#!/usr/bin/python
#Bioinformatics 3 : Wiebke Schmitt & Thibault Schowing
from ScaleFreeNetwork import ScaleFreeNetwork
from DegreeDistribution import DegreeDistribution
from RandomNetwork import RandomNetwork
import time
import matplotlib.pyplot as plt
import Tools as Tools


if __name__== "__main__":

    # TASK 2.1 a AND b
    # Number of nodes and link per node
    SMALL = 1000
    BIG = 10000
    NB_LINK = 2

    # Create first network
    time1 = time.time()
    sf_net = ScaleFreeNetwork(SMALL,NB_LINK)
    time2 = time.time()
    print("Network created -> Time elapsed: ", (time2 - time1)/60, " minutes")

    # Create second network
    time1 = time.time()
    sf_net2 = ScaleFreeNetwork(BIG,NB_LINK)
    time2 = time.time()
    print("Network created -> Time elapsed: ", (time2 - time1)/60, " minutes")

    # Create random network
    rand_net = RandomNetwork(1000, 10000)

    # Network's normalized distributions
    sf_degree = DegreeDistribution(sf_net).getNormalizedDistribution()
    sf_degree2 = DegreeDistribution(sf_net2).getNormalizedDistribution()
    rand_degree = DegreeDistribution(rand_net).getNormalizedDistribution()

    # Plot the degree distributions
    # Small vs Big scale-free network
    legend1 = str(SMALL) + "Scale-Free"
    legend2 = str(BIG) + "Scale-Free"
    Tools.plotDistributionComparisonLogLog([sf_degree, sf_degree2],[legend1,
        legend2], "Plot Degree Distribution of ScaleFree networks")

    # Big scale-free vs random network
    Tools.plotDistributionComparisonLogLog([sf_degree2, rand_degree], [legend2
        , "Random (1'000 x 10'000"],"Plot Degree Distribution ScaleFree vs 
        Random Network")

    # TASK 2.1 c
    # reuse sf_net2 (BIG)
    sf_net_c = sf_net2
    sf_net_c_degree = DegreeDistribution(sf_net_c).getNormalizedDistribution()

    k = len(sf_net_c_degree)

    gamma_distance = []

    # Foreach gamma, calculate the KS distance
    steps = [x * 0.1 for x in range(10, 30)]
    for gamma in steps:
        theoretical_dist = Tools.getScaleFreeDistributionHistogram(gamma, k)
        distance = Tools.simpleKSdist(theoretical_dist, sf_net_c_degree)
        gamma_distance.append((gamma, distance))
    # Sort the distances-gamma tuples
    gamma_distance.sort(key=lambda x: x[1], reverse=False)

    print("All gamma-distance: ", gamma_distance)
    print("Best gamma: ", gamma_distance[0][0])

    # Optimal theoretical distribution (powerlaw) with the best gamma
    optimal_theoretical = Tools.getScaleFreeDistributionHistogram(
        gamma_distance[0][0], k)
    Tools.plotDistributionComparisonLogLog([sf_net_c_degree,
        optimal_theoretical], ["Scale Free Network" + str(BIG), 'PowerLaw'],'
        Plot Compare theory to practice')
```

(c) *The degree distribution of a scale-free network follows a power law, which has the form $P(k)\ k^{-\lambda}$ To simplify the exercise, we assume $P(k)\ Ck^{-\lambda}$ with C being a fixed normalization constant to obtain a proper distribution. Try to fit this theoretical distribution to the degree distribution of a random network using the Kolmogorov-Smirnov distance.*

Listing 3: Tools.py

```
import matplotlib.pyplot as plt
import math
from itertools import accumulate


def plotDistributionComparison(histograms, legend, title):
    '''
    Plots a list of histograms with matching list of descriptions as the
        legend
    '''
    # determine max. length
    max_length = max(len(x) for x in histograms)

