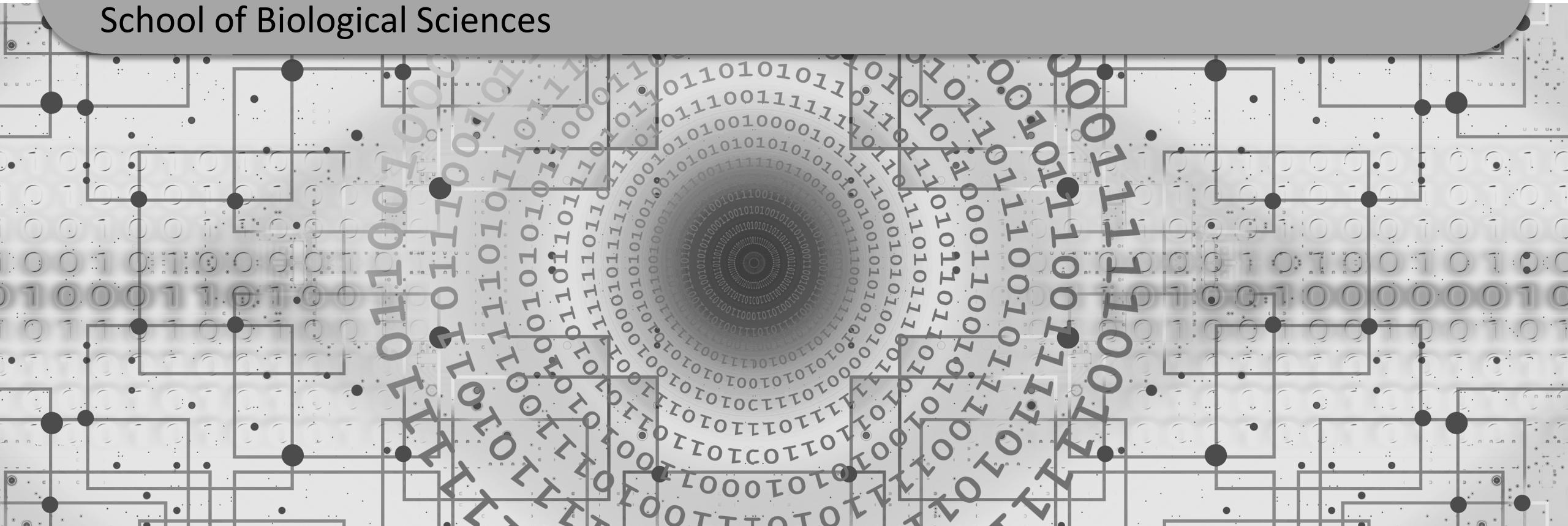


Network Theory and Network Biology

BS0004 Introduction to Data Science

Dr Wilson Goh

School of Biological Sciences

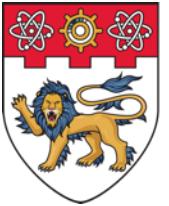


Learning Objectives

By the end of this topic, you should be able to:

- Define a network.
- Describe a network in terms of its mathematical formalisms.
- Perform simple network-based statistical calculations.
- List examples of social and biological networks.
- Describe examples of social and biological networks.
- Explain how networks are a form of guilt-by-association analysis (biological context).





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What is a Network?

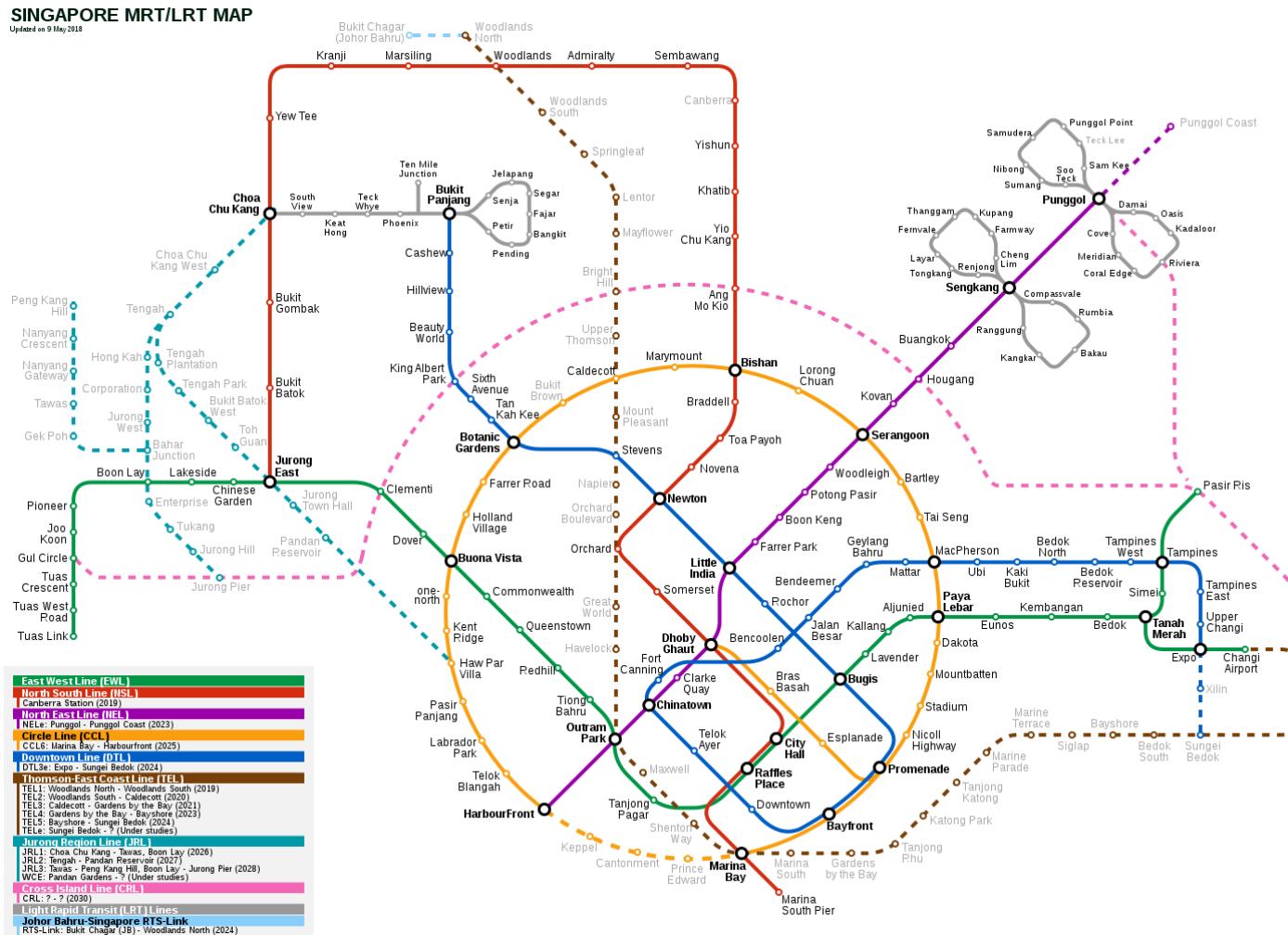
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What is a Network?

You just got off school. And you want to go home from Boon Lay to Jurong East. You should be familiar with the following map.

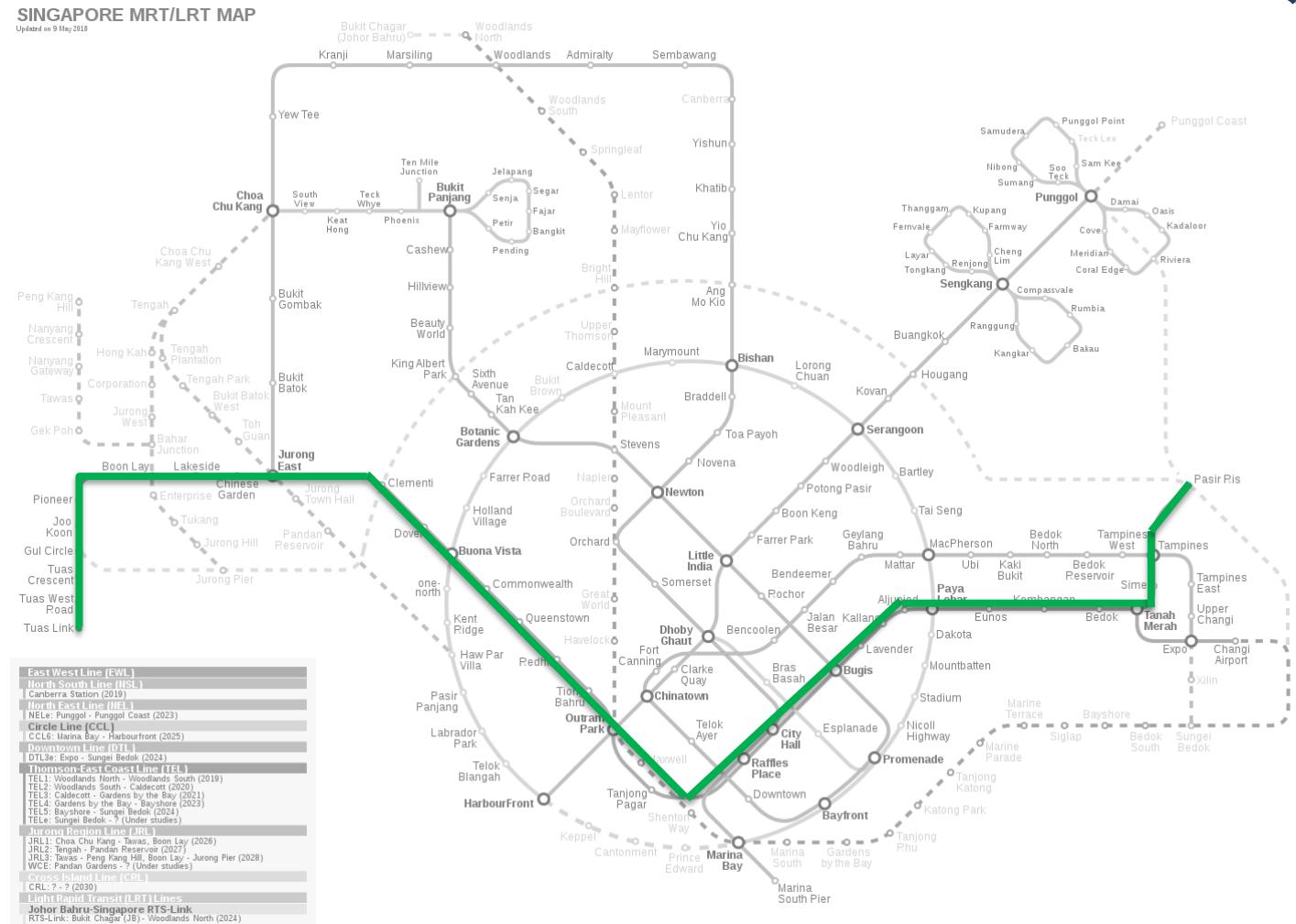


Every station is a point. Every station is connected to another. Some stations are inter-changes --- connecting different lines.

What is a Network?

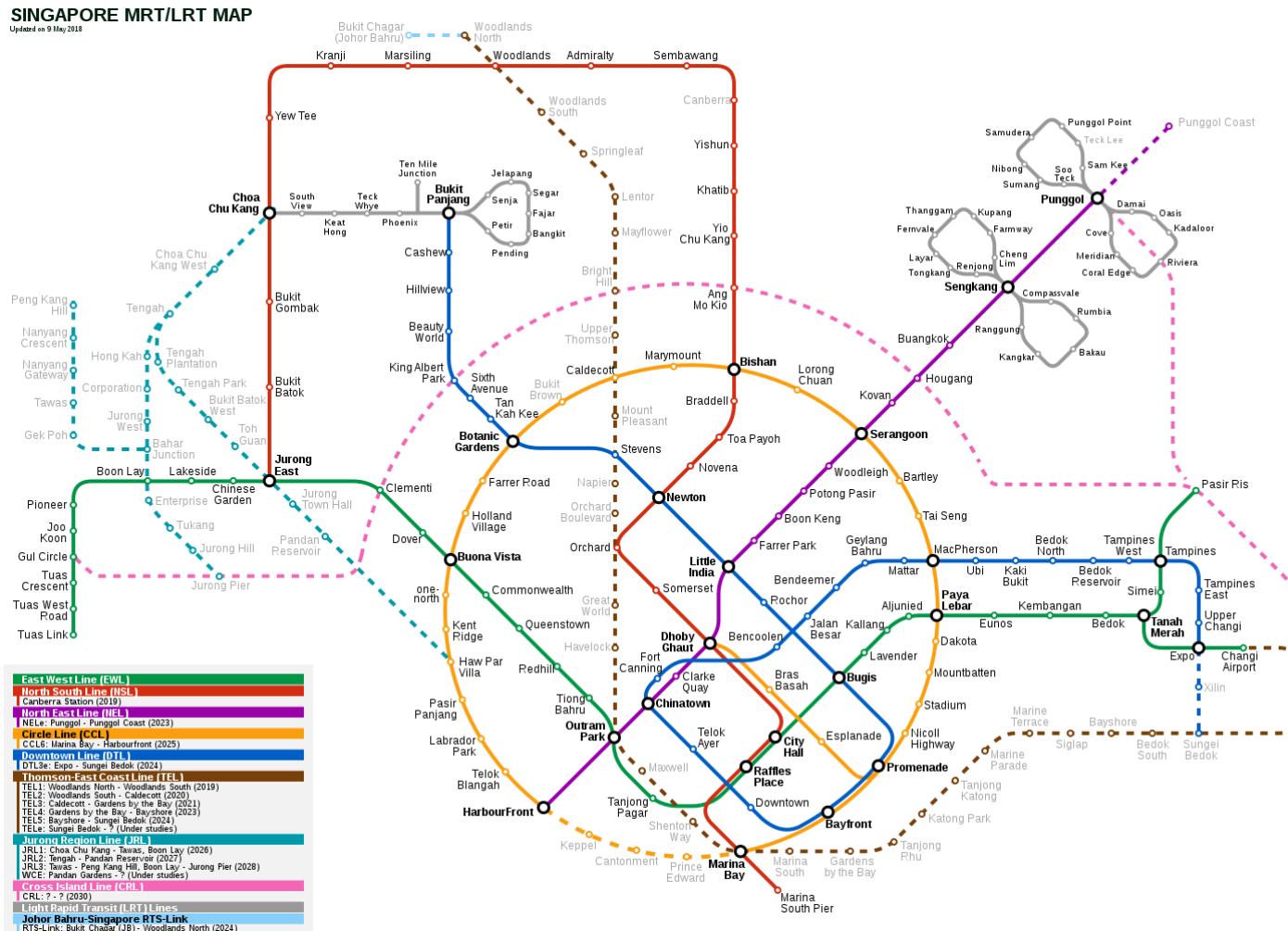
To get home. You do not need to consider the entire train system. You only need to consider your starting point, which is on the green line. And the end point, which is also on the green line.

