**Gene essentiality (https://en.wikipedia.org/wiki/Essential\_gene), definition**

When people started studying essentiality (first knockout Gene Recombination in the Bacterium *Escherichia coli*), first experiments and results, why they were important.

Why they are essential?

Essential protein domains!!

Origins of essentiality..

The questions involved

1. Minimal number of genes for an organism (Kooning)
2. Essential processes of life
3. ???

Move to large scale - Essentiality.

1. Explanation of the experiments.
2. First, collections of experiments and data in different model organisms,
   1. First knock-out of a gene!!!!!
   2. Synthetic leathality
   3. RNAi
   4. First Protein – Protein interaction experiment, yeast two hybrid (1987).
   5. Individual studies
3. second, the era of high throughput technologies, large scale experiments.
   1. The first large scale experiment, -omics era
   2. Protein interactions screens
   3. First Protein interaction network, which organism,
   4. What followed
4. System biology.
   1. List - table of the high throughput/ large scale experiments in molecular biology

Databases with essentiality. Data table.

Also Synthetic lethality.

Question the term essentiality. In terms of :

1. Evolvability (Redefine paper)
2. Differential/ conditional essentiality
3. Modular essentiality in protein complexes, in general modular biology

Essentiality across scales

1. Before??
2. Protein domains
3. Proteins
4. Protein complexes
5. After?

Systems biology approach, computational approach

1. Laborious experiments, not feasible in humans among other species.
2. Homology (after the sequencing of whole genomes),
3. Network (first protein networks, first experiments ???) , others), why is important.
4. ???

**In this work, we focus on the network approach of gene essentiality.**

1. First uses, centrality lethality rule
2. All current methods for network-based essentiality (2-4 paragraphs). Review paper (A comprehensive review)
   1. The best centrality method. How can we include it in our analysis?
3. Protein networks, organisms, data description and limitations
   1. Different levels of protein networks
      1. Protein residue networks (protein folding)
      2. Protein – protein Interaction networks
      3. Protein complex interaction network
   2. The different use of centralities! Influential nodes detection.
4. Structure and function problem (~ Structure, Dynamics, Function problem).. Network approach as structure approach..
5. General view of molecular network biology (this can be really long)
   1. Include microarrays?
   2. Use the list of high throughput techniques

Directions to overcome the current limitations concerning network science and molecular biology in general and to the centrality lethality rule specifically.

1. Integration of different types of data for more biologically correct and rich network construction, still static.
2. Network annotation for complexes and functions (the modular essentiality problem)
3. Temporality of interactions across time and in different responses of the organism
4. Network dynamics (the evolvability problem of essentiality)
5. Multiplex networks. Different networks, with different links of the same nodes
   1. Biological essentiality example…. And importance..
   2. How to analyze them?
6. Hypernetworks
   1. How to use them, added value?
   2. Protein complexes?? Overlapping genes?

**Our aim**

Further, we aim in this work to provide more insight to the centrality lethality rule by expanding the uses of the centralities in signed networks.