

Comparing the Circadian Rhythm Cell Signalling Pathways of *Neurospora crassa* and *Aspergillus flavus* Using CMP

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Figure 1: *Aspergillus flavus*. Image from Medmyco (https://commons.wikimedia.org/wiki/File:Aspergillus_flavus.jpg, cropped to fit)

ABSTRACT

Cell signalling pathways are an extremely helpful tool for learning and analyzing how proteins interact within a cell and how those small interactions correlate to bigger systems. However, the creation of these pathways are usually done manually and require specific data or preprocessing of the data. In this paper, we use a program we created and a graphing tool to automatically graph the circadian rhythm cell signalling pathways of *Neurospora crassa* and *Aspergillus flavus*. We compare these using the orthology of the proteins in the pathways and discover that the circadian rhythms of *Neurospora crassa* and *Aspergillus flavus* have a lot in common.

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CCS CONCEPTS

- Applied computing → Biological networks.

KEYWORDS

fungi, orthologous, circadian rhythm, cellular signalling pathway, protein-protein interactions (ppi)

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1 INTRODUCTION

Due to the interestingness of circadian rhythms and complexity of cellular signalling pathways, for our humble project we compare the circadian rhythm pathways of only 2 fungi, *Neurospora crassa* and *Aspergillus flavus*. Using the CMP program, we compared what proteins are and aren't orthologous between the pathways

and graphed this visually so we could see which parts of the circadian rhythm pathways were significantly different or similar between fungi. Finally, we analyzed why sections of the pathway were similar, simpler or more complex and what the benefits of each were.

1.1 Circadian Rhythms

Even with varying bedtimes and wake up times, people typically live on a 24-hour cycle. This process is known as the circadian rhythm. The circadian rhythm is an internal and natural process which repeats roughly every 24 hours and is known for regulating the sleep-wake cycle [1]. Many organisms have some form of circadian rhythm and have been observed in animals, plants and even fungi and cyanobacteria [1]. Circadian rhythms are adjusted by external cues called zeitgebers, and these include light, temperature, and redox cycles [1]. The driving force of the circadian rhythm is the circadian clock. The circadian clock is a biochemical oscillator which cycles using a stable phase while also being synchronized with solar time [2]. Circadian clocks consist of three major components, a central biochemical oscillator, input pathways to the central oscillator, and output pathways tied to distinct phases of the oscillator [2]. These are all put together using cell signalling.

1.2 Cell Signalling Pathways

Cell signalling is how the cells of an organism signal to each other what to do. Signals are usually propagated using different types of proteins, although other molecules are also used. The way the signal is propagated from a protein to another protein to yet another protein can be mapped to a directional pathway. Pathways are not always linear and can be very complex as sometimes multiple different proteins are needed at the same time to propagate signals and signals can be propagated at the same time to different proteins. Visually mapping the pathways is very important for helping scientists and doctors understand how biological systems work at the cellular level and how different medicines affect the pathways at a chemical level.

2 CMP PROGRAM

To achieve our goal, we developed a Python program that reads in and compares the list of proteins of 2 organisms, the orthology between the 2 organisms and other data. There were 3 different databases used for this:

- Circadian Gene Database (CGD)
- Orthologous MAtrix Project (OMA)
- STRING Database

CGD was used to find the lists of circadian rhythm proteins [3]. OMA was used to find orthology between the proteins of organisms [16-33]. STRING was used to graph the output of the program for better visualization and analysis [4-15].

For 2 organisms A and B, the program outputs 8 different sets of proteins as text files: Imperfect Union (A,B), Perfect Union (A,B), Imperfect Except (A,B), Perfect Except (A,B), Imperfect Union (B,A), Perfect Union (B,A), Imperfect Except (B,A) and Perfect Except (B,A). The next few sections will explain, first, the reason why the

Union sets are ordered, then what Union and Except sets are, and, finally, the difference between Imperfect and Perfect sets.

