Using Circuit Structural Analysis Techniques for Networks in Systems Biology

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ABSTRACT

The cell contains numerous networks for information processing. These networks are responsible for carrying out all cell functions including gene transcription, signal transconduction, and metabolic activities. Many of these networks process information similar to digital logic circuits and classical logic methods have been successfully used to analyze their behavior. The objective of this paper is to investigate the potential of circuit structural analysis techniques in analyzing the topologies of cellular networks arising in systems biology context. Rent's rule has been in particular a classical method that is used in analyzing the topologies of digital circuits. We investigate the applicability of Rent's rule to systems biology networks, and we outline the structural similarities and differences between circuit networks and systems biology networks. We compute Rent's rule parameters and classify systems biology networks according to their Rent's exponent. Interestingly, networks that process information in a logical fashion have Rent exponents that are similar to that of logic circuits. To provide a basis for our results we utilize recent advancements in graph theory to create random artificial networks with the same degree sequences as real networks and extend our experiments to those circuits as well. Our results open the door for other researchers to further investigate topological circuit analysis techniques for networks in systems biology.

ACM Categories & Subject Descriptors
B.7.1 [Integrated Circuits]: Types and Design Styles
General Terms: Design, Algorithms.
Keywords: Rent's rule, networks, systems biology.

1. INTRODUCTION

The main purpose of digital circuits is information processing which is carried out using logic gates and intercommunication wires. The cell is an integrated device made of thousands/millions of interacting proteins. The cell monitors its internal and external environment and accordingly responds using different proteins that exercise various cell functionalities. The interactions among genes, proteins and various signal molecules form complex information processing networks that map the cell's signals and molecules into functions. Cellular networks are at the center of the study of the field of systems biology [1].

Networks arising from electronic circuits and systems biology contexts share many similarities. At their core they both process information. Much of this information processing is carried out in systems biology in a logical manner (e.g., using conjunction, disjunction and negation operators) similar to digital circuits. In both networks computation occurs distributively at the nodes of the network and communication is carried out between the nodes of the network to realize the network's function. In electronic circuits, metal wires transfer electrons in the circuit for communication purposes. In systems biology, proteins and various biochemical molecules floating in the water-based medium of the cell carry out the required communication. Just as nodes in circuit networks can be grouped into modules (e.g., flip-flops, adders) based on their functionalities, nodes in systems biology can be also grouped into *motifs* that are used to carry out specific recurring functionalities (e.g., feed-forward loops and autoregulation).

The recent years have seen a flurry of research into analyzing the structure of systems biology networks [19, 20, 1]. Previous research focused on many structural aspects of such networks including: motif finding, identification of motif functionality, determining the statistical properties of node degree distribution, and investigating the applicability of scale-free laws. Given the similarities between systems biology networks and electronic circuits, this paper seeks to investigate the applicability of circuit topology and structure analysis techniques to systems biology networks. In particular, electronic circuits have shown unique properties as displayed by the famed Rent's rule [9, 17]. Does Rent's rule also extend to systems biology networks? What are the structural similarities and differences between systems biology networks and electronic circuits? These questions and their answers are the focus of this paper. The main contributions of this paper can be summarized as follows.

- This paper is the first to investigate the applicability of circuit topological analysis techniques for networks arising in systems biology. We study the applicability of Rent's rule for systems biology networks. We explain the structural similarities and differences between electronic circuits and cellular networks in systems biology.

- To provide a basis for comparing different networks, we utilize some of the latest results in graph theory to construct random networks with the same number of edges, nodes and node degree sequences as the experimented real networks. We also investigate the applicability of Rent's rule to these random networks.

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- We provide comprehensive experimental results on large selection of representative networks from systems biology. We classify these networks based on their functionality, and we show that the Rent's exponent range depends on the functionality of the network. Networks that process information in a logical fashion have Rent exponents that are in the same range as in electronic circuits.

The organization of this paper is as follows. Section 2 reviews Rent's rule as a classical method for structural circuit analysis. Section 3 overviews new techniques that synthesize random networks with the same characteristics as real networks. Section 4 reviews various network types arising in systems biology contexts. Section 5 provides all experimental results and conclusions. Finally Section 6 summarizes the main results of this paper.

2. NETWORKS IN INTEGRATED CIRCUITS

Rent's rule is a classical relationship that is observed when analyzing the structure or topology of computing circuitry [9, 17, 7]. The rule relates the number of external wires emanating from a block of computational cells to the number of cells within the block as illustrated in Figure 1. The rule has been observed and validated on many real circuit designs. It has many applications in circuit design and implementation including wirelength estimation, congestion estimation and interconnect power estimation [14, 21, 3, 18, 8]. Rent's rule is a power-law relationship that exists for logic circuits [9, 17, 10]. Rent's rule is given by

$$P = TB^r, \tag{1}$$

where

- P is the average number of external nets per block, where a block is a cluster or partition of cells.
- B is the average number of cells per block.
- $0 \leq r \leq 1$ is the Rent exponent.
- T is the average number of pins per cell.

