Dynamic network rewiring determines temporal regulatory functions in Drosophila melanogaster development processes

Man-Sun Kim, Jeong-Rae Kim and Kwang-Hyun Cho*

The identification of network motifs has been widely considered as a significant step towards uncovering the design principles of biomolecular regulatory networks. To date, time-invariant networks have been considered. However, such approaches cannot be used to reveal time-specific biological traits due to the dynamic nature of biological systems, and hence may not be applicable to development, where temporal regulation of gene expression is an indispensable characteristic. We propose a concept of a “temporal sequence of network motifs”, a sequence of network motifs in active sub-networks constructed over time, and investigate significant network motifs in the active temporal sub-networks of Drosophila melanogaster. Based on this concept, we find a temporal sequence of network motifs which changes according to developmental stages and thereby cannot be identified from the whole static network. Moreover, we show that the temporal sequence of network motifs corresponding to each developmental stage can be used to describe pivotal developmental events.

Keywords:
- gene regulatory network; nested feedback loop; static network motif; temporal sequence of network motifs; time-varying network

Introduction

Biological processes are regulated via complex gene regulatory networks (GRNs) [1, 2] and hence expression levels of genes are tightly controlled by complex interactions in large-scale networks. It is therefore important to understand the intrinsic characteristics (e.g., stability, oscillations, and robustness) of large-scale GRNs in order to unveil the governing principles behind the biological processes.

One efficient way to analyze complex networks is to divide them into components or “network motifs,” which are patterns (sub-graphs) that recur within a network much more often than expected in random networks [3, 4]. More frequently observed sub-networks are considered to have been selected because of their evolutionary advantages. There are numerous case studies of network motifs which consider a variety of interaction data (e.g., genetic or protein interaction) in order to investigate the abundance of particular feedback structures (e.g., feedback loops [5, 6], signaling cascades [7, 8], and feed-forward loop in GRNs [9, 10]).

Gene regulatory networks have been extensively studied as a tool for understanding the organization within cells and their dynamics [11]. The majority of research on network motifs has considered only time-invariant biological networks [12–14]. Hence, time-evolving network and time-specific biological traits cannot be found by such an approach, and thereby current network motif approaches are not applicable to the analysis of the network structures of time-evolving...
networks or the developmental traits that require temporal regulation of gene expression. Indeed, it was shown that the “active regulatory paths” in a gene expression network of yeast exhibit dramatic topological changes and hub transience during a cellular process [15]. In more recent studies, Papatsenko [16] analyzed the network motifs for spatial stripe pattern formation and Ahmed and Xing [17] analyzed the rewiring patterns among interacting gene ontology (GO) groups in four development periods, but the time-evolving network structure has not been considered. On the other hand, Seo et al. [18] presented the dynamical roles of hub genes with feedback loops in the overall developmental process, but the relation between time-varying network structures and their biological meaning in each developmental stage has not yet been explored.

We propose a new concept, “temporal sequence of network motifs,” which can be used to study the topologic structures and biological roles of time-varying networks (Fig. 1A).

**Figure 1.** The conceptual illustration of a temporal sequence of network motifs and static network motifs. (A) Time-varying network [36] and its temporal sequence of network motif (lower). Filled circles and unfilled circles denote active and inactive nodes, respectively. Each time-specific network has its own network motifs and the network motifs change over time. A temporal sequence of network motif is given like {Motif A, B} → {Motif A} → {Motif B, D} → {Motif A}. (B) Time-invariant network and its static network motifs. In this approach, some network motifs of the static network may not be active. For example, Motif C (green) is not observed in the time-varying network. (C) The procedure of reconstructing time-varying sub-networks. Black arrows and circles denote the active links and nodes, respectively, and white arrows and circles denote the inactive links and nodes, respectively.
In contrast to previous methodologies for motif analysis (Fig. 1B), in this article we reconstruct the active sub-networks from differentially expressed (overexpressed or repressed) genes (DEG) at each developmental stage and analyze the resulting network motifs. We applied this temporal sequence of network motifs analysis to the developmental network of Drosophila melanogaster since its dynamic properties are well characterized, and we identified the time-evolving network motif pattern of the time-varying network. From both static (time-invariant) and dynamic (time-varying) network approaches, we discovered four network motifs including a nested feedback loop where one feedback loop is nested inside another feedback or feed-forward loop (Fig. 2). We note, however, that ID 9 and ID 12 were identified only in the static network, whereas ID 11 is found only in the time-varying network.

How do the particular types of motifs perform specific functions that are essential to development? To investigate the regulatory roles of temporal sequence of network motifs, we have analyzed their dynamical properties and found that feedback loops are more important in late embryogenesis than in early embryogenesis and that nested feedback loops induce enhanced robustness compared to single feedback loop. Furthermore, we have also unraveled the dynamical properties of coupling structures of feed-forward and feedback loops. Finally, we have associated the temporal sequence of network motifs with some pivotal developmental events in D. melanogaster embryogenesis. These results suggest that additional insights can be obtained from the analysis of the temporal sequence of network motifs, including time-dependent activity of genes which cannot be uncovered from the static network motif approach.

