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ASSORTATIVITY OF AGING KEY PLAYERS IN THE DYNAMICAL NETWORKS

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Abstract: Human aging is the main social and medicinal challenge where it is one of the factors lead to disease. Understanding the process will be advantageous in the drugs and medicinal fields. In this study, we analyze the process through dynamic protein-protein interaction (PPI) networks by observing the topological changes of the network across ages. The dynamic networks consist of 14 ages, they are within 80 – 99 years, where we call aging-related protein networks. In each of the network, we analyzed the property of assortativity as proposed by recent study. Assortativity in PPI network is a measure to quantify the tendency of proteins to communicate with other similar proteins in the network. However, recent study proposes local assortativity for individual nodes in the network. Consequently, we are able to analyze the characteristics of aging network; i) Aging-related protein networks are disassortative with positive non-linear local assortativity, ii) there are strong and weak assortative key-players, iii) assortative key players are not close to all proteins in aging network, and iv) assortative hubs decrease the robustness of the networks.

Keywords: local assortativity; aging; dynamic network.

2010 AMS Subject Classification: 92B20.

1. INTRODUCTION

Aging is a phenomenon in all living things and a fundamental biological process across a life span.

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Aging process continues from younger to older people as many factors contribute to accelerate or decelerate the process. However, this biological process is poorly understood and therefore, aging-related genes gain more attraction from academician and medicinal field. Studies on aging in recent years are highly increasing as the awareness of relation of disease and aging are connected and therefore will be advantageous in the drugs and medicinal fields. Aging is a process where organs and tissues in our body physiologically lose its integrity where our body starts to lose coordination between parts and the systems begin to malfunction over time [1]. Aging consist of strong genetic components [2] and therefore understanding of aging through protein-protein interaction (PPI) network representation is very helpful to understand the aging process through network topology. In this study, we employ the older ages of 80 years until 99 years as the obvious aging process happen in these ages. This is due to the facts that half of all people aged 80 years will suffer from frailty where they experienced low physical activity, low social interactions and several chronic diseases that needs medical attention [3].

In biological system, proteins interact with each other to carry out their functions. According to this feature of proteins, it is necessary for us to study the assortativity of the network as to observe the tendency of individual protein to connect with similar protein [4]. Assortativity is defined as the tendency of an individual node to connect or link with other nodes that shares similar property in term of degree [5 – 7] based on degree-degree correlation of the nodes [6, 7]. The network with positive correlation coefficient indicate that the network is assortative while negative correlation indicate the disassortativity of the network [7]. Assortative network consist of high degree nodes connected with high degree nodes and vice versa while disassortative network consist of high degree nodes connected with low degree nodes [28]. Recently, as the assortativity is a quantity of network, a few studies have introduced local assortativity of nodes in the network where the nodes can also exhibit assortative or disassortative tendencies [8].

In rich-club phenomena, the highly connected nodes tend to connect with other highly connected nodes not automatically imply the network is assortative because the high degree nodes can either be connected assortatively or disassortatively [8]. Therefore, Piraveenan et al. proposed local assortativity which measures the impact of each nodes to the network assortativity [9]. In this paper, we aim to investigate the local assortativity of aging key-players protein in the dynamical network.

A network commonly used as a representation of a complex systems, social, technological, and biological systems. In biological systems such as PPI network, nodes represent proteins while their connections represent interaction between proteins. Correlation of proteins is an approach to

characterize the structure of the network. The correlation also known as assortative mixing [4]. This approach allows us to observe the behavior of the network assortativity.

Assortativity has been defined as a tendency of nodes to connect with other similar nodes. Therefore, a social network tends to be assortative because the connections between friends with similar background, while a food web tends to be disassortative as predator connects to prey. However, the social network could be either assortative or disassortative depends on the specific interest. Film actors network could be assortative as they collaborate with other actors in the same movie, but people dating network could be disassortative as they date with an opposite gender. Therefore, in this case of assorativity, it is specified that the similar property of nodes are referring to the degree centrality of the nodes [10].