    # extend "shorter" distributions
    for x in histograms:
        x.extend([0.0]* (max_length-len(x)) )

    # plots histograms
    for h in histograms:
        plt.plot(range(len(h)), h, marker = 'x')

    # remember: never forget labels!
    plt.xlabel('degree')
    plt.ylabel('P')

    # you don't have to do something stuff here
    plt.legend(legend)
    plt.title(title)
    plt.tight_layout()
    plt.show()


def plotDistributionComparisonLogLog(histograms, legend, title):
    '''
    Plots a list of histograms with matching list of descriptions as the
        legend
    '''
    fig = plt.figure()
    ax = plt.subplot()
    # determine max. length
    max_length = max(len(x) for x in histograms)

    # extend "shorter" distributions
    for x in histograms:
        x.extend([0.0]* (max_length-len(x)) )

    ax.set_xscale("log")
    ax.set_yscale("log")

    # plots histograms
    for h in histograms:
        ax.plot(range(len(h)), h, marker = 'x', linestyle='')

    # remember: never forget labels!
    plt.xlabel('degree')
    plt.ylabel('P')

    # you don't have to do something stuff here
    plt.legend(legend)
    plt.title(title)
    plt.tight_layout()

    # Uncomment the line below to display normally
    # plt.show()

    # Comment the 2 lines below to display normally
    filename = title + ".png"
    fig.savefig(filename)


def getScaleFreeDistributionHistogram(gamma, k):
    '''
    Generates a Power law distribution histogram with slope gamma up to degree
        k
    '''
    histogram = []
    # NORMALISATION_CONSTANT \
    # Todo here or in ScaleFreeTest.py

    for i in range(1, k+1):
        histogram.append(i**-gamma)

    #Normalisation

    norm_hist = [i / sum(histogram) for i in histogram]

    return norm_hist


def simpleKSdist(histogram_a, histogram_b):
    '''
    Simple Kolmogorov-Smirnov distance implementation
    '''
    histograms = [histogram_a,histogram_b]

    max_len = max(len(x) for x in histograms)

    for x in histograms:
        x.extend([0.0] * (max_len - len(x)))

    for i in range(0, 2): # accumulative distribution
        histograms[i] = list(accumulate(histograms[i]))

    ksdist = []

    for i in range(max_len):
        ksdist.append(abs(histogram_a[i] - histogram_b[i]))

    return max(ksdist)
```

Use the KS distance to determine a γ (between 1 and 3, 0.1 steps sufficient) that fits best to the degree distribution of a scale-free network with 10 000 nodes and two new links per iteration. Compare the empirical distribution of the network to the theoretical distribution with optimal γ in a double-log. plot. Comment on the quality of your fit, reason why it may *fail and how it could be vastly improved.*

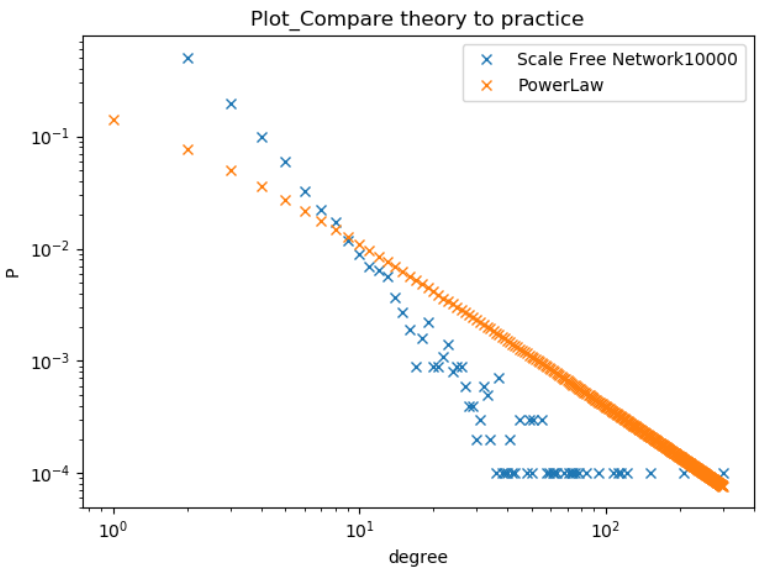


Figure 5: We can see that the theoretical distribution fits the Scale-Free network like linear regression. This doesn't get the information that really few nodes will have high degrees. By fitting the Power-Law distribution only to the lower-degree nodes (consider big hubs as outliers), the power-law would fit the distribution more accurately, at least for the first part. The higher degree nodes would fit a more linear function.

Exercise 2.2: Classify real-world network examples

(a) File sharing services

The two first listed services, Megaupload and Rapidshare, are more server oriented. The servers host the content, and the client download it. This is more like a scale-free network with a few big central servers around the world (so also like a clustered-network). About directions, each client can upload and download files (media like music and movies are certainly the most famous example). Of course, people uploading files are rarer than people downloading the contend. The traffic, so the directions, are more oriented from the hubs to the leaves/final client.

(b) Social networks

These are undirected networks. Two people are friends or not, but there is no directionality to the relation. A social network can be considered to be a scale-free network, because people with many friends are more likely to make new friends than people who are not as active socially. It can therefore also be considered to be a clustered network, because there tend to be people that are much more connected than others for geographical reasons.

(c) Broadcasting networks

This is hierarchical networks. Main TV/Radio companies send contents over cables or satelite connexion. For cables, city-relays, neighbourhood-relays or other structure can transmit the information stream from the central node, to the final one (TV or radio). The signal is directed from the broadcasting company to the client, so is the network.

Exercise 2.3: Real interaction networks

(a) Here is the implementation of the BioGRIDReader-class

Listing 4: BioGRIDReader.py