The Rent exponent reflects that there is intra-communication among the cells of a block and thus fewer than TB terminals are available for communication with the external world outside the block. The higher the Rent exponent, the more complex is the wiring of the circuitry. Memory structures with local interconnects have low r values while logic circuits for microprocessors have a r that is usually in the range of $0.4 - 0.7$. Generally circuits with mainly local wires lead to lower r, while circuits with larger shares of global wires lead to higher r [6, 15].

There are two general approaches to calculate Rent exponent [13, 23]. One method is based on recursive-based partitioners and the other method is based on placers.

- **Partitioning-based Calculators.** In this method a min-cut partitioning algorithm is used to recursively partition the network of cells. At each partitioning level, the average number of cells per partition and the average number of nets external to a partition are computed. These pair of numbers constitute a point on the log-log graph of Rent's rule. After all points are plotted, linear regression is used to estimate, r, the rent exponent.

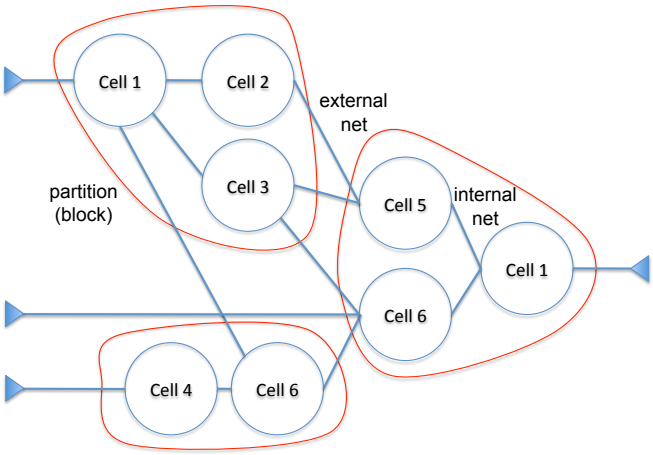

Figure 1: Example illustrating the blocks (or partitions), cells and external nets of a circuit network.

- **Placement-based Calculators.** In this method a circuit is placed using some "good" placement algorithm. Then the placement area is divided into several regions. The average number of cells per region and the average number of external nets per region are then computed. These two numbers constitute a point on the log-log graph of Rent's rule. The process of dividing the placement area into regions is attempted with various sizes for the regions to give more points on the log-log graph. Then the Rent exponent, r, is computed through a linear regression using the computed points

In this paper we use partitioning-based calculators based on multi-level partitioners. We build our own Rent calculator based on the multi-level partitioning tool `hMETIS` (version 1.5) [16]. For example, Figure 2 gives the partitioning results of the s838 circuit from the ISCAS '89 benchmark suite [5]. We apply the `hMETIS` in a recursive fashion to obtain the average values of P when the average values of $B = 256, 128, 64, 32, 16, 8, 4, 2, 1$ corresponding to the various levels of recursive partitioner. The plot is in semilog scale for both axes. The plot can be generally partitioned into two regions where the first region (Region I) is the one that exhibits the linear relationship between B and P [7]. As the number of cells

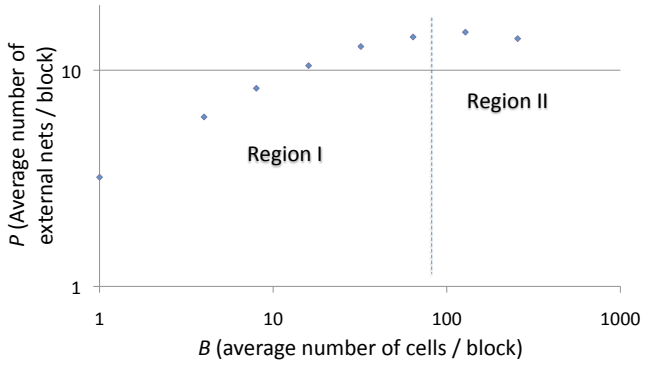

Figure 2: Rent's rule plot for the s838 circuit of the ISCAS '89 circuits.

per block approaches the total number of cells in the circuit, the number of external nets becomes constrained by the limited number of I/O terminals at the circuit periphery. This restriction leads to a rapid reduction in the value of P which defines Region II of the Rent's rule plot. The Rent exponent can be calculated using linear regression from the points in Region I. From our results the Rent exponent of this circuit is equal to 0.367. As previously discussed in the literature [13, 23], the numerical value of the Rent exponent of a circuit can slightly vary depending on the optimality of the partitioner or placer used.

