Characterizing Building Blocks of Resource Constrained Biological Networks

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ABSTRACT

Identification of motifs—recurrent and statistically significant patterns—in biological networks is the key to understand the design principles, and to infer governing mechanisms of biological systems. This, however, is a computationally challenging task. This task is further complicated as biological interactions depend on limited resources, i.e., a reaction takes place if the reactant molecule concentrations are above a certain threshold level. This biochemical property implies that network edges can participate in a limited number of motifs simultaneously. Existing motif counting methods ignore this problem. This simplification often leads to inaccurate motif counts (over- or under-estimates), and thus, wrong biological interpretations. In this paper, we develop a novel motif counting algorithm, *Partially Overlapping MOTif Counting (POMOC)*, that considers capacity levels for all interactions in counting motifs. Our experiments on real and synthetic networks demonstrate that motif count using the *POMOC* method significantly differs from the existing motif counting approaches, and our method extends to large-scale biological network in practical time.

CCS CONCEPTS

• Applied computing → Biological networks; Bioinformatics; Systems biology;

KEYWORDS

Motif counting; partial overlap; reaction capacity; biological networks

INTRODUCTION

One of the most fundamental challenges in computational network studies is the motif counting problem. A network motif is a pattern of local interconnections (i.e., a small subnetwork) observed significantly more frequently in a given network than in a random network of the same size [1]. Existing studies have already uncovered existence of network motifs such as feed forward loop and bifan [6]. Motifs utilize the basic control mechanisms to govern biologically important dynamic behaviors, such as oscillations, generation of molecular pulses, and rapid or delayed responses [1, 11]. Thus, the presence or relative abundance of motifs in biological networks is often used to characterize their topology, function, and robustness [7]. Network motifs have been effectively used to study

Figure 1: (a) A network with eight nodes and eight edges. (b) A motif pattern. (c) A network with edge capacities. $x(y)$ denotes the edge x has the capacity y . (d) - (i) six motif embeddings in the network.

the biological processes that regulate transcription and to find the genetic factors that impact various diseases [3, 6].

Identifying motifs and counting them in biological networks is a computationally challenging task as it requires solving the subgraph isomorphism problem, which is NP-complete [2]. Several methods have been developed to count instances of a motif in a given network [4, 9]. These methods could be categorized into two classes [4]. The first class counts all instances of a given motif ignoring the fact that some motifs may share edges (F_1 measure) [9]. The second class counts all non-overlapping instances of a given motif, i.e., those which do not share any edge (F_2 measure). Figure 1 shows the difference between these two frequency measures on a hypothetical network G . Consider the motif pattern M in Figure 1b. Our input network G in Figure 1a yields six possible embeddings of M shown in Figures 1d-1i. Thus, F_1 measure of M in G is six. However, out of these six embeddings at most two can be chosen without picking the same edge multiple times (e.g., Figures 1d and 1i). Thus, F_2 measure of M in G is two.

Notice that both F_1 and F_2 measures make opposite, yet very strong assumptions regarding how the cells realize interactions. The former one assumes that the same interaction can participate in an arbitrary number of motif instances at the same time. The latter one limits the participation of an interaction to a single motif instance. Although, these two assumptions simplify the motif counting problem, they rarely reflect how cells operate interactions. Each interaction utilizes the molecules participating in that interaction. Thus the abundance of the interacting molecules makes it

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possible to include the corresponding edges appear in multiple (yet limited) number of motif instances. For example, depending on the concentration level of a metabolite, an enzymatic reaction may take place in one (low reaction/edge capacity) or many metabolic pathways (high edge capacity) [12]. We use the term *capacity* of an edge to denote the number of motif instances that edge can participate simultaneously. Thus, even if two cells have the same underlying biological network topology, they may yield different number of motifs of the same topology. For example, if we allow partial overlap of the motif M in the network G (see Figures 1b and 1c), we find four possible embeddings of motif M in G (Figures 1d, 1g, 1h and 1i). *A motif counting approach that ignores the edge capacities will lead to unrealistic motif counts, and wrong biological interpretations. Motif counting approaches that take edge capacities into account are needed.*