To get to Jurong East, you need to traverse 3 stops from Boon Lay to Jurong East. But what if you want to go to Dhoby Ghaut, which is on both the red and yellow line? You then have to consider more options. You may change at the circle line or the red line (at Jurong East, Raffles Place or City Hall).



What is a Network?

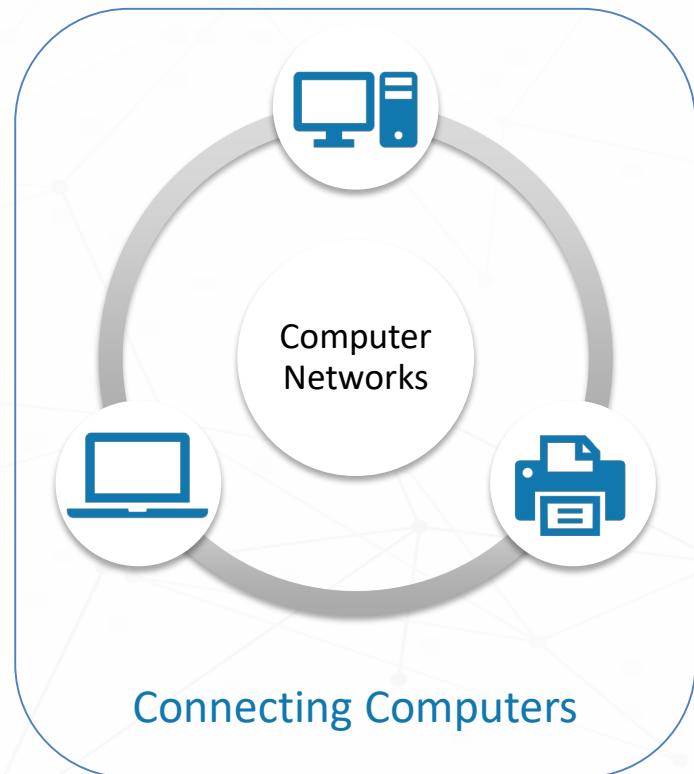
The MRT system is an example of a network. A network is a complex system, which shows you the relationship amongst entities.



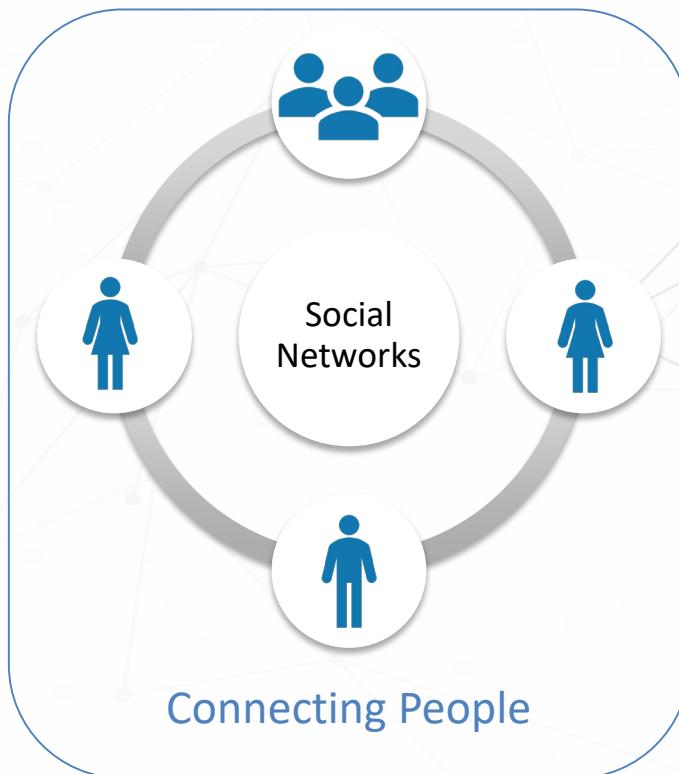
In a train system (train network), the entities are the stations, and the relationships are the tracks connecting the stops.

What is a Network?

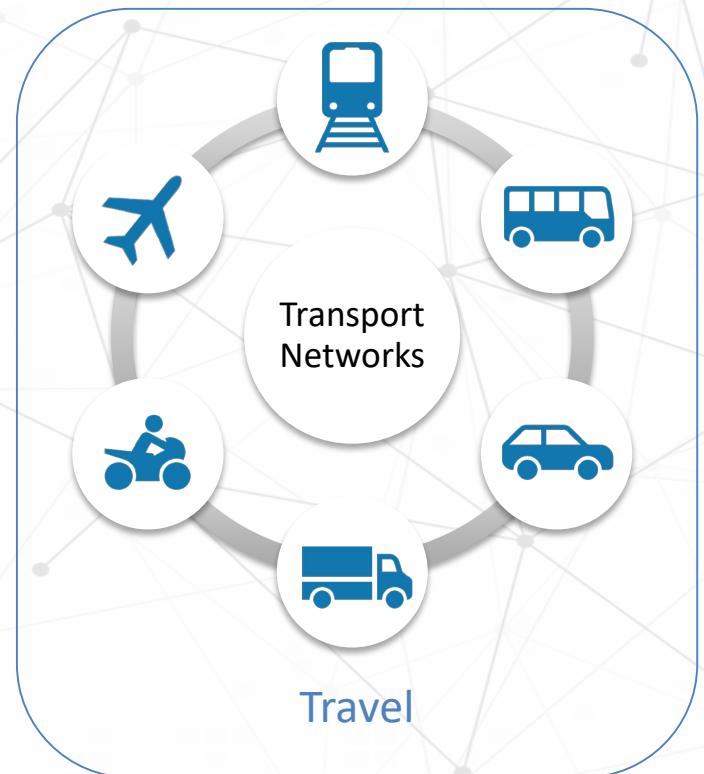
Networks are all around us.



Connecting Computers



Connecting People

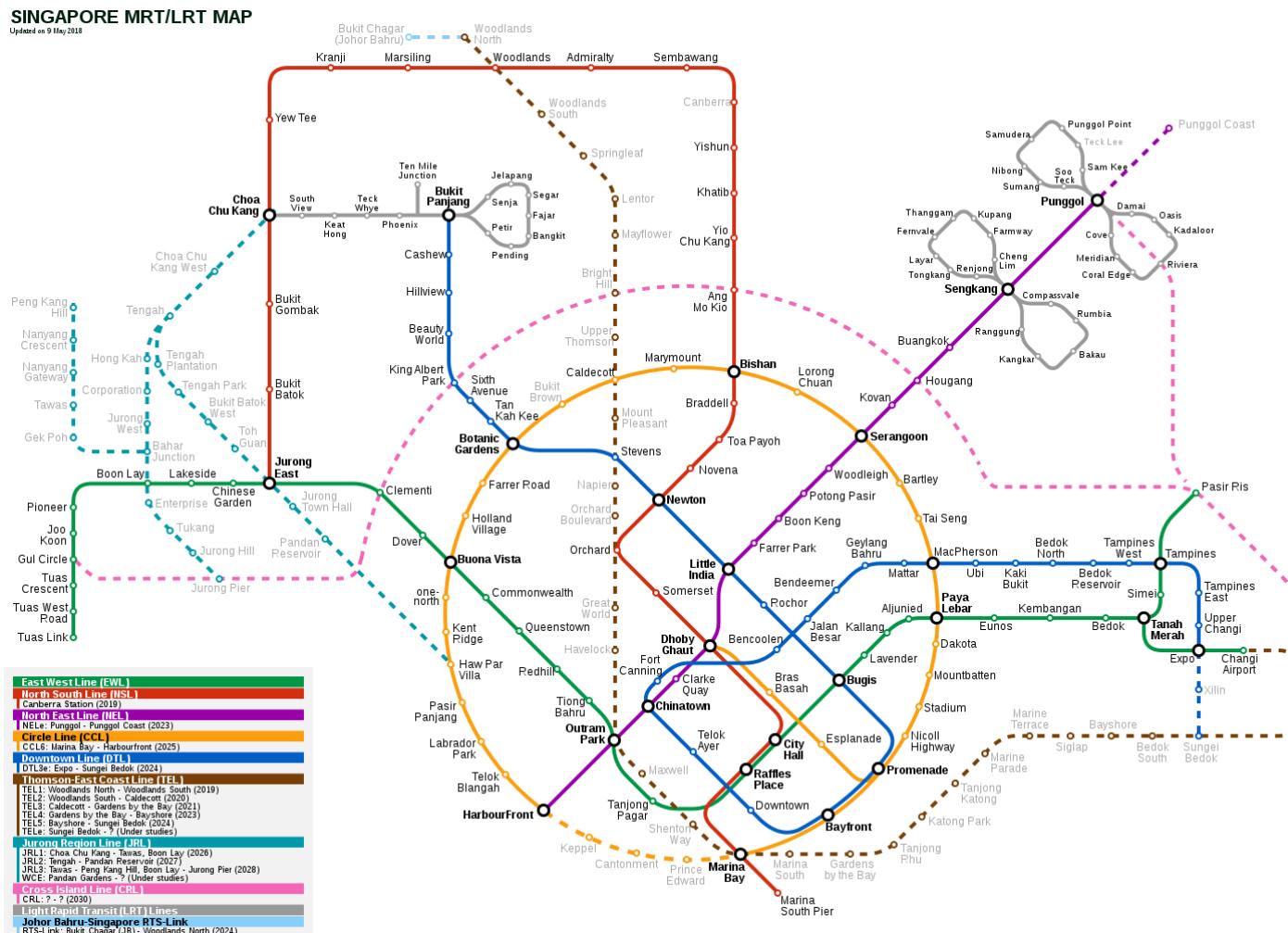


Travel

Have you ever wondered how things are connected to one another?
And whether these intricate system of connections mean anything?

What is a Network?

The network representation of the train system helps you plan your journey --- as its architecture acts as a constraint.



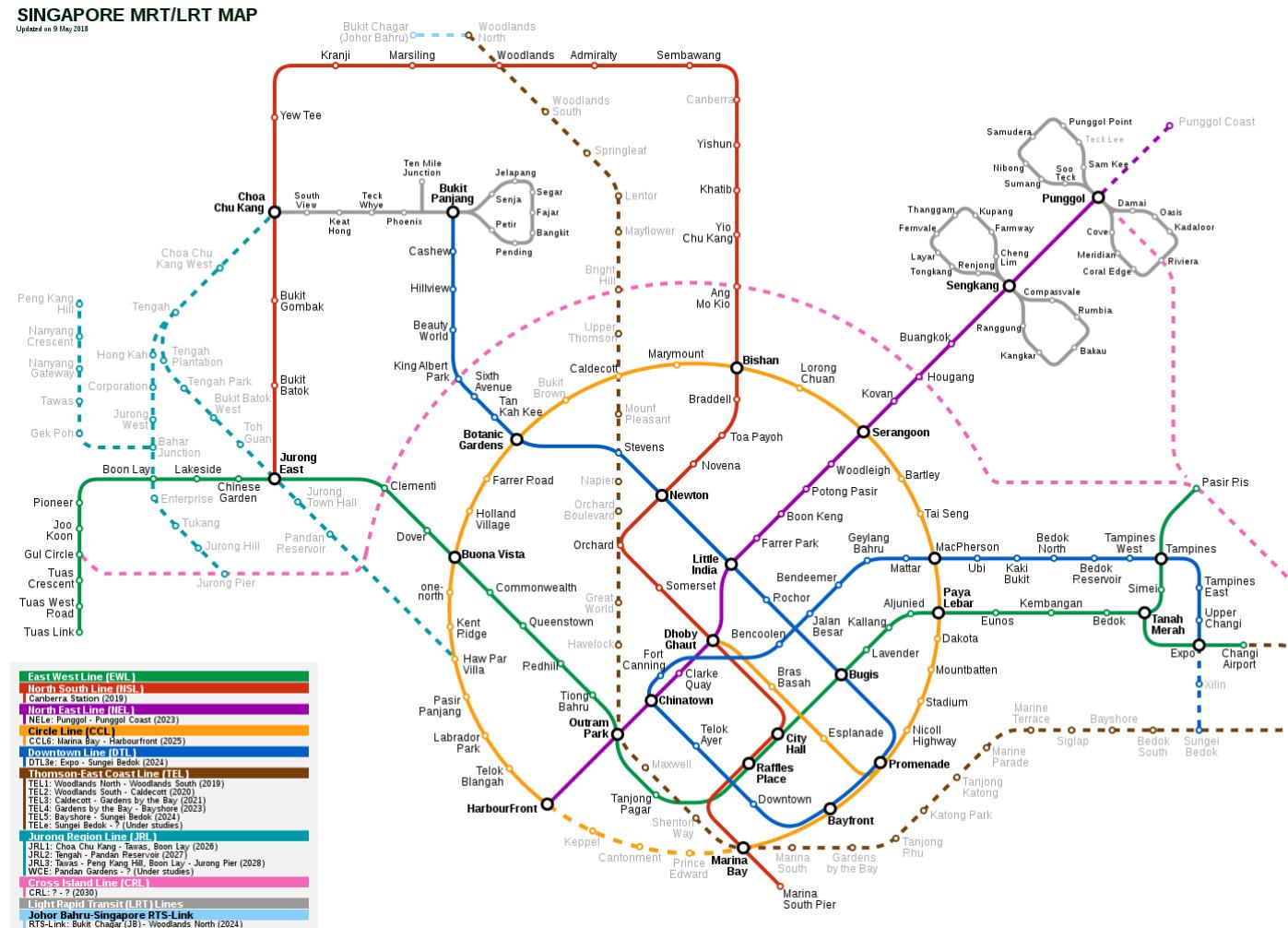
You cannot simply say, I want to go from Yishun to Boon Lay in one stop. A direct connection does not exist.

Source: By Afrol. - Own work, CC BY-SA 3.0, <https://commons.wikimedia.org/w/index.php?curid=31339406>

What is a Network?