2.1 Why Order Matters for Union Sets

Some proteins of organism A can be orthologous to many proteins in organism B and vice-versa. Therefore, for the union of orthologous proteins in A and B the program would have to create a node that combines all proteins orthologous with each other. This was infeasible as for the graph part STRING only takes a list of proteins so we would need to create or use some other graphing software for the project. Simplifying the graph of the pathway may also be destructive to information about the proteins. Instead, Union (A,B) is the set of proteins in A that are orthologous to some protein in organism B and Union (B,A) is the set of proteins in B that are orthologous to some protein in organism A.

2.2 What are Union and Except Sets

There are 2 set operations this program performs on the proteins of the 2 selected organisms: Union (U) and Except (-). As mentioned in the previous section, the Union operation is slightly different from the well-known set operation as it does not consolidate the 2 input sets. The Union operation takes the sets of proteins for 2 organisms, A and B, and the orthology between them and returns the subset of proteins of organism A that are orthologous to some protein of organism B. The Except operation takes the same input but does the opposite of the Union function: it returns the subset of proteins of organism A that are not orthologous to any protein of organism B.

2.3 Imperfect vs. Perfect

The difference between Imperfect and Perfect sets is that Imperfect sets have proteins that are orthologous to proteins that may not be part of the circadian rhythm pathway in the other organism. If that did not make sense, here is the explanation again in logical form.

Protein A from Organism X is orthologous to a set of proteins P of Organism Y. For some protein Q in P, Q may or may not be a protein of the cellular signalling pathway being studied in Organism Y. Suppose Q is not. Do we keep that A is orthologous to Q? The Imperfect set keeps the orthology between A and Q and the Perfect set does not.

2.4 Output

Now that that has all been explained, let us go back to the overview of the algorithm. So the program outputs to the ./output/text directory the 8 different sets of proteins as text files. Each protein in the text file is represented by its OMA id and the proteins are separated by newlines. For Union set text files, each protein also lists the set of proteins orthologous to it using OMA ids and with orthology scores. The program also outputs to the ./output/graphs directory the 8 different sets of proteins and the full set of proteins for each organism, but this time it skips the extra Union set stuff and outputs STRING ids instead of OMA ids. These text files can be directly input to the STRING database to get a graph of the set of proteins, which there are some examples of in the next section [4-15]. Along with all of that, the program also outputs how many

proteins are in each set.

We used the program to compare and analyze the phylogeny of the circadian rhythm pathways of the fungi, *Neurospora crassa* and *Aspergillus flavus*.

In this paper we use the program to compare and analyze the phylogeny of the circadian rhythm pathways of the fungi, *Neurospora crassa* and *Aspergillus flavus*.

3 RESULTS

The STRING database can provide a graph of proteins which shows the connection between proteins and the confidence of which the nodes are connected [4-15]. For the edge confidence the thickness of the line determines the confidence of the connection, STRING uses the following four values for confidence, 0.150 (low), 0.400 (medium), 0.700 (high), and 0.900 (highest) [4-15]. The value of 0.150 represents the thinnest line, while 0.900 represents the thickest line. STRING provided an average clustering coefficient, which indicates how connected the graph is, with higher values meaning higher connectivity [4-15]. Finally, STRING provided an average degree node value, which indicates how many interactions a protein has on average in the network [4-15]. The full graphs for *Neurospora crassa* and *Aspergillus flavus* are drastically different.

The *Neurospora crassa* graph contains 1150 protein nodes with not all nodes being connected. The majority of these nodes are densely packed into the middle. The reason these nodes are arranged this way is due to the fact that each of them have an extremely high number of connections, and the average node degree was 20.7 which is clearly located in the middle. The average clustering coefficient was 0.276 which isn't very high meaning a lower connectivity.