3. RANDOM NETWORKS

To provide a basis for comparison, our objective in the section is construct random networks. Motivated by recent developments in graph theory, our objective is to generate random graphs with the same node degree sequences as real circuits in addition to the typical requirement of having the same number of nodes and edges. A node here could be either a cell or an I/O terminal. The *degree sequence* of a graph is defined as the non-increasing sequence (repetitions allowed) of its node degrees. The outline of the random graph generation algorithm is as follows [12, 22]:

1. Generate a graph with the given sequence. This step is iterative in nature. The residual degrees of nodes, where *residual degree* is the difference between the current degree and the final degree of a node, is maintained. In each iteration, an arbitrary node u is picked and edges are added from u to r_u nodes of highest residual degree, where r_u is the residual degree of u. The residual degrees of u and all affected r_u nodes are updated accordingly. The iterations are repeated until the residual degrees of all nodes are equal to zero.

Before explaining Step 2, a handy lemma is first proven.

Lemma 1. If the graph constructed from the Step 1 is unconnected, then at least one of the connected subgraphs must contain a cycle.
Proof: Assume the original connected circuit had n nodes. Since the circuit is connected by definition then it must have at least a total of $n-1$ edges or $2(n-1)$ degrees. Assume Step 1 leads to to an unconnected graph with m connected subgraphs or components where each component has n_i nodes for $i = 1 \ldots m$. If none of the components has a cycle then the the total number of edges in all components is equal to $\sum_{i=1}^{m}(n_i - 1) = n - m$. This leads to a contradiction as $n-m$ is less than $n-1$ since there are $m \geq 2$ components.

2. Connect the graph while keeping all the degrees of its nodes the same. If Step 1 leads to an unconnected graph then this step converts the graph to connected one. If the graph constructed from the previous step is unconnected, then at least one of the connected subgraphs must contain a cycle as proven in Lemma 1. Let (u,v) be an edge in that cycle and let (s,t) be an edge in a different connected subgraph. Deleting the edges (u,v) and (s,t) and inserting the edges (u,s) and (v,t) will merge the two subgraphs into a connected graph. This step is illustrated in Figure 3. Note that the resulting graph still satisfies the given degree sequence. This step can be repeated until the entire graph is connected.

3. Switch the edges to make the graph random while still being connected. The graph can be randomized as follows. Pick two edges at random, say (a,b) and (x,y) with distinct endpoints. If (a,x) and (b,y) are not edges then produce a new graph by deleting the edges (a,b) and (x,y) and inserting the edges (a,x) and (b,y) as long as this switching operation leaves the new graph connected.

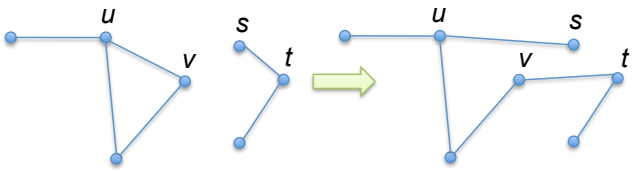

Figure 3: An illustration of Step 2.

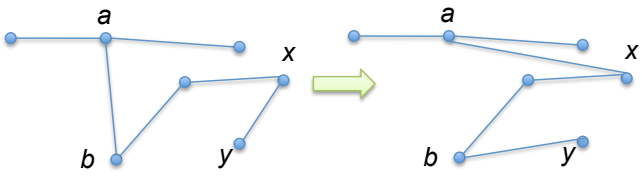

Figure 4: An illustration of Step 3.

This step is illustrated in Figure 4. Using the switching operation, any connected graph can be transformed to any another connected graph satisfying the same degree sequence.

Note that the outlined method can be to generate random synthetic circuits for other purpose like benchmarking or driving physical synthesis tool chains.

4. NETWORKS IN SYSTEMS BIOLOGY

The cell function is based on complex networks of interacting biochemical reactions that respond to events inside and outside the cell environment and produce observable cellular function. These networks occur at multiple levels including gene-protein interactions, protein-protein interactions, signals-protein interactions and biochemical interactions for metabolism. In the upcoming subsections we briefly overview the structure of the major networks inside the cell.

4.1 Transcriptional Networks

A cell can sense many signals within its internal and external living environment, and it can respond to these signals by producing the appropriate proteins. These proteins are produced from expressed genes within the cell. *Transcription factors* regulate the rates of production of proteins by controlling the expression levels of the individual genes that produce the proteins. A transcription factor itself is a protein that binds to specific DNA sequences and thereby regulates the transcription of genetic information from DNA to RNA (RNA eventually gets translated to protein). For example *E. coli* has about 300 transcription factors that regulate the rates of production of about 4000 proteins. Transcriptional factors transit between active and inactive states as determined by the input signals from the environment.