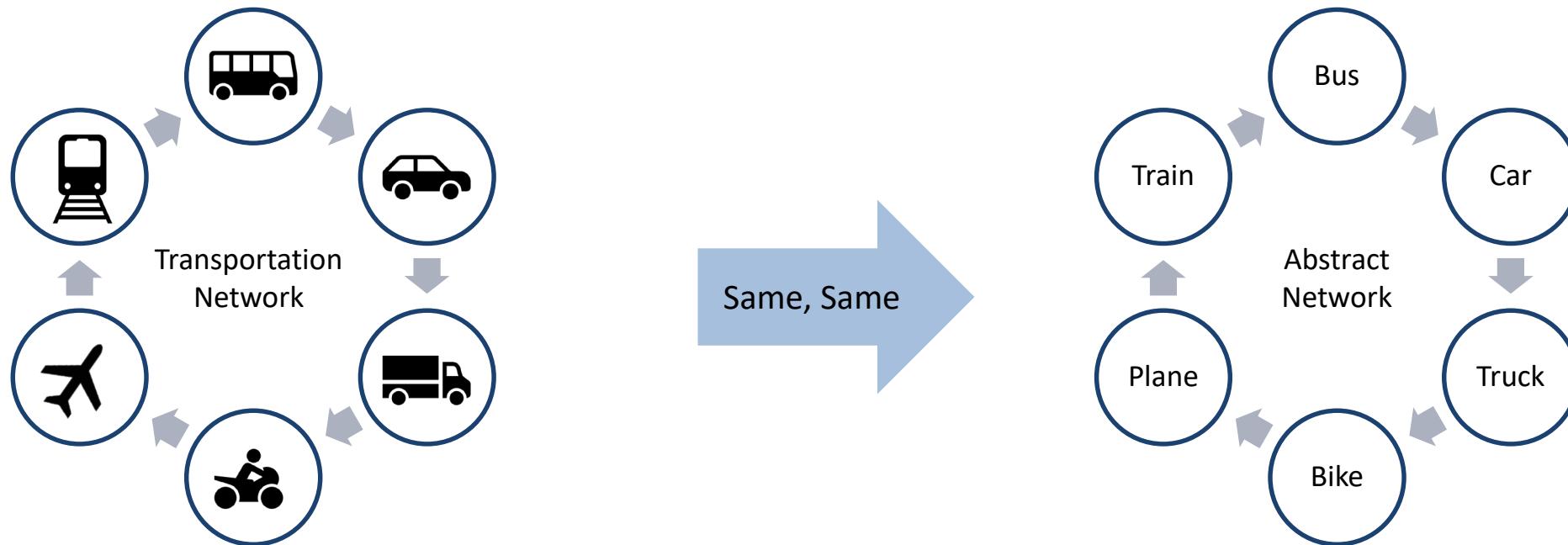
The network map given here is not actually how the real train system looks like. Connections may vary by travel time and also distance. The map may also not be geographically correct. Cannot superimpose on Singapore map.

The train network model is an abstraction.



What is a Network?

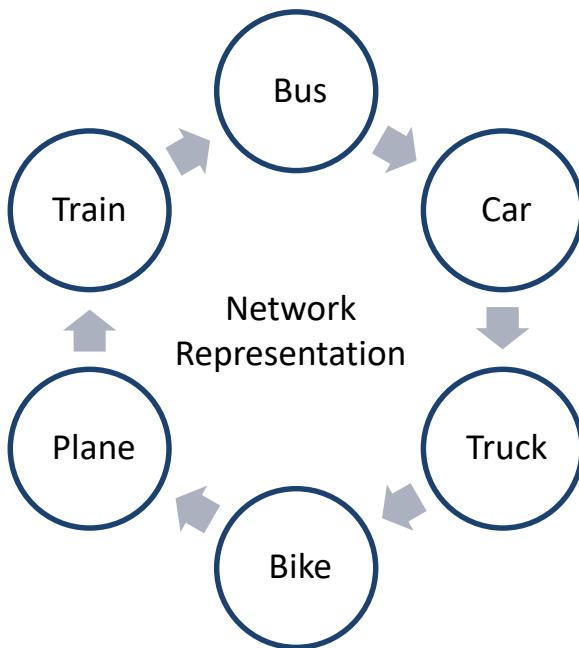
A network is an abstraction. An abstraction involves removing unnecessary detail. Leaving behind only relevant information that is sufficient for our analytical purposes.



It doesn't matter what the entities really are. They are all supposed to be 'equivalent'. At its most basic level, it might as well be circles connected by lines. Ditto for the relationships. Although they are all 'lines': some are sea routes, some are air routes, and there may be stopovers as well.

What is a Network?

Concept of nodes and edges: Formally in network theory, an entity is called a node. And the relationships connecting the nodes are called edges.



- Node represents an entity
- Edge represents a relationship

What is a Network?

A network is:

- An abstraction of a complex system describing the relationships amongst a set of nodes.
- In a network, seemingly different entities are reduced to homogeneous nodes.
- The relationships are also simplified, and may not include full details.
- We analyze how entities are connected to reveal useful insights.

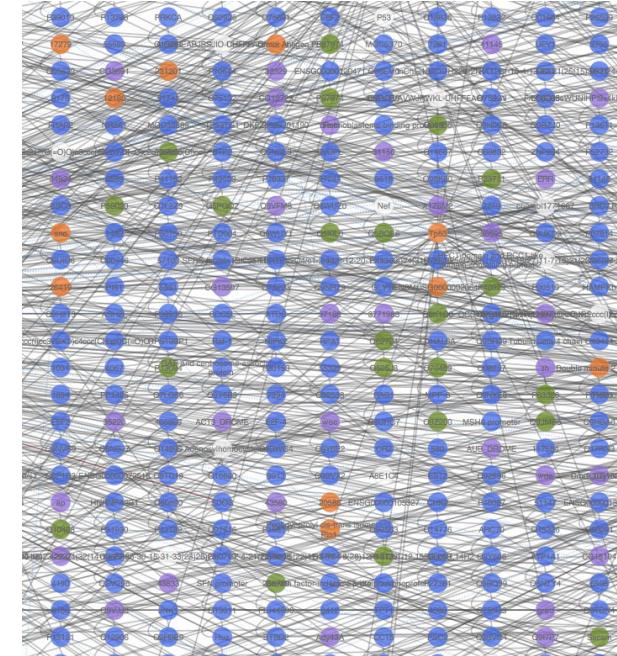
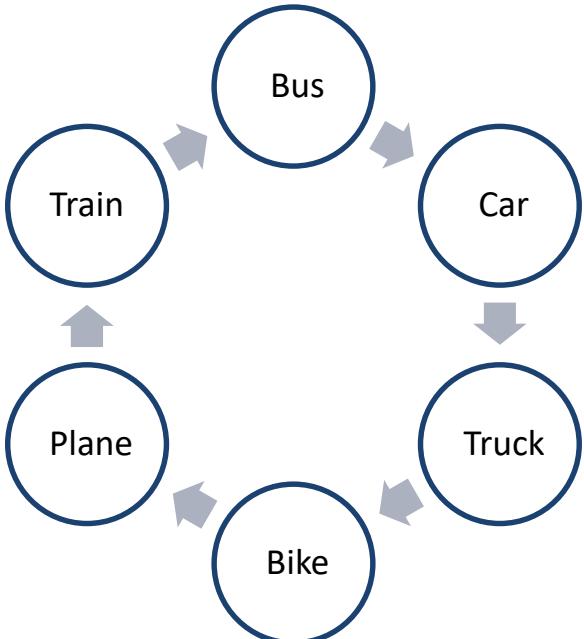
What is a Network?

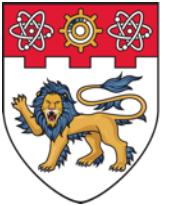
So why study networks?

- Analysis of the network architecture allows you to understand the limitations of the system.
- When planning how to get home, you have to work within the constraints of the system. But more importantly, it also tells you how well-connected the system is.
- Do you remember how ‘good’ the MRT system was before the circle line?
- A well-connected system should allow you to identify viable alternative routes when one part breaks down.
- You cannot do this if you only look at train stations by themselves.
- Interesting information emerges when you look at how entities are connected, and not just by themselves alone.
- This property where the “whole is greater than the sum of its parts” is called **emergence**.

What is a Network?

Networks can be simple or complex: While useful for describing small simple systems, the true power of a network emerges when applied on large, complex systems which are otherwise impossible to study empirically.





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Mathematical Formalisms

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Networks are mathematical constructs

A single network may be represented by the notation G.

- The set of its nodes may be represented by V
- The set of its edges may be represented by E

Together, they may be expressed as follows:

$$G = \langle V, E \rangle$$

This representation, while simple, isn't very useful. The list of nodes V is easy to store and represent. However, storing and representing relationships in the form of edges E is not so straightforward. There are several options: The set E(G), of relations for a network G, can be stored as an adjacency matrix, an adjacency list or an edge list.

Adjacency matrices

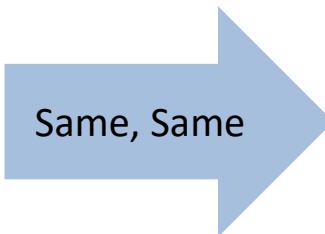
The set $E(G)$, of relations for a network G , can be stored as an adjacency matrix. In an adjacency matrix, given n nodes, an $n \times n$ matrix is used. Suppose we have a small network G with nodes A, B and C. Edge information $E(G)$ can be represented in an adjacency matrix as:

$$E(G) = \begin{bmatrix} & A & B & C \\ A & 0 & 1 & 0 \\ B & 1 & 0 & 0 \\ C & 0 & 0 & 0 \end{bmatrix}$$

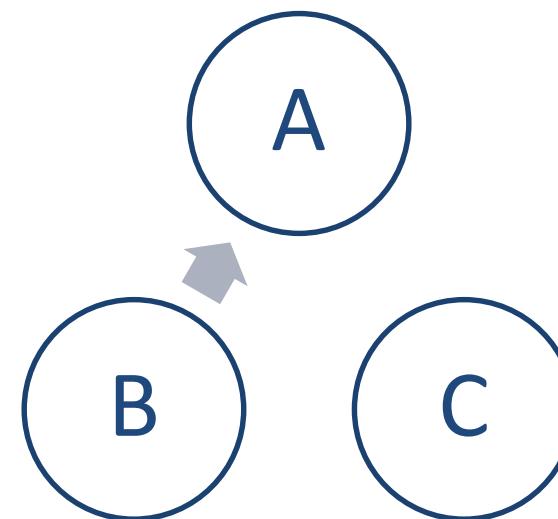
In $E(G)$ above, A is connected to B and vice versa, and neither A nor B is connected to C. There are no self-connections; hence none of the nodes have a positive value along the diagonal.

Adjacency matrices

$$E(G) = \begin{bmatrix} A & A & B & C \\ A & 0 & 1 & 0 \\ B & 1 & 0 & 0 \\ C & 0 & 0 & 0 \end{bmatrix}$$

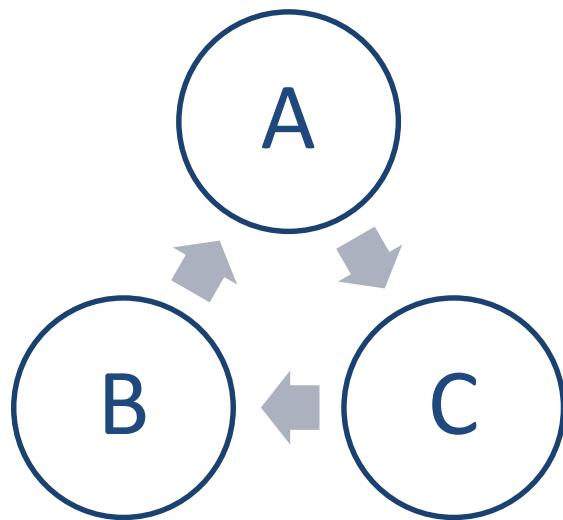


Same, Same



Notice that an adjacency matrix is symmetrical. A – B and B – A connections are repeated.

Exercise 1



Same, Same

$$E(G) = \begin{bmatrix} A & B & C \\ A & B & ? \\ B & C & \end{bmatrix}$$

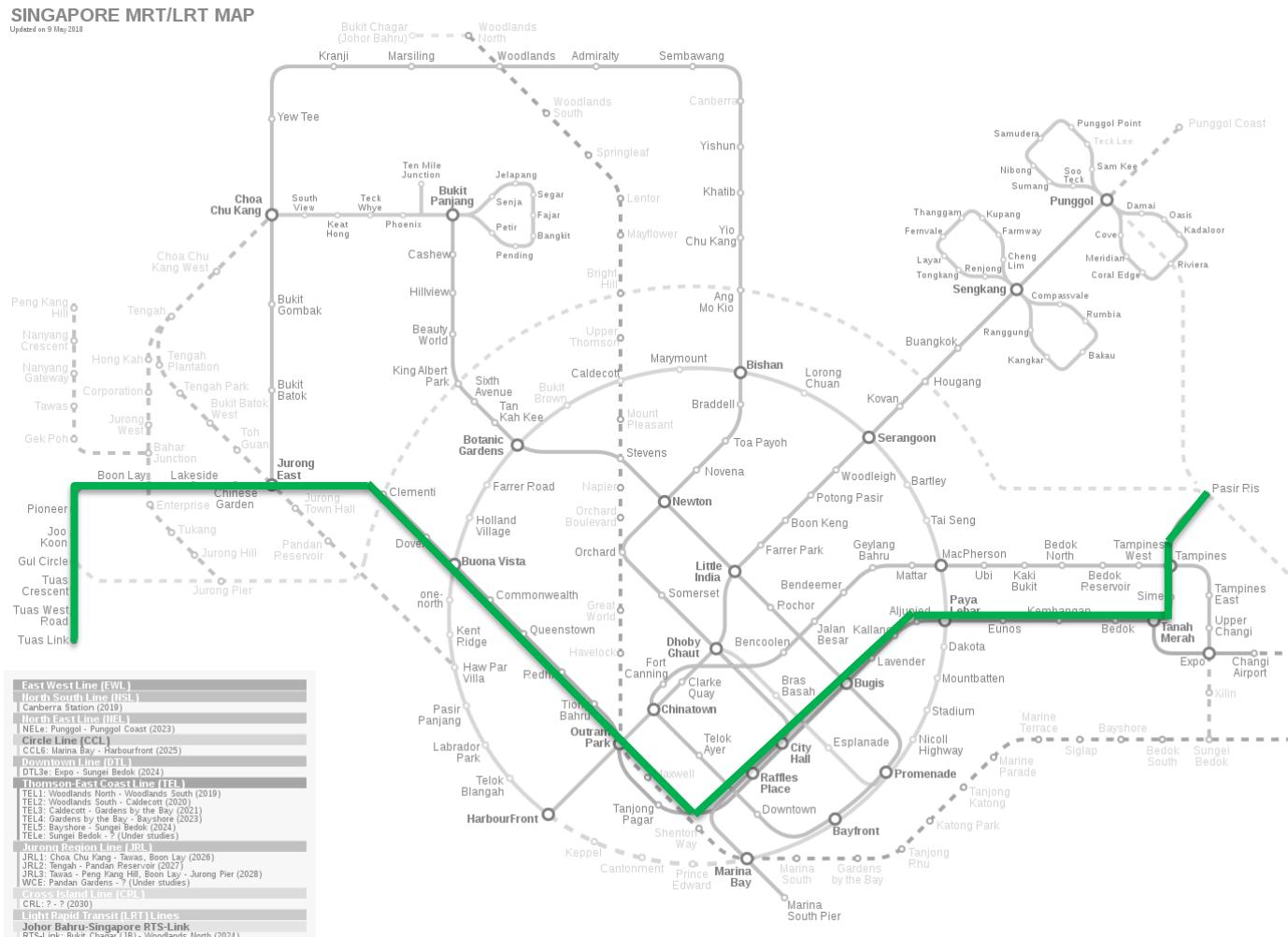
Write the adjacency matrix to illustrate relations A, B and C. Use 1 if there is a connection, and 0 otherwise. Hint: Use an Excel Spreadsheet to help you.