Network assortativity, *r* of most real world networks are globally disassortative with negative value [11]. The positive value of *r* indicate the network is globally assortative. Study by Piraveenan et al. (2009) shows that there are two types of disassortative classes of real world networks that have been identified, i) networks that have assortative hubs and non-linear local assortative profiles and ii) networks that have disassortative hubs and linear-local assortative profiles [11]. However, study by Piraveenan et al. (2010) in their paper of unbiased local assortativity, emphasized that there are four classes of complex networks. They are; i) assorttative network with assortative hubs, ii) assortative network with disassortative hubs, iii) disassortative network with disassortative hubs and iv) disassortative network with assortative hubs [7]. Biological network such as PPI network falls into the category of assortative network with disassortative hubs while most of metabolic network is assortative network with assortative hubs [7]. Fig. 1 shows the hubs are locally assortative in human PPI network while Fig. 2 shows the hubs are locally disassortativity in Internet AS network.

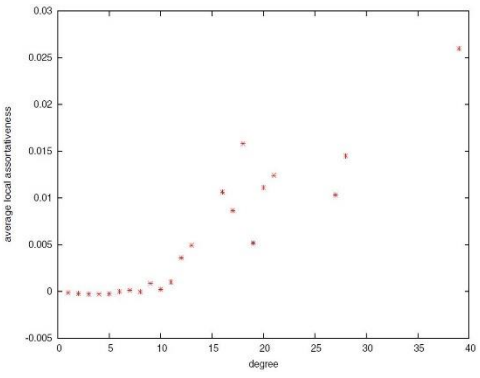


Fig. 1. Local assortativity distribution of H. Sapien (human) PPI network [11].

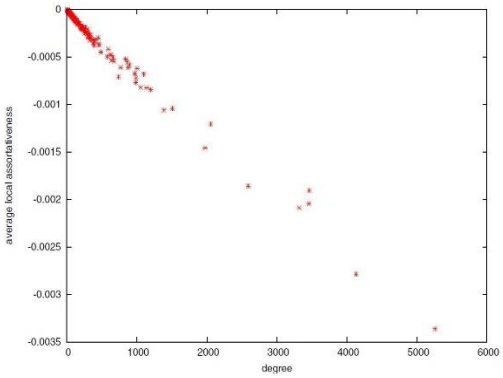


Fig. 2. Local assortativity distribution of Internet at the AS level, in 2007, December [11].

Assortativity coefficient is commonly used to evaluate the assortativity [4] by measuring the average mixing pattern of the network. The single measure is insufficient to characterize heterogeneous network [12], therefore recent study proposed the calculation of assortativity for individual nodes as it would be meaningful to observe the characteristics for each nodes. In this study, we employ the local assortativity to aging-related proteins network for further understanding of aging through dynamical network.

2. MATERIALS AND METHODS

2.1 Data Sources

2.1.1 Aging-related gene expressions data

We use a microarray human brain gene expression data set containing 173 samples from 55 individuals, with 14 different ages from 80 until 99 years [13].

2.1.2 PPI data set

Human PPI data set is obtained from Database of Interacting Protein (DIP) consist of 7794 PPI with self-interactions as downloaded on 31/7/2016 [14]. However, after considering the unique protein with no self-interactions, the number of PPI reduced to 7285. The ID used in this study is uniprot kb.

2.2 Development of Dynamical Network

Microarray human brain gene expression data is obtained via Affymetrix Hg-U133plus 2.0 microarray experiments using 54675 probes in each individual sample. The probe is then converted into protein id using uniprot mapping ids for mapping the probes into PPI network. Detection of p-value < 0.04 is used to determine status (Present/Absent) of the probe [15] using Negative Probesets (PANP) in R software package [16]. Based on majority vote rule, gene m will be considered as expressed at age n if more than 50% of $x \times y$ probes are found to be expressed at age n (or at least $\frac{x \times y}{2} + 1$ probes) [17]. Fig. 3 illustrate the integration of static PPI with gene expression data. Dynamic network in this study consist of 14 subnetworks. Size of each network is within range of 913 – 1156 interactions with 883 – 1027 proteins.

