CLASSIFYING SIGNS OF REGULATORY INTERACTIONS IN GENE NETWORKS

SMU

Jessica Otah • Rachel Crusius • Dr. Brandilyn Stigler

Introduction

Gene regulatory networks control many life processes. An important problem in systems biology is to reconstruct a model of the network from existing laboratory data. A major challenge is to validate predictions made by these data-driven models. While designing new experiments would be the most desirable, the cost involved is often prohibitive. Gold standard networks (GSNs), which are knowledge-driven models built from existing knowledge, have become necessary tools for validation. Therefore building **comprehensive** GSNs is imperative.

We extended an existing GSN for *C. elegans* by
1. classifying interactions as either positive or negative (***signs***).
2. distinguishing between direct and indirect regulation (***directedness***).

Background

Tissue development in *C. elegans* has been well studied. In [2] the authors presented a preliminary, biological model for the regulatory network based on a wildtype time course data. In [5], the authors extended the model to include interactions from knock-out data; however the authors did not include signs or directedness.
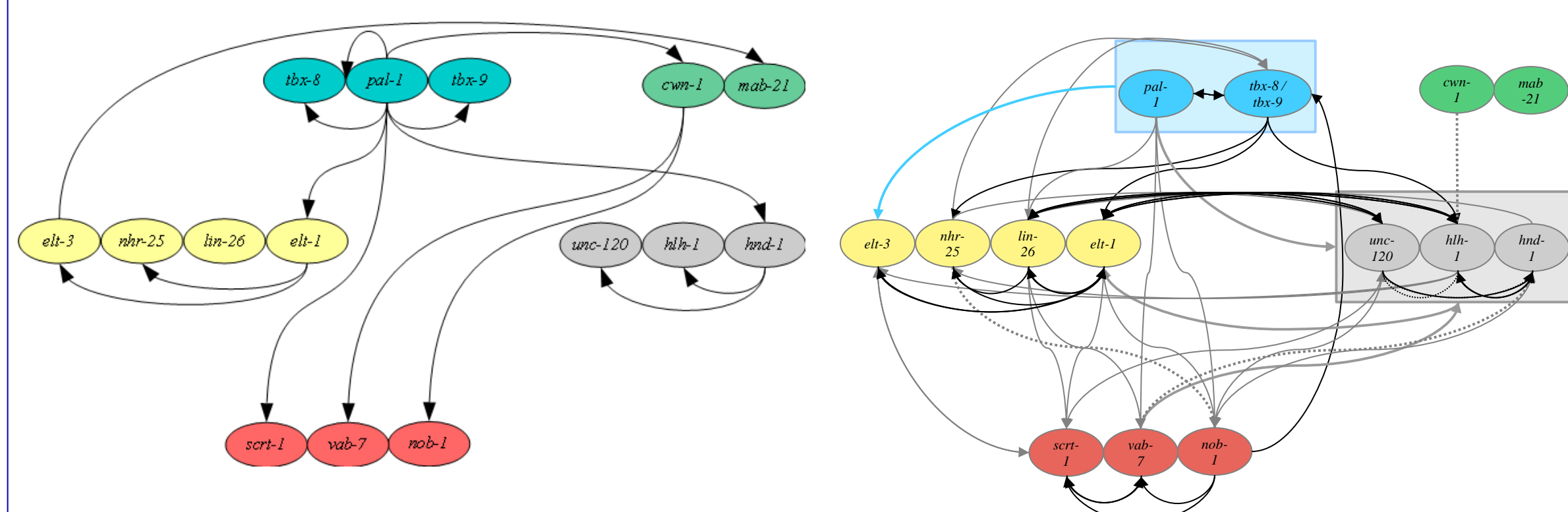

Fig. 1: First GSN, presented in [2].   Fig. 2: Second GSN, presented in [5].

