

ABSTRACT

Title of dissertation: PHASE TRANSITIONS
IN GENE NETWORKS
EVOLVED UNDER DIFFERENT
SELECTION RULES

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Applied Mathematics, Statistics,
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Mathematical models of gene regulation are a powerful tool for understanding the complex features of genetic control. While various modeling efforts have been successful at explaining gene expression dynamics, much less is known about how evolution shapes the structure of these networks. An important feature of gene regulatory networks is their stability in response to environmental perturbations. Regulatory systems are thought to have evolved to exist near the transition between stability and instability, in order to have the required stability to environmental fluctuations while also being able to achieve a wide variety of functions (corresponding to different dynamical patterns). We study a simplified model of gene network evolution in which links are added via different selection rules. These growth models are inspired by recent work on ‘explosive’ percolation which shows that when network links are added through competitive rather than random processes, the connectivity phase transition can be significantly delayed, and when it is

reached, it appears to be first order (discontinuous, e.g., going from no failure at all to large expected failure) instead of second order (continuous, e.g., going from no failure at all to very small expected failure). We find that by modifying the traditional framework for networks grown via competitive link addition to capture how gene networks evolve to avoid damage propagation, we also see significant delays in the transition that depend on the selection rules, but the transitions always appear continuous rather than ‘explosive’.

Phase Transitions in Gene Networks
Evolved Under Different Selection Rules

by

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List of Abbreviations and Notations

Undirected networks

GC Giant component

Directed networks

SCC Strongly Connected Component

IN(i) In component of the node i

OUT(i) Out component of the node i

GOUT Giant OUT component

GBT Giant Bow-tie

GSCC Giant Strongly Connected Component

Chapter 1: Introduction and Background

Changes to gene regulatory networks are thought to be a major driver of evolutionary innovation. While various mathematical modeling efforts have been useful for understanding the dynamics of gene regulatory networks, much less is understood about how these networks have evolved. In order to gain insights into this process, we study simple models of gene network evolution in which links are added according to various selection rules. This chapter provides relevant background for this thesis. In Section 1.1, we discuss Boolean network models of gene regulation. In Section 1.2, we highlight important structural properties of gene regulatory networks. In Section 1.3 we review recent work by Pomerance et al. that demonstrates how complex network topology influences stability in Boolean models of genetic control. In Section 1.4 we highlight how major components of the network change when the network is directed. In Section 1.5, we discuss how the transition to dynamical instability in Boolean networks can be mapped to a percolation problem. In Section 1.6, we discuss recent studies of ‘explosive’ percolation and how this phenomena may be relevant in the study of gene network evolution.

1.1 Boolean models of gene regulation

Boolean networks have been widely used as mathematical models of gene regulation since their introduction by Kauffman in 1969 [20]. In these models, genes exist in one of two states: ‘on’, meaning that the gene is expressed or ‘off’, meaning that the gene is unexpressed. Gene states are synchronously updated at discrete time steps, and the state of a gene at time t is determined by the states of its inputs at time $t - 1$. The interactions between genes are given by a directed network and a set of deterministic *update functions*. The network and update functions are meant to capture the complex biological rules of gene regulation. The update rule for each gene specifies its state at time t for all possible combinations of its inputs at time $t - 1$. For example, the network in figure 1.1 shows that the states of genes B , C and D can influence the expression of the gene A . Figure 1.1 shows an example update function (or truth table) for gene A .

Kauffman’s original $N - K$ networks consisted of N nodes (genes), each with K inputs randomly drawn from the set of $N - 1$ other genes. In this model, the update functions are *time-independent* truth tables in which the 2^K entries in the output column are randomly filled in with a bias b (probability of zero). The *state of the network* at each time step t can be represented by an N -vector whose i th component, x_i^t , 0 or 1, indicates whether gene i is off or on at time t . There are 2^N possible network states. Because the system is finite and deterministic, for each initial condition the system must eventually return to a previously visited state and the subsequent dynamics will be the same as before. The periodic orbit (or fixed

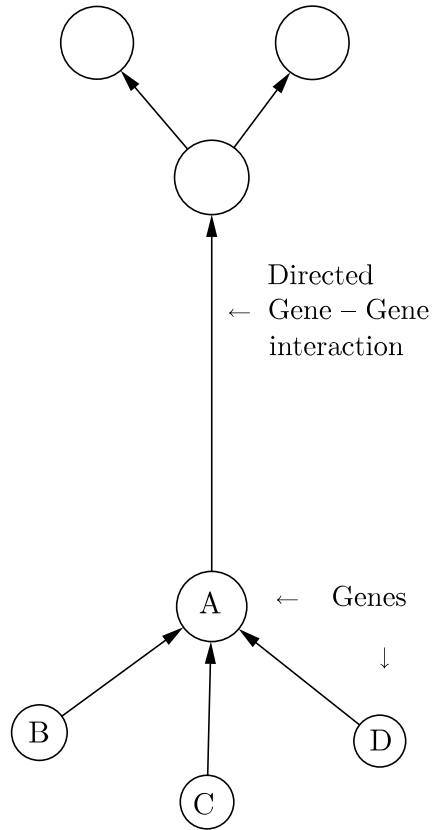


Figure 1.1: An example of a network that models a gene A by a corresponding node. It has three incoming nodes that model genes B , C and D .

time t			time $t + 1$
gene B	gene C	gene D	gene A
0	0	0	1
1	0	0	0
0	1	0	0
0	0	1	1
0	1	1	1
1	0	1	0
1	1	0	1
1	1	1	0

Figure 1.2: Example of a truth table of node A in the network in Figure 1.1. The first three columns denote the values of the nodes B , C and D . The sets values of the nodes are listed in lexicographic order by rows.

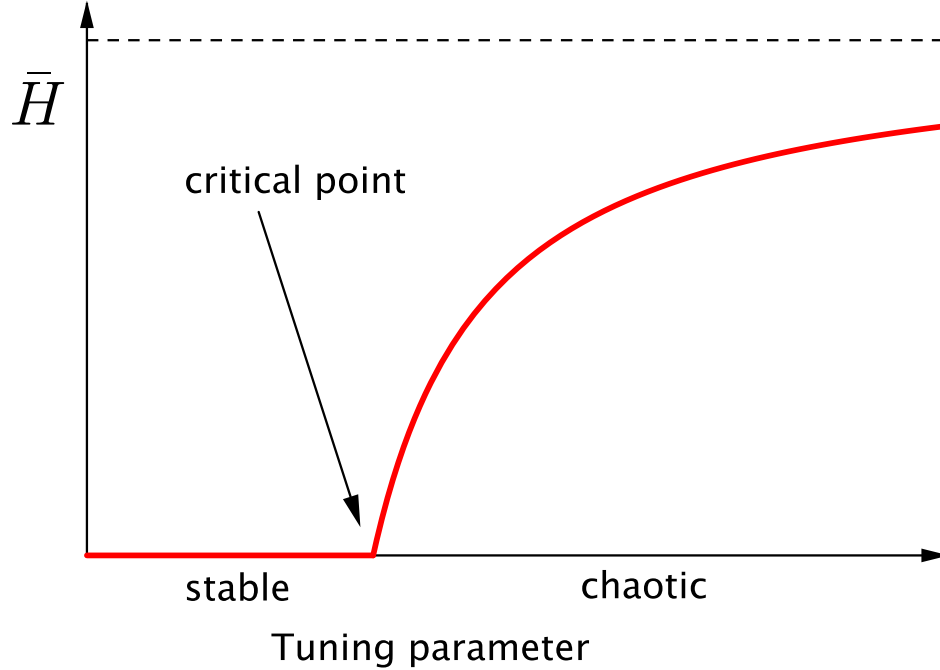


Figure 1.3: As the tuning parameter goes through value P_c the order parameter goes through a phase transition.

point) that is eventually reached is called the ‘attractor’ of the initial condition. Depending on the parameters K and b , these models can exhibit stable or ‘chaotic’ (unstable) dynamics separated by a critical region (Figure 1.3).

Stability is measured by tracking the normalized Hamming distance, \bar{H} , (i.e., fraction of genes whose states differ) as a function of time between two systems evolved from initially close network states, \mathbf{x}^0 and $\tilde{\mathbf{x}}^0$:

$$\bar{H}(\mathbf{x}^t, \tilde{\mathbf{x}}^t) = \frac{1}{N} \sum_i^N |x_i^t - \tilde{x}_i^t|. \quad (1.1)$$

In stable systems, the Hamming distance decays in time, while for ‘chaotic’ systems, it grows in time until a saturated level is reached.

In terms of their biological interpretation, the attractors are thought to corre-

spond to different cell states or different cell types. Real gene networks are thought to exist near the border between stability and instability. Since cells in general shouldn't change state in response to small perturbations like chemical fluctuations, we expect them to have some degree of stability. At the same time, we also expect that cells should be able to achieve a variety of different dynamical patterns (which are mapped to different functions). The combination of these two desired features suggests that gene networks may have evolved their structure and dynamics so that they occupy the 'critical' regime.

1.2 Complex structure of regulatory networks

While networks described by Kauffman's $N - K$ model have simple random structure, empirically derived gene regulatory networks exhibit much more complex structures [14] [15] [16] and illustrated in Figure 1.4. In this Section, we discuss important structural features that are relevant to gene regulatory networks.

For example, many networks, gene regulatory networks included, have degree distributions that are heavy-tailed [6]. The degree of a node is the number of other nodes to which it is connected. In heavy-tailed degree distributions, the median degree is substantially less than the average degree because some nodes have very high degree even though most have relatively low degrees. In undirected networks, the distribution of degrees is prescribed by the values p_k which specify the probability that a randomly chosen vertex will have degree k . In directed networks, the distribution of incoming edges $p_{k_{in}}$ can be different from the distribution of

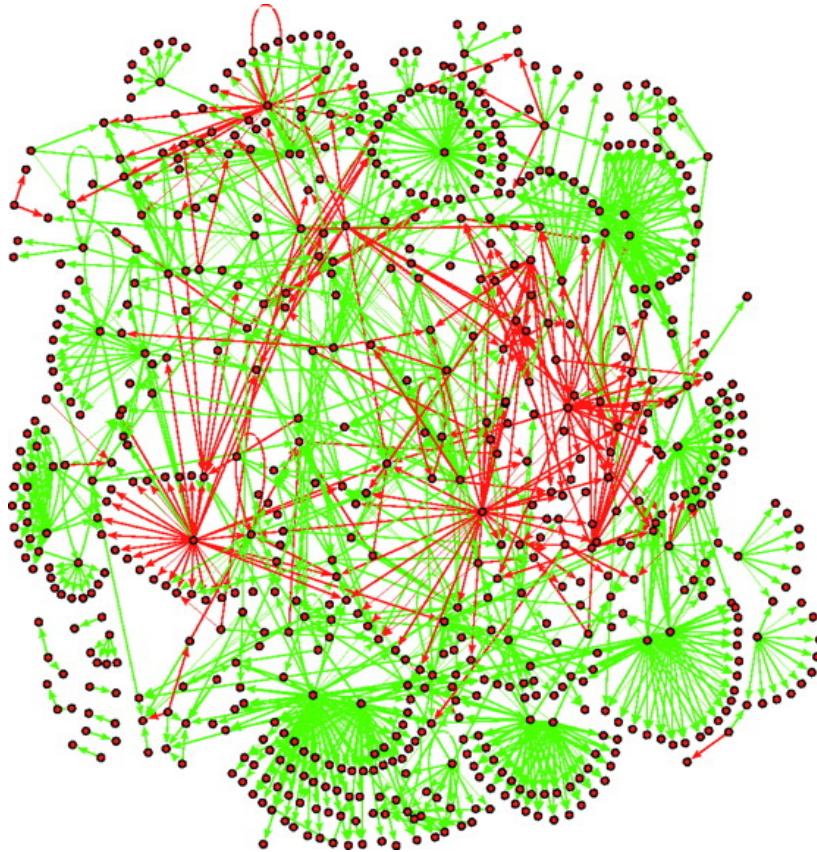


Figure 1.4: Empirically derived gene regulatory network for yeast. The green directed edges indicates that the origin gene promotes expression of the target gene, red edges indicates that the source gene inhibits expression of the target gene. Taken from [13].

outgoing edges $p_{k_{out}}$.