Exercise 2

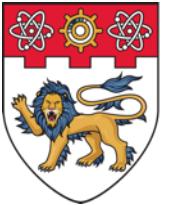
Write the adjacency matrix to illustrate relations between Chinese Garden, Jurong East and Clementi.

Use 1 if there is a connection, and 0 otherwise. Are these 3 stations very highly interconnected?

Hint: Use an Excel Spreadsheet to help you.



Source: By Aforl. - Own work, CC BY-SA 3.0, <https://commons.wikimedia.org/w/index.php?curid=31339406>



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Network Statistics

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Dr Wilson Goh
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The Degree (Connectivity)

The degree k , of a node is the sum of its connections to other nodes.

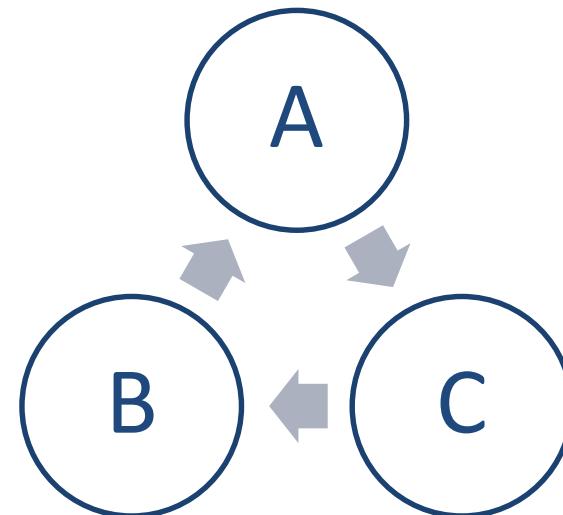
The degrees of the network shown here (k_i , where $i \in \{A, B, C\}$)

$$k_A = 2$$

$$k_B = 2$$

$$k_C = 2$$

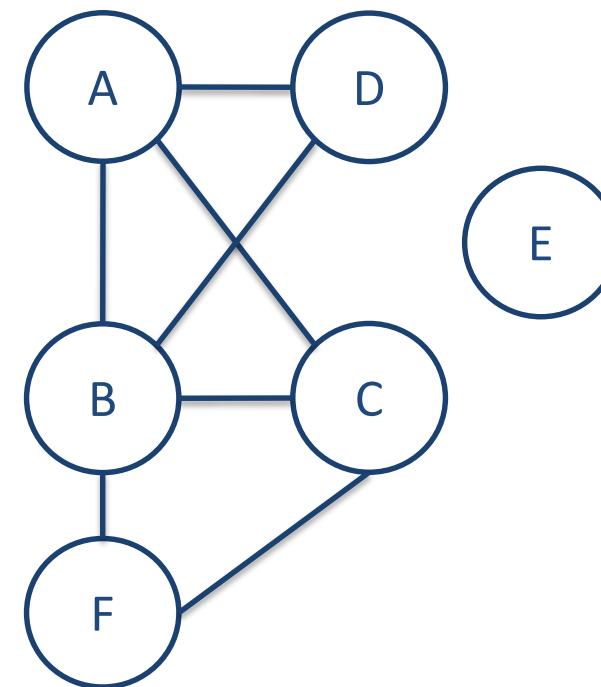
The intuition conveyed here is that the more connected a node is, the more important it is.



Exercise

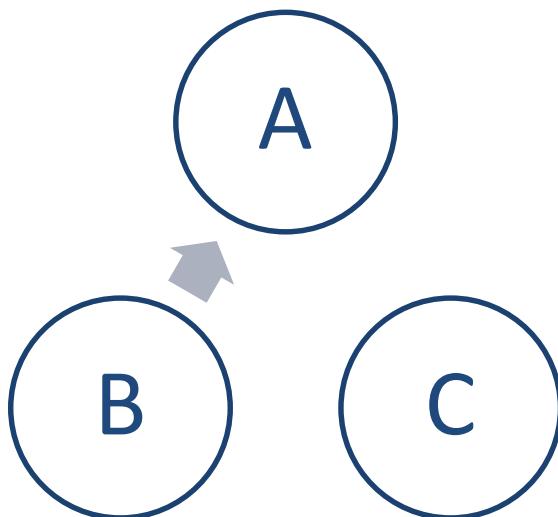
Write down the degrees for each of the nodes shown here:

- $k_A =$
- $k_B =$
- $k_C =$
- $k_D =$
- $k_E =$
- $k_F =$



The Degree (Connectivity)

You can also get the degree from the sum of columns or rows in the adjacency matrix.



$$E(G) = \begin{bmatrix} A & B & C \\ A & 0 & 1 & 0 \\ B & 1 & 0 & 0 \\ C & 0 & 0 & 0 \end{bmatrix} \quad k = 1, 1, 0$$
$$k = 1, 1, 0$$

The Degree (Connectivity)

Based on the degree k (and what you actually know about the SMRT system), what does this tell you about the importance of each of these stations?



Dhoby Ghaut

$$k_{\text{Dhoby Ghaut}} = 5$$



Buona Vista

$$k_{\text{Buona Vista}} = 4$$



Tuas Link

$$k_{\text{Tuas Link}} = 1$$

A highly connected entity in the network system is called a hub.

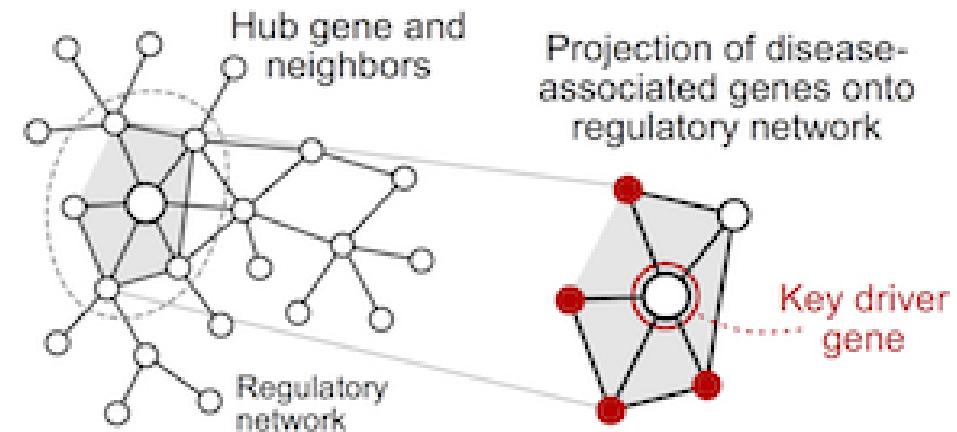
Hubs are important

The degree is an example of a measurement of centrality. The more connected a node is, the higher its degree, and therefore, the more ‘central’ the position it occupies in the network. A highly connected node is called a ‘hub’.



The most popular people in a friendship network

Source: <https://www.fotolia.com/id/164890588>



The genes that controls many other genes in some biological context

Source: <http://mergeomics.research.idre.ucla.edu/>

The Clustering Coefficient (Transitivity)

The clustering coefficient CC, of a node is the proportion of connections amongst the direct neighbors of a node over total number of possible connections.

$$CC_i = \frac{2n_i}{k_i(k_i - 1)}$$

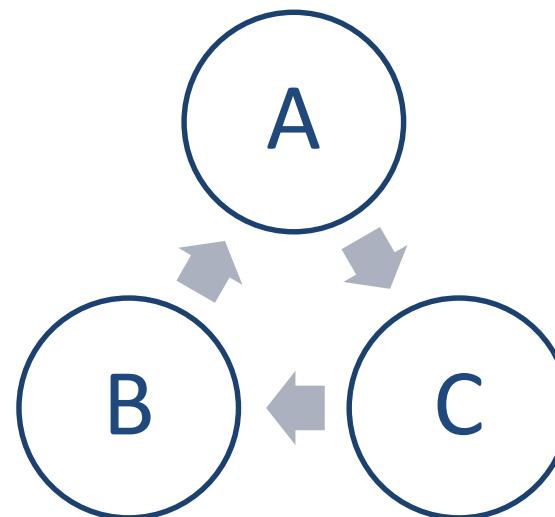
The CC of the network shown here (C_i , where $i \in \{A, B, C\}$)

$CC_A = 1$ [Neighbors of A are B and C]

$CC_B = 1$ [Neighbors of B are A and C]

$CC_C = 1$ [Neighbors of C are A and B]

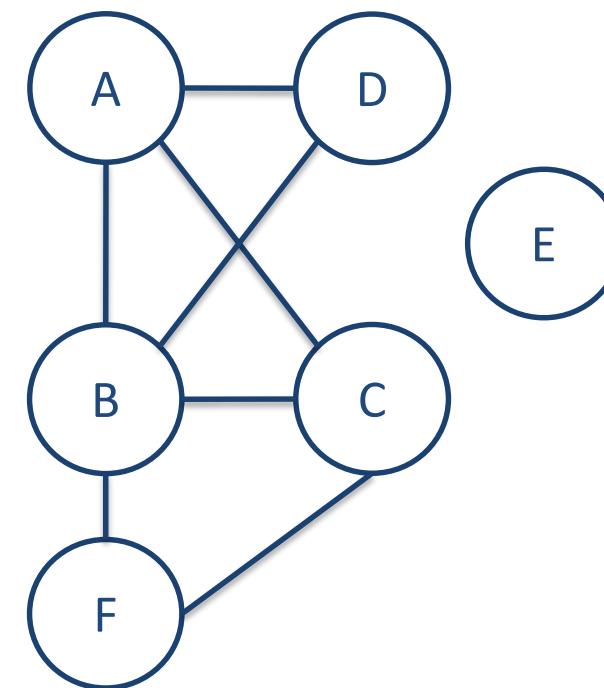
The intuition conveyed here is that the more highly connected the neighbours of a node is, the ‘more protection’ this network has in its structure (removing any node will not adversely affect the connections amongst other nodes).



Exercise

Write down the clustering coefficient for each of the nodes shown here:

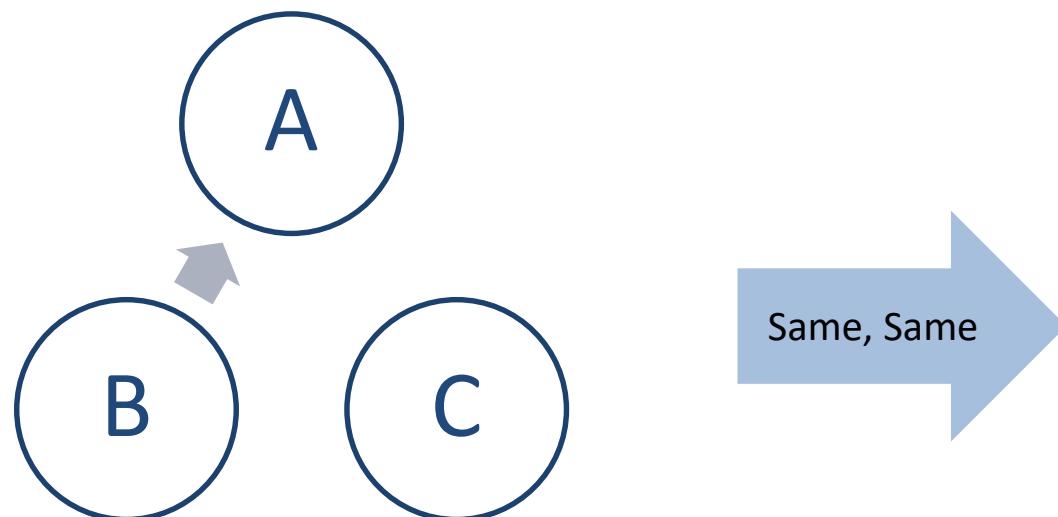
- $CC_A = 2 * 2 / (3 * 2) = 2/3$
- $CC_B =$
- $CC_C =$
- $CC_D =$
- $CC_E =$
- $CC_F =$



The Clustering Coefficient (Transitivity)

Getting CC from the adjacency matrix is not as direct as getting the degree.

1. For each given node i , you need to first check its direct neighbors, n_i (given by 1 along the rows)
2. The maximum number of connections, Max_{ni} is denoted by $(n_i \times (n_i - 1))/2$
3. Next, for each direct neighbor in n_i , check if an edge exists. If yes, add 1 to the sum of observed edges amongst first degree neighbors
4. Return the sum of observed edges, S_{ni}
5. Divide S_{ni} by Max_{ni} to obtain CC_i



$$E(G) = \begin{bmatrix} & A & B & C \\ A & 0 & 1 & 0 \\ B & 1 & 0 & 0 \\ C & 0 & 0 & 0 \end{bmatrix}$$

Question: Why do you think Max_{ni} is not denoted by n_i^2 ?

The Clustering Coefficient (Transitivity)

Based on the clustering coefficient CC, you will realize that there are no connections amongst first neighbors of any station in the SMRT system.