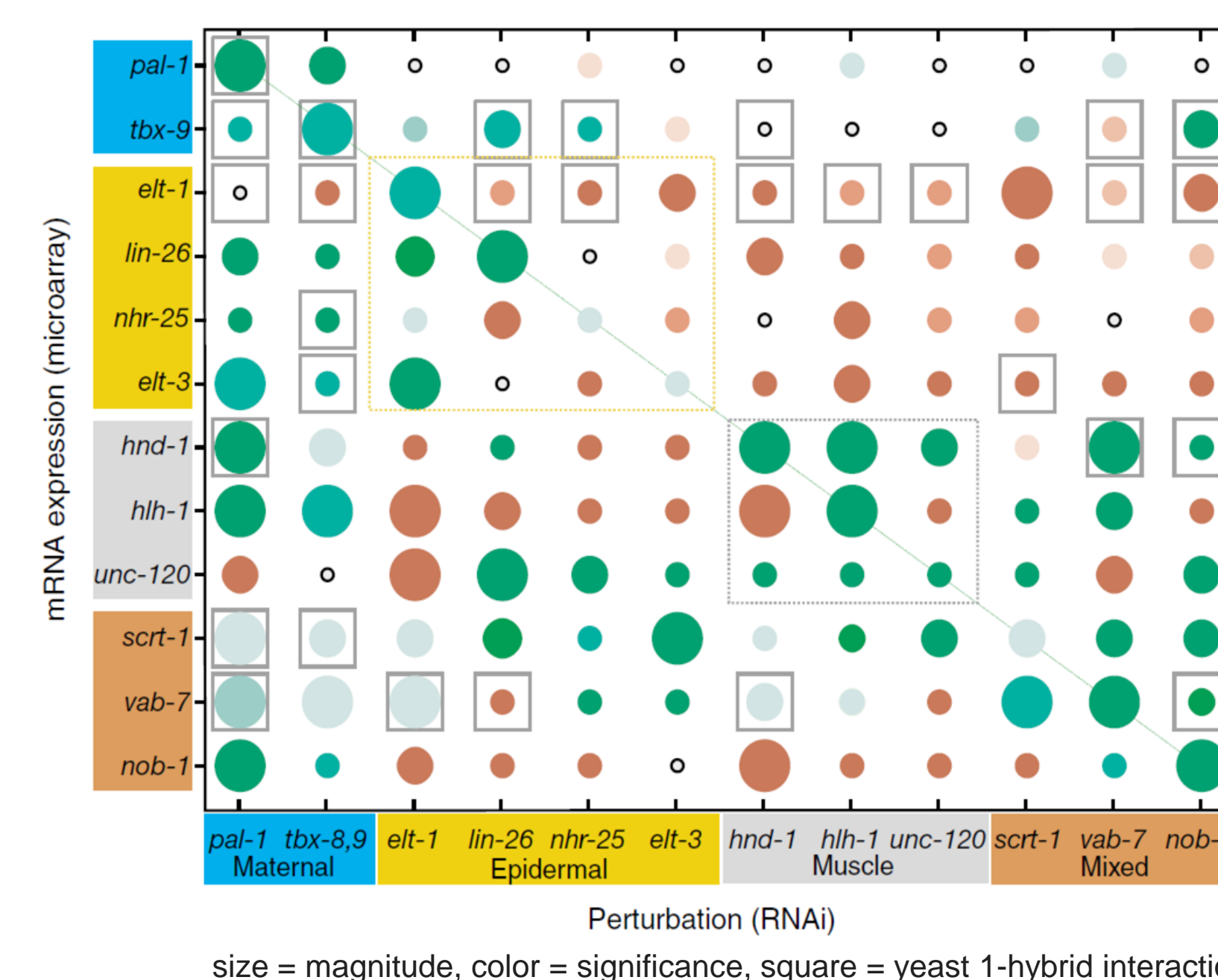The genes in the network can be categorized as follows:
- Blue = maternal genes
- Yellow = ectoderm (skin) genes
- Grey = mesoderm (muscle) genes
- Brown = genes of mixed activity
- Green = other

Data

Several sources were used to infer signs and directedness of the interactions. Most inferences were made from the pairwise knockout experiments shown in the matrix [6].

We also used the following references for targets of the genes listed below. Most experiments were conducted using reporter genes.