In $N - K$ networks, the $p_{k_{in}}$ is given by a delta function:

$$p_{k_{in}} = \delta(k_{in}, K) \quad (1.2)$$

In the the limit of large N , the out degree distribution is described by a Poisson distribution:

$$p_{k_{out}} = \exp(-K) \frac{K^{k_{out}}}{k_{out}!}. \quad (1.3)$$

Another important structural property relevant to gene regulatory networks is assortative mixing. Assortative mixing by degree occurs when nodes connect preferentially to other nodes with similar degree. A network is said to be disassortative if high degree nodes connect preferentially to low degree nodes. The assortativity coefficient, r , captures the Pearson correlation of degrees of node pairs connected by edges. For undirected networks, the assortativity coefficient [6, 7, 8] can be written as:

$$r = \frac{\sum_{jk} jk(e_{jk} - q_j q_k)}{\sigma_q^2}, \quad (1.4)$$

where e_{jk} is the fraction of the links connection a node with remaining degree k with a node with remaining j . The remaining degree represents the number of connections from a node reached by following a link, not including the link arrived on. The variable q_k specifies the distribution remaining degree and is given by:

$$q_k = \frac{(k+1)p_{k+1}}{\sum_j j p_j} \quad (1.5)$$

σ_q is the standard deviation of this distribution. The value r is 0 for random (neutral) networks, $r > 0$ for assortative networks with positive degree correlations

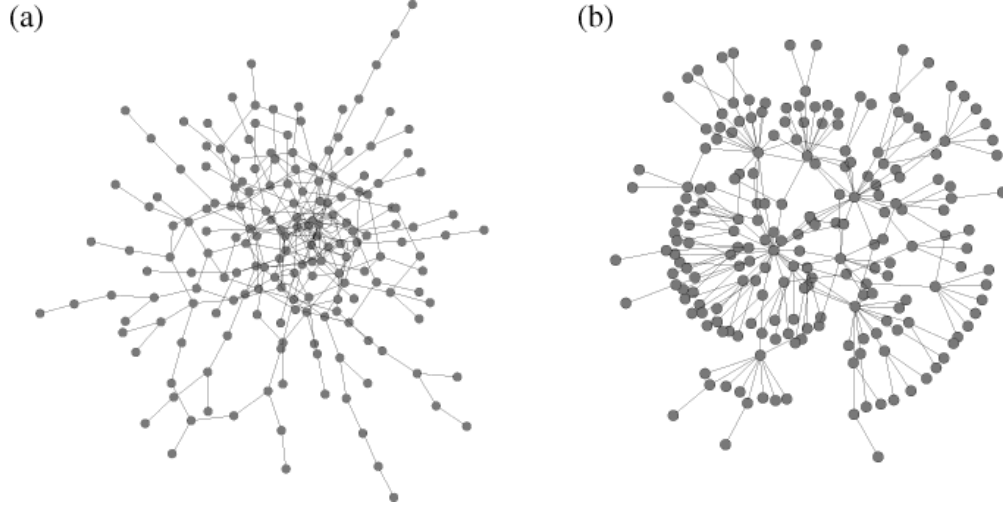


Figure 1.5: a) Assortative and b) disassortative network examples. Taken from [5].

between edge-connected node pairs, and $r < 0$ for disassortative networks with negative degree correlations. Figure 1.5 illustrates two networks with the same degree distribution but different levels of assortative mixing.

For directed networks, we can measure the correlation between the in degree and out degree of source and target nodes connected by a directed link. In addition to these in-out correlations, we can measure in-in, out-in, and out-out correlations for source-target pairs connected by edges. In this way, a generalized assortativity [9] can be defined as follows:

$$r(\alpha, \beta) = \frac{\sum_i (j_i^\alpha - \bar{j}^\alpha)(k_i^\beta - \bar{k}^\beta)}{\sqrt{\sum_i (j_i^\alpha - \bar{j}^\alpha)^2} \sqrt{\sum_i (k_i^\beta - \bar{k}^\beta)^2}} \quad (1.6)$$

where $\alpha, \beta \in in, out$, and \bar{j}^α and \bar{k}^β are the average degrees of α degree of sources and the β degree of targets, respectively, with the averages calculated over edges. The value $r(in, out)$ coincides with the directed version of the Newman assortativity coefficient, r [6]:

1.3 How network topology affects stability in gene networks

Network topology is known to affect the transition from stability to instability in Boolean networks, described above in Sec. 1.1. For $N - K$ networks, Derrida and Pomeau showed that, for a given value of the bias b , there is a critical number of connections K_c at which the transition occurs:

$$K_c = \frac{1}{2b(1-b)}. \quad (1.7)$$

For networks with no correlation between in-degree and out-degree, the same expression determines the critical average in-degree (and out-degree), $\langle k_{in} \rangle_c$ [24]. Aldana and Cluzel showed that if correlation exists between node in- and out- degree, a similar result to Eq. 1.7 holds [12]:

$$\frac{\langle K^{\text{in}} K^{\text{out}} \rangle}{\langle K \rangle} = \frac{1}{2p(1-p)} \quad (1.8)$$

Note that the equation above considers the correlation between the in and out degrees for individual nodes, not the correlation between the in degree and out degree of pairs of nodes connected by edges, which is measured by the assortativity coefficient.

The above results were derived using what is called an ‘annealed’ approximation: at each time step the output entries of the truth table and randomly redrawn subject to the bias b and the incoming links are randomly chosen from the set of remaining nodes.

Pomerance *et al.* introduced a *semi-annealed* approximation in order to calculate stability. Their goal was to understand the stability of random update functions

for a *specific* network. In the *semi-annealed* approximation the update functions are randomized at each time step, but not the topology of the graph. They considered a generalized model in which the expression bias b_i could vary from gene to gene. An important quantity in the semi-annealed analysis is the sensitivity of a gene, $q_i = 2b_i(1 - b_i)$ which reflects the probability that a node changes state at time t given a change in the state of one its inputs at $t - 1$. Because the truth table entries are randomized at each time step, subject to the bias b_i , q_i does not depend on time.

If y_i^t represents the probability that the state of i at time t is different along two trajectories \mathbf{x} and $\tilde{\mathbf{x}}$ evolved from very close initial conditions, the following update equation for y_i holds for the semi-annealed approximation:

$$y_i^t = q_i \left(1 - \prod_{j \in \mathcal{K}_i} (1 - y_j^{t-1}) \right), \quad (1.9)$$

where \mathcal{K}_i denotes the set of nodes with incoming links to i .

The equation is linearized around $y(t) = 0$ for small perturbations:

$$y_i^{t+1} \approx q_i \sum_{j=1}^N A_{ij} y_j \quad (1.10)$$

And thus for $Q_{ij} = q_i A_{ij}$ we have a linear equation $y^{t+1} = Qy^t$. Then the stability is defined by the largest λ_Q :

- $\lambda_Q > 1$, then the zero fixed point is unstable,
- $\lambda_Q = 1$, then the zero fixed point is critical,
- $\lambda_Q < 1$, then the zero fixed point is stable.

This result holds for locally tree-like networks.

1.4 Connected components in directed and undirected networks

Before we discuss how the transition between stability and instability in Boolean networks can be mapped to a percolation problem in directed networks, we first briefly discuss connected components in directed networks and undirected networks.

This set of all nodes that are reachable via a directed path (of any length) starting at node i is called the OUT component of i and is defined as follows:

$$\text{OUT}(i) = \{j | i \rightarrow j\}$$

Similarly, a dual concept to OUT, the set of all nodes j from which there is a directed path (of any length) to node i :

$$\text{IN}(i) = \{j | j \rightarrow i\}$$

For undirected networks,

$$\text{C}(i) \equiv \text{OUT}(i) = \text{IN}(i).$$

For directed networks, the strongly connected component of i is the maximal set of nodes, including i , such that, for every pair of nodes, u and v in the set, there exists a directed path from u to v and also a directed path from v to u .

$$\text{SCC}(i) = \text{IN}(i) \cap \text{OUT}(i)$$

The bow-tie of node i is denoted $\text{BT}(i)$ and illustrated in Figure 1.6:

$$\text{BT}(i) = \text{IN}(i) \cup \text{OUT}(i).$$

We denote the cardinality of the set as $|\cdot|$.

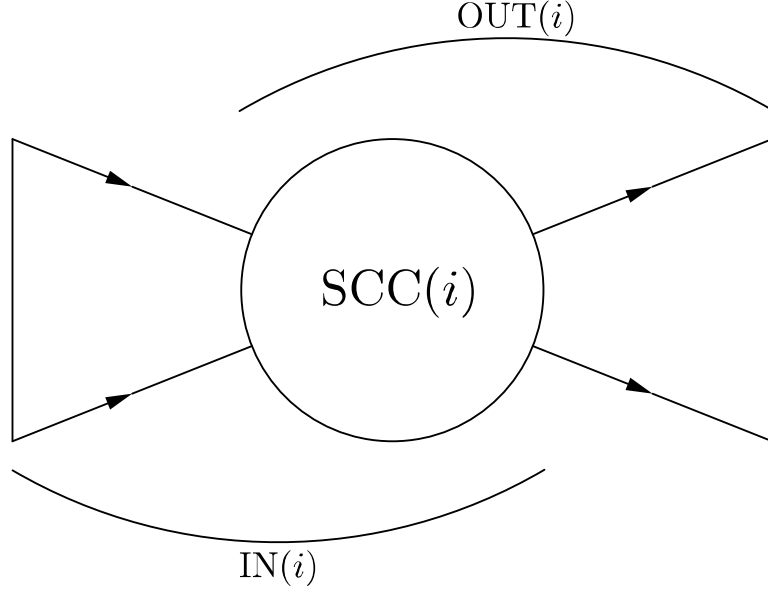


Figure 1.6: Bow-tie structure of node i , in terms of $SCC(i)$, $OUT(i)$, and $IN(i)$.

In the limit of large N , a network is said to percolate if its largest connected component scales with N . For undirected networks the largest connected component is called the giant component (GC). For directed networks, we track the sizes of three different types of components: the giant out component (GOUT), the giant bow-tie (GBT) and the giant strongly connected component (GSCC):

- $|GOUT| = \max_i(|OUT|(i))$
- $|GBT| = \max_i(|BT(i)|)$
- $|GSCC| = \max_i(|SCC(i)|)/N$

We can consider site or edge percolation on complex networks. In edge percolation, we track the growth of the largest connected component as edges are added to the systems. In site percolation, we start with a pre-defined network of ‘empty’

nodes and edges, and we track the growth of network components as nodes are ‘filled in’. Since we are interested in damage propagation in gene networks, we consider a node to be ‘filled in’ if it is damaged.

1.5 Mapping Boolean network dynamics to percolation

In 2012, Squires *et al.* showed that the transition from stability to instability in the *dynamics* of Boolean networks can be mapped to an appropriately defined *static* site percolation problem [2]. They showed that Eq.1.9 has a similar form to the condition for site percolation on directed networks.

To begin, Eq. 1.9 can be rewritten without the time dependence:

$$y_i = q_i \left[1 - \prod_{j \in \mathcal{K}_i} (1 - y_j) \right]. \quad (1.11)$$

Then $\bar{H} = \langle y_i \rangle$ represents the fraction of nodes that get damaged in the steady state. We emphasize that this relation relies on the semi-annealed approximation of the Boolean dynamics.

Restrepo *et al.* gave a similar condition for site percolation, also for locally treelike directed networks:

$$\eta_i = 1 - q_i + q_i \prod_{j \in \mathcal{K}_i} \eta_j, \quad (1.12)$$

where η_i is the fraction of site-deleted networks for which node i is not in the giant out component (GOUT) and q_i is the probability that each node is filled in. $|\text{GOUT}|/N$ is the fraction of the nodes in the largest out component in the network and its expected value is given by $\langle 1 - \eta_i \rangle$.

The equivalence between Eq. 1.11 and Eq. 1.12 shows that if we set $\langle y_i \rangle = \langle 1 - \eta_i \rangle$, that also means $\bar{H} = |\text{GOUT}|/N$. Hence, the transition from stability ($\bar{H} = 0$) to instability ($\bar{H} > 0$) can be mapped onto the percolation transition for damage propagation in directed networks in which each site is damaged with probability q_i . The percolation transition occurs when $|\text{GOUT}|$ scales with N in the limit of large N , i.e. the transition from $|\text{GOUT}|/N = 0$ to $|\text{GOUT}|/N > 0$. Here, GOUT is the largest OUT component in the subnetwork of damaged nodes.