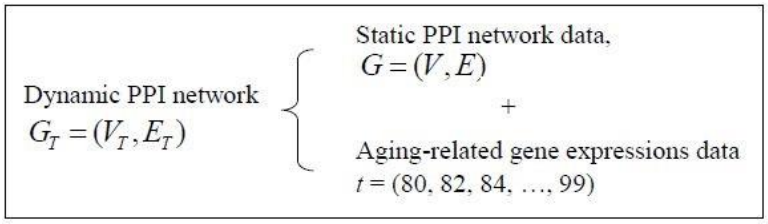


Fig. 3. Integration of gene expressions data with static PPI data.

2.3 Network Assortativity

Assortativity of a network has been defined as correlation function [4],

$$r = \frac{1}{\sigma_q^2}\left[\sum_{jk} jk(e_{j,k} - q(j)q(k))\right] \tag{1}$$

where $e_{j,k}$ is the link distribution of network while $q(k)$ is the network's excess degree distribution and σ_q is the standard deviation of the network excess degree distribution.

2.4 Local Assortativity

LA of a protein is defined as

$$LA(v) = \frac{j(j+1)(\bar{k} - \mu_q)}{2n\sigma_q^2} \tag{2}$$

where $\bar{k}$ is the remaining degree of node's neighbor, n is the number of links in the network, μ_q and σ_q are the mean and standard deviation of remaining degree distribution of a network while $q(k)$ is given by

$$q(k) = \frac{(k+1)p(k+1)}{\sum_j jp(j)} \tag{3}$$

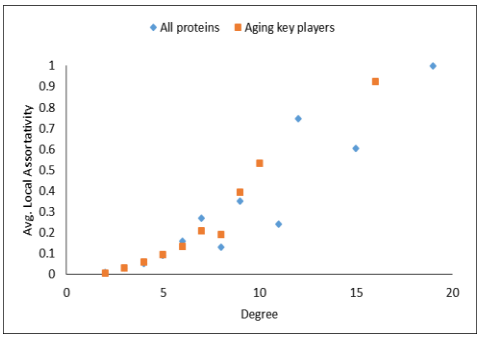
where j and is the excess degrees of protein v while k is the excess degree of protein v's neighbor [7].

3. RESULT AND DISCUSSION

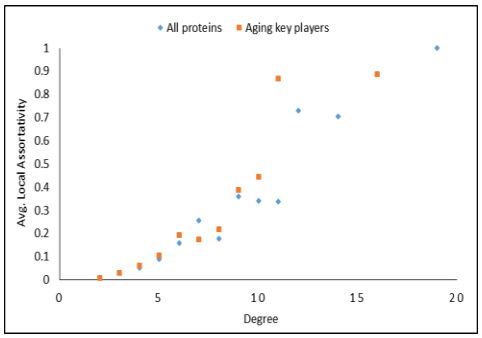
Some of the PPI networks show a different kind of assortativity. For example, essential proteins in baker's yeast are locally disassortative where the local assortativity and protein's degree have a negative correlation. However, essential proteins in *Escherichia coli* and *Drosophila melanogaster* are locally assortative [5]. In this study, proteins in aging-related protein networks are locally assortative as the average local assortativity of proteins are positively correlated with the degree as shown in Fig. 4. The local assortativity of all networks show the characteristics of proteins where there is a higher density of connections among hubs and vice versa. Therefore, the aging key-player proteins have been observed and studied for further understanding of aging process through dynamical network.

3.1 Assortativity of Dynamical Networks

Study by Piraveenan et al. shows that real world networks are divided into four classes of assorativity [7]. In this study, we show that aging-related protein networks have characteristics of disassortative with proportional non-linear local assortative profiles. The aging-related protein networks are disassortative with negative value of r = -0.0713 to -0.0254 where the proteins have correlations between other dissimilar degree characteristic to carry out their functions, as some of the proteins are involved in the formation of variety different protein complexes. In context of aging, aging key-players protein play an important role that contribute to the disassortativity of the network in communications among different functional modules as studied by Zhang et al. [18].