Figure 5 illustrates the process of gene regulation through transcription factors. In general, genes are transcribed to mRNA when RNA polymerase binds to the promoter region of a gene. RNA gets translated to proteins by ribosomes. Transcription factors of a gene control the binding of RNA polymerase to the promoter region. There are two possible modes of regulation:

- *Activation* $X \rightarrow Y$. In this case when the transcription factor

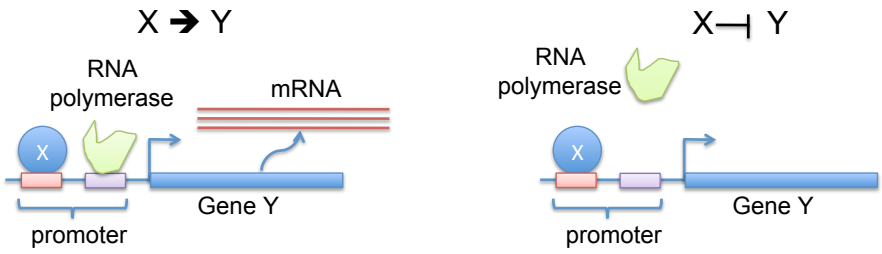

Figure 5: Illustration of gene transcription regulation.

X binds to the promoter region of gene Y, it enables RNA polymerase to bind to the promoter region. Once the RNA polymerase is bound, gene Y is expressed and its transcribed into mRNA. If the transcription factor is not present then RNA polymerase will not bind to the promoter region and thus gene Y will be inactive.

- *Repression* $X \dashv Y$. In this case when the transcription factor X binds to the promoter region of gene Y, it disables RNA polymerase from binding to the promoter region. Once the RNA polymerase is unable to bind, gene Y becomes inactive and no transcription to mRNA occurs. If the transcription factor is not present then RNA polymerase will bind to the promoter region and thus gene Y will be activated and the transcription process to mRNA occurs.

Transcription factors themselves are expressed by genes which are regulated by other transcription factors, which are in turn regulated by some transcription factors and so forth. These set of interactions between transcription factors and their target genes form a *transcriptional network*. In such network nodes represent genes and directed edges represent transcriptional regulation of one gene by another gene. A gene can be regulated by multiple of transcription factors. The primary inputs (using circuit terminology) are the signals that carry information from the external or internal environment of the cell, and the primary outputs are proteins that act upon the environment. Transcriptional networks are largely composed of a small set of network *motifs*; motifs are patterns of interactions that significantly recur in these networks than in randomized networks [19]. Each motif performs a specific information-processing role in the network just as logic gate modules perform particular information processing functions in digital circuits.

Consider the example network of Figure 6 which is part of the developmental transcription network[1] of the *B. subtilis* spore. In this network:

- Gene Z_1 is expressed if both the transcription factor expressed from gene X_1 is active and the transcription factor expressed from gene Y_1 is repressed or inactive. The transcription factor expressed from Y_1 is active (repressed) when the transcription factor expressed from X is active (repressed). The *feed-forward* motif consisting of Z_1, X_1 and Y_1 behaves as a pulse generator where Z_1 is expressed for a short duration only when X_1 is expressed.

- Genes Z_2, Y_2 and X_2 form a feed-forward motif that behaves as a pulse generator when X_2 is expressed. X_2 is expressed in turn when the transcription factors expressed from both X_1 and Y_1 are activated.

- Gene Z_3 is expressed when the transcription factors expressed from both X_2 and Y_2 are active.

4.2 Protein-Protein interaction Networks

Protein-protein interactions are one of the most abundant inside the cell and they are used to carry out many of the essential cell functions. Examples of protein interactions include a protein interacting with another protein to form part of a larger protein complex, or a protein interacting with another protein (say by phosphorylation) to modify it. In protein-protein interaction networks nodes correspond to relevant proteins and edges correspond to protein - protein interactions among the nodes.