1.6 Explosive percolation transitions in growing networks

Recent work by Achlioptas *et al.* [19] shows that if edges are added competitively (described in more detail below) the edge percolation transition appears to be discontinuous (first-order) instead of continuous (second-order), as is the case if edges are added randomly. In our study, we explore how growth of gene networks through edge selection can be used as a simple model of gene network evolution. We consider extended versions of the competitive processes studied by Achlioptas that take into account both the directed nature of gene regulatory networks and their need to avoid the kind of damage propagation discussed in the previous Section. Our extensions are described in the next chapter. Here, we review the well-studied Achlioptas process.

As with traditional edge percolation, the process starts with N nodes and zero edges, and then edges are added one at a time. If the edges are added in random order, we see a continuous phase transition in the growth of the largest connected

component, i.e., the giant component. In the Achlioptas *competitive process*, also called the Achlioptas Process (AP) links are chosen competitively so as to delay the onset of the percolation transition. At each step, the best edge is selected from $m = 2$ or 3 candidates; $m = 1$ is the basic random Erdős - Rényi process. For undirected networks we consider a following process at each time step t :

1. Two candidate edges are chosen at random, $i_1 - j_1$ and $i_2 - j_2$,
2. If one of the two edges connect nodes in the same connected component, it is added automatically,
3. Otherwise chose the edge that minimizes the

$$|C(i_k)| \times |C(j_k)|, \quad k \in \{1, 2\} \tag{1.13}$$

This process exhibits what is called *explosive* percolation, meaning that the phase transition appears discontinuous and is illustrated in Figure 1.7.

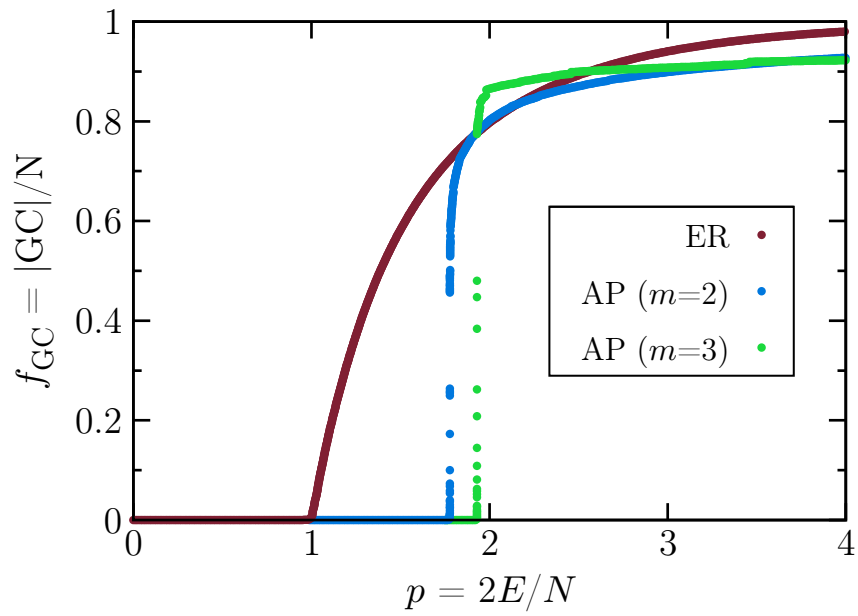


Figure 1.7: Normal and explosive phase transitions, taken from [1]. ER denotes Erdős – Rényi (Random) process, AP denotes Achlioptas process (Competitive). The value m denotes the number of candidate edges considered at every step.

Chapter 2: Methods

In this chapter we discuss different growth processes as evolution models of gene regulatory networks. We consider three different kinds of network growth processes:

1. Random, in which directed links between nodes are added between randomly chosen pairs of nodes.
2. Competitive link addition, in which two ‘potential’ edges are considered and the one that is expected to delay the transition to instability is added to the system.
3. Direction selection, in which two nodes are randomly chosen to have an edge added between them and the direction is selected in order to delay the transition to instability.

Each of the growth models begin with a specified number of genes N , with each gene having an bias b_i and a corresponding sensitivity q_i , which indicates the propensity for that gene to spread damage through the network. The bias values are used for damage based processes.

We consider the growth of these networks in two different conditions.

1. Damage propagates through all genes.

2. Damage spreads probabilistically through the network, based on the sensitivity values, q_i . In this case, link additions take into account the probabilities of damage spreading.

In each case we add one edge at a time according to a rule. We then compare resulting network properties for the different growth rules.

2.1 Random Growth

For the case of random link addition, the growth process proceeds as follows at each time step:

1. Add a new edge between two randomly selected nodes i and j that are not already connected by an edge.
2. Keep track of the order parameter, S .

For undirected networks, we consider S to be the size of the the giant component, $|\text{GC}|$. The giant component is defined as largest connected component in the network. For directed networks, S is the size of the giant out component, $|\text{GOUT}|$, where GOUT is the largest out component of the network.

Each time we start the growth process, we begin with a set of N nodes with no edges between them.

2.2 Growth under Selection

As compared to Random link addition, we now consider network growth selection in which each link is added via a selection process whose objective is to delay the transition to instability.

2.2.1 Edge Competition

We first consider a rule for Edge Competition in directed networks that is inspired by the Achlioptas process [19] discussed in Section 1.6. This rule was previously studied by Squires *et al.* In this thesis, we extend the results of [1] by analyzing the structural properties of networks grown according to this rule and also studying damage propagation in grown networks using a related rule (Section 2.3).

The growth rule for each successive link addition is implemented as follows:

1. Choose two new candidate edges randomly, $i_1 \rightarrow j_1$, $i_2 \rightarrow j_2$, such that both of them are not in the network already.
2. If there is already a path from i_k to j_k for one of the k , we choose this edge to add to the network. If a path exists for both $k = 1$ and $k = 2$, we choose one of the edges at random.
3. Otherwise we choose the more optimal candidate edge based on a fitness function:

$$\min_{k=1,2} \{|IN(i_k)| \times |OUT(j_k)|\} \tag{2.1}$$

Where $|\text{IN}(i_k)|$ is the size of the in component of node i_k and $|\text{OUT}(j_k)|$ is the size of the out component of node j_k .

2.2.2 Direction Selection

Here, we consider a process alternative to choosing between two candidate edges in order to delay the onset of instability, a selection process that minimizes the growth of GOUT by choosing the direction of the edge between two randomly selected nodes. For that we choose the edge to go from the node with lower sensitivity to higher sensitivity.

1. Choose a new edge $i \rightarrow j$ randomly.
2. If $q_j \geq q_i$ connect the edge in the direction $i \rightarrow j$.
3. If both i and j are damaged update the GOUT.

2.3 Damage Propagation

In the previous section, we considered the growth of GOUT as edges are added according to different selection rules, assuming that all genes (nodes) are capable of damage propagation. Here, we study what happens when the genes have different propensities for propagating damage, which are given by their sensitivity values, q_i . Recall that the sensitivity q_i tells us how likely it is for gene i to change state in response to a change in state of one of its inputs. As before, for growth by selection, edge are added according to a rule that is designed to delay the onset of global

damage propagation. Unlike before, the rule now incorporates the gene propensities for damage propagation.

When we consider probabilistic damage propagation, we grow the network by adding edges according to the process described below for Random, Edge Competition, and Direction Selection, and mark each node i as damaged with probability $q_i = 2b_i(1 - b_i)$. Here, we modify our definition of GOUT to track the size of the largest out component for the subnetwork of nodes that are damaged. We assign biases uniformly ($b \sim U[0, 1]$), which then gives that the expected value of q , $\langle q \rangle = 1/4$, meaning that approximately a quarter of the nodes will be damaged.

For the Random growth process with probabilistic damage:

1. Each of the N nodes i are marked ‘damaged’ with probability q_i . The total number of damaged nodes is denoted N^* ($N^* \approx N/4$).
2. A random link addition is implemented, as discussed in Section 2.1.
3. When each link is added, the $|GOUT|/N^*$ of the damaged subnetwork is calculated. The subnetwork is the set of damaged nodes, and all the edges that connect pairs of damaged nodes.

Growth via Edge Competition process proceeds as follows:

1. All nodes are marked damaged or not as described above.
2. At each step choose two candidate edges $i_1 \rightarrow j_1$ and $i_2 \rightarrow j_2$.
3. Choose a new edge based on:

$$\min_{k=1,2} \{q_{i_k} q_{j_k} |IN(i_k)| \times |OUT(j_k)|\} \quad (2.2)$$

4. If both nodes in the added edge are damaged update $|\text{GOUT}|/N^*$.

Since the growth via Direction Selection described in Section 2.2.2 already incorporates the sensitivity values q_i , we don't need to modify the rule, we just need to keep track of the size GOUT in the subnetwork of damaged nodes.

For both Edge Competition and Direction Selection, the growth rules take into account the gene sensitivities in order to limit the damage spread (measured by the growth of GOUT). In Edge Competition, edges are more likely to be included if both genes have low sensitivity values (meaning they are less prone to damage propagation). In Direction Selection, the direction of the edge is selected to run from the lower sensitivity gene to the higher sensitivity gene because this directionality reduces the likelihood of damage spreading. We track the growth of GOUT as well as assortativity coefficients and distribution of strongly connected components (SCCs). The results are presented in the next chapter.

Chapter 3: Results

In this chapter we present and analyze numerical results for the growth models introduced in the previous chapter. In Section 3.1 we show delayed percolation in undirected network for competitive as compared with random growth processes. We study the growth of directed networks for both random and selective growth processes, under the assumption that damage propagates through all nodes in Section 3.2. We consider the two types of selective growth processes: Edge Competition and Direction Selection (described in Section 3.2.1 and 3.2.2). In order to compare the different processes, we study network properties like component sizes and distributions, and we also track assortativity coefficients during the growth processes. In Section 3.3, we study growth processes that take into account probabilistic damage spreading based on the node sensitivity.

3.1 Random and Selective Growth Processes in Undirected Networks

For comparison with the growth of directed networks, our primary interest, we first recreate the growth of undirected networks for random and competitive processes, as studied in [1], and described in Section 2.1

Figure 3.1 shows the growth of the giant component as edges are added to the

system via Random and Competitive processes, for different system sizes ($N = 500, 5000, 10000$). We see that, compared with the Random growth process, the Competitive process exhibits a delayed transition in the growth of the giant component, and this transition is more abrupt (or ‘explosive’) when it finally does occur. We also observe that, as expected, the transition becomes sharper for larger values of N .

3.2 Random and Selective Growth Processes in Directed Networks

In the previous Section we introduced growth processes for undirected networks. Now we generalize to directed networks. We consider Random growth and two types of growth by selection in directed network.

1. Edge Competition – for each step of the growth process two candidate edges are picked randomly, and one of them is chosen in order to minimize the normalized size of the giant OUT component, $|G_{OUT}|/N$, (described in Section 2.2.1).
 2. Direction Selection – at each step of the growth process an edge is randomly picked, and the direction is determined, (described in Section 2.2.2).
- picked based on maximizing stability of the network.

The Edge Competition growth process was described in [1], but some of the structural features we investigate here, like assortativity (described in Section 1.2) were not shown.

Here, we consider the case in which all nodes spread damage (as described in Section 2.3) before tackling the case of probabilistic damage spreading in Section 3.3.