Dhoby Ghaut

$$CC_{Dhoby\ Ghaut} = 0$$



Buona Vista

$$CC_{Buona\ Vista} = 0$$



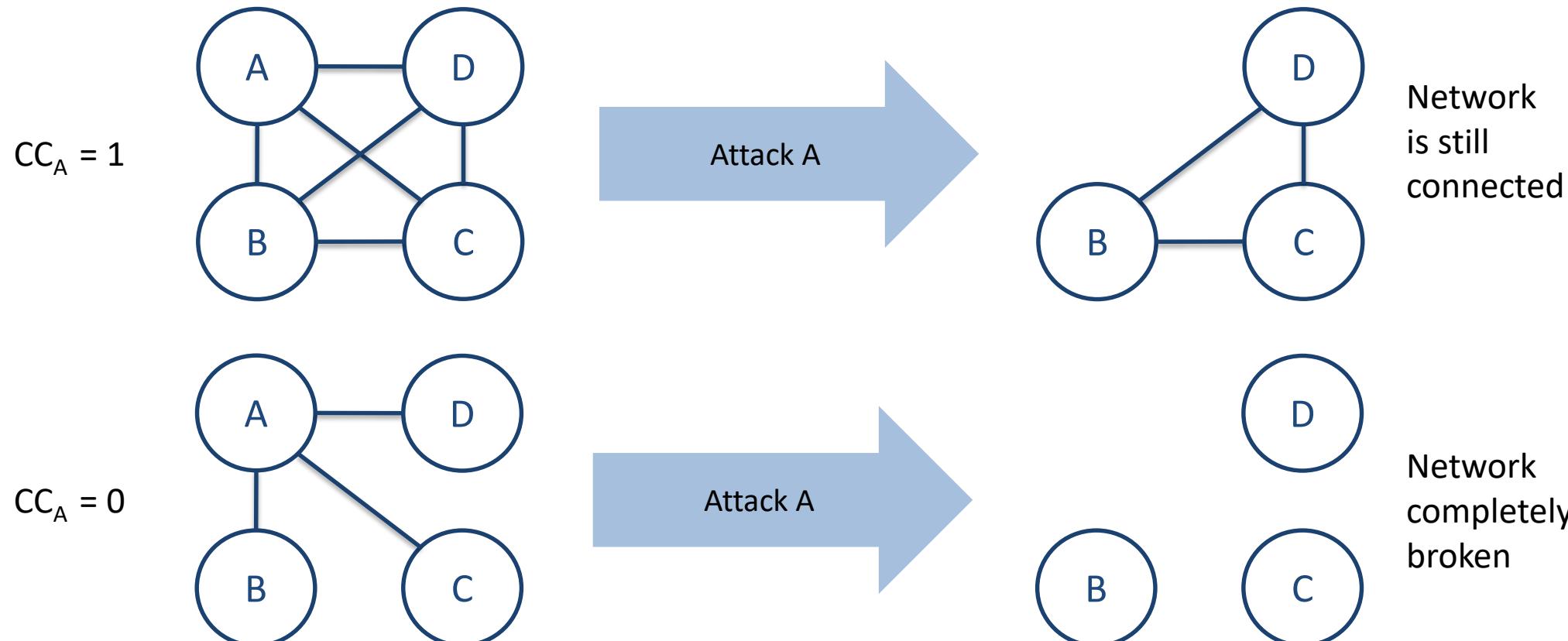
Tuas Link

$$CC_{Tuas\ Link} = 0$$

(Almost) All stations in SMRT system have 0 clustering coefficient.
So what do you think happens when any station breaks down?

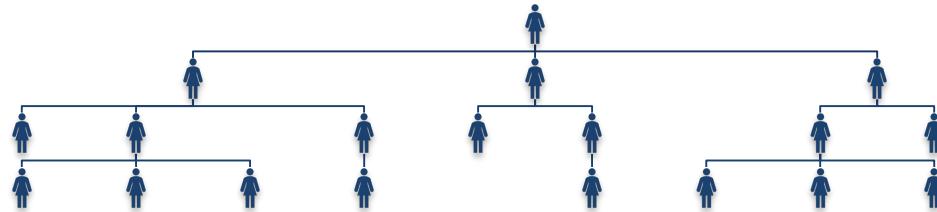
Highly clustered networks are resistant to attacks

The clustering coefficient is an example of a measurement of robustness. The more highly connected the neighbors node is, the higher its clustering coefficient, and therefore, the more ‘robust’ it is against attacks (i.e., eliminating nodes from the network).

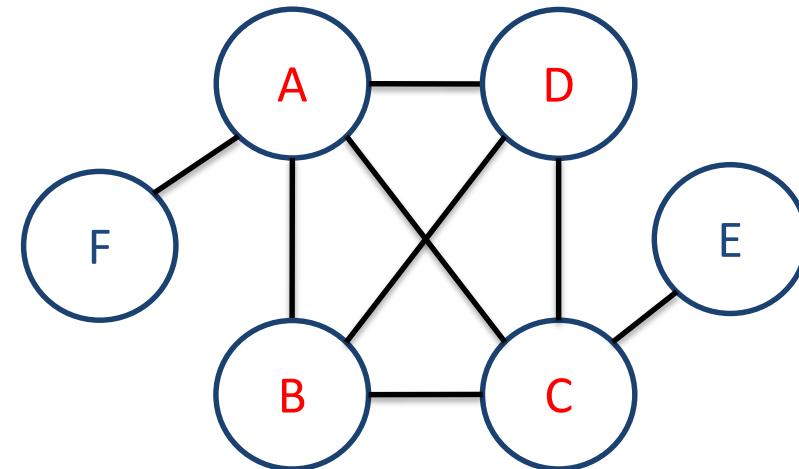


Inter-connectivity is important in real life examples

The clustering coefficient is an example of a measurement of robustness. The more highly connected the neighbors node is, the higher its clustering coefficient, and therefore, the more ‘robust’ it is against attacks (i.e., eliminating nodes from the network).



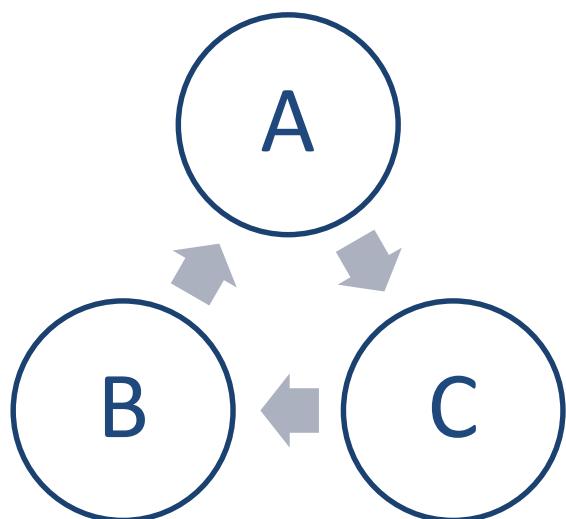
Can your company survive without you?



Biological Complexes

Global Network Statistics

The degree k and clustering coefficient of any single node is a local statistic. But nodes are part of a large network system, and so we need global statistics to tell us something about the system. 2 simple global statistics based on the degree and clustering coefficient is to merely calculate their respective averages.



$$k_A = 2$$

$$k_B = 2$$

$$k_C = 2$$

$$CC_A = 1 \text{ [Neighbors of A are B and C]}$$

$$CC_B = 1 \text{ [Neighbors of B are A and C]}$$

$$CC_C = 1 \text{ [Neighbors of C are A and B]}$$

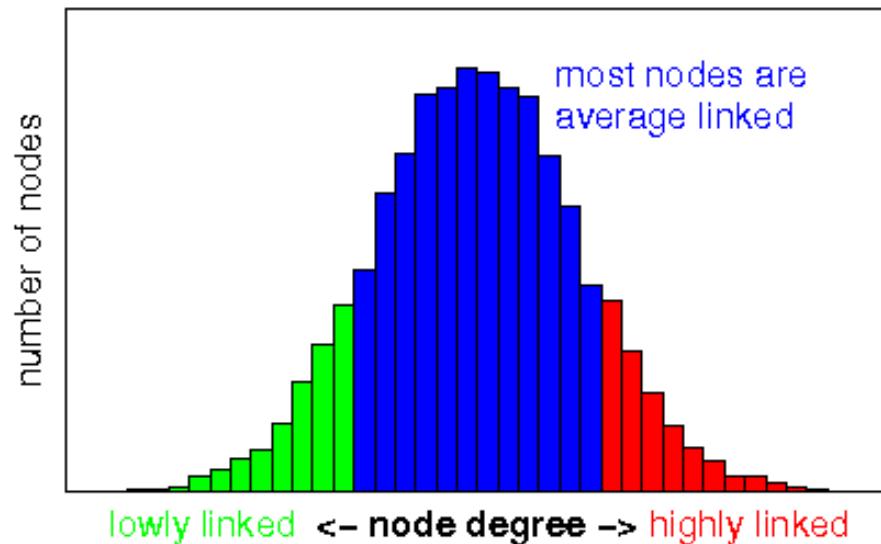
$$\text{Average degree } \langle k \rangle = 2+2+2/3 = 2$$

$$\text{Average clustering coefficient } \langle CC \rangle = 1+1+1/3 = 1$$

Global Network Statistics

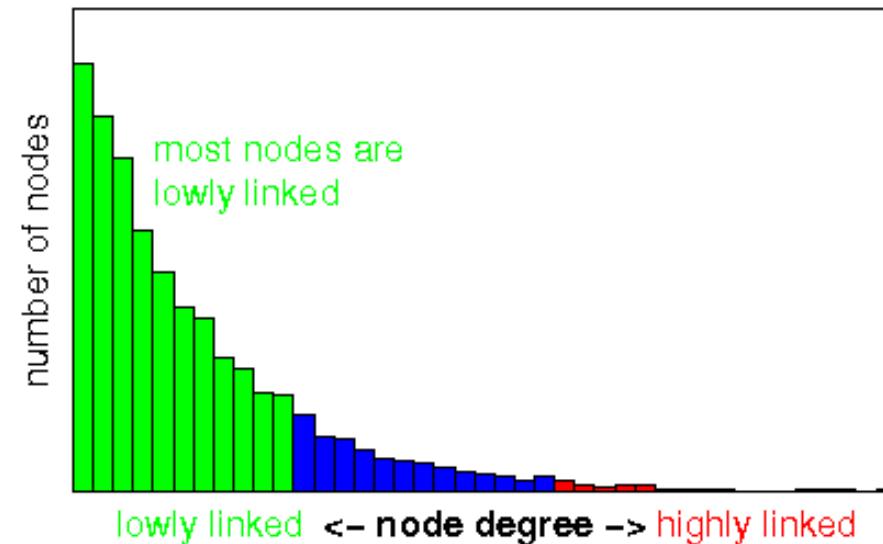
Note however, that averages are not useful global metrics, especially when the metric distributions are non-symmetrical. Many natural networks do not have normally distributed/symmetrical distributions.

random networks



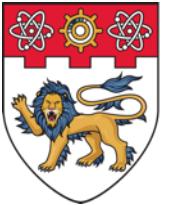
Symmetrical
Average is meaningful

real networks (power-law, scale-free)



Non-Symmetrical
Average is not meaningful

Source: <http://www.network-science.org/>



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Social Networks

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Friendship Networks (Karate Club)

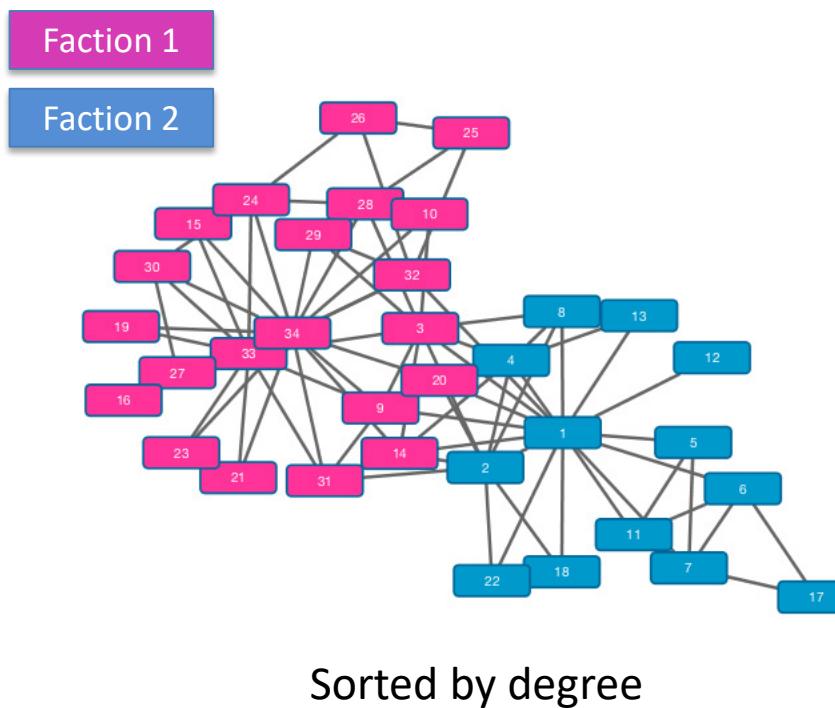
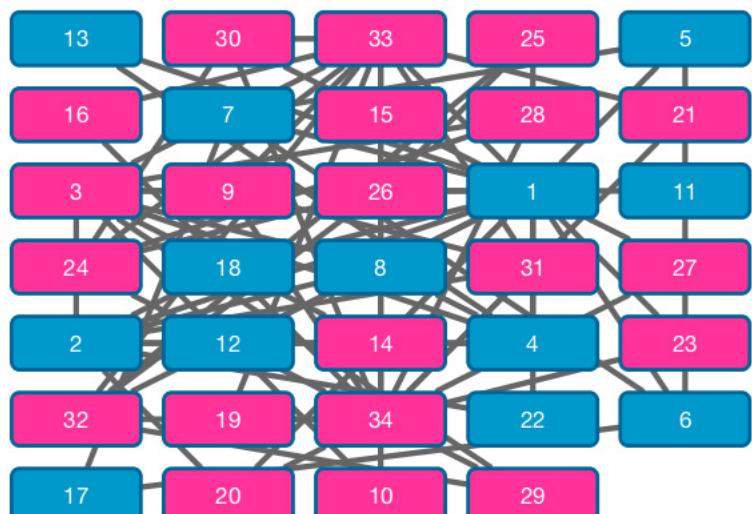
Zachary Karate Club (1977) <http://www.networkdata.isc.uci.edu>

- This network represents friendship between members of a university-based karate club. The club was observed for over a period of three years from 1970 to 1972. Two individuals in the network are considered to be friends if the two individuals consistently were observed to interact outside the normal activities of the club (karate classes and club meetings). That is, an edge exists if the individuals could be said to be friends outside the club activities.
- This friendship network consists of 34 individuals.
- At the beginning of the study there was an incipient conflict between the club president and karate instructor over the price of karate lessons. As time passed, the entire club became divided over this issue. The factions were merely ideological groupings, however, and were never organizationally crystallized. There was an overt sentiment in the club that there was no political division, and the factions were not named or even recognized to exist by club members. Rather, they were merely groups which emerged from the existing network of friendship among club members at times of political crisis because of ideological differences. There was no attempt by anyone to organize or direct political strategies of the groups, and, in general, there was no barrier to interaction between members of opposing factions.