The *Aspergillus flavus* graph only contains 148 protein nodes with not all nodes being connected. *Aspergillus*'s nodes were also located more in the middle, but had more of a spread to them instead of being densely packed. The average node degree was 5.8 which is significantly less than *Neurospora*. The average clustering coefficient was 0.335 which isn't very high meaning a lower connectivity, but more connected than *Neurospora crassa*.

The nodes which were not connected in both graphs were due to CGD saying they were, while STRING did not think they were.

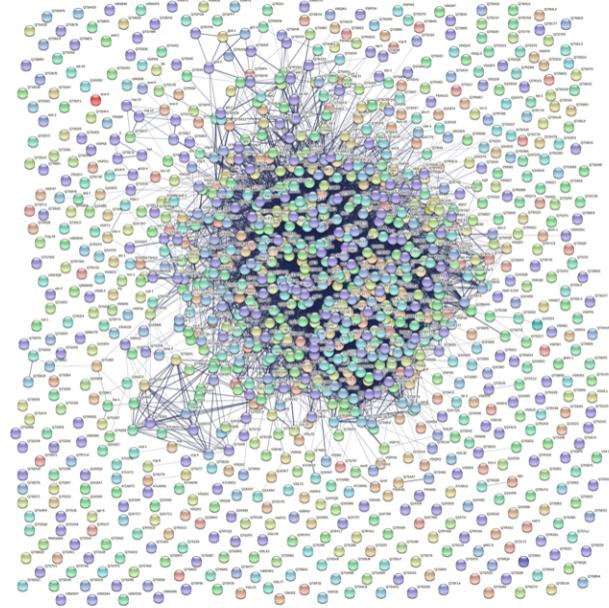


Figure 2: *Neurospora crassa*

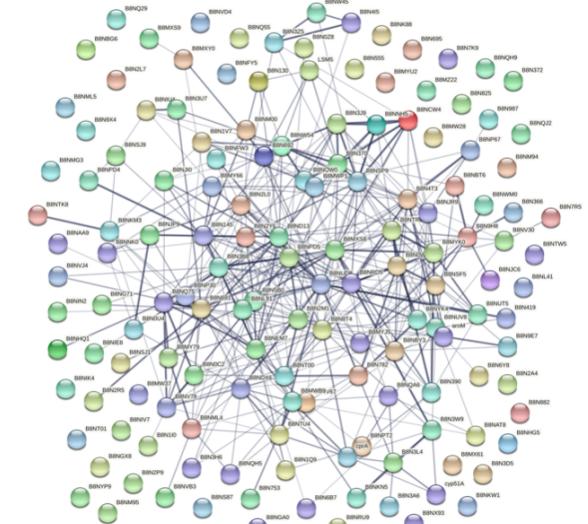
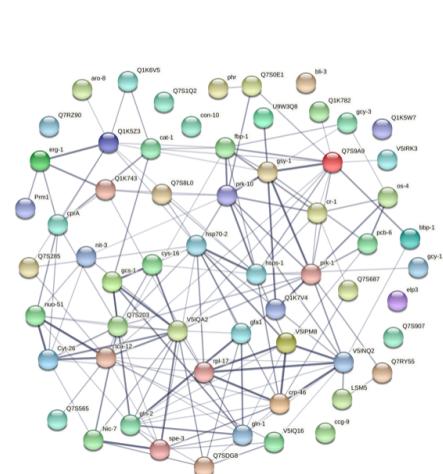


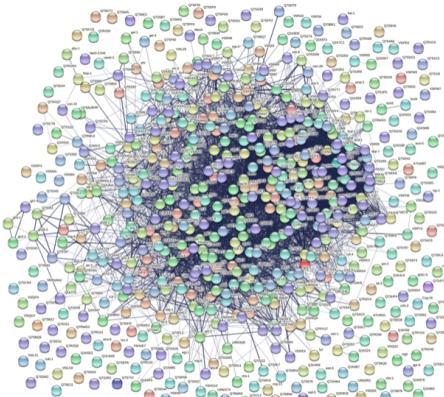
Figure 3: *Aspergillus flavus*

3.1 Order: (*Neurospora crassa*, *Aspergillus flavus*)

While many of the proteins of the *Neurospora crassa* are orthologous to proteins in *Aspergillus flavus*, not many are orthologous to proteins in *Aspergillus flavus*'s circadian rhythm (52.5% of proteins in Imperfect Union → 5.8% of proteins in Perfect Union). This is either because the proteins of the imperfect set but not of the perfect