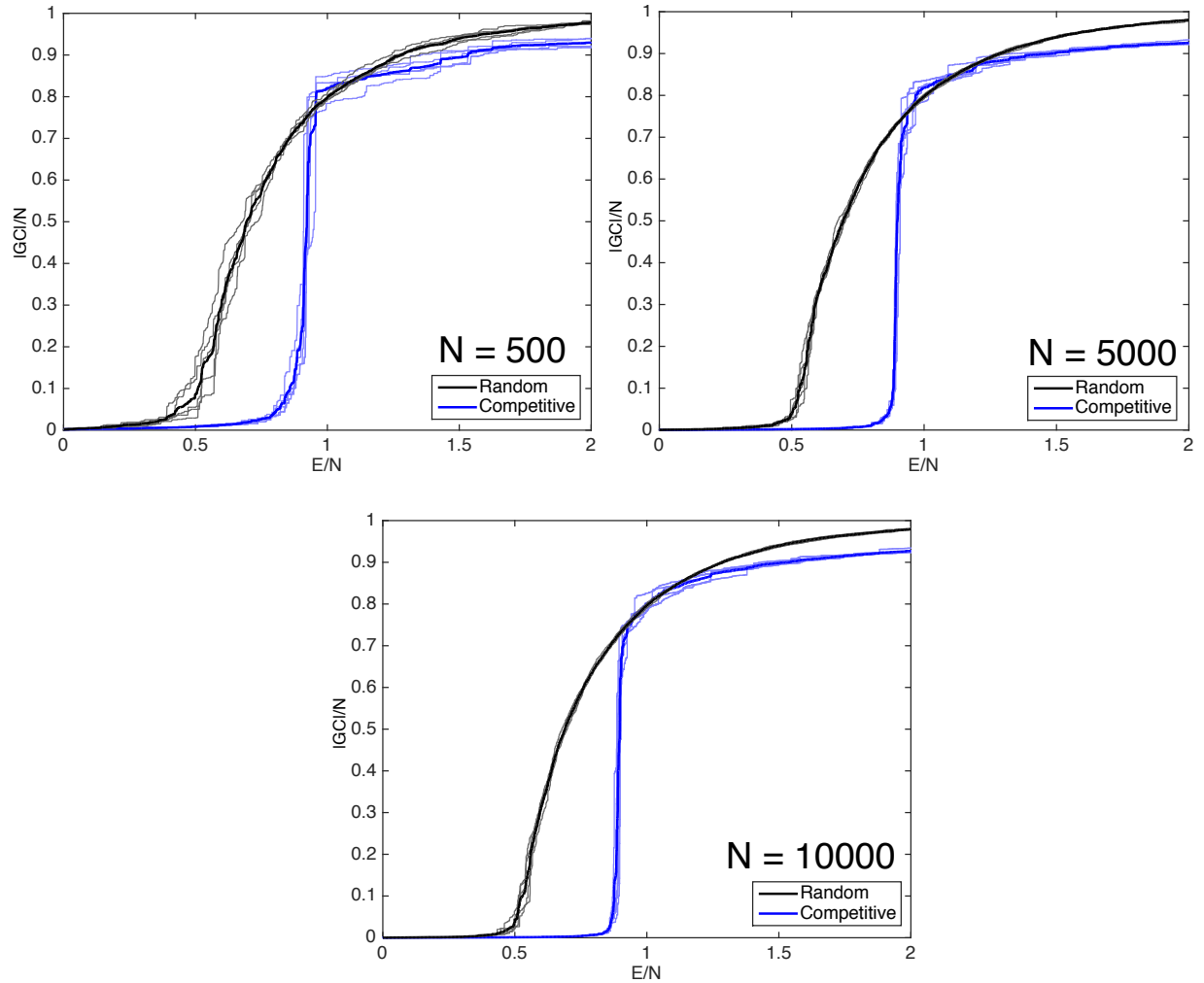


Figure 3.1: In blue is the Competitive growth process. We see that it exhibits a delayed and more abrupt transition, as compared with the Random process (shown in black). The thin lines show individual growth processes for individuals networks, and thick lines show averaged result over 5 runs.

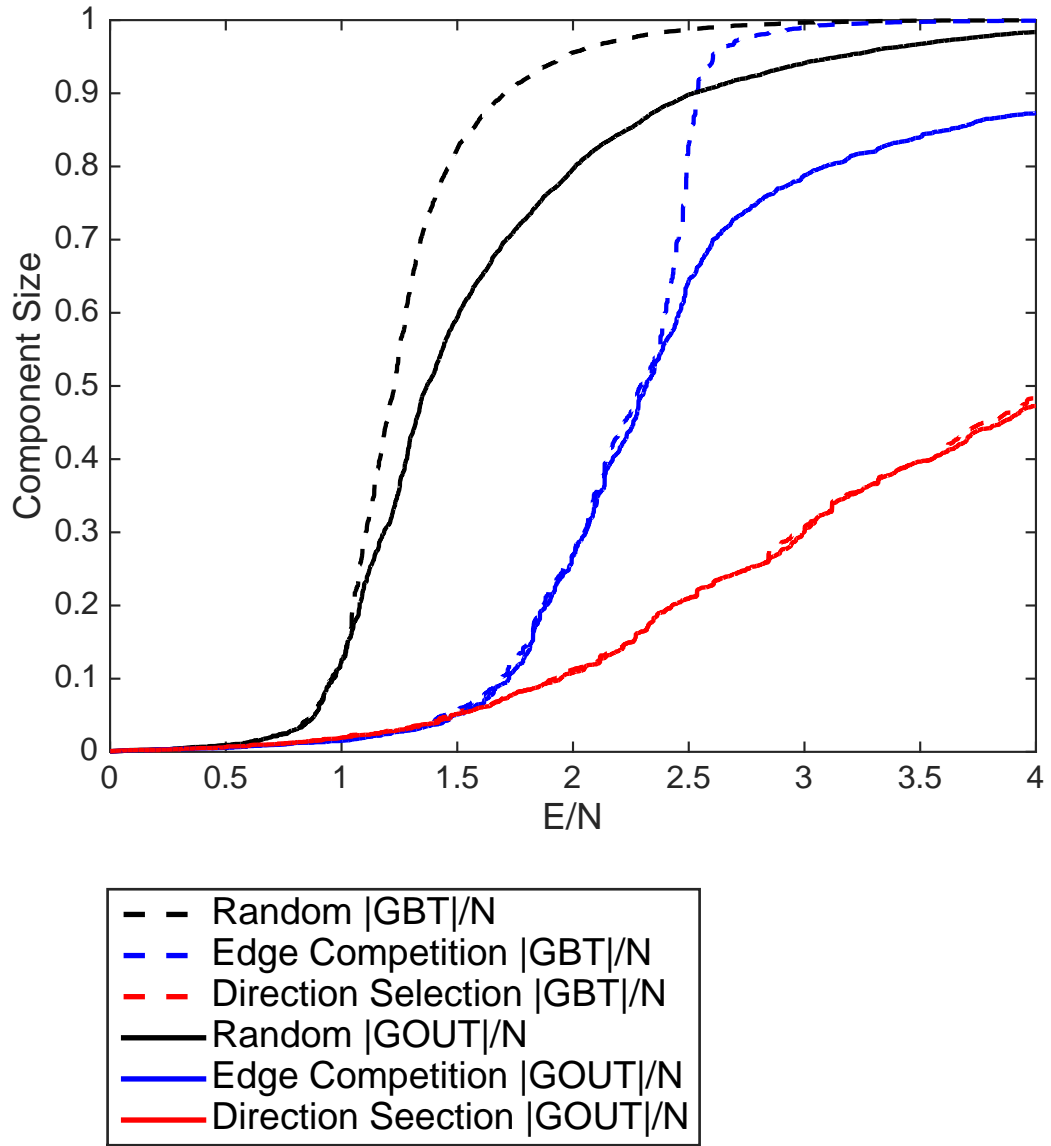


Figure 3.2: Transitions for all growth processes for $N = 5000$ nodes, averaged over five growth processes. The $|GOUT|/N$ is shown in solid line, and the bow-tie, $|BT|/N$, is dashed. The five individual growth processes are illustrated with thin lines, and the average is illustrated by thick lines.

In Figure ?? we see the growth of the giant out component, GOUT, and the giant bow-tie, GBT, by selection in red (direction selection) and blue (edge competition) and the Random growth for comparison in black. We see that compared with the undirected case the Edge Competition growth process the transition does not appear look as abrupt (although it is still delayed), and in the case of Direction selection we see that the growth of GOUT and GBT is even further suppressed. For the Random growth process the transition is smooth for both the growth of GOUT and GBT with a slightly steeper slope for GBT right after the transition point. In comparison, for Edge Competition growth model, the GBT size increases more dramatically at the transition point. The Direction Competition growth process is very different. Since there are no loops in the network, other than self loops, there are no SCCs with size greater than one. As a result, the GBT is almost the same size as the size of the GOUT.

To better understand the structure of the networks growth according to the different growth rules, we track the in-out assortativity coefficients, $r(in, out)$ (Eq. ??), throughout the growth processes (Figure ??). For Random growth, we see that the assortativity stays near zero, as expected. For Edge Competition, the assortativity starts around zero and decreases until about $E/N = 2$. This is the approximate location of the transition in GOUT that we observed in Figure ?. After the transition, the assortativity begins to increase, but remains negative even after $5N$ edges have been added to the system. (We discuss this phenomena in more detail in Section 3.2.1). In contrast, for the case of Direction Selection, after some initial fluctuations, the assortativity coefficient decreases almost monotonically.

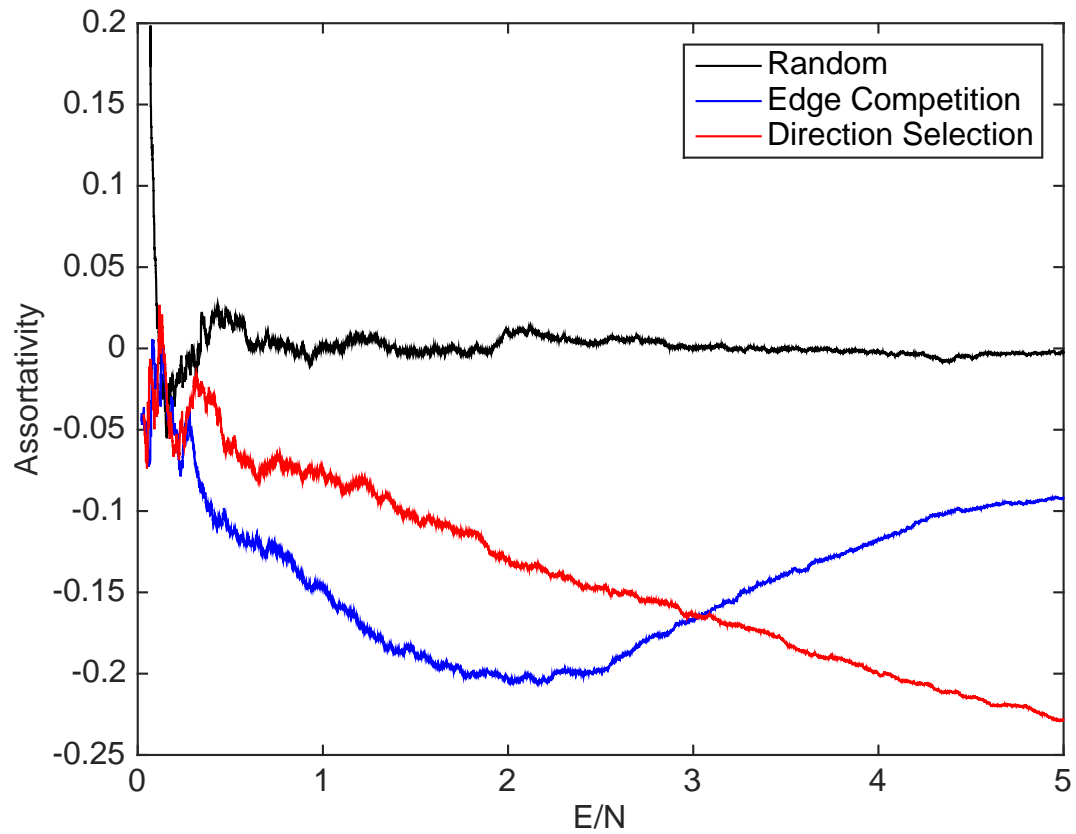


Figure 3.3: In-out assortativity coefficients, $r(in, out)$, for average of three growth processes for $N = 2000$.