- *pal*–1: [1], [2]
- *elt*–1: [2]
- *lin*–26: [4]
- *hnd*–1: [2]
- *hlh*–1: [3]

size = magnitude, color = significance, square = yeast 1-hybrid interaction

Methods

The interactions in Figure 2 were classified according to signs and directedness. Signs and directedness were determined from the matrix above as follows:

- **Positive** regulation was assigned to nodes with a green dot
- **Negative** regulation was assigned to nodes with a red dot
- **Direct** regulation was assigned to nodes with a square
- **Indirect** regulation was assigned to nodes w/o a square

Signs and directedness were determined from the other sources by reading the articles and consulting with an expert [7].

References

1. J. Ahringer (1997). *Development* 124.
2. L. R. Baugh *et al* (2005). *Development* 132.
3. T. Fukushige and M. Krause (2005). *Development* 132.
4. R. Pocock *et al* (2004). *Development* 131:10.
5. B. Stigler and H. Chamberlin (2012). *BMC Systems Biology* 6:1.
6. I. Yanai *et al* (2008). *Molecular Systems Biology* 4:163.
7. H. Chamberlin, Prof. of Mol. Gen., The Ohio State University.

Results
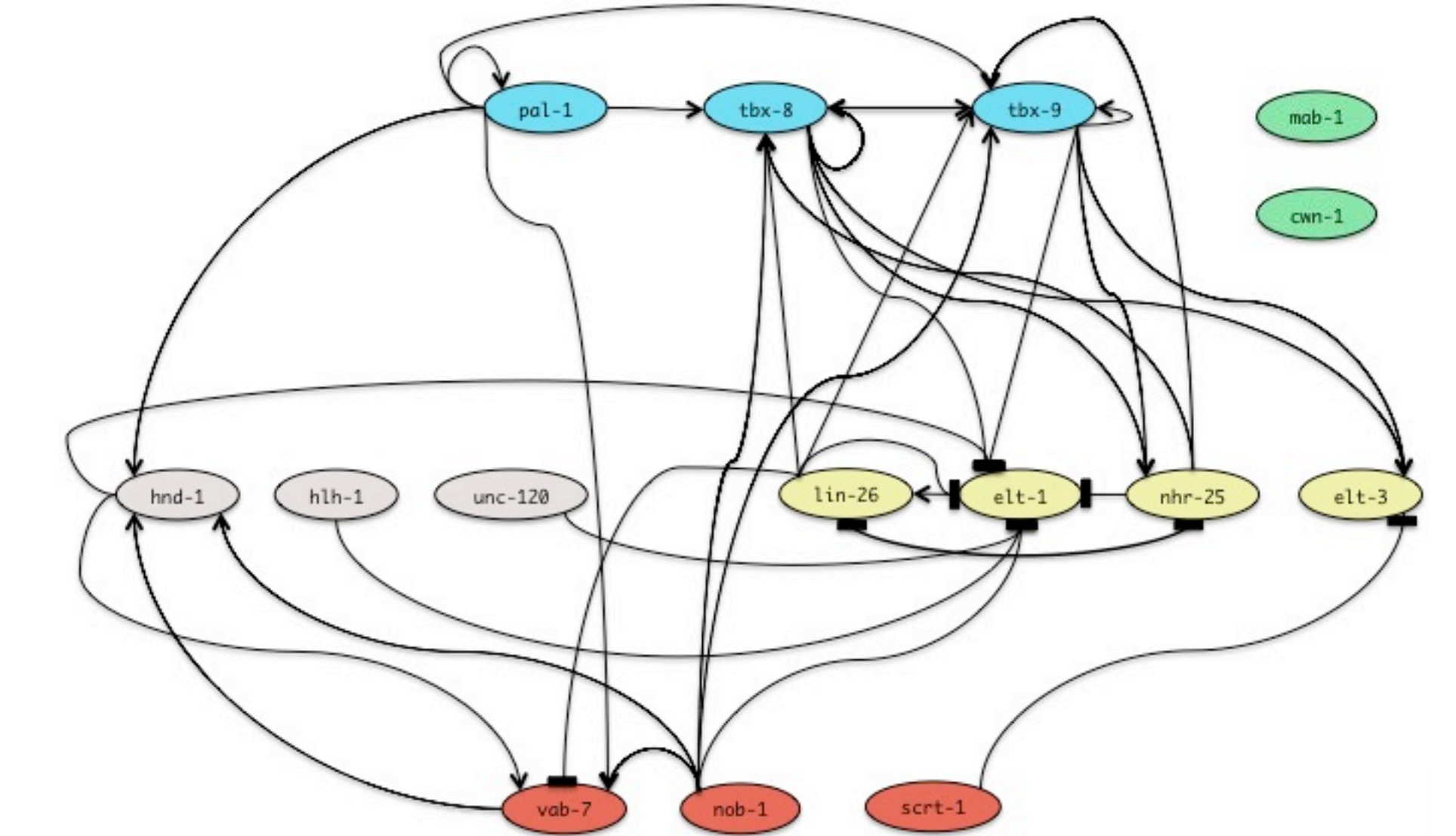
Interactions from Figure 2 proposed to be direct are shown in the figure above along with their signs:
- Arrow end = positive
- Blunt end = negative