Source: W. W. Zachary, An information flow model for conflict and fission in small groups, Journal of Anthropological Research 33, 452-473 (1977).

Friendship Networks (Karate Club)

Networks are useful for visual analysis. You can detect "weak spots" or "clusters" that may be used to explain or predict phenomenon.



In this case, by studying how people interact generally in this club, you will find that two factions already exist. However, it wasn't until a dispute that occurred when this underlying social structure began to exert its "muscle". Notice also that some individuals are actually friends with both factions?

Source: W. W. Zachary, An information flow model for conflict and fission in small groups, Journal of Anthropological Research 33, 452-473 (1977).

Small World Effects (6 Degrees of Separation)

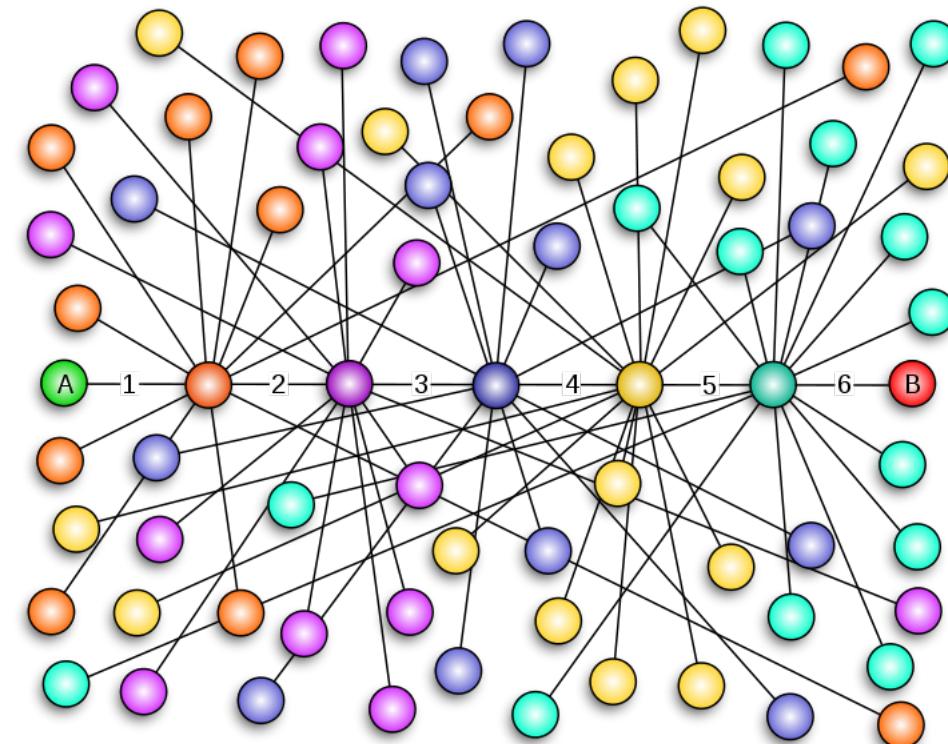
The world is full of seeming ‘coincidences’

Ever wondered how you always seem to know someone who shares a common friend with you?

Six degrees of separation is the idea that all living things and everything else in the world are six or fewer steps away from each other so that a chain of "a friend of a friend" statements can be made to connect any two people in a maximum of six steps.

The sheer inter-connectedness of our underlying social networks can surprise us.

If the network is very big, but all connections between nodes are less than 6 steps away, this is termed a small world network.



Source: <https://www.nature.com/articles/30918>

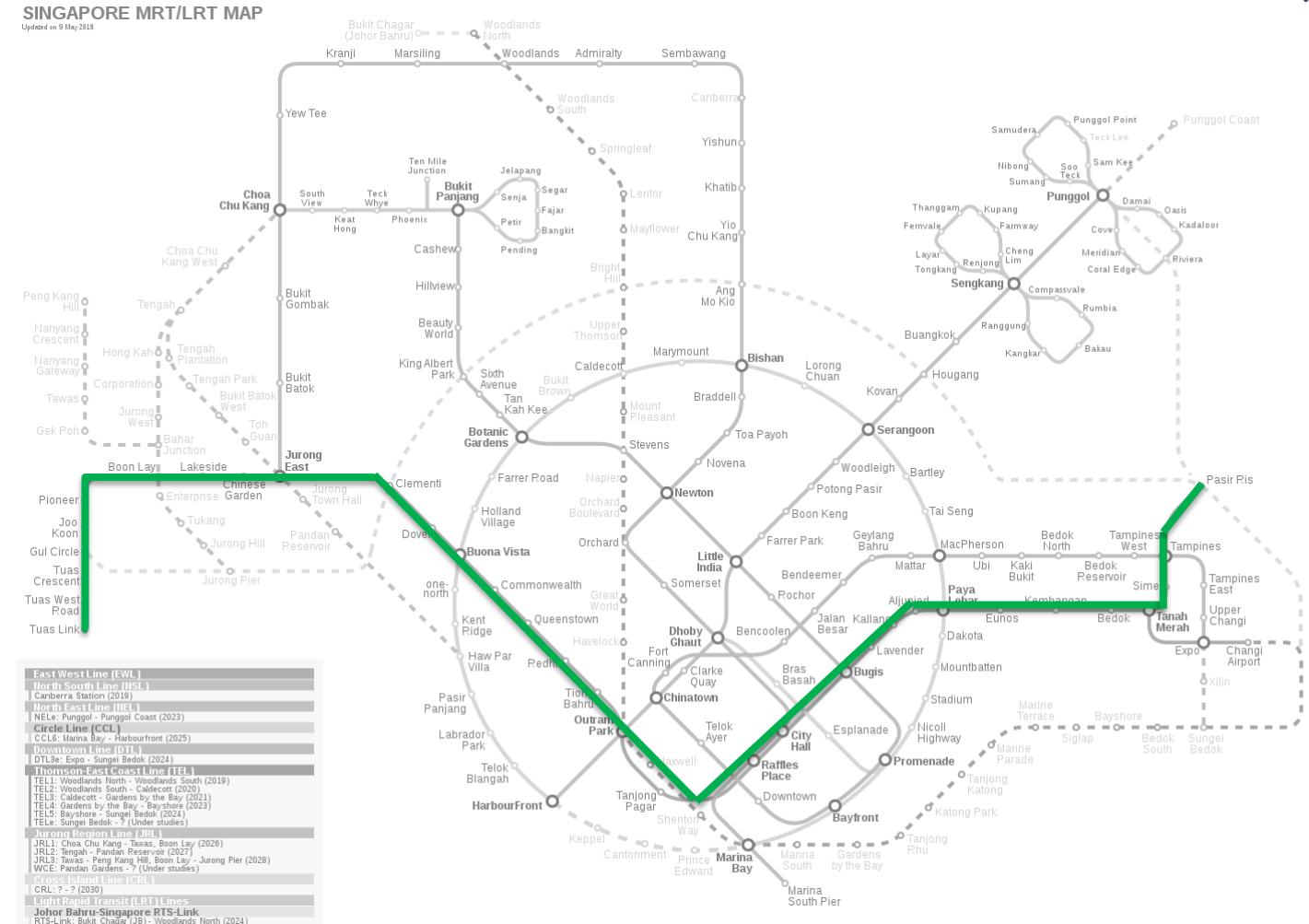
Small World Effects (6 Degrees of Separation)

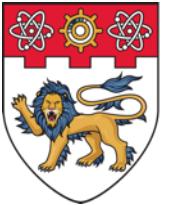
Is the east-west line a small world network?

Try counting the number of stops you need to pass through for every pair of stations.

What do you notice? Is it fast to go from Tanjong Pagar to Outram Park? How about from Kembangan to Boon Lay?

It is not a small world network. For example, the path between Boon Lay to Pasir Ris is exactly equals to the longest connection path in the entire network. It is definitely way greater than 6 degrees of separation.





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Biological Networks

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Types of Biological Networks

Commonly studied networks:

- Protein-protein interaction (PPI) networks
- Transcriptional networks
- Metabolic networks

Other biological networks:

- Neural networks
- Phylogenetic trees
- Gene ontology
- Correlation networks (e.g., gene expression)
- Disease – “disease gene” association networks
- Drug – “drug target” networks

Protein-Protein Interaction Networks

- Captures physical interactions between proteins e.g. A binds to B.
- Physical interactions suggests shared functionality e.g components in a complex.
- Tested in vitro --- e.g. Yeast-2-Hybrid (Y2H), Affinity purification (AP).

Protein-Protein Interaction Networks

Where to find them?

DATABASES OF PROTEIN-PROTEIN INTERACTION NETWORKS (STATISTICS AS OF 2016).

Database	# nodes, # edges	URL	Build Focus
BioGRID	10k, 40k	http://thebiogrid.org	Literature
DIP	2.6k, 3.3k	http://dip.doe-mbi.ucla.edu	Literature
HPRD	30k, 40k	http://www.hprd.org	Literature
IntAct	56k, 267k	http://www.ebi.ac.uk/intact	Literature
MINT	30k, 90k	http://mint.bio.uniroma2.it/mint	Literature
STRING	5200k, ?	http://string-db.org	Literature, Prediction

Source: Goh and Wong, Network-Based Proteomics, Imperial College Press

Protein-Protein Interaction Networks

- Need to distinguish between transient and stable interactions (70% of interactions are stable and 30% are transient).
- Loss of time and spatial effects (not all interactions occur at the same time, or in same space).
- Unknown False Positive, False Negative rates.
- Network structure may be misleading due to bias in studies.

Gene Regulatory (Transcriptional) Networks

- Captures information between transcription factor and target gene.
- Is usually a bipartite system:
 - 2 types of nodes (TFs, target genes)
 - 1 type of edge (regulation)
 - TFs bind to genes, TFs do not bind to each other, genes do not bind to each other)
 - Typically tested using Chromatin-Immunoprecipitation (ChIP) assays

Gene Regulatory (Transcriptional) Networks

- Need to distinguish between True Positives and False Negatives.
- Loss of time and spatial effects.
- Difficult to establish if a physical interaction is indeed meaningful.
- Ambiguous regulatory elements.
- Hard to detect weak binding effects.
- Usually difficult to study due to the lack of bipartite network analysis methods.

Gene Regulatory (Transcriptional) Networks

Where to find them?

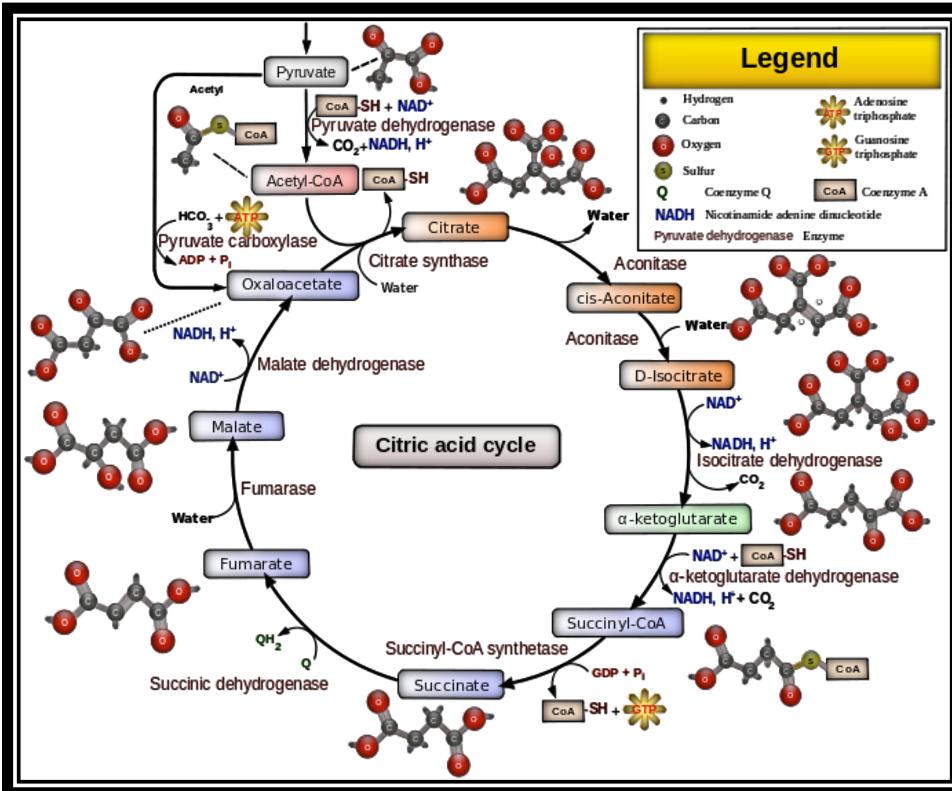
- GeneNet
- EcoCyc
- KEGG
- RegulonDB
- Reactome
- TRANSPATH
- TRANSFAC

Metabolic Networks

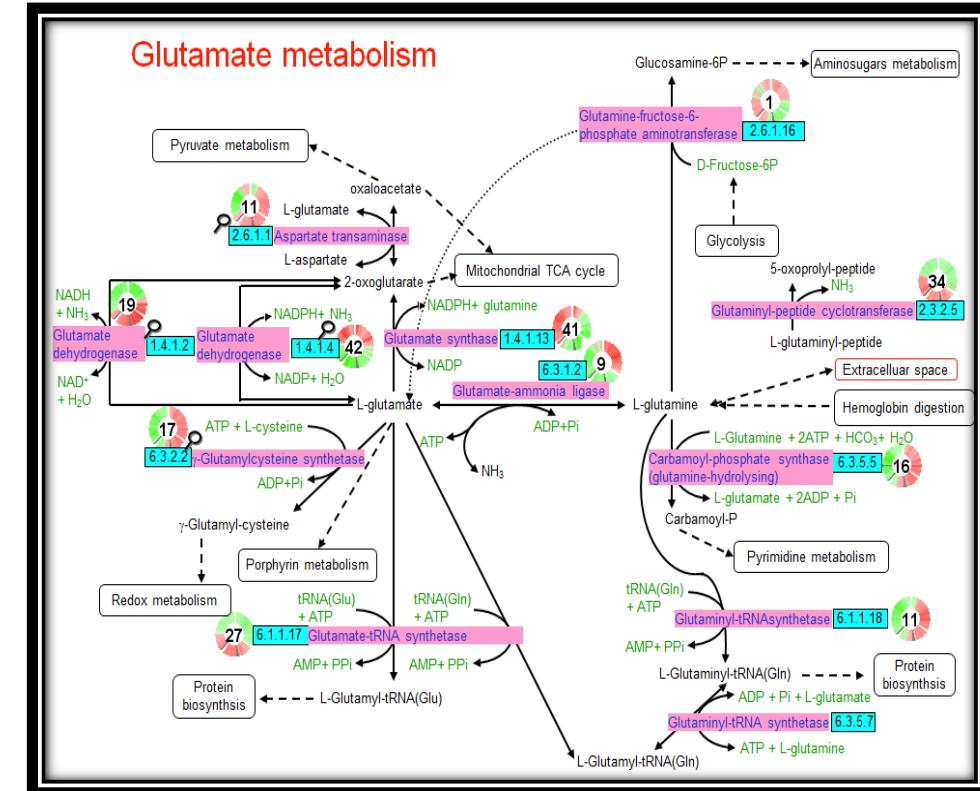
- Processes involved in energy generation, growth, maintenance, etc.
- Can comprise of proteins linked together by a metabolite e.g in Protein A->B, the substrate of B is the product of A.

