

# Predicting phage-host relationships using network fusion

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## 1 Introduction

Here we propose a method for predicting the phage-host relationships by combining different sources of information using network fusion techniques.

### 1.1 Motivation

Bacteria are under a constant barrage of phages that act as viruses and integrate their DNA into the bacteria so that the phages can multiply themselves. This is a parasitic relation where the bacteria act as host to carry out the multiplication of the phage DNA. ??

The bacterial communities are very diverse and almost all suffer from attacks by phages. Next to that, there is a lot of information about these attacks found in the DNA of both the phages and the bacteria. This gives interesting ways to indirectly infer what phages attack bacteria. It is an interesting subject to learn more about ecological networks on the micro scale.

In addition, there has been increased interest in the use of phages against bacterial infection. This is caused by an increasing number of antibiotic resistant bacteria. Using phages to kill bacteria can help to better combat bacterial infection. ??

### 1.2 Representing the phage-host relationships in a bipartite graph

Here, we will model the phage-host relations as a bipartite graph. In this graph we model the bacteria and the phages as nodes in a graph. So, in the resulting graph we will have two kinds of nodes. One group of nodes that each represent a kind of bacteria and another that represent a kind of phage.

Phage-host relationships are usually represented as a relation matrix or interconnection matrix in which an edge represents the possibility for a phage to be able to infect the bacteria. We will refer to this matrix as  $C$ . The dimensions of this matrix are  $f \times b$ , where  $f$  indicates the amount of phages and  $b$  indicates the amount of bacteria. Now, each entry of the matrix represents a relation with one particular phage and one particular bacteria.

In addition to the relation matrix, we will also make use of the similarity matrices. We have two similarity matrices. One that indicates the similarity of phages with other phages. This matrix we call  $F$  and has dimensions  $f \times f$  where  $f$  indicates the amount of phages. The other matrix indicates the similarity of the bacteria with the other bacteria. This matrix we call  $B$  and has dimensions  $b \times b$ . Unlike the relation matrix  $C$ , the similarity matrices are symmetrical.

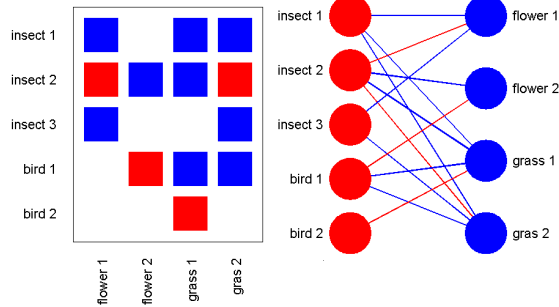


Figure 1: Another example of a bipartite network in ecology. What animals eat what plants. Source: [2]

### 1.3 Modularity and nestedness

Phage-host relationship graphs are often non-random and instead have certain characteristics that are called its modularity and its nestedness.

When we call a bipartite graph modular it means that we can define certain groups that mostly have connections with other nodes in that group, but have less connections with nodes outside the group. Biological, this probably indicates that these bacteria and phages are living together and therefore the phages have mostly evolved to target those specific group of bacteria they can't

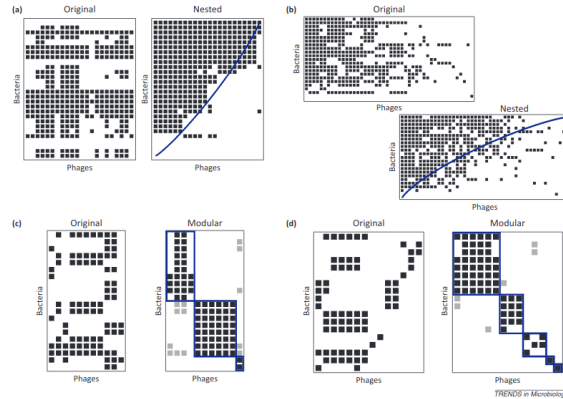


Figure 2: Nestedness vs. modular infection matrices. Source: [6]

When investigating published relation matrices of phage-host relationships based on empirical data, you will find that these matrices are mostly nested. However, they note that this observation might be biased by the environments that have been analyzed in those experiments. Low resource environments for example might eliminate the general phages. Another bias they discovered is that network analysis of microbial communities in food production is often more modular. These communities are most likely selected by those food producers as they are more robust against phage attacks [6].

## 1.4 What data is available

The proposed method tries to use information that is available for as well phage-host relationships as well as phage-phage and bacterium-bacterium relationships / similarities. Here summarized what these kinds of sources of information are.