Similar to transcription networks, as protein interaction networks become increasingly large and complex, it becomes more important to break them down into manageable structural modules or motifs. These motifs represent clusters of proteins that together contribute to the same cellular function, where the clustering is derived from

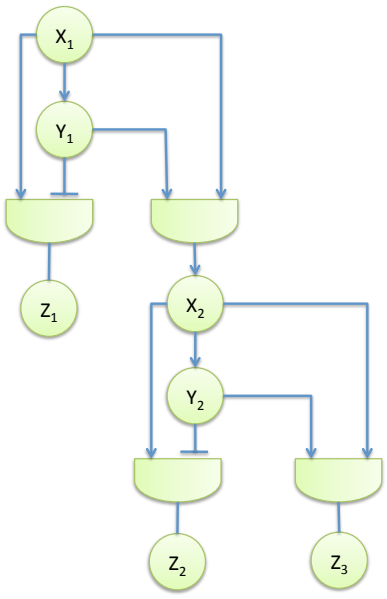

Figure 6: A simplified transcription network that guide the development of the *B. subtilis* spore (adapted from [11, 1]).

[1]Developmental transcriptional networks govern the fate of cells as an egg develops into a multi-cellular organism. These networks are required to create the required differentiation between cells as they develop into different types within an organism.

the topology of the network [4]. Protein interaction networks function together with other cell networks (e.g., signal transduction networks and transcription networks) and thus these interacting networks can be described using one integrated network. For example, one protein can modify another protein which allows the latter to regulate the transcription of a gene, or a transcription factor can regulate two genes whose protein products interact.

4.3 Signal Transduction Networks

These networks involve the transduction of a signal from the outside of a cell to the inside. Signaling networks transmit signals from the external environment of the cells to the inside of cell, to the nucleus, or to other cellular organelles and functions [20]. Signal transduction involves the binding of an extracellular signaling molecules (*ligands*) to cell-surface receptors. This binding triggers intracellular signaling cascades within the cell. The main steps that occur with signal transduction include: (1) the binding of the signal molecule (*ligand*) to an extracellular receptor; (2) the subsequent phosphorylation of an intracellular enzyme; (3) the amplification and passage of the signal; and (4) an eventual change in the cellular function. In signal transduction networks, nodes represent proteins and molecules and edges represent reactions and processes (e.g., ligand binding).

4.4 Metabolic Networks

Cell metabolism is the mechanism that converts raw materials into energy as well as the elementary blocks needed to produce biological structures, to maintain cells and to conduct various cellular functions [20]. Metabolic imbalance is associated with major human disease, such as diabetes and obesity. Metabolism is usually divided into phases. The first phase is *catabolism* where input substrates to cells are broken down into common *metabolities*, and the second phase is *anabolism* that converts the metabolites into amino acids, nucleic acids and other needed elementary blocks. A metabolic network shows the interactions between enzymes and metabolites in a cell. In these networks enzymes and metabolites form the nodes of the network and interactions between them form the edges.

4.5 Neural Networks

Neural networks generally do not belong to the category of systems biology networks; however, we include one such network in our experimental results. A neural network describes a collection of physically interconnected neurons whose inputs and output signaling targets define a circuit. Communication between neurons often involves an electrochemical process. Each neuron interact with other neurons through several input collections called *dendrites*, which are connected via *synapses* to other neurons, and one output connection called *axon*. If the sum of the input signals surpasses a certain threshold, the neuron sends an action potential that propagates along the axon. Neural networks are used for information processing in the brain and the nervous system. Our experimental neural network comes from the *c. elegans* worm.

5. EXPERIMENTAL RESULTS

In this section we study the applicability of circuit structural analysis techniques to systems biology networks and to random network with degree sequences as real networks. We carry out two sets of experiments. In the first set of experiments we investigate a number of representative systems biology networks and then graph the Rent plot (i.e., average of nodes per block versus the number of external nets per block on a log-log scale). We also calculate the Rent exponent and provide observations on the similarities and differences between electronic circuits and systems biology networks. In the second set of experiments we construct random graphs with the same degree sequences as the real networks and then graph the Rent plot and compute the rent exponent. We also discuss the differences between such networks and the real networks. First we describe the tools used in the experiments of this study.

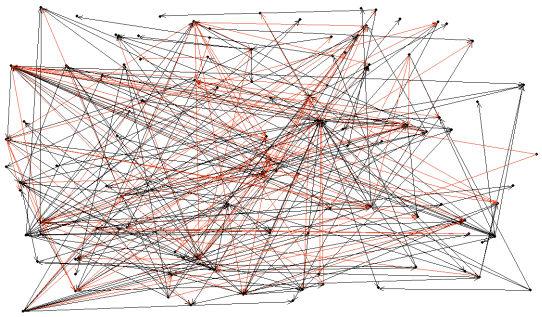

Figure 7: Visualization of the dros network.

- We construct a tool that calculates P and B of the Rent rule based on the hypergraph partitioning tool `hMETIS` (version 1.5) [16].
- We use the tool `gengraph` [22] to generate random graphs with the same number of edges and nodes and with the same degree sequence as the experimental networks.
- We use the tool `mDraw` for network visualization [2].