Metabolic Networks

Some examples



Source:
[https://med.libretexts.org/Bookshelves/Nutrition/Book%3A_Intermediate_Nutrition_\(Lindshield\)/10%3A_Macronutrient_Metabolism_Micronutrients/10.4%3A_Riboflavin/10.4A%3A_Riboflavin_Functions](https://med.libretexts.org/Bookshelves/Nutrition/Book%3A_Intermediate_Nutrition_(Lindshield)/10%3A_Macronutrient_Metabolism_Micronutrients/10.4%3A_Riboflavin/10.4A%3A_Riboflavin_Functions)



Source: <http://mpmp.huji.ac.il/maps/glutamatemetpath.html>

Metabolic Networks

- Incomplete coverage -> many pathways are incompletely covered e.g. in apoptosis 11%-16% (Gene Pair Agreement Percentage) and 32%-46% (Gene Agreement Percentage).
- For all pathways, the ranges are 0%-88% (Gene Agreement Percentage) and 0%-61% (Gene Pair Agreement Percentage).
- Integration across pathway databases is a non-trivial problem.

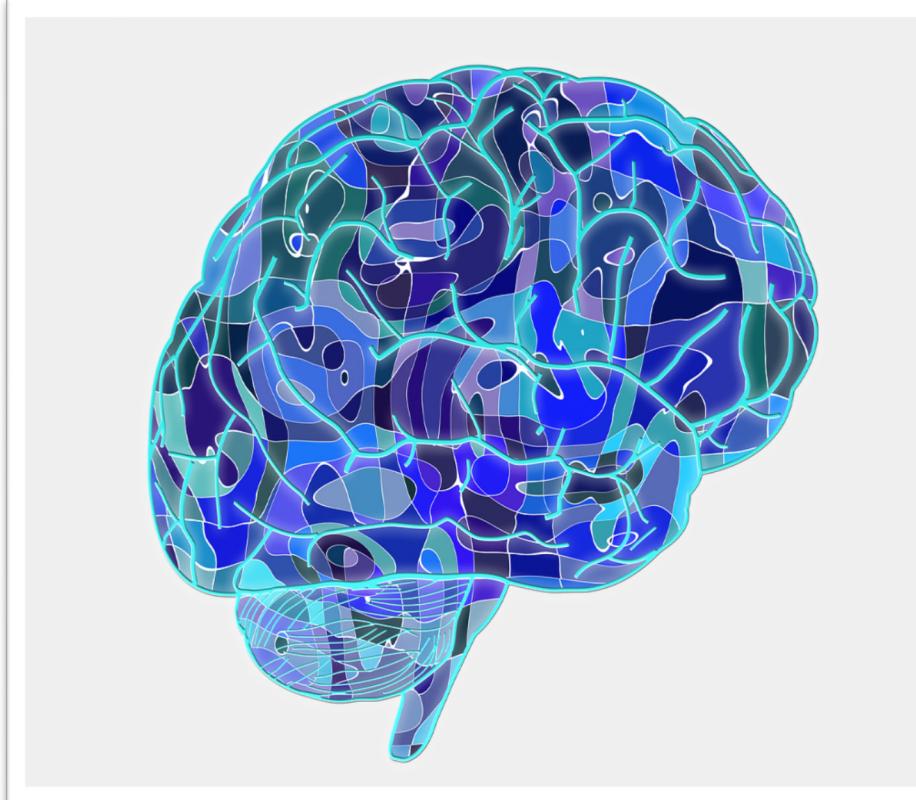
Metabolic Networks

Where to find them?

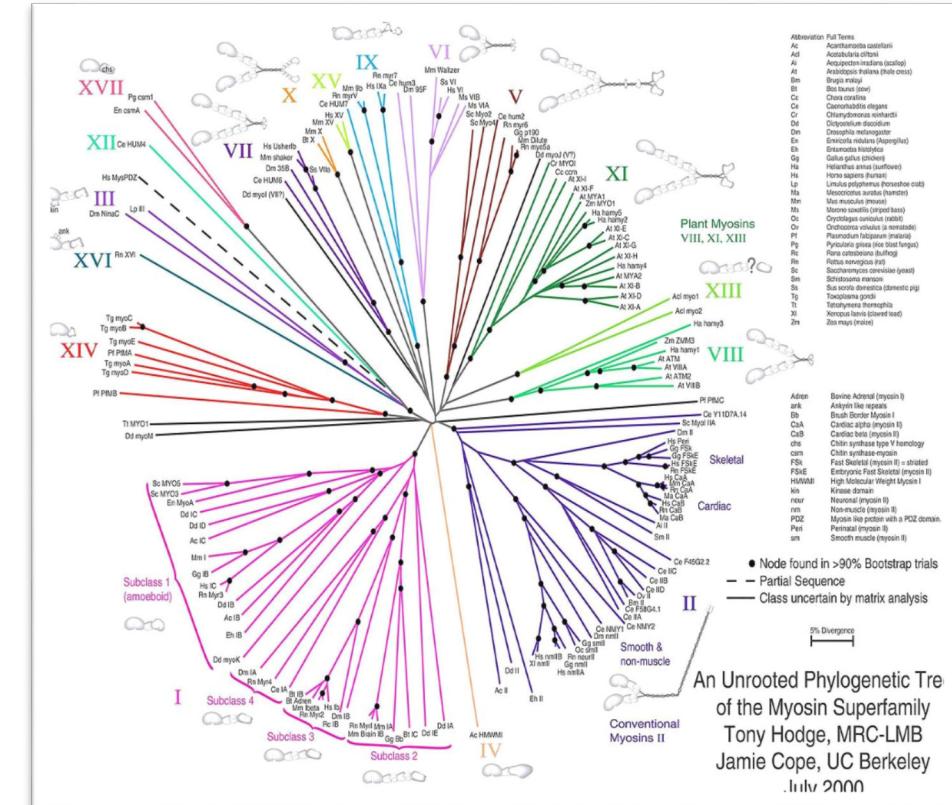
- KEGG (Kyoto Encyclopedia of Genes and Genomes)
- WikiPathways
- BioCyc, EcoCyc, MetaCyc
- WIT, renamed to ERGO
- PathwayAPI
- IntPath
- Ingenuity Pathways (IPA)

Other Networks

Neural Networks



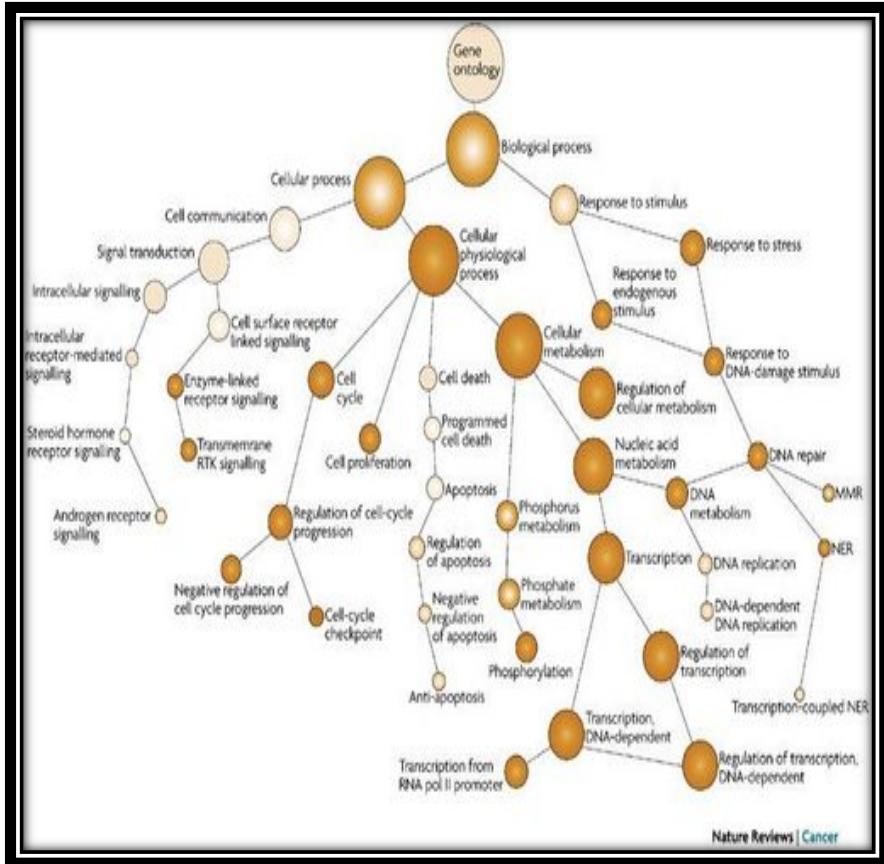
Phylogenetic Trees



By T. Hodge and M.J.T.V. Cope - [<http://www.mrc-lmb.cam.ac.uk/myosin/trees/trees.html>] T. Hodge and M.J.T.V. Cope (2000). "A Myosin Family Tree". Journal of Cell Science 113: 3353-3354., CC BY 1.0, <https://commons.wikimedia.org/w/index.php?curid=1343805>

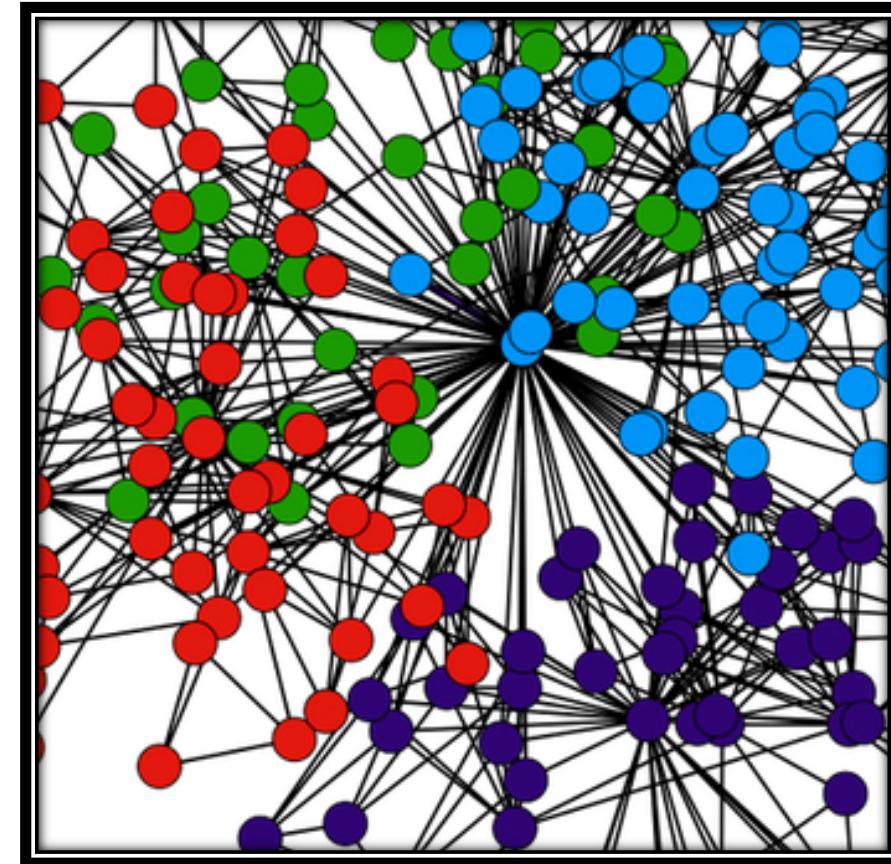
Other Networks

Gene Ontology



Source: <https://www.nature.com/nrc/#search-menu>

Correlation Networks



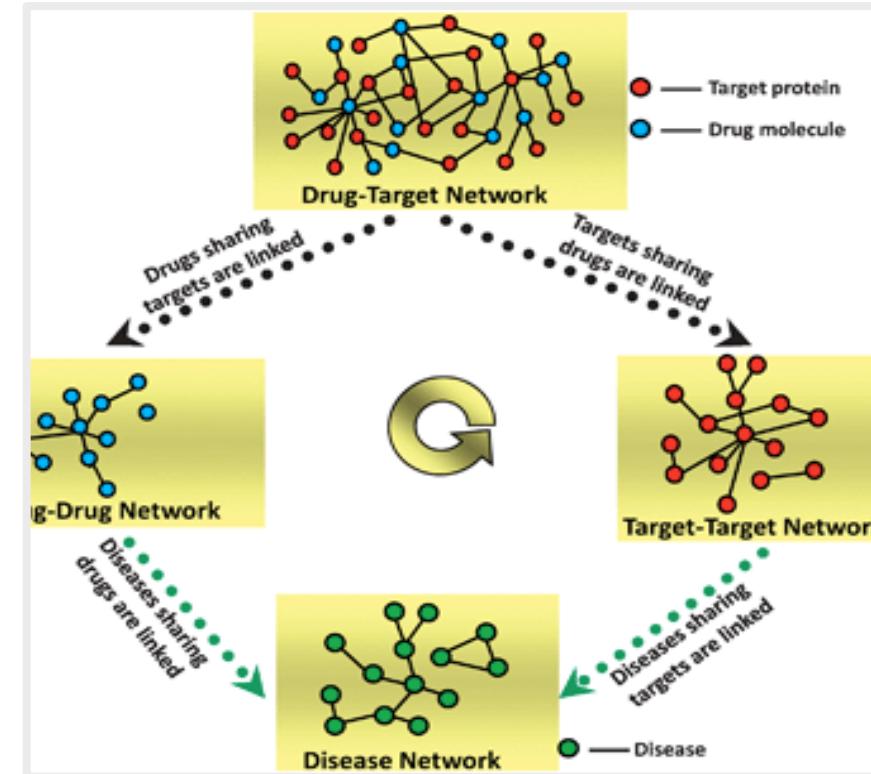
Other Networks

Disease Network



By Empetrisor - Own work, CC BY-SA 4.0,
<https://commons.wikimedia.org/w/index.php?curid=68603787>

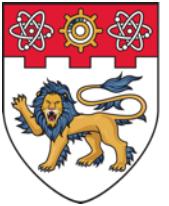
Drug Target Network



Janga, S. and Tzakos, A. (2009). Structure and organization of drug-target networks: insights from genomic approaches for drug discovery. *Molecular BioSystems*, 5(12), p.1536.