(a)



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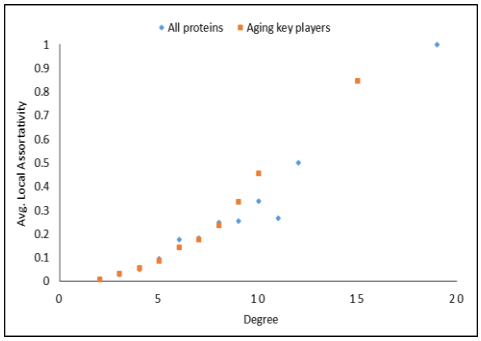
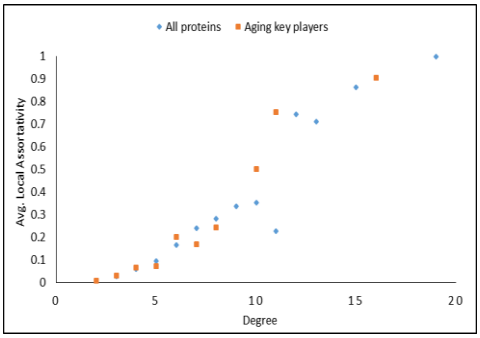
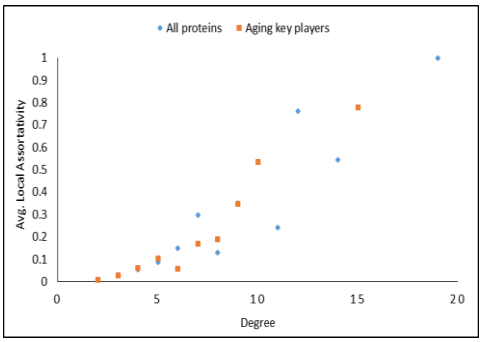

All proteins
Aging key players
Avg. Local Assortativity
Degree

(c)


All proteins
Aging key players
Avg. Local Assortativity
Degree

(d)


All proteins
Aging key players
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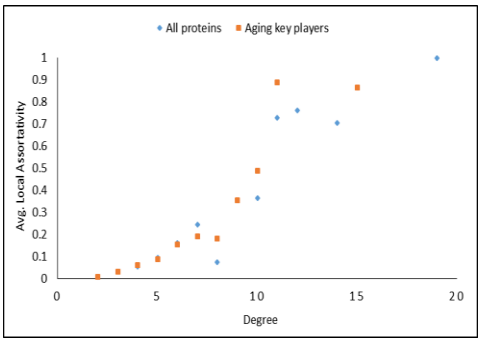
All proteins
Aging key players
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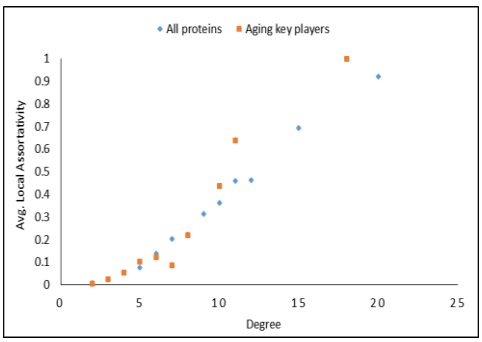
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Aging key players
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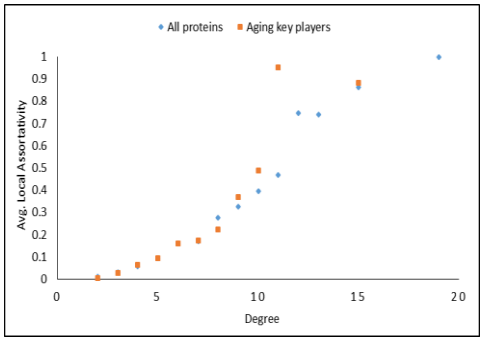
All proteins
Aging key players
Avg. Local Assortativity
Degree