METHODS

In this study, we build a new motif counting algorithm that allows partial overlap between different embeddings of a given motif on the target network. Briefly, given a target network, a motif topology, and a positive capacity value for each interaction in the target network, we count the maximum number of ways to place the motif on the target network, so that no edge appears in more motif embeddings than its capacity. Notice that the classical counting measures F_1 and F_2 are special instances of our measure [5, 10]. If we set the capacity of all edges to one, our motif counting problem reduces to non-overlapping motif counting with F_2 measure. Similarly, if we set the edge capacities to infinity our problem reduces to motif counting using F_1 measure.

We develop a novel motif counting method called *Partially Overlapping Motif Counting (POMOC)*, that computes the number of partially overlapping instances of a given motif in a given network. *POMOC* first finds all instances of a given motif M in the network G , then it chooses the motif instances that are guaranteed to exist without using any edge more than its capacity. For a given motif embedding, if the capacities of its edges are more than the number of embeddings those edges are part of, this embedding exists in our solution. Next, for the remaining motif instances, *POMOC* randomly adds some embeddings whose edges are not more than the capacity constraints, into the resulting embedding set. It gradually expands the resulting set by taking one embedding out of the resulting set and inserting another two embeddings to the set. For further details on our method see [8].

RESULTS

Our experiments on both synthetic and real networks demonstrate that motif count using *POMOC* significantly differs from the existing motif counting approaches, and our approach extends to large-scale biological networks in practical time. Our results show that *POMOC* finds substantially different number of motifs than that with F_1 and F_2 measures on a *S. cerevisiae* transcription regulatory network (see Table 1). We observe that there is a massive variation in the abundance of different motif topologies from only one up to over two thousand. There is only one instance of cascade. Thus, this motif instance occurs in all three measures as it has no other instance to overlap with. More importantly, partially overlapping motif counting varies greatly in the interval defined by F_1 and F_2 measures for different motif topologies. For instance, for biparallel, it is closer to F_1 measure, while it is closer to F_2 measure for bifan, and equally distant to F_1 and F_2 measures for feed forward loop. This demonstrates that the amount of overlap among different embeddings of a motif depends not only on the network topology but also the motif topology. Similar to Milo *et al.* (2002) [6], we find that bifan and feed forward motifs are the most abundant motif

Table 1: Average and standard deviation of the motif counts for four motif topologies using the *POMOC* method and, motif counting with F_1 and F_2 measures.

	Feedforward	Bifan	Biparallel	Cascade
F_1	73	2026	11	1
F_2	24	137	5	1
<i>POMOC</i>	54 ± 0.5	426.4 ± 7	10 ± 0	1 ± 0

types in this network. These two motif topologies also show small variation across the 14 *S. cerevisiae* transcription networks for the *POMOC* method. The running times for motif counting with F_1 and F_2 measures are less than 1 second in all real network experiments. *POMOC* method's running time—in average 22 seconds—is comparable to those of F_1 and F_2 measures. For a detailed description of our results see [8].

CONCLUSIONS

Motif counting in biological networks is an important tool to decipher the topology of biological networks and its function. Existing motif counting approaches either count all or non-overlapping instances of a given motif. This results in either over- or under-estimation of the motif counts. In this paper, we presented a novel motif counting method, *POMOC*, based on edge capacities of a given network. Since biological interactions are resource limited, leading to varying edge capacities, we hypothesize that our method provides a more accurate approach to counting network motifs in biological networks than existing methods. Although, the *POMOC* method is slightly slower than motif counting with F_1 and F_2 measures, our method remains to be practical for all network sizes and motifs we test here. Our results on a *S. cerevisiae* transcriptional regulatory network suggest that oxidative stress is more disruptive to abundance and organization of network motifs than genetic mutations. Our analysis also suggests that by focusing on the edges that lead to variation in motif counts, our method can be used to find important genes, and to reveal subtle topological and functional differences of the biological networks under varying genetic backgrounds and growth conditions.

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