What to do with all these biological networks?

- It is important to recognize that all of these biological networks are in themselves abstractions. Each focuses on 1 aspect of biology.
- The ‘true’ biological network comprises all possible entities (DNA, mRNA, proteins, metabolites), and all types of edges e.g. regulation, physical binding, etc).
- What do you think is the problem with modelling a ‘true’ network?
- What will the network statistics tell us?



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Networks Leverage on Biological Context

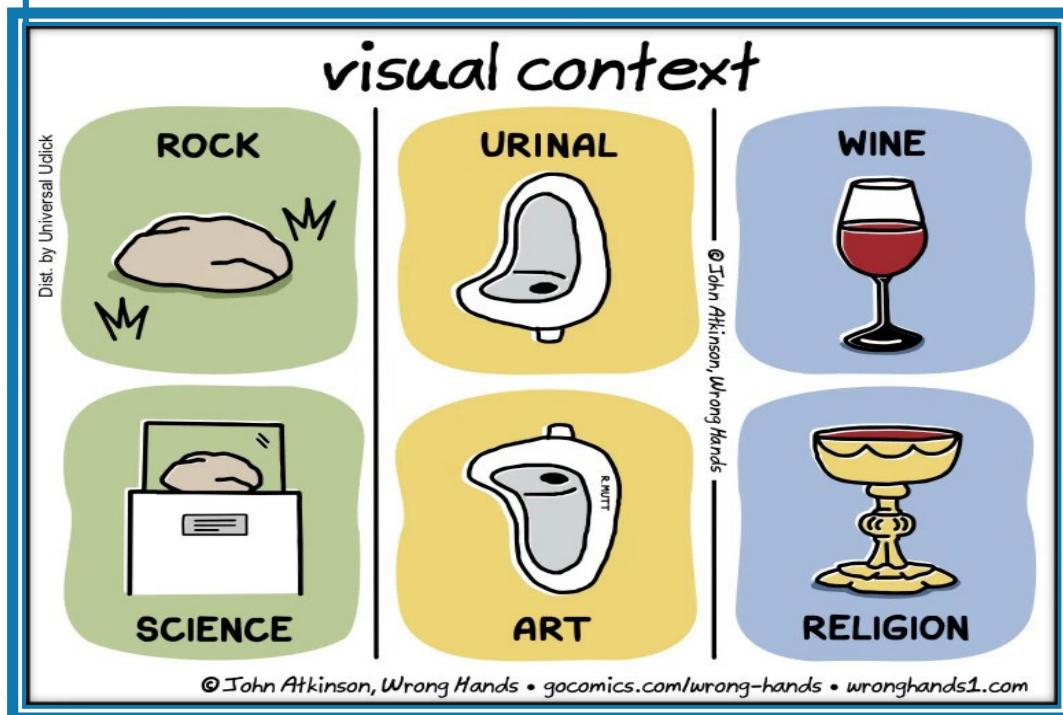
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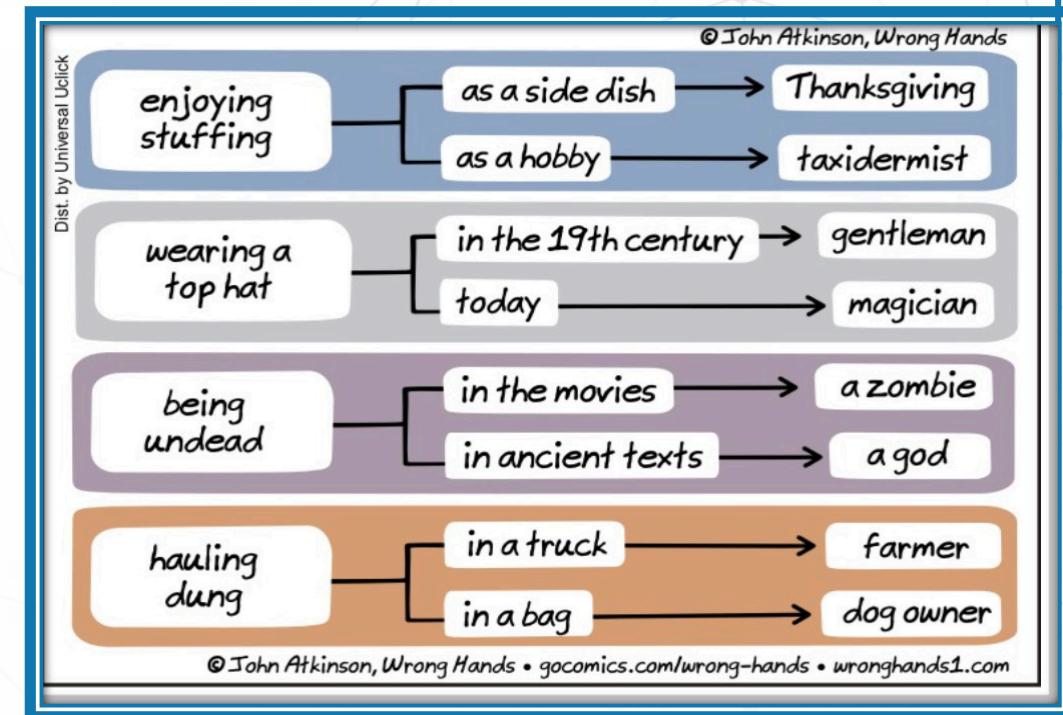
Context

The term ‘context’ is a noun. It is the circumstances that form the setting for an event, statement, or idea, and in terms of which it can be fully understood.



Source: Creative Common License

<https://wronghands1.files.wordpress.com/2017/07/visual-context.jpg>



Source: Creative Common License

<https://wronghands1.files.wordpress.com/2017/02/contextual.jpg>

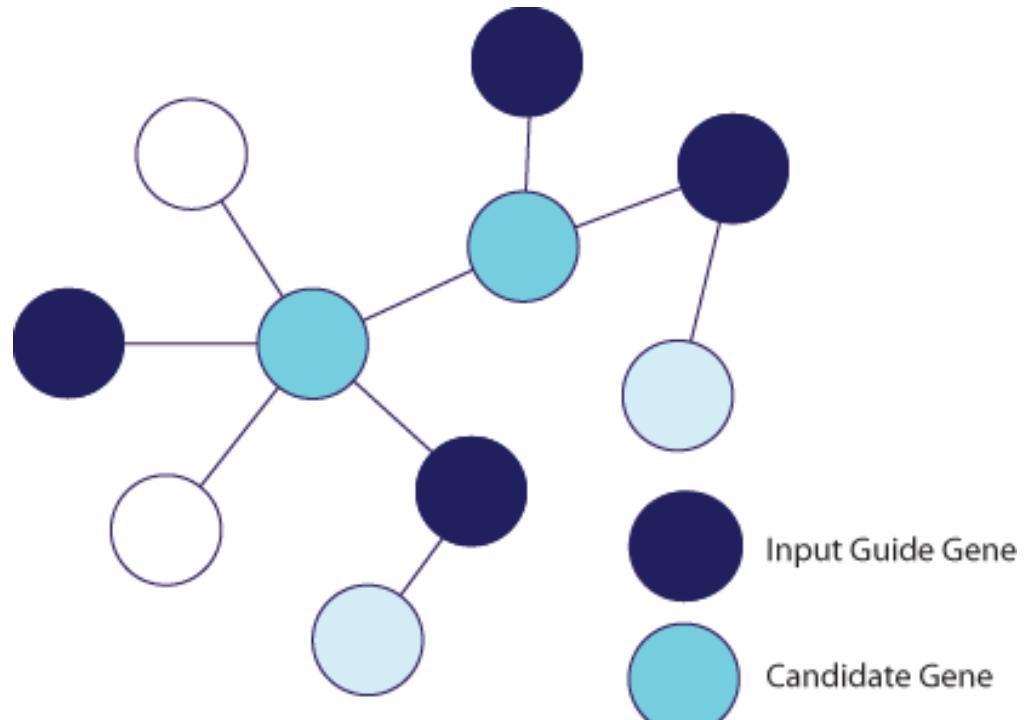
Context

Gene networks:

- Genes do not function independently of each other but rather in networks (such as a biochemical pathway or protein interaction network).
- When several components of a single network are affected, we can generally deduce that this network (including the unobserved components) is important to the phenotype.
- We may leverage on this context to perform better analysis.

Networks are a form of “guilt-by-association” analysis

Predicting “new” candidate genes



<https://www.inetbio.org/wheatnet/search.php>

Predicting new candidate genes for your biological pathway of interest can be accomplished by exploiting direct linkages. To predict candidate genes of your interest, submit a set of genes that are known to participate in a particular biological pathway. These submitted genes are used as '**guide genes**' to search for novel candidate genes. The predicted candidate genes are prioritized by summing the edge scores that are directly connected to guide genes. Highly ranked candidate genes are potentially new members of a pathway. The MaxLink algorithm uses this intuition.

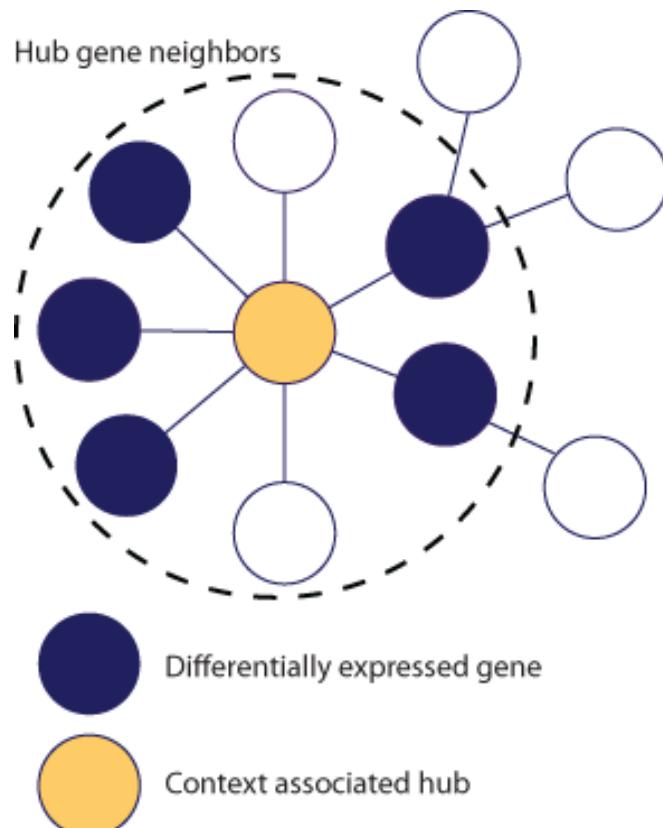
<http://www.mcponline.org/content/9/4/648.full>

<https://academic.oup.com/bioinformatics/article/30/18/2689/2475609>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3784647/>

Networks are a form of “guilt-by-association” analysis

Identifying “invisible causes”

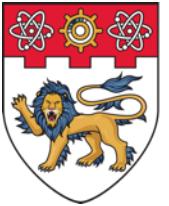


<https://www.inetbio.org/wheatnet/search.php>

Many differentially expressed genes (DEGs) are derived from expression measuring experiments with specific conditions reflecting particular biological contexts. However, DEGs are often results of a treatment rather than the cause. To elucidate the causal genes, we search for ***Context associated hubs***.

Context associated hubs are genes that have dense linkages to a set of DEGs. Since the hub genes have significantly enriched number of DEGs as neighbors, it has a high possibility of being a regulator of a biological context (“Guilt-by-Association”). The Functional Class Scoring algorithm uses this intuition.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3805323/>
<https://doi.org/10.1093/bib/bbx128>



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Summary

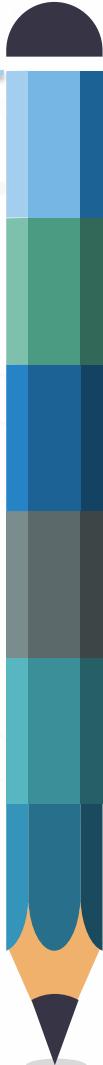
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Key Takeaways from this Topic

- 
1. A network is an abstraction of a complex system describing the relationships amongst a set of nodes.
 2. A network G may be described as its set of nodes, V and set of edges, E i.e., $G = \langle V, E \rangle$.
 3. The degree is a measure of centrality based on the number of connections of each node to others.
 4. The clustering coefficient is a measure of robustness based on how connected a node's neighbours are.
 5. There are many different kinds of social and biological networks.
 6. Network analysis is a form of 'guilt-by-association' analysis. We can use this for predicting missing components or underlying causes.

References (Recommended)

Books

- Newman, M. Networks: An introduction. Oxford University Press, 2010.

Batch Effects

- Goh WWB, Wong LS. Integrating networks and proteomics: moving forward. *Trends in Biotechnology*, 34(12):951-959, Dec 2016.