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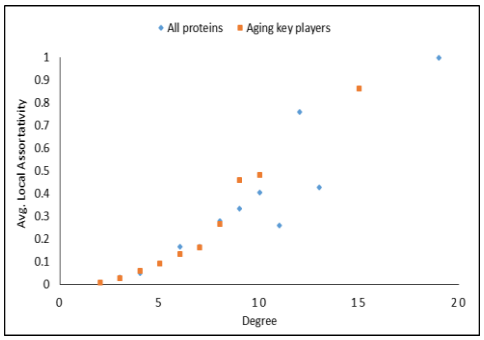
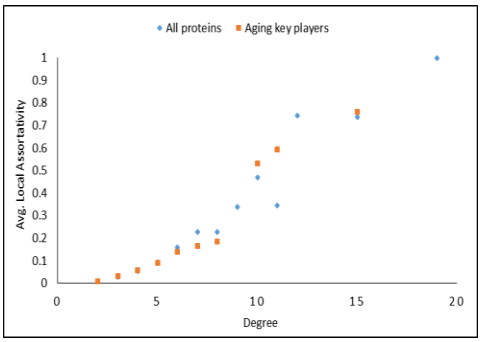

All proteins
Aging key players
Avg. Local Assortativity
Degree

(i)


All proteins
Aging key players
Avg. Local Assortativity
Degree

(j)