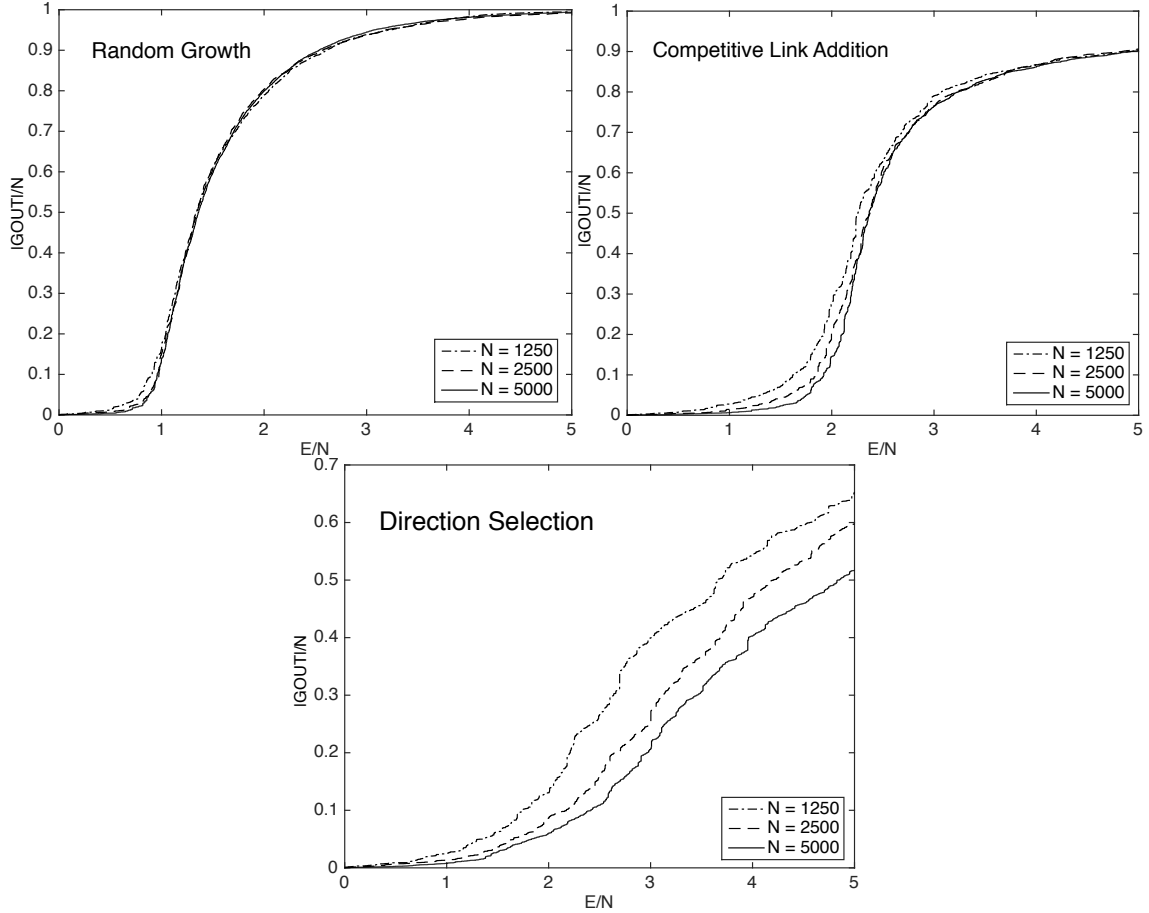


Figure 3.4: Growth processes in terms of network size. Dotted line denotes $N = 1250$, dashed $N = 2500$, $N = 5000$ nodes accordingly. Each is the result of averaging over 3 independent experiments (growth processes).

The size of the network is an important feature that affects the accuracy of the results, as was illustrated in Figure 3.1 for undirected networks.

In Figure 3.4, for the Random case the transition becomes sharper with larger N , and the difference between the transition for $N = 1250$ and $N = 2500$ is visually much larger than the difference between $N = 2500$ and $N = 5000$. Compared with Random growth for Edge Competition and Direction Selection, the transition occurs later in the growth process, but does not appear much steeper as in the undirected

case. In subsequent results, we mostly use $N = 5000$, unless indicated otherwise. In this work we do not simulate very large networks, but rather focus on networks on the order of 1000 nodes, because we are specifically interested in the application to gene regulatory networks, which are approximately this size.

The rest of the of the chapter provides a more detailed analysis of the processes introduces above.

3.2.1 Growth via Edge Competition vs. Random Growth

In this Section, we provide more detailed comparison of Random growth process and Edge Competition growth process. To visualize the difference, we generate snapshots of the process for a small value of N , keeping in mind that we expect small network effects. We see differences in the processes, illustrated in Table 3.1.

In Table 3.1 we see that in the beginning of the growth processes at $E = 25$ the inputs are mostly random, and the competitive process (in this example) has a larger GOUT component, but in general process at this point (see Figure ??) we expect to be smaller $|\text{GOUT}|$ is smaller for the competitive process before the transition.

In the later stages of the process, when $E = 75$, the difference between the sizes of GOUT are visible the network for the random process is beyond transition point, and the network for the competitive process is not. In the last row example in Table 3.1, with $E = 125$, the network of the competitive process has more nodes not in the GOUT component, than for the random process.

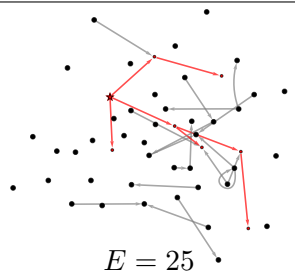
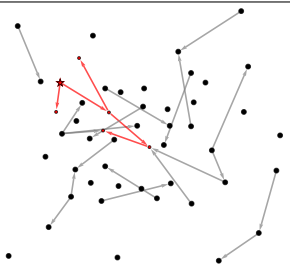
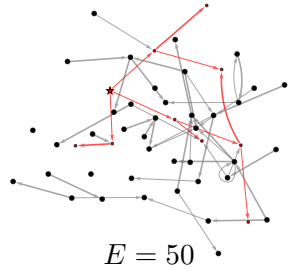
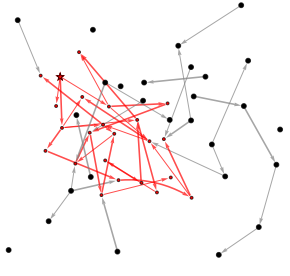
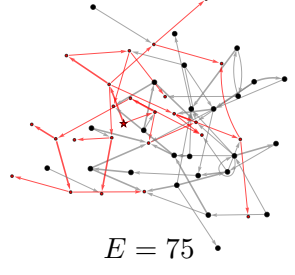
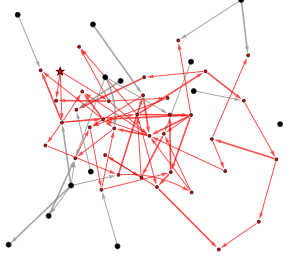
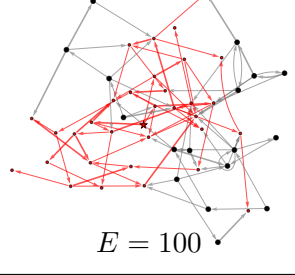
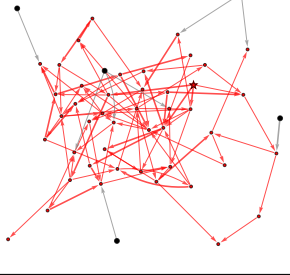
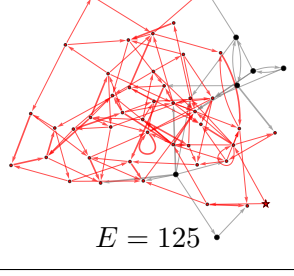
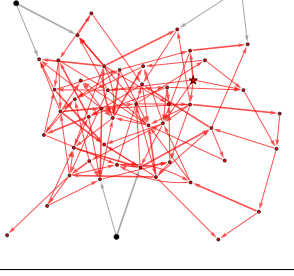
Properties	Edge Competition	Random
$r_c = -0.0827$ $r_{rd} = 0.0045$ $ \text{GOUT} _c/N = 0.16$ $ \text{GOUT} _{rd}/N = 0.12$	 <p style="text-align: center;">$E = 25$</p>	
$r_c = -0.2547$ $r_{rd} = 0.1097$ $ \text{GOUT} _c/N = 0.2$ $ \text{GOUT} _{rd}/N = 0.46$	 <p style="text-align: center;">$E = 50$</p>	
$r_c = -0.2730$ $r_{rd} = 0.0064$ $ \text{GOUT} _c/N = 0.5$ $ \text{GOUT} _{rd}/N = 0.74$	 <p style="text-align: center;">$E = 75$</p>	
$r_c = -0.3446$ $r_{rd} = -0.1050$ $ \text{GOUT} _c/N = 0.66$ $ \text{GOUT} _{rd}/N = 0.9$	 <p style="text-align: center;">$E = 100$</p>	
$r_c = -0.2568$ $r_{rd} = 0.0770$ $ \text{GOUT} _c/N = 0.88$ $ \text{GOUT} _{rd}/N = 0.94$	 <p style="text-align: center;">$E = 125$</p>	

Table 3.1: Edge Competition and Random growth process, with networks shown for $E = 25, 50, 75, 100, 125$ edges and $N = 50$ nodes. The edges added in the current steps (new edges) are thick, the ones added earlier in thin. The edges in GOUT are shown in red. The values r denotes assortativity, rd denotes Random, and c – Edge Competition.

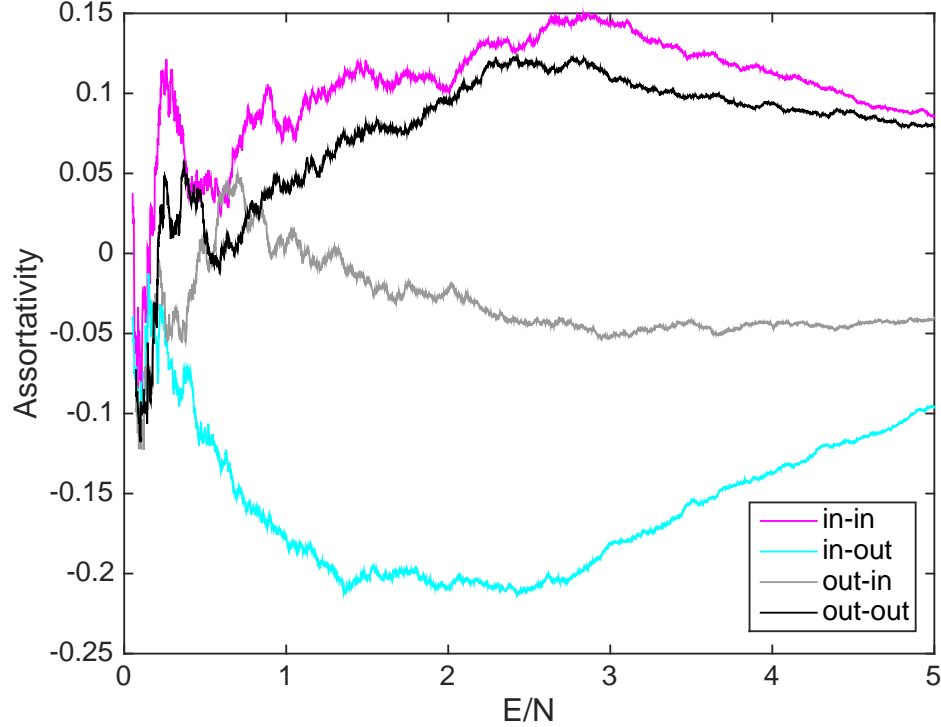


Figure 3.5: Assortativity coefficients averaged over 10 growth processes of network with Edge Competition for $N = 5000$.

We consider the assortativity coefficients of the Edge Competition process to understand the structural properties after transition, in order to quantify the structural properties of the grown network. In order to do that we trade the assortativity coefficients $r(in, in)$, $r(in, out)$, $r(out, in)$, and $r(out, out)$, defined in Section 1.2 in Equation 1.2. The result is shown in Figure 3.5.

Before the transition, that happens at $E/N \cong 2$ (see Figure ??) assortativity coefficients $r(in, in)$ and $r(out, out)$ are slightly positive, $r(out, in)$ is near zero, and $r(in, out)$ is slightly negative. When E/N is low, the in-out assortativity coefficient, $r(in, out)$, is negative because the competitive rule minimizes the connections between nodes with high in-degree and high out-degree. However, the competi-

tive rule for edge selection has two major parts, each contributing to the in-out assortativity coefficient in opposite ways:

1. Add the edge that minimizes the $|IN(\cdot)| \times |OUT(\cdot)|$,
2. Add an edge between a node pair if it is already connected by a path,

The first rule contributes to assortativity being smaller, as it minimizes the added edges with the $|IN(\cdot)| \times |OUT(\cdot)|$ parameter. The second contributes to making the assortativity coefficient larger, as in this case the network is being filled, and the edges are added regardless of the IN and the OUT components of the according edges.