### 1.4.1 Data sources for phage-host relationships

### 1.4.2 Data sources for phage-phage relationships

### 1.4.3 Data sources for bacterium-bacterium relationships

## 1.5 Network fusion

When creating a network from biological data, a common challenge involves being able to combine multiple sources of information. This problem is known as network fusion.

There are multiple different strategies to solve the network fusion problem. Here we propose to make use of an existing method called similarity network fusion (SNF) [4] with more details here [5]

For a full explanation of the algorithm, consult the papers, but in short, you have to create a similarity network for each source of information and then combine the networks using the following algorithm:

First generate a similarity matrix  $W$  for each of your information sources, then normalize this matrix to create the status matrix. Take the self-similarity as  $\frac{1}{2}$ . Then create a kernel matrix  $P$  by normalizing using the k-nearest neighbours  $N_i$  which results in a sparse matrix  $P^*$ . We will keep using the  $*$  to indicate sparseness by nearest neighbour selection.

$$P(i, j) = \begin{cases} \frac{W(i, j)}{2 \sum_{k \neq i} W(i, k)} & j \neq i \\ \frac{1}{2} & j = i \end{cases} \quad (1)$$

$$P^*(i, j) = \begin{cases} \frac{W(i, j)}{\sum_{i \in N_j} W(i, j)} & i \in N_j \\ 0 & else \end{cases} \quad (2)$$

Here are the update formulas to fuse the different status matrices  $P_v$  and  $P_w$  that represent two different information sources. Repeat the formulas till convergence.

$$\begin{aligned} P_{v,t+1} &= P_{w,t}^* \times P_{v,t} \times P_{w,t}^{*,T} \\ P_{w,t+1} &= P_{v,t}^* \times P_{w,t} \times P_{v,t}^{*,T} \end{aligned} \quad (3)$$

This can be extended to account for more than 2 information sources.

## 2 Related work

As far as I can find, the only computational work done on phage-host relationships involves a single metric which is used to measure the possibility of a phage-host relationship [1]. I could

not find references to an attempt to combine this result or to combine it with phage-phage or bacterium-bacterium similarity. There is however a paper that reports using “iterative weighted distributed averaging” to apply network fusion on bipartite graphs [3].

### 3 Proposed method

#### 3.1 Combining different information

First, the different sources of information for both the phages as the bacteria networks are combined to present a similarity graph for both the phages and the bacteria. For this the standard SNF method can be used.

#### 3.2 Diffusion of the phage-host relationship

Now we have a similarity network for both the phages as the bacteria. The next step will be to ‘diffuse’ the information that exist for phage-host relationships (the connection graph) to other phage-host connection that don’t have this information available. We diffuse the weights to other connections that have the most similar phages or the bacteria.

To do this we first pick what network to use (either the phage-phage  $F$ , or the bacterium-bacterium  $B$ ). (It is probably best to make use of the sparse similarity matrix here,  $F^*$  and  $B^*$ ). Then multiply this with the connection matrix ( $C$ ). This will then move the weights over the strongest connection for each phage or bacterium. When working out the math it will become clear that this method can be done in a single step and has much resemblance to the previous discussed SNF algorithm.

$$\begin{aligned}
C_{t+1} &= F^* \times C_t \\
C_t &= (B^* \times C_{t-1}^T)^T \\
&= C_{t-1} \times B^{*,T} \\
\text{Combined :} \\
C_{t+1} &= F^* \times C_{t-1} \times B^{*,T}
\end{aligned} \tag{4}$$

##### 3.2.1 Alteration to ensure convergence

Since we are alternating between two different similarity matrices, I don’t think it will converge. To make sure the algorithm converges, I propose to alter the similarity matrices every iteration by gradually reducing the percentage of weight that gets moved around until it reaches zero per-cent.

This can be mathematically be accomplished by changing the normalization function so the self-similarity start at some point ( $a(0) = \frac{1}{2}$ ) and gradually grows to one in which case all similarity is the self-similarity (i.e. the similarity matrix is an identity matrix) and no weight is shifted anymore.

$$P^*(i, j) = \begin{cases} (1 - a(t)) \times \frac{W(i, j)}{\sum_{i \in N_j} W(i, j)} & i \in N_j \\ a(t) & i = j \\ 0 & \text{else} \end{cases} \quad (5)$$

$$a(0) = \frac{1}{2}$$

$$a(T) = 1$$

Additionally, this adjustment can help to prevent weights drift to far away and can thereby preserve some nestedness. It is probably also best that this function that is responsible for reducing the amount of shifted weight is convex so that most of the change happens in the first iteration. I believe this will be best to prevent disrupting the nestedness too much.