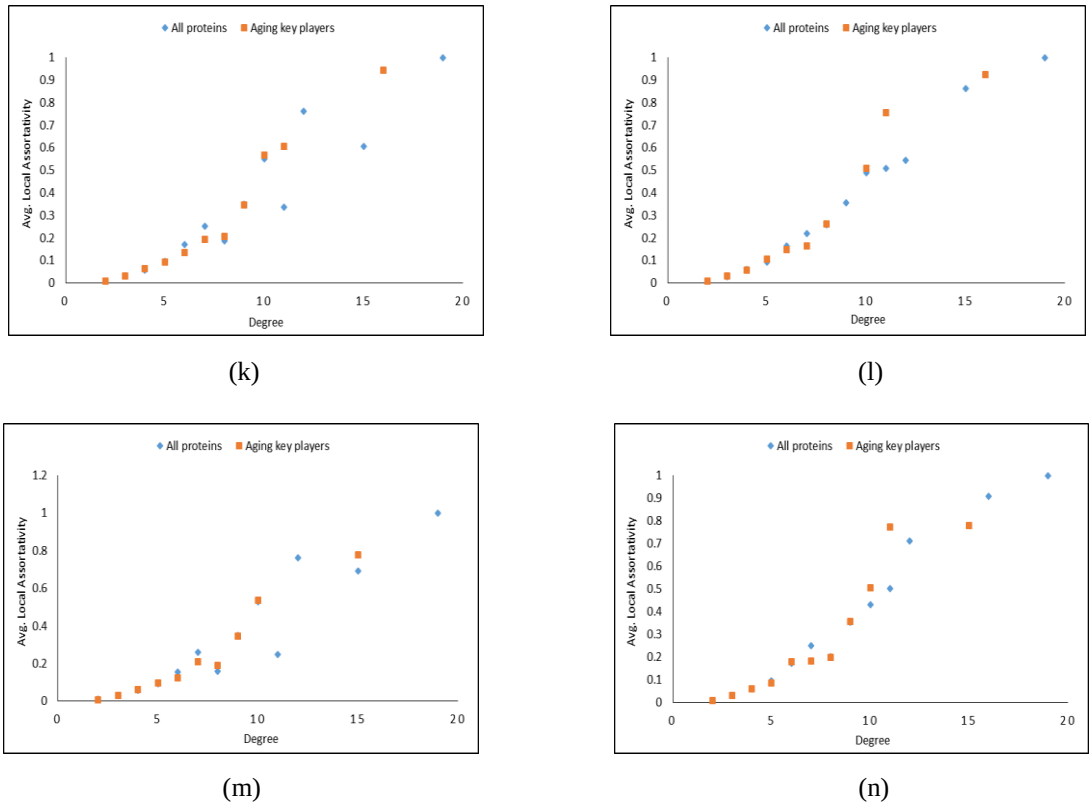


Fig. 4. Local assortativity of Aging-related Proteins Network in Respective Age. (a) 80, (b) 82, (c) 83, (d) 84, (e) 85, (f) 86, (g) 87, (h) 90, (i) 91, (j) 92, (k) 95, (l) 96, (m) 97, (n) 99.

Local assortativity the networks from 80 years until 99 implies that each protein interacts with similar degree characteristic. The outliers in the profiles are the high degree proteins with high average local assortativity. Furthermore, there are some fluctuations in the profiles as the average local assortativity does not increase uniformly with degree. The profiles fluctuate in different degree at different ages. However, there are some parts in the distributions that shows a linear profiles as no fluctuation occur. The characterization of the networks have been proven theoretically by Piraveenan et al. [7] This indicates that the proteins are locally assortative and the hub proteins form clusters among them. The clusters are then connected to each other by lower degree proteins [19] as shown in Fig. 5.

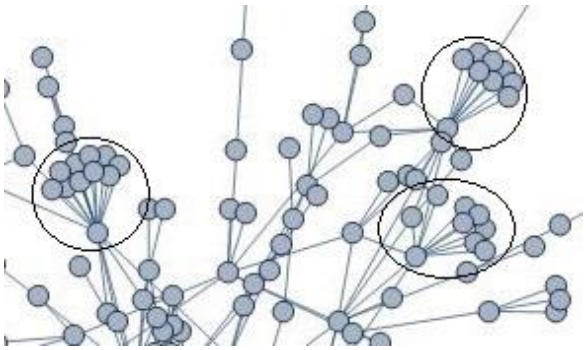


Fig. 5. Hub proteins are connected by low degree proteins

3.2 Characteristics of Aging Key-Players Protein

From Fig. 4, aging key players have a proportional non-linear local assortative profiles in each network. However, key players that have degree below than 5 shows a positive linear profiles as the value of LA increases uniformly. The profiles start to fluctuate at proteins with the degree of 5 and above for some of the networks. Network of 80, 83, 86, 87, 91, 92, 95, 96 and 97 years continue the linear profiles until 6 or 7 degree of proteins. For the proteins with degree of 10 and above, the profile in network of 80, 83, 84, 85, 87, 91, 92, 95, 96 and 97 years increase without any fluctuations. However, the profiles for the networks of 86, 90 and 99 years fluctuate at key players that have degree of 15.

Average local assortativity increase for degree above 10 as high degree key players are strongly connected to other high degree proteins. In all networks, the key players are the outliers in the profiles where the average local assortativity are different between them (high degree key players) and the other key players. The difference shows that high degree key players have high average local assortativity and vice versa. The circumstance indicate the ‘Rich-Club phenomena’ where the hubs have higher connections among them.

From previous discussions, high degree key-player proteins have the highest average local assortativity. However, in network 86, 90 and 99 years, the high degree key-player proteins with degree of 15 do not have the highest average local assortativity. Instead, key player proteins that have degree of 11 have highest average local assortativity. These key player proteins are both high average local assortativity and also the outliers in the profiles. Therefore, high degree key players not only have higher degree but also have a strong assortativity.