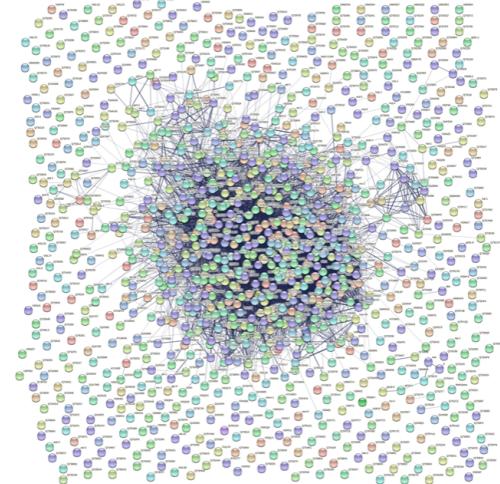
(a) Perfect Union



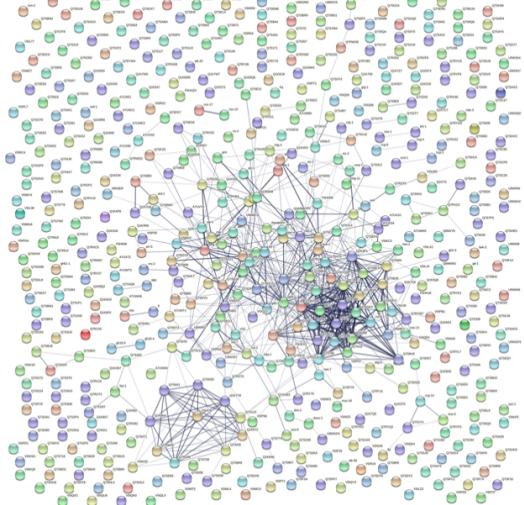
(b) Imperfect Union

Figure 4: Union of *Neurospora crassa*, *Apergillus flavus*

set are loosely connected to the circadian rhythm and propagate input and output signals, and would evolve to or from proteins in other pathways. Or this is because the list of circadian rhythm proteins used is unfortunately out-of-date. If the first is true, then it means more pathways or evolved, more complex pathways use the circadian rhythm in *Neurospora Crassa* than in *Aspergillus flavus*.



(a) Perfect Except

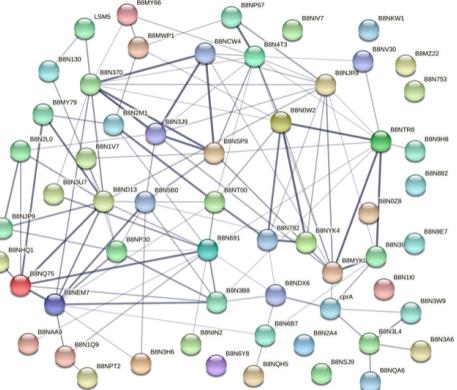


(b) Imperfect Except

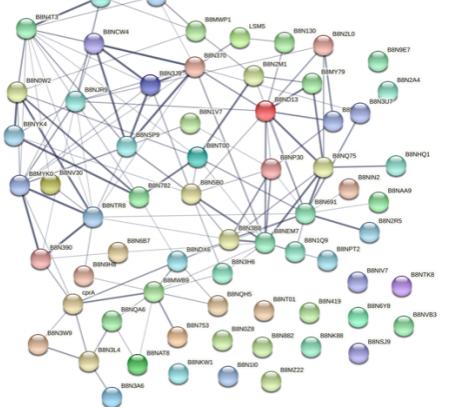
Figure 5: Union of *Neurospora crassa*, *Apergillus flavus*