```
import operator
from GenericNetwork import GenericNetwork
from DegreeDistribution import DegreeDistribution
import Tools as Tools

class BioGRIDReader:
    '''Reads BioGRID tab files'''
    def __init__(self, filename):
        '''
        Initialization, read in file and build any data structure that makes
            you happy
        '''

        content_start = False

        # Temporary tab -> contains one line
        line_tab = []

        self.INTERACTOR_A = []
        self.INTERACTOR_B = []
        self.OFFICIAL_SYMBOL_A = []
        self.OFFICIAL_SYMBOL_B = []
        self.ALIASES_FOR_A = []
        self.ALIASES_FOR_B = []
        self.EXPERIMENTAL_SYSTEM = []
        self.SOURCE = []
        self.PUBMED_ID = []
        self.ORGANISM_A_ID = []
        self.ORGANISM_B_ID = []

        with open(filename, "r") as f:
            for line in f:
                if line.startswith("INTERACTOR_A"):
                    content_start = True
                    continue
                if content_start:
                    # Process data
                    line = line.rstrip()
                    line_tab = line.split('\t')

                    self.INTERACTOR_A.append(line_tab[0])
                    self.INTERACTOR_B.append(line_tab[1])
                    self.OFFICIAL_SYMBOL_A.append(line_tab[2])
                    self.OFFICIAL_SYMBOL_B.append(line_tab[3])
                    self.ALIASES_FOR_A.append(line_tab[4])
                    self.ALIASES_FOR_B.append(line_tab[5])
                    self.EXPERIMENTAL_SYSTEM.append(line_tab[6])
                    self.SOURCE.append(line_tab[7])
                    self.PUBMED_ID.append(line_tab[8])
                    self.ORGANISM_A_ID.append(line_tab[9])
                    self.ORGANISM_B_ID.append(line_tab[10])

        # The file has now been read and all infos are in lists
        # Tuples can store pairwise interactions



    def getMostAbundantTaxonIDs(self, n):

        interact = {}
        organism_pairs_list = zip(self.ORGANISM_A_ID, self.ORGANISM_B_ID)

```

```python
        for A, B in organism_pairs_list:
            if not A in interact:
                interact[A] = 1
            else:
                interact[A] += 1