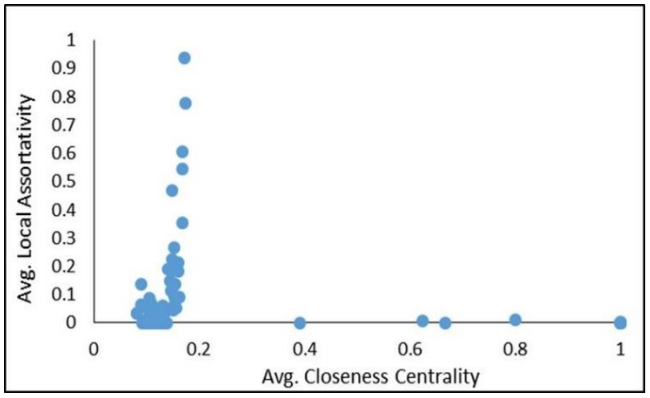


Fig. 6. Local assortativity distribution of network for age 99.

3.3 The Closeness of Key Players

Closeness centrality measures the average distance from a protein to other proteins in the network. If the value of closeness centrality is high, then the protein close to all others. Fig. 6 shows the distribution of LA against closeness centrality for aging key players. The key players accumulate mostly within range 0 – 0.2 of closeness centrality value and within the bigger range 0 – 1 of LA value. Besides that, there are four points at 0.39, 0.63, 0.67, 0.8 and 1 of closeness centrality value have almost 0 of LA value. On the other hand, the key players clogged mostly below 0.1 of LA value and below 0.2 of closeness centrality value.

From Fig. 6, higher average local assortaitivity have lower closeness centrality values. Key players that have high value of LA are highly connected to hub which is not possible to be centralized (closest to all proteins) in network as they are not able to reach low degree members directly. The pathways are longer to reach others because the hubs form clusters among themselves and the low degree key players are the main connector between the clusters. The low degree key players are centralized in network as they can reach both degree characters of proteins; high degree and low degree key players directly. Therefore, the hubs are assortative, but assortative key players are not close to all proteins in aging network. In addition, the pro-longevity genes (aging-related proteins) tend to form cluster than anti-longevity genes [20] explains why assortative proteins are not centralized, instead they form cluster among themselves.

3.4 Assortativity vs Degree of Key Player Proteins

Assortative hubs and disassortative hubs are hardly recognized but the local assortative profiles allow us to recognize the difference in both of the behavior [7]. Average local assortativity profile in all networks are proportional to protein's degree which imply the proteins are locally assortative. The high degree key players have high average local assortativity represent a strong assortativity where there is a higher density of connections among them. Low degree key player with low average local assortativity represents a weak assortativity indicate a low density of connections among them. However, both characteristics of the key players are assortative. From this situation, it is proven that assortative high degree proteins formed clusters that are connected with low degree key players. In addition, the key players have more interactions among them, provided with the high degree proteins [18].

Table 1. Value of LA in proteins P35222 and Q13547 in respective age.

Age	Degree of protein P35222	Value of LA of protein P35222	Degree of protein Q13547	Value of LA of protein Q13547	Lowest value of CC
80	16	0.9260	10	0.6780	0.0812
82	16	0.8878	11	0.8698	0.0830
83	15	0.8470	-	-	0.0817
84	16	0.9059	11	0.9544	0.0820
85	15	0.7779	10	0.6780	0.0815
86	15	0.8643	11	0.8892	0.0805
87	18	1.0000	11	0.8051	0.0971
90	15	0.8816	11	0.9509	0.0791
91	15	0.8643	9	0.5730	0.0815
92	15	0.7609	10	0.7393	0.0816
95	16	0.9446	10	0.7002	0.0826
96	16	0.9240	11	0.7550	0.0822
97	15	0.7779	10	0.6891	0.0819
99	15	0.7779	11	0.9386	0.0820

From Fig. 4, the profiles seems punctuated as there are differences between average local assortativity of high degree key players and other key players. Therefore, the high degree key players are strongly assortative at degree >10 with higher average local assortativity. In Table 1, the highest degree key player, P35222 has highest value of LA in most of the networks except in network 84, 86, 90, 96 and 99 years where protein Q13547 have highest value of LA. P35222 shows a strong assortative high degree key player as it has highest value of LA within range 0.78 – 1. A study emphasized that high degree key player plays an important role in aging process as

the process is associated by the failure of hubs [1]. The key player P35222 functions as coactivator for transcription factors leading to activate certain gene [21]. It is proven by Auley et al. that this function is a vital mechanism of aging for a human being [22].