To show that in Figure 3.6 we consider the fraction of the edges that are added due to (2), i.e. when the edge $i \rightarrow j$ is added because there is already a path between i and j .

We see that the fraction of edges that are added between nodes that already have a directed path connecting them increases at transition point, and stays at a large values. The fact that the fraction is large contributes to the in-out assortativity coefficient growing, because the adding paths between those nodes 'fills in' the network and draws edges that have a high $|IN(\cdot)| \times |OUT(\cdot)|$ value, causing an increase of assortativity.

Next we study the 'main building block', Strongly Connecting Components, SCC, of the network at each step of the growth process in order to quantify differences between the randomly built graph and the network built with edge competition process. First we consider the SCC size distribution. The SCC's themselves are

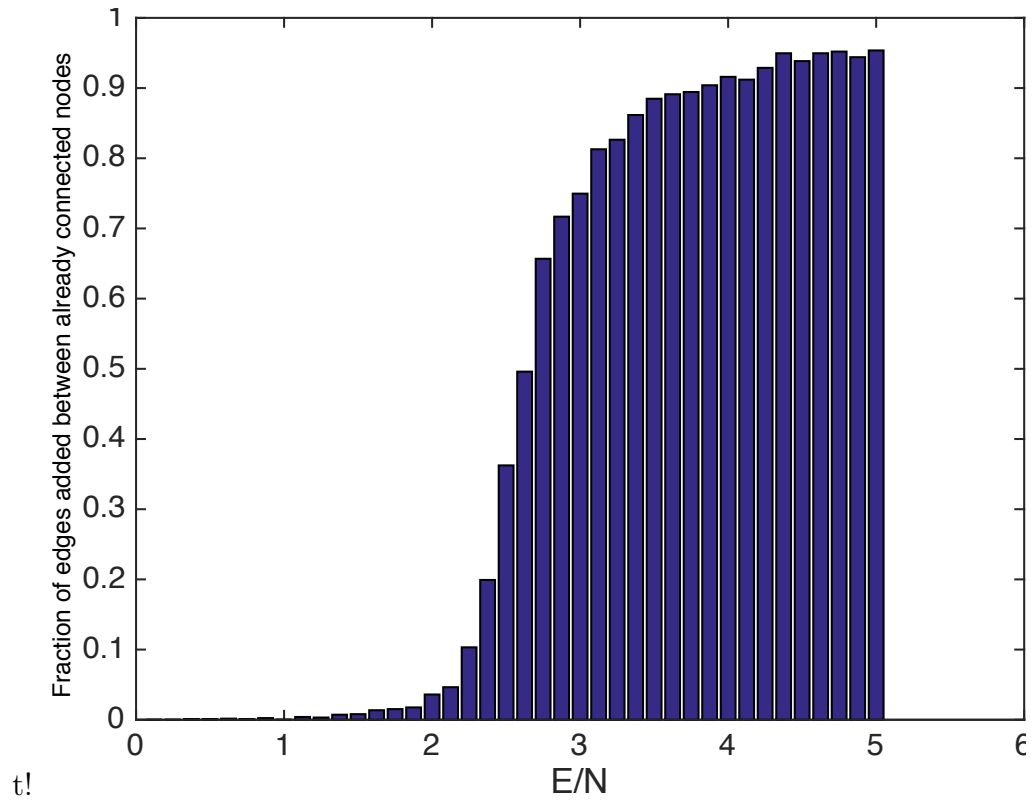


Figure 3.6: For Edge Competition, the fraction of edges added between already connected nodes, for groups of edge additions in increments of $N/8$.

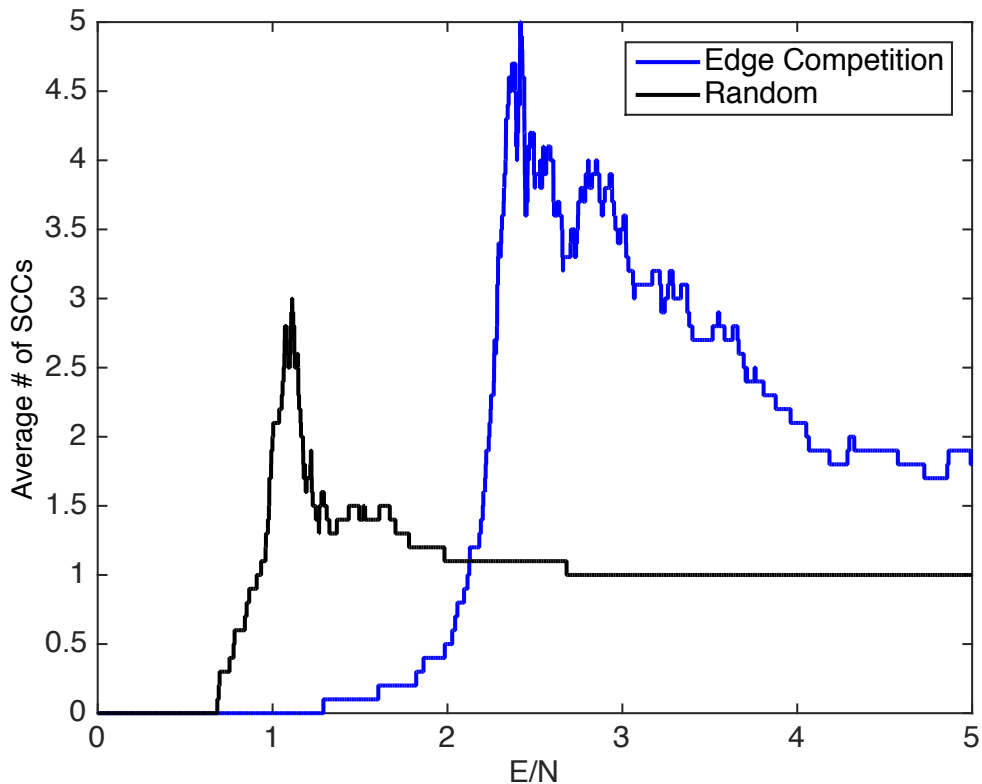


Figure 3.7: Number of SCC's averaged over 10 growth processes of network size 5000. Black color shows random growth average, and blue shows edge competition.

thought to control network dynamics, as the interdependence of the nodes within a given SCC is larger than for nodes in different SCC's. Notice that in this work we consider SCC's of size two or larger.

In Figure 3.7 is a plot of the number of SCC's for the Random and the Edge Competition processes, averaged over a number of growth processes. Notice that for each individual growth process the value is integer, but the average could be non-integer.

Figure 3.7 illustrates how the number of SCC's is different for Random and Competitive growth processes: at the point of the transition the Edge Competition

exhibits a large burst of SCC formation, while there are only a small number of SCCs at the transition point of the random process.

Edge competition by design delays transition, but here we also see that the competition affects the SCC distribution of the network much well beyond transition point. After the transition we see that there are more SCC's for Edge Competition processes, which means that the non-giant SCC's delay joining the GSCC.

We also consider in Figure 3.8 the size of the largest SCC for both processes, and illustrate the average size of the components, that are not the Giant Strongly Connected Component.

The Figure 3.8 shows that for Random growth process the average size of non-giant SCC's is small. For the Edge Competition growth process, the average size of the non-giant SCC is much larger, on the order of 0.2, meaning that the competition not only contributes to delay of transition, but also to the delay of adding new components after percolation. After transition the new edges are more prone to adding edges between non-giant SCC's, further delaying growth of the giant SCC.

3.2.2 Growth via Direction Selection vs. Random Growth

The Direction Selection model introduced in the previous chapter has much different topology than the previous models. As opposed to the random and the competitive models, the networks in the Direction Selection has tree structure: there are no loops in the network aside from self-loops, or any SCC's of size larger than one. This occurs

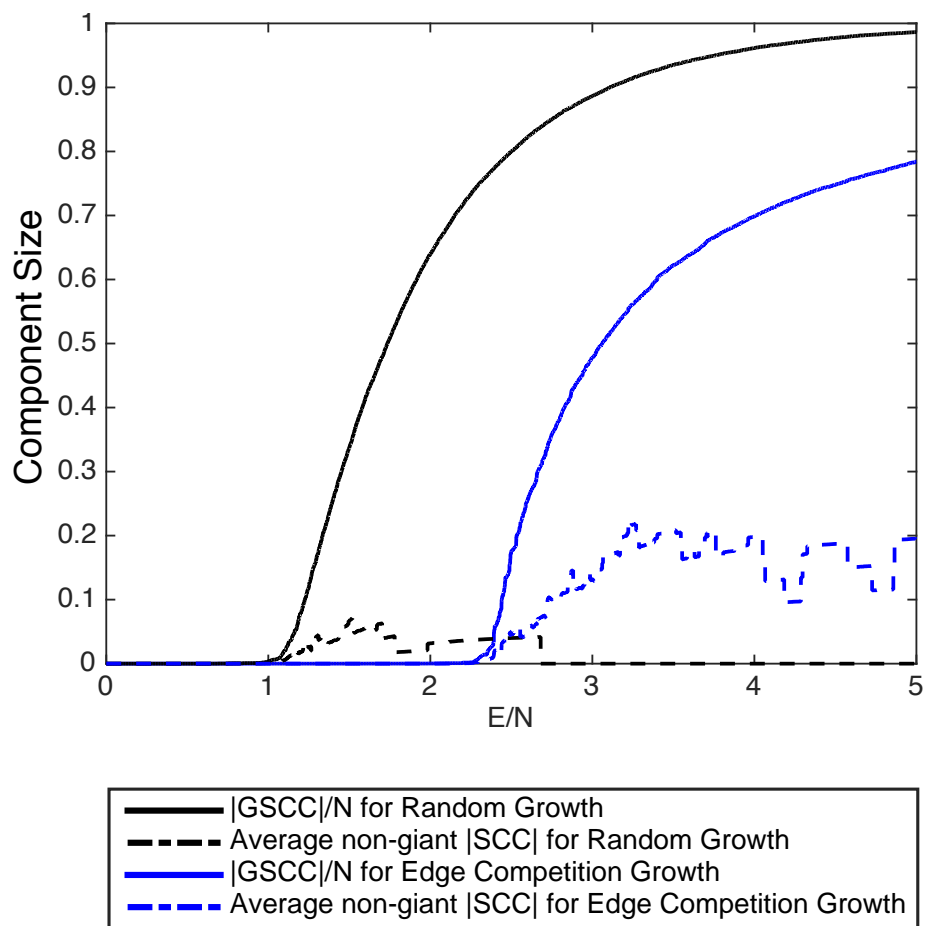


Figure 3.8: Maximum normalized SCC size and average of the non-giant normalised SCC sizes, for the same process as in Figure 3.7.

because the growth rule forbids adding an edge from a higher sensitivity node to a lower sensitivity node.

For Direction Selection case the edges only go from nodes with higher sensitivity values to nodes with lower sensitivity values. So in the network below, in Table 3.2 we consider the network with nodes ordered by sensitivity ascending order. For comparison we also consider the Random growth process with nodes plotted in a line with random ordering (as there are no sensitivity values in the Random growth process). To measure we keep track of the assortativity coefficient and the $|GOUT|/N$ parameter.

Properties	Direction Selection	Properties	Random Graph
$ GOUT_d /N = 0.25$ $r_d = -0.25$		$ GOUT_{rd} /N = 0.25$ $r_{rd} = -0.6202$	
$ GOUT_d /N = 0.35$ $r_d = -0.2325$		$ GOUT_{rd} /N = 0.55$ $r_{rd} = 0.5199$	
$ GOUT_d /N = 0.8$ $r_d = -0.4710$		$ GOUT_{rd} /N = 0.8$ $r_{rd} = 0.2860$	
$ GOUT_d /N = 0.9$ $r_d = -0.428$		$ GOUT_{rd} /N = 0.9$ $r_{rd} = -0.0879$	

Table 3.2: The Direction Selection growth process networks, with 20 nodes, for snapshots of the growth process with $E = 10$, $E = 20$, $E = 30$ and $E = 40$ edges. The properties reported are the normalized size of GOUT and the in-out assortativity coefficient, d stands for Direction Selection growth process, and rd stands for Random growth process.