            # If both are the same, the interaction must be counted only once
            if A != B:
                if not B in interact:
                    interact[B] = 1
                else:
                    interact[B] += 1
        # Sort the dict to retrieve the n first
        # https://stackoverflow.com/questions/613183/how-do-i-sort-a-
            dictionary-by-value

        sorted_interact = sorted(interact.items(), key=operator.itemgetter(1))


        nFirst = []
        for i in range(1, n+1):
            nFirst.append(sorted_interact[-i])

        return nFirst

    def getHumanInteraction(self):
        # Search for human-human interactions
        nb_human_human_interact = 0

        organism_pairs_list = zip(self.ORGANISM_A_ID, self.ORGANISM_B_ID)
        for A, B in organism_pairs_list:
            if A == B == "9606":
                nb_human_human_interact += 1

        print("HUMAN_INTERACTIONS\n")
        print("\nNumber of Human-Human interactions (human_id = 9606): ",
            nb_human_human_interact)

        # Now we need the indices of the human - human interactions
        # The code below extract the indices where ORGANISM A / ORGANISM B are
             human and take the intersection
        # Order dict: https://stackoverflow.com/questions/16772071/sort-dict-
            by-value-python

        # Get Indexes
        indexesA = [i for i, x in enumerate(self.ORGANISM_A_ID) if x == '9606'
            ]
        indexesB = [i for i, x in enumerate(self.ORGANISM_B_ID) if x == '9606'
            ]

        # Get intersection
        indexes = list(set(indexesA).intersection(indexesB))

        proteins = [self.OFFICIAL_SYMBOL_A[i] for i in indexes]
        proteins.extend([self.OFFICIAL_SYMBOL_B[i] for i in indexes])

        proteins_count = {}
        for prot in proteins:
            if prot not in proteins_count:
                proteins_count[prot] = 1
            else:
                proteins_count[prot] += 1
        proteins_count = sorted(proteins_count.items(), key=lambda x:x[1])

        # Obtain the n most used proteins
        n = 10
        nFirst = []
        for i in range(1, n + 1):
            nFirst.append(proteins_count[-i])

        print("\nThe ", n, " proteins with the highest degree are: ")
        print(nFirst)

    def writeInteractionFile(self, taxon_id, filename):

        organism_pairs_list = zip(self.ORGANISM_A_ID, self.ORGANISM_B_ID)
        file = open(filename, "w+")

        # Get Indexes
        indexesA = [i for i, x in enumerate(self.ORGANISM_A_ID) if x ==
            taxon_id]
        indexesB = [i for i, x in enumerate(self.ORGANISM_B_ID) if x ==
            taxon_id]

        # Get intersection
        indexes = list(set(indexesA).intersection(indexesB))

        for i in indexes:
            file.write(self.OFFICIAL_SYMBOL_A[i])
            file.write("\t")
            file.write(self.OFFICIAL_SYMBOL_B[i])
            file.write("\n")

        file.close()


if __name__== "__main__":

    path = "../../../../Bioinformatics3_data/assignment2/BIOGRID-ALL-3.4.159.
        tab.txt"
    bio = BioGRIDReader(path)
    abundantTaxon = bio.getMostAbundantTaxonIDs(5)
    print("The most abundent TaxonIDs are (id, qty): ", abundantTaxon)
    bio.getHumanInteraction()

    # Export human interactions to a file
    EXPORT_FILE_NAME = "humanFile.txt"
    EXPORT_ORGANISM = "9606"
    bio.writeInteractionFile(EXPORT_ORGANISM, EXPORT_FILE_NAME)

    # Create GenericNetwork with previously exported file
    gen = GenericNetwork(EXPORT_FILE_NAME)
    print(str(gen))
    print("The network has ", gen.degreeSum(), " links.\n")