The names of the networks used in our experiments together with their characteristics are given in Table 1, where we provide the number of edges, nodes and the average node degree of each network. We use the `mDraw` tool to draw the dros network in Figure 7. The average node degree of electronic logic circuits is usually around $3-4$ due to technology limitations on the number of fan-in and fan-outs of nodes. The average node degree for most systems biology networks (especially the ones that are similar to logic circuits) are within the range of logic circuits. However, some other networks like neural networks require high connectivity which increases the average node degree.

In addition to average node degrees, we consider the node degree sequence. Figure 8 shows the degree sequence of a number of networks. We first notice that except for nodes with degree one, systems biology networks exhibit the general trend that as the degree increases, the number of nodes with the degree decreases. However, circuits typically have few nodes (basically I/O terminals) with degree one which is due to the limitedness of the perimeter of the circuit. Networks from systems biology do not have necessarily such limitation. The difference in the number of nodes with degree one will impact the shape of Region II in the Rent plot. We will shortly study the implications of the number of nodes with degree one as part of the first experiment.

Exp 1: Experiments with Systems Biology Networks. In the first set of experiments we asses the validity of Rent's rule to networks from systems biology. We use the recursive-partitioned based developed flow for calculating B (the average number of nodes per block) and P (the average number of external nets per block) at various partition levels. We plot our results for four networks in

Network	Description	nodes	nets	av. degree
s838	an electronic circuit network	512	819	3.20
sea_urchin	a developmental transcription network from sea urchin	45	83	3.69
coli1	a transcription interactions between regulatory proteins and genes in the bacterium E. coli	418	519	2.45
human	a human signal transduction network	181	312	2.75
yeast	an integrated transcription and protein interaction network in the yeast S. cerevisiae	685	1052	3.07
s9234	an electronic circuit network	5844	8197	2.81
dros	a drosophila developmental transcription network in Drosophila fly	110	306	5.14
tong	a transcription genetic interaction network of yeast	685	1052	3.07
c_elegans	a neuronal synaptic circuitry network in the C. elegans worm	280	2170	15.50
ccsb	a protein-protein interaction network	687	2608	7.59
dip	a protein-protein interaction network for S. cerevisiae	4716	15114	6.41

Table 1: Characteristics of networks in experimental results.

Figure 9; other networks display similar trend. Our plots show that systems biology network display a clear linear Region I trend as the case for electronic circuits. Thus, we conclude that Rent's rule is generally applicable to networks from systems biology.

While Region I of the Rent graph is the region of interest in calculating the Rent exponent, Region II is characteristic of computational circuits as it shows the impact of the limited number of I/Os. One of the differences between Rent graphs for electronic circuits and biological systems lies in Region II. In many of the plots of Figure 9, Region II does not clearly exist. There are a number of reasons for such behavior.

- Some of the experimented networks are actually subnetworks that are extracted from larger cell networks. In many cases cell networks are gigantic and researchers focus on only mapping subnetworks of an original network, and thus it is reasonable to expect a large number of "I/O" terminals and consequently the lack of Region II.

- The number of I/O signals for the cell are limited by the surface area of its volume, and thus it has more capacity to handle I/O than circuits that are constrained either by their perimeter or their surface area (in case of flip-chip packaging).

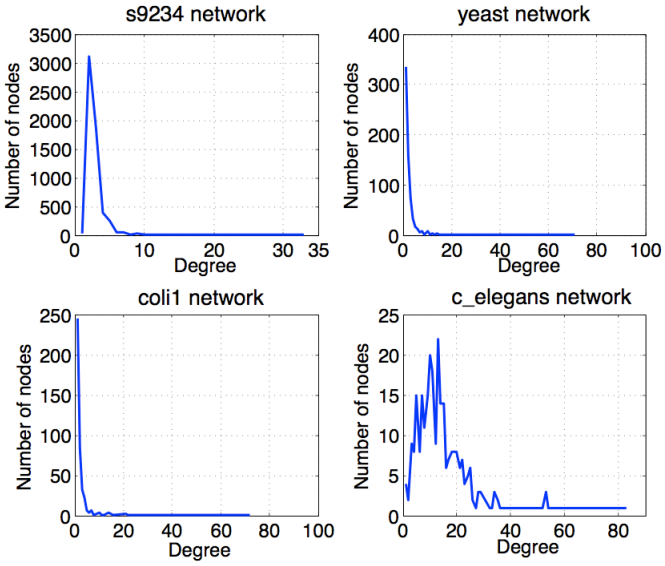

Figure 8: Degree distribution (sequence) for four networks.

network	Rent	Rent random	diff
s838	0.367	0.671	0.304
sea_urchin	0.448	0.588	0.140
coli1	0.463	0.568	0.105
human	0.431	0.665	0.234
yeast	0.489	0.708	0.219
s9234	0.500	0.777	0.277
dros	0.601	0.721	0.120
tong	0.621	0.775	0.154
c_elegans	0.781	0.878	0.097
ccsb	0.827	0.858	0.031
dip	0.827	0.896	0.069

Table 2: Rent exponent for the studied networks and the random networks with the same degree sequence as their real counterparts.