Notice, that in the Table 3.2 above, in the column with Directed Selection, as the number of edges increases, the nodes on the left with high sensitivity parameter has a high out-degree and low in-degree. The nodes with low sensitivity parameters on the contrary have high in-degree and low out-degree. We see that the network becomes more and more disassortative, as high in-degree nodes connect to low in-degree and high out-degree nodes connect to low out-degree nodes. The increased propensity toward disassortativity is also illustrated in Figure 3.3.

3.3 Damage Spreading for Different Growth Processes

In the previous Section, we showed how different selection rules resulted in different transitions in component sizes, for GOUT, GSCC, and GBT, assuming that all nodes spread damage. In this Section, we consider probabilistic damage spreading based on the node sensitivity values.

For the Edge Competition growth process in the context of damage propagation, we modify the growth rule of equation 2.1 to select the edge

$$\min_{k=1,2} \{q_{i_k} q_{j_k} |IN(i_k)| \times |OUT(j_k)|\} \quad (3.1)$$

For $k = \{1, 2\}$. The value q_{i_k} is the sensitivity value of i_k .

Independent of edges have been added according to the growth process rule, we go designate each node i as damaged with probability q_i . This means that approximately 0.25 of the nodes will be designated as damaged and nodes with higher sensitivity will be more likely to be damaged. Using this damage demarcation, we track the sizes of the connected components only including damaged nodes.

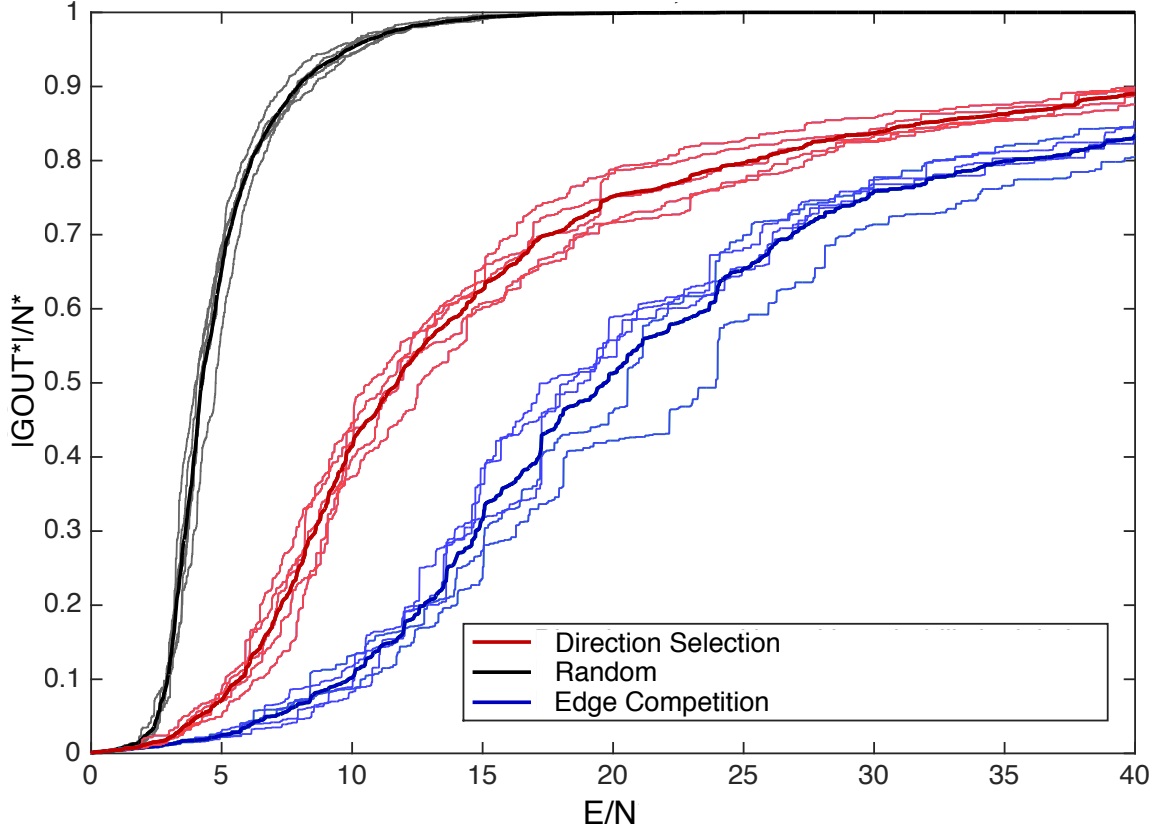


Figure 3.9: Transitions for damage sensitive networks, for network size $N = 50000$, with averaging over five growth processes. Individual processes are shown in thin, the average is shown in thick color.

In Figure 3.9 consider the the $|GOUT^*|/N^*$, where N^* is the size of the sub-network of damage-sensitive nodes, and $GOUT^*$ is the the biggest OUT component for only damaged nodes of the network. The competitive process and the damage spread process can correlate significantly, which we illustrate below.

Notice that in Fig 3.9 the order transitions moments are interchanged from the order of transitions without damage propagation in Fig ??.

The transition happens at a much larger value of E/N , than non-damaged process does. The damage based process has transition at $E \approx 4N$ for random

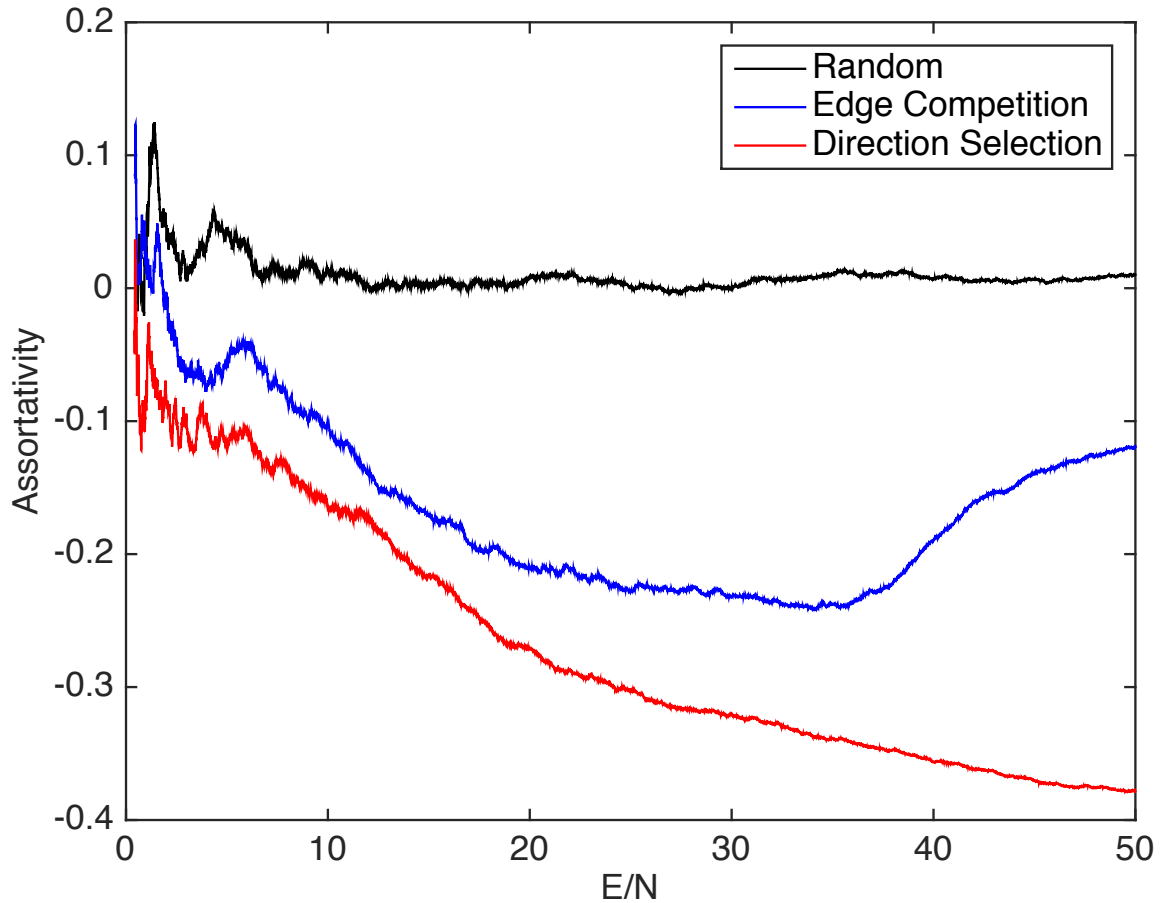


Figure 3.10: Assortativity for damage spread networks. Edge Competitions is considered with probabilistic damage spread.

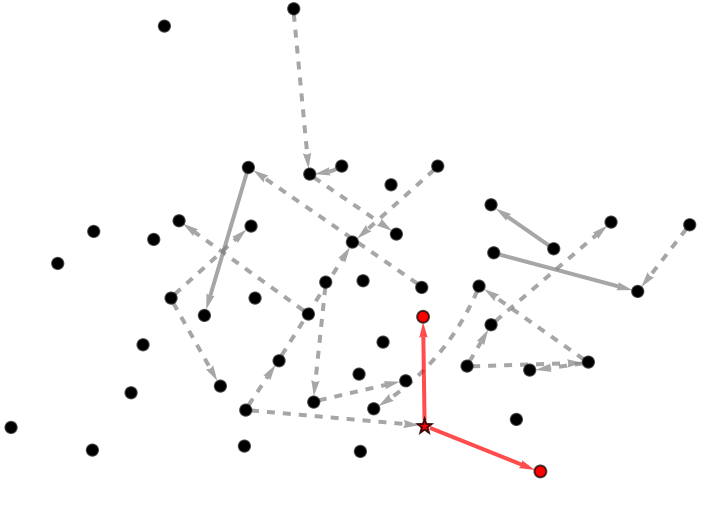
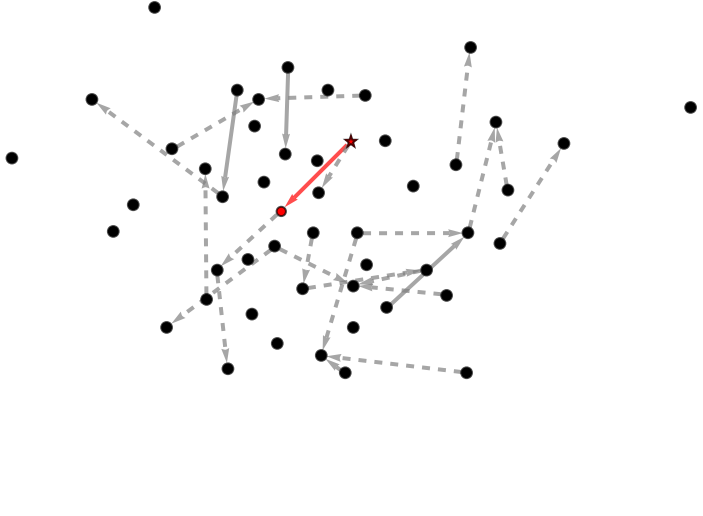
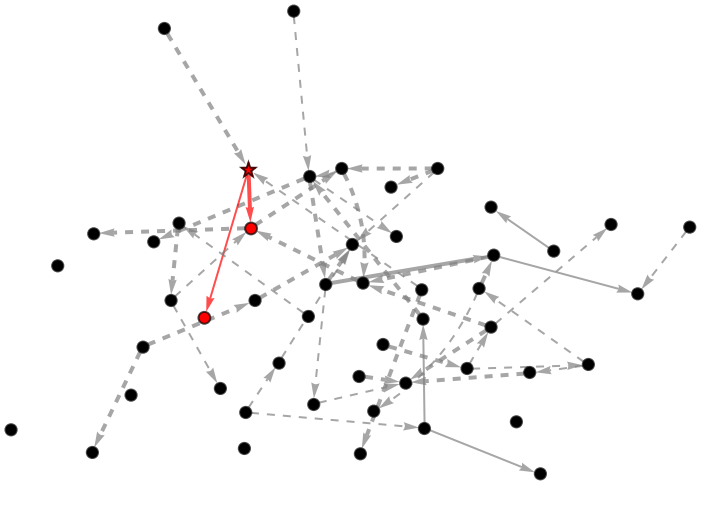
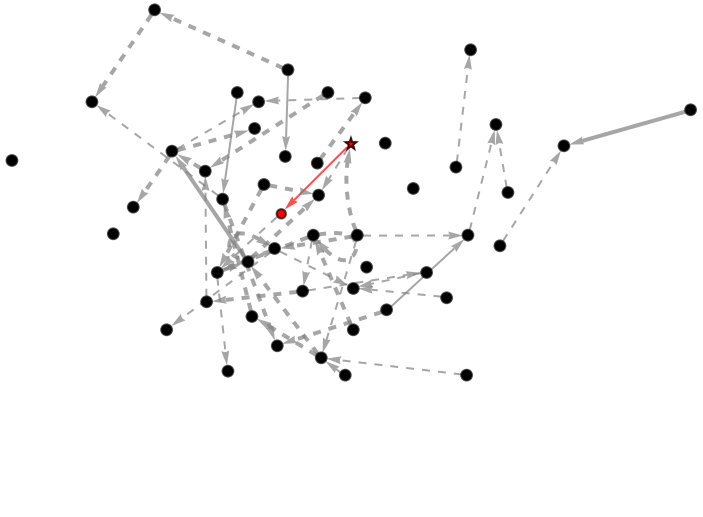
growth process, at $E \approx 10N$ and at $E \approx 15N$. As discussed in the background, the size of the damage sensitive subnetwork is on average four times smaller than the original network, $N^* \approx N/4$. This means that for the random case the percolation will happen on average four times slower than in the un-damaged case, $E/N \approx 4$.