All other interactions are indirect and not shown.

Predictions
- Maternal gene interactions are all direct and positive.
- *pal*–1 only directly regulates *hnd*–1 and *vab*–7.
- Regulation between mesoderm genes is indirect.
- All negative interactions involve ectoderm genes.
- Ectoderm genes could be key in negative feedback loops which drive oscillations.

Analysis
Our GSN corroborates several interactions proposed to be direct in [6]:
- *lin*–26 ➜ *elt*–1
- *elt*–1 ➜ *lin*–26
- *lin*–26 ➜ *nhr*–25
- *nhr*–25 ➜ *elt*–1
- *pal*–1 ➜ *hnd*–1
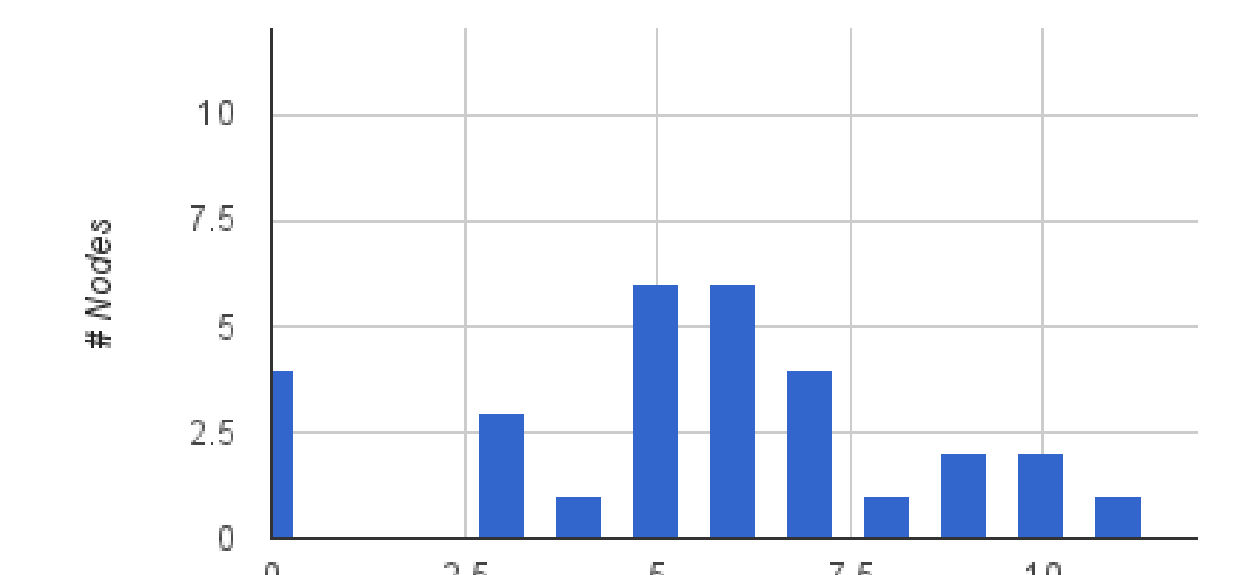
The distributions of the total degree (shown), in-degree, and out-degree for all interactions (shown) and direct interactions suggest that this network does not exhibit scale-free dynamics, as is expected in gene networks.

Discussion

1. We present a more comprehensive knowledge-driven model for *C. elegans* tissue development than currently exists.
2. It can improve validation for data-driven models.
3. It can used in building consensus models.