- For signal transconduction networks, the cell has the capability to transport multiple ion types through the same ion channels effectively multiplexing its I/O and increasing its communication capabilities.

To calculate the Rent exponents of all networks, we perform linear regression on our partitioning results. We tabulate the results for various circuits in column 2 of Table 2. The results show that the Rent exponent varies between $0.4 - 0.8$ depending on the circuit's type. Circuits with larger wiring complexity and higher average node degree (e.g., c_elegans, ccsb and dip) display higher Rent exponents. Interestingly, transcription networks that function in a manner similar to logic circuits have Rent exponents that are in the $0.4 - 0.6$ range, which is similar to electronic logic circuits.

In electronic circuits, the correctness of Rent's rule is a result of the fact that designers build their designs in a hierarchical fashion, imposing the same complexity at each level of the hierarchy [21]. Such hierarchy leads to self-similarity of the designs [21, 7]. Given the presented results, one might wonder whether evolution has eventually led to biological networks with such hierarchical organization.

Exp 2: Real Networks vs. Random Networks. In the second set of experiments we study the applicability of Rent rule to random networks that have the same degree sequence as real networks. For each network in Table 1, we use the tool `gengraph` [22] to generate a random network with the same (1) nodes, (2) edges, and (3) degree sequence as its real counterpart. Then we use our partitioning-based flow to calculate B and P at various partitioning levels. We plot in Figure 10 the partitioning results for both the real network and the random counterpart. In all cases the random network has the upper plot (i.e., the one with larger Rent exponent).

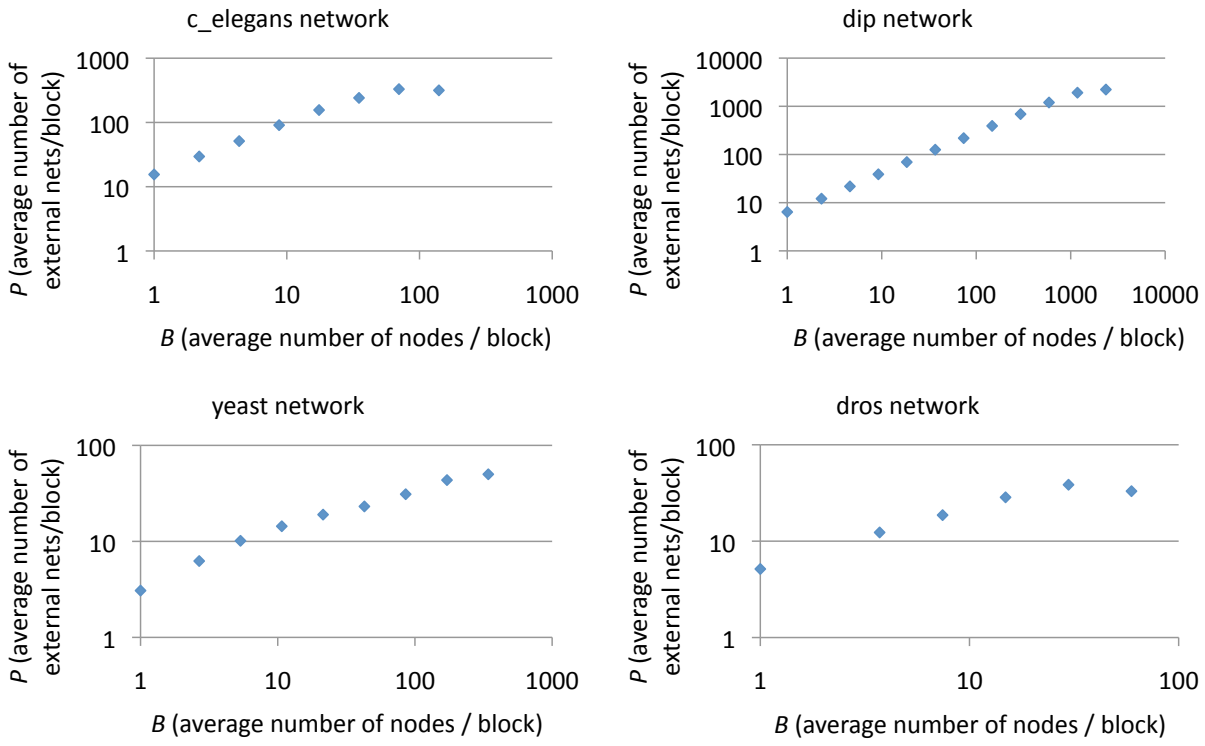

Figure 9: Rent plot for selected networks.