The subnetwork of the original evolved network that consists of damage sensitive nodes has its own structural properties. In Figure 3.10 we consider the assortativity coefficients.

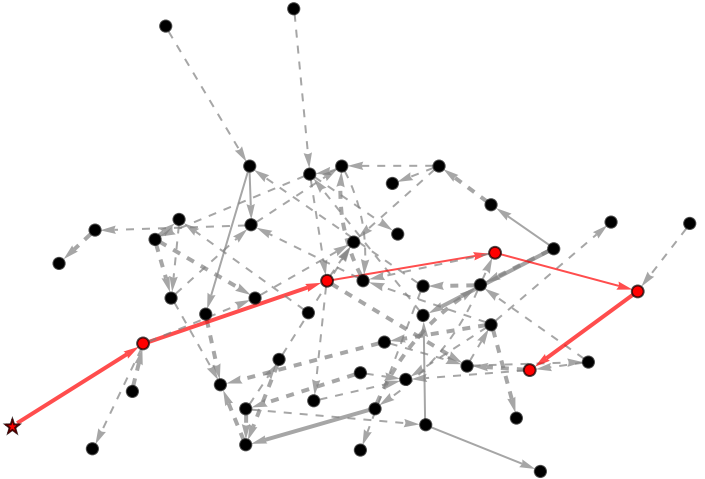
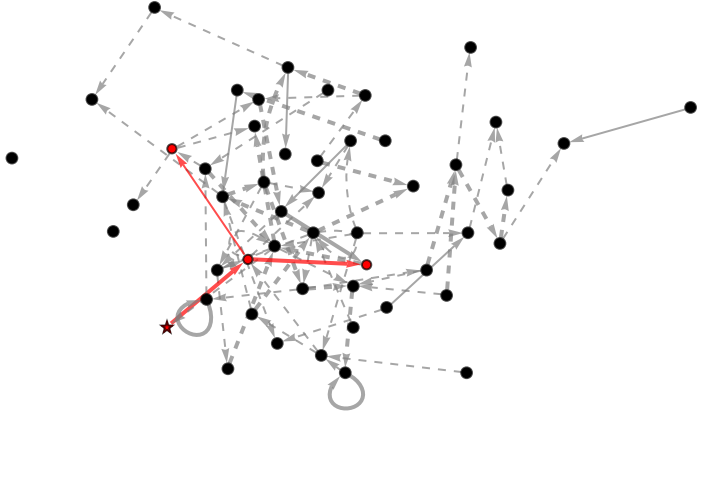
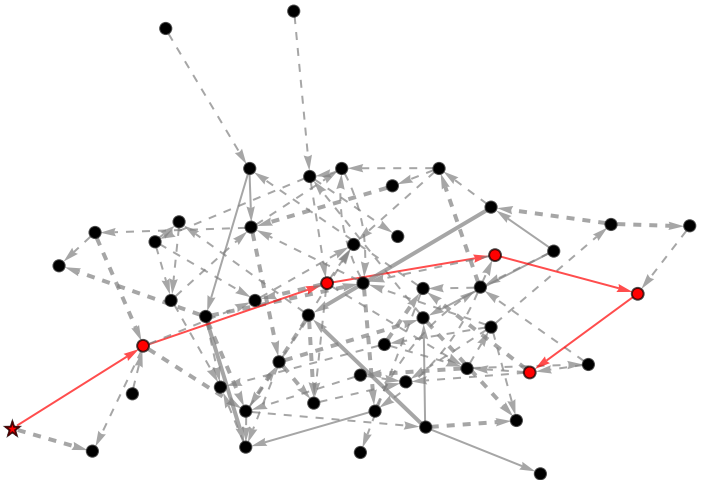
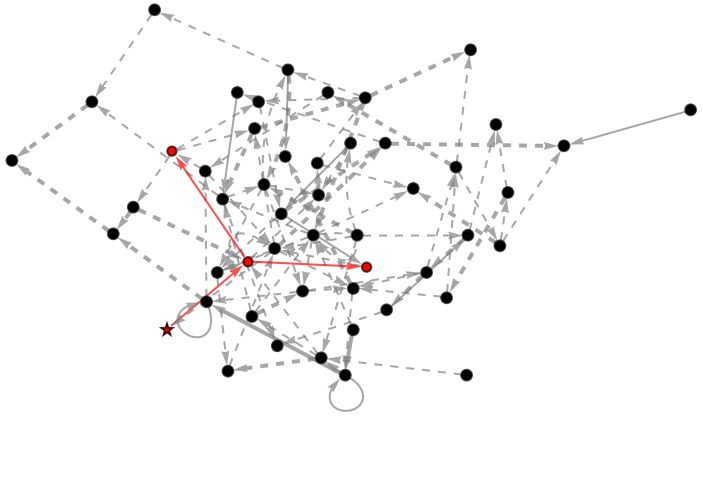
We see a similar behavior as in networks without damage spread (in Figure

3.3), but with larger values of assortativity in absolute values. The process is much longer, goes up to $E = 50N^*$.

In Table 3.3 we illustrate the structure of the Edge Competition growth process.

Properties	Random Graph	Competitive link addition
$r_{rd} = -0.42$ $ \text{GOUT} _{rd}/N = 0.15$ $r_c = \text{NaN}$ $ \text{GOUT} _c/N = 0.1053$		
$r_{rd} = 0.05$ $ \text{GOUT} _{rd}/N = 0.15$ $r_c = \text{NaN}$ $ \text{GOUT} _c/N = 0.1053$		

(Continued on next page)

Properties	Random Graph	Competitive link addition
$r_{rd} = 0.14$ $ \text{GOUT} _{rd}/N = 0.3$ $r_c = 0.3889$ $ \text{GOUT} _c/N = 0.2105$		
$r_{rd} = 0.06$ $ \text{GOUT} _{rd}/N = 0.3$ $r_c = 0.3858$ $ \text{GOUT} _c/N = 0.2105$		

(Continued on next page)

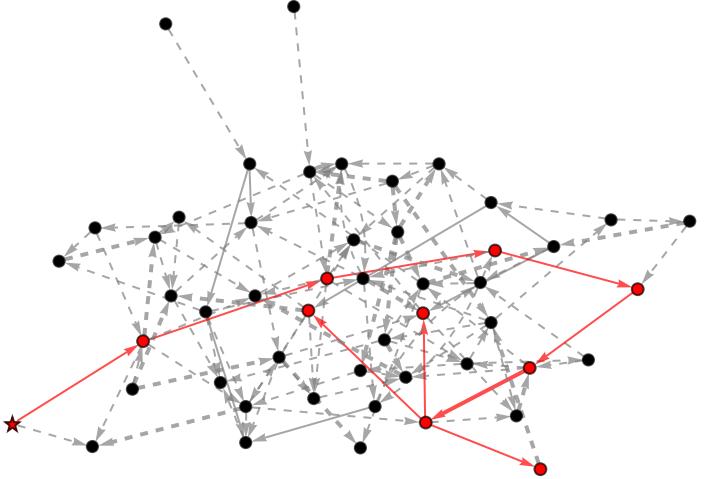
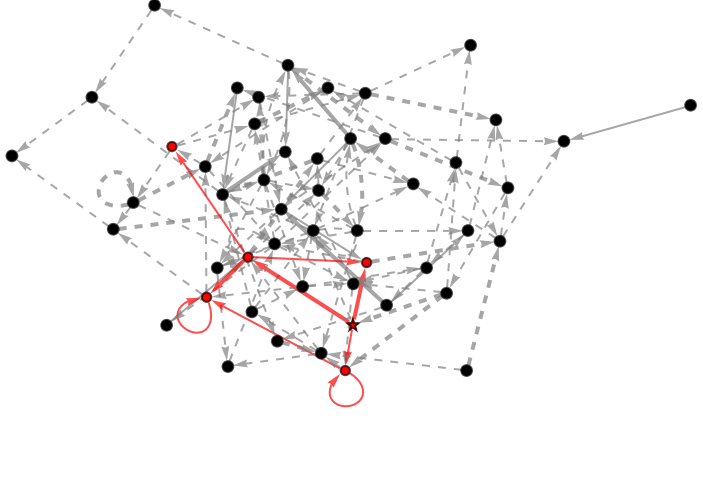
Properties	Random Graph	Competitive link addition
$r_{rd} = -0.11$ $ \text{GOUT} _{rd}/N = 0.5$ $r_c = 0.1724$ $ \text{GOUT} _c/N = 0.3158$	 <p>A network graph with approximately 40 nodes. Nodes are represented by black dots. Edges are shown as dashed gray lines. A subset of nodes and edges is highlighted in red, forming a connected subgraph. A red star is located at the leftmost node of this red subgraph.</p>	 <p>A network graph similar to the random graph, but with additional red edges and nodes. Some nodes are now red circles, and some edges are solid red lines. There are also red circles around some nodes, possibly indicating self-loops or specific states. The overall structure is more complex than the random graph.</p>

Table 3.3: (Continued from previous page). Random network and competitive link addition. The edges between damaged nodes are non-dashed, others are dashed. The red nodes and edges are showing the largest OUT component in the damaged subgraph. Index c stands for Competitive, index rd stands for Random.

Chapter 4: Conclusions

In this thesis, we studied the growth processes of Boolean networks as simple models of evolution of gene regulatory networks. The models are based on growth models in which links are added via different selection rules. The models are inspired by recent work on ‘explosive’ percolation, which shows that when network links are added through competitive rather than random processes, the connectivity phase transition can be significantly delayed, and when it is reached, it appears to be first order instead of second order. We find that by modifying the traditional framework for networks grown via competitive link addition to capture how gene networks evolve to avoid damage propagation, we also see significant delays in the transition that depend on the selection rules, but the transitions always appears continuous rather than ‘explosive’. We consider two different selection rules for network growth: Edge Competition and Direction Selection. We see that both Edge Competition and Direction Selection delay the onset of the transition to global damage propagation. If we consider the case in which all genes propagate damage, the damage propagation is more suppressed for Direction Selection than for Edge Competition. If we consider that nodes propagate damage probabilistically based on their sensitivities, and that these sensitivity values influence the growth process, then the reverse is

true: damage propagation is more suppressed for Edge Competition than for Direction Selection. For both Edge Competition and Direction Selection, we see that the networks become more and more disassortative as the system approaches the transition to global damage spreading. For Edge Competition, the assortativity coefficient begins to increase after the transition, while for Direction Selection, it continues to decrease even after the transition.

Glossary of Frequently Used Notation

N	number of nodes in a network
E	number of edges in a network
k_{in}	in-degree
k_{out}	out-degree
A	adjacency matrix of network
b_i	bias of node i
q_i	sensitivity of node i
r	assortativity coefficient of a network
\bar{H}	Hamming distance
m	number of choices for next generation of the growth process
S	order parameter
κ	maximum jump
t	time
p_k	degree on node k

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