### 3.2.2 Performing network fusion on the connection matrix

Now we only are left with multiple connection matrices for each source of information on the phage-host relationships. We can however transform the connection matrix in a square matrix ( $M$ ) by adding the missing edges between bacteria and phages as an edge with zero. So, in essence we stack the connection matrix with the similarity matrix of the phages and the bacteria. The resulting matrices can then be fused using the aforementioned SNF fusion algorithm. This can in fact be reduced to applying something similar to the SNF fusion algorithm to the connection matrix directly:

*Full matrix from connection matrix:*

$$M = \begin{bmatrix} 0 & C^T \\ C & 0 \end{bmatrix}$$

*Update rules:*

$$M_{v,t+1} = M_{w,t}^* \times M_{v,t} \times M_{w,t}^{*,T}$$

$$M_{w,t+1} = M_{v,t}^* \times M_{w,t} \times M_{v,t}^{*,T}$$

$$\begin{aligned} M_{v,t+1} &= M_{w,t}^* \times M_{v,t} \times M_{w,t}^{*,T} \\ &= \begin{bmatrix} 0_b & C_w^{*,T} \\ C_w^* & 0_f \end{bmatrix} \times \begin{bmatrix} 0_b & C_v^T \\ C_v & 0_f \end{bmatrix} \times \begin{bmatrix} 0_b & C_w^{*,T} \\ C_w^* & 0_f \end{bmatrix} \\ &= \begin{bmatrix} 0_b & C_w^{*,T} C_v C_w^{*,T} \\ C_w^* C_v^T C_w^* & 0_f \end{bmatrix} \\ C_v &= C_w^{*,T} C_v C_w^{*,T} \end{aligned}$$

### 3.2.3 A note on the order and combination of steps

As can be seen, there are a few different ways to combine all the information. You can for example also apply the network fusion on the connection matrix first and then diffuse it using the similarity matrices. This is also faster because then the diffusion is only applied to one connection matrix and not multiple. I think this might be a worthwhile alternative to investigate.

On the other hand, you can even apply the diffusion using the different sources of the similarity matrices. I, however, don't think that is the best way as it then will start to mix different kinds of information too much too early.

Finally, you can also create the square matrix from the connection matrix by including the similarity weights already instead of setting those edges to zero. I also think that such an approach tries to combine too much information too early. However, it might still be interesting to investigate the affect between forcefully setting the similarities between bacteria and phages to zero or to let them grow as well, or even initialize them to some value (fixed or otherwise).

### 3.2.4 A note on computational complexity

To reduce the computational I propose to make the similarity matrices sparse by only looking at the k-nearest neighbours for each similarity neighbour. This is also done in the SNF algorithm and can also trivially be applied to the aforementioned formulas.

### 3.2.5 Notes on modular vs. nestedness

The approach relies on the assumption that phage-host networks are modular. I assume it would work best in situations where one wants to place unknown bacteria or phages in a spot with already fairly known relationship.

However, it should also work for relative nested networks, but only if it is true that generalized phages and general bacteria are relatively very similar to a lot of other resp. phages and the specialized phages / less targeted bacteria are more unique.

## 4 Summary

The discussed method can be summarized in four steps (not necessarily in this order):

- Find similarity matrices for phage-phage and bacterium-bacterium using network fusion.
- Find connection matrix for phage-host.
- Diffuse the phage-host matrix using the phage-phage and bacterium-bacterium matrix.
- Apply network fusion to the resulting diffused phage-host relationships.

## 5 Further ideas

### 5.1 Maximizing modularity

Although modularity is not an end in itself, a good modular network is something what we expect. That's why it might be worth looking into methods that focus on maximizing the weights on the different information sources, instead of applying the network fusion algorithm. This can be done on the connection matrix alone (and so still have the ability to perform network fusion and diffusion first), but can also be done on the combined matrix with all the phage-phage and bacterium-bacterium information already included. This might however, force the modular network a bit too much.

## 5.2 Using experimentally proven phage-host relationships

There is various experimentally proven phage-host relationships available. These experimental data can be used to enhance the network fusion or to validate our method.

Still, it is important to note that those experimentally reported phage-host relationships might be biased and using it needs caution.

### 5.2.1 Enhancing the proposal with some semi-supervised method

It might be possible to use this as an alternative information source that can make certain relationships more important than others because of it being experimentally proven, or can be used in some semi-supervised learning way.

### 5.2.2 Validation

This source of information can however also be used a way to validate our method.

It is perhaps also a good idea to see if certain assumptions we make in this proposal or true for the real world. Especially the idea that phages that infect the same bacteria are more similar to each other and bacteria with the same phages as viruses are more similar to each other.

## References

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