For space limitations, only a sample of networks are plotted; other networks exhibit similar behavior. The plots show that Rent rule is well applicable into random networks with the same degree sequence as the real networks. We also calculate the Rent exponent for all networks and tabulate the results in the third column of Table 2. From our results we observe that random networks display Rent exponents with higher values than their real counterpart networks with the same degree distribution. In general the difference between the Rent exponent of a real network and that of its random network decreases in magnitude as the Rent exponent increases in magnitude.

6. CONCLUSIONS

In this paper we have discussed the applicability of the structural circuit analysis techniques to network arising in other contexts like systems biology. Information processing networks in system biology bear striking resemblance to their physically-engineered ones, and thus it is natural to investigate whether circuit topological properties are also valid for them. We have investigated Rent rule as a key property of electronic circuits. We have examined its applicability to systems biology network and to also random graphs with the same properties as their circuit counterparts (nodes, edges and degree sequences). We have discovered that Rent's rule is also well applicable to systems biology network, and furthermore the Rent exponent of biology networks that carry out logic-based information processing fall within the same range as engineered electronic circuits. Random networks with the same degree sequence as real networks also obey Rent's rule but consistently have higher Rent exponent than their real counterparts.

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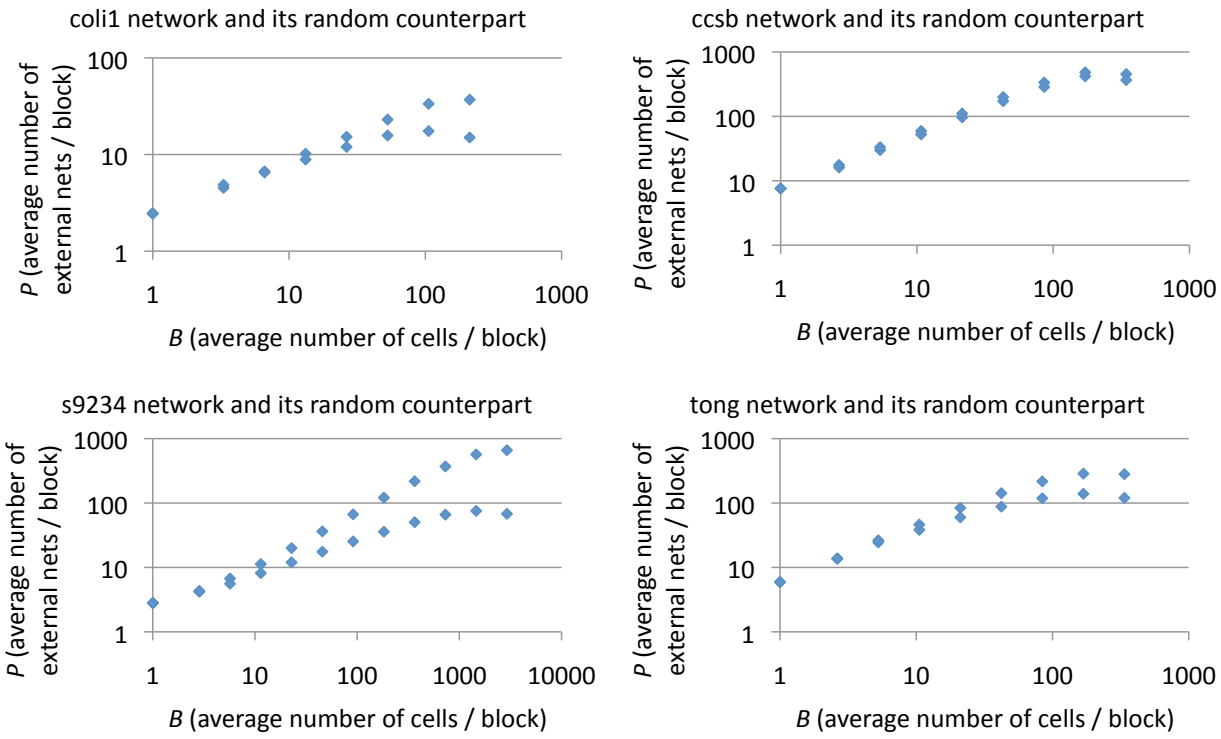

Figure 10: Rent plot for selected networks and their random counterparts. In all plots, the random network has the trend with the larger slope (i.e., rent exponent).

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