In addition, Q13547 shows a strong assortative high degree key player. There are five networks of 84, 86, 90, 96 and 99 years where the key player have highest value of LA within range of 0.80509 – 0.93856 with degree of 11 as shown in Table 1. The key player has high connections of hubs compare to P35222 as the value of LA in P35222 is lower than Q13547. Therefore, Q13547 has an important role in aging network not only as a hub, but also as assortative key player. This is due to its function in transcriptional regulation, cell cycle progression and developmental events [23]. The failure of the functions will lead to an abnormal system or disease in human [24]. Therefore, the perturbation of P35222 and Q13547 will fragment not only the pathways, but also the whole networks. This aging key players play significant role in the networks as it may affect the pathways in the network if the perturbation happens.

The key players with degree below than 6 have lower average local assortativity with value below than 0.5. This indicates that low degree key players have a weak assorativity. The key players are not highly connected with other low degree proteins as they have connections with hub proteins. Besides that, these key players are the main connectors between clusters of hub proteins. This findings is supported with their high closeness centrality values as shown in Figure 5. High closeness centrality value imply they are centralized in network.

In this study, high degree key players are highly assortative as they have more connections among hub proteins but less connections with low degree proteins, thus they form clusters in the network. This clusters lay vital role as the influence on process of human aging development. Study by Xue et al. on aging network have found that aging network consist of major network modules by molecular explanations [25]. Besides the high degree key players, the low degree key players show a significant role in network though they have lower value of local assortativity. Instead, they also have connections among high degree proteins. This situation explains that the network characteristic of disassortative with assortative proteins where the low degree key players keep the disassortativeness of the network by having connections among higher degree proteins.

3.5 Vulnerability of the Network

Vulnerability of aging-related proteins network from perturbations are measured through the impact or effect of perturbation towards activites of the network [18], [26]. In this study, local assortativity shows a high connections among hubs, which may lead to the network fragmentation if these hubs been perturbed. The perturbation not only effect the proteins activity but also the connections among other proteins, therefore it will leads to the changes of the activity of their neighbors [26]. Thus aging-related proteins network are vulnerable to perturbations as it may lead to alteration of their links and subsequently, change the network topology. This is contradict from Gnana et al., where they stated that assortative hubs may increase the robustness as the hubs can function and support for each other [8]. However, it may be true to other real world networks.

On the other hand, the robustness of the network increase when the interaction among hub proteins are suppressed as it decrease the likelihood crosstalk between different functional modules of cell [27]. However, aging-related proteins network in this study is obviously different as it is enriched by the interactions among hub proteins as it the hubs are strongly assortative. Aging key-player proteins tend to be intermediaries for crosstalk which may lead to decrease the robustness of the networks. This feature is significant in the aging-related proteins network as the network will be vulnerable to attacks as the effect of deleterious spread across pathways. The vulnerability of the network contributes to the aging process where the interactions among aging-related proteins are perturbed and the network topology also altered. Therefore, assortative hubs decrease the robustness of network from perturbation which lead to aging process.

4. CONCLUSION

In this study, we successfully analyzed the characteristics of aging-related protein networks; globally disassortative with proportional non-linear local assortative profiles. We found out that the networks are globally disassortative while the proteins individually are locally assortative. As the profile of local assortativity shows a proportional non-linear, the key players are divided into two features; strong assortative and weak assortative. On the other hand, the assortative aging key-player proteins are not close to all proteins as they have lower value of closeness centrality. Besides that, assortative hubs decrease the robustness of network from perturbation which lead to aging

process. In conclusion, this study successfully analyzed the assortativity of aging-related proteins network which could help in understanding the aging process further.

5. ACKNOWLEDGEMENT

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Conflict of Interests

The authors declare that there is no conflict of interests.

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