    # Get distribution
    gen_degree = DegreeDistribution(gen).getNormalizedDistribution()
    # Plot the degree distribution
    Tools.plotDistributionComparisonLogLog([gen_degree], ["Human's proteins 
        interactions"],"Plot Degree Distribution Generic Network ")
```

(b) The class getMostAbundantTaxonIDs(n) is listed in the listing 4 above.

The most abundent TaxonIDs are (id, qty): [('559292', 704012), ('9606', 414501), ('316407', 184023), ('284812', 72149), ('7227', 67935)]

- 559292: Saccharomyces cerevisiae (Baker's Yeast)
- 9606: Human (Homo sapiens)
- 316407: Escherichia coli
- 284812: Schizosaccharomyces pombe (Fission yeast)
- 7227: Drosophila melanogaster

(c) *How big is the human interaction network and which are the 10 proteins with the highest degree? Take one of them as an example and briefly explain the biology behind the connectivity.*

Number of Human-Human interactions (human id = 9606): 386192

The 10 proteins with the highest degree are: [**('TP53', 3024), ('TRIM25', 2559), ('APP', 2454), ('EGFR', 2134), ('UBC', 2042), ('NTRK1', 2002), ('MDM2', 1939), ('BRCA1', 1876), ('ELAVL1', 1840), ('HDAC1', 1646)**]

The gene/protein P53 is the most present in the data. The protein's full name is "Cellular Tumor Antigen p53". "p53 has many mechanisms of anticancer function and plays a role in apoptosis, genomic stability, and inhibition of angiogenesis."[1] This protein interacts with many cellular processes and thus, has many interactions with many other genes/proteins.

In our case, the human interaction network has **17087** nodes and **772384** links.

(d) Generic network distribution and implementation

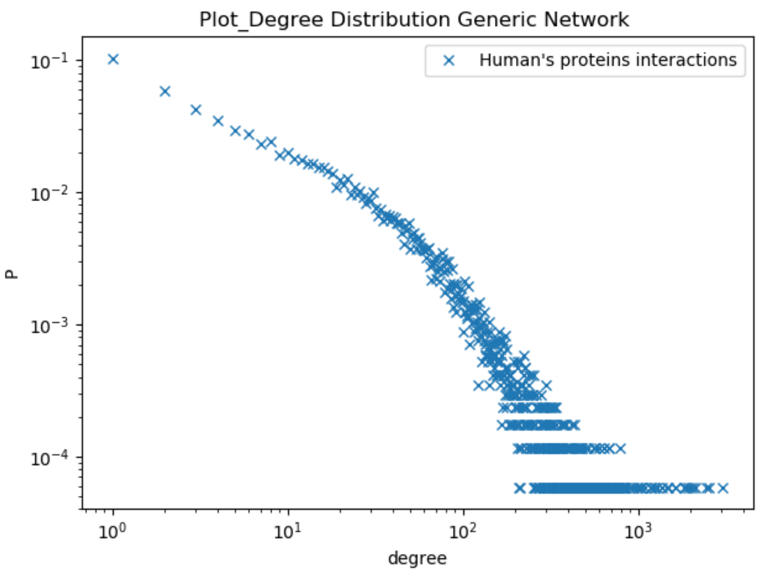


Figure 6:

Figure 7:

Listing 5: GenericNetwork.py

```
from AbstractNetwork import AbstractNetwork
from Node import Node

# from standard library module
from itertools import islice
import sys

class GenericNetwork(AbstractNetwork):


    def __init__(self, filename):
        """
```

[1] https://en.wikipedia.org/wiki/P53

```
        Create a network from a file
        """

        self.nodes = {}
        # We first need to create all Nodes (unique)
        allEntries = []
        pairs = []
        with open(filename) as f:

            # Run through the entire file to make a set of entries
            for line in f:
                line = line.rstrip()
                line_tab = line.split('\t')
                pairs.append(line_tab)
                allEntries.extend(line_tab)

            allUniqueEntries = set(allEntries)
            for n in allUniqueEntries:
                self.appendNode(Node(n))

            for pair in pairs:
                self.getNode(pair[0]).addLinkTo(self.getNode(pair[1]))
                self.getNode(pair[1]).addLinkTo(self.getNode(pair[0]))
```