3.2 Order: (*Aspergillus flavus*, *Neurospora crassa*)

In comparison to the huge disparity between the Imperfect and Perfect Union sets of *Neurospora crassa*, *Aspergillus flavus*'s Imperfect and Perfect Union sets are not very different at all (44.6% of proteins in Imperfect Union → 39.2% of proteins in Perfect Union). This disparity seems to be evidence of a lack of up-to-date knowledge about circadian rhythm pathways by the CGD, or at least an inconsistency in the way the CGD considers some proteins of the circadian rhythm pathway and others not. Thus the previous idea that other pathways have evolved from a few output-signal-propagating proteins is inconclusive for these graphs, but it may still pertain to future, more accurate graphs.



(a) Perfect Union



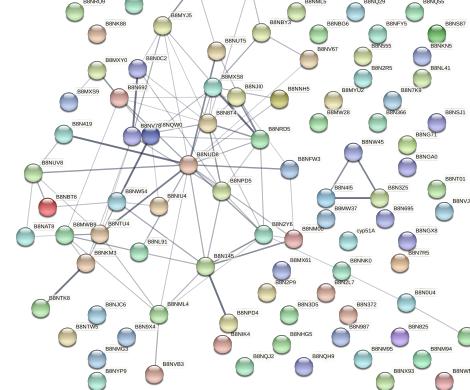
(b) Imperfect Union

Figure 6: Union of *Aspergillus flavus*, *Neurospora crassa*,

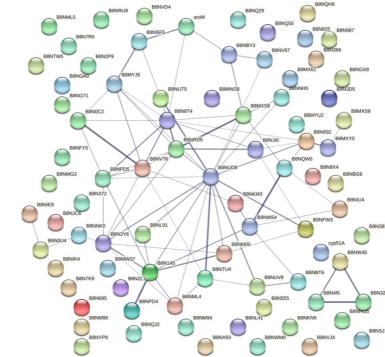
4 DISCUSSION

The project had multiple issues as a result of using 3 databases together. Other than using each protein's sequence, there was no way to map which protein was which in each database and each database didn't always have every protein. On occasion, one database's organism's list of proteins would include proteins from different variants of that organism. Some proteins were labelled as interacting with each other as part of the circadian rhythm pathway according to CGD but had no interactions with other proteins according to STRING. Due to these issues, the process of extracting, comparing and graphing the data was not ideal.

For the future, it would be best to use better curated or not out-of-date databases. The next step in the CMP program that was



(a) Perfect Except



(b) Imperfect Except

Figure 7: Except of *Aspergillus flavus*, *Neurospora crassa*,

infeasible for this project would be to develop a graphing application which would display the pathway similar to STRING. However, instead of assigning the colours to each node as STRING does, we would assign nodes 1 of 2 colours, red and green. Red would indicate proteins are not orthologous, or that the proteins are from the Except set. Green would indicate proteins are orthologous, or that the proteins are from the Union set. This would allow a user to easily see which parts of the pathway are orthologous and which are not. It would also be good if the graph was zoomable and the nodes of the graph were clickable so users can find more information about the protein.

5 CONCLUSION

In conclusion, the CMP Program outputs and the STRING graphs showed that there is indeed quite a bit of overlap of circadian rhythm pathways of *Neurospora crassa* and *Aspergillus flavus*. Graphs of pathway comparisons, along with the numbers, are great tools for analysis and will help scientists and doctors better understand the difference and similarities between and evolution of cellular signalling pathways. By comparing the pathways between organisms, it may also become easier to predict the effects of medicine or the chances of a disease that affects one organism.

affecting another. As a difficult topic currently being researched, furthering our understanding of cell signalling pathways in all their complexity is one of the next steps in the field of Bioinformatics.

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