The concept of a temporal sequence of network motifs

In order to reconstruct time-varying sub-networks from a whole static GRN, we need two kinds of information: gene expression time-course data and an integrated GRN (Fig. 1C). Here, we have used two published datasets to illustrate the proposed concept of a temporal sequence of network motifs. First, we have utilized the Gene Expression Omnibus database to obtain the gene expression time series data with the accession number GSE6186 [19]. This dataset contains almost all the genes expressed over the time course of D. melanogaster embryogenesis. Second, for an integrated GRN, we have used the GRN obtained from the TRANSFAC database, which consists of 245 nodes and 350 links. Using normalized values of the expression data, we selected DEG at each time point (see Methods Section for details). We have identified the active sub-network at each time point by integrating the information of each DEG set and the GRN as follows: if two genes connected by an edge in the GRN are also included in the DEG set, then both of the genes and the connecting link constitute the active sub-network. By repeating these procedures, we can obtain a set of time-varying active sub-networks (Fig. 1C).

To identify network motifs of the time-varying sub-networks, we first examined small-scale interaction patterns by determining the statistically significant network sub-graph at each time point. The statistical significance of each sub-graph was evaluated based on the probability (p-value), which represents the significance compared to randomized cases. A network motif is usually chosen when it is both frequent and significant, but most of the network motifs in this report were chosen based on significance, since the size of active sub-networks at specific time points is usually small. The transcription network was scanned for three-node motifs, which were determined to be statistically significant if the p-value was less than the cut-off threshold of 0.05 (note that this threshold is frequently used in motif analysis [20, 21]). The randomized networks were generated through a random local rewiring algorithm which preserves the vertex degrees [22]. We considered only motifs of size 3 (which corresponds to the number of sub-network nodes) and randomizations of 1,000 times in order to get reliable statistics, since it is difficult to handle the tremendous number of sub-networks with more nodes.

A temporal sequence of network motifs can reveal pivotal development events

Development proceeds through a series of stages and processes [23]. We have used the concept of a temporal sequence of network motifs to investigate the developmental network of D. melanogaster. Embryogenesis, the first developmental phase, requires the delicate orchestration of complex events.
We have investigated the network motifs of the integrated ("static") GRN (to be called static network motifs; see Fig. 2B) and the time-varying network (to be called the temporal sequence of network motifs; see Fig. 2C). We identified the following temporal sequence of network motifs: 

\{Motif ID 4, 6\} \rightarrow \{Motif ID 4\} \rightarrow \{Motif ID 10\} \rightarrow \{Motif ID 4\} \rightarrow \{Motif ID 4, 10\} \rightarrow \{Motif ID 4\} \rightarrow \{Motif ID 4, 5, 10, 11\} \rightarrow \{Motif ID 4, 5, 10, 11\} \rightarrow \{Motif ID 4, 5\} \rightarrow \{Motif ID 4\} \rightarrow \{Motif ID 4, 10\} \rightarrow \{Motif ID 4\} \rightarrow \{Motif ID 4, 5\} \rightarrow \{Motif ID 4\} \rightarrow \{Motif ID 4, 5, 6, 10\} \rightarrow \{Motif ID 4, 5, 10, 11\} \rightarrow \{Motif ID 4, 10, 11\}.

Motif ID 4, 6, and 10 are commonly found in both static network and temporal sequence of network motifs approaches, but using the temporal sequence of network motifs approach, one extra motif, ID 11, is found to be statistically significant, whereas ID 9 and ID 12, found in the static network, are no longer significant.

In the temporal sequence of network motifs, a feed-forward loop (ID 4) is found ubiquitously, whereas feedback loops (ID 5, 6, 10, and 11) are found across stages 11–16. In order to investigate the biological significance of these network motifs, we have analyzed the GO of those genes comprising each network motif. First, we considered a set of three genes related to the feed-forward loop and investigated their biological processes (Table 1). For instance, triple genes, bicoid (bcd), Kruppel (Kr), and hairy (h), in the early embryo are related with the trunk segmentation (GO: 0035290) where bcd included in various gene triples is critical for proper embryonic patterning and two gap genes, Kr and h, affect the overall development process [24–26]. At stage 14, the triple genes Enhancer of split (E(spl)), scute (sc), and achaete (ac) were identified as comprising ID 4. These triple genes are associated with the development of the peripheral nervous system (GO: 0007422), one of major division processes in the nervous system [27]. Another triple genes, tinman (tin) [28], Kr, and h, at this stage are related to the tube development (GO: 0035295).

Second, we considered a set of three genes related to the feedback loop motifs identified mostly at late stages. As a result, we found that those triple genes are related to some GO terms.

### Table 1. Illustration of the GO analysis for triple gene components of sample motifs

<table>
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<tr>
<th>Motif</th>
<th>Triple genes (X, Y, Z)</th>
<th>GO terms</th>
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<tbody>
<tr>
<td>FFL</td>
<td>bcd, Kr, h</td>
<td>GO:0035290 trunk segmentation</td>
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<td></td>
<td></td>
<td>GO:0003002 regionalization</td>
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<tr>
<td></td>
<td></td>
<td>GO:0035282 segmentation</td>
</tr>
<tr>
<td>FBL</td>
<td>eve, tin, mus209</td>
<td>GO:0048646 anatomical structure formation involved in morphogenesis</td>
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<td></td>
<td>eve, tin, abd-A</td>
<td>GO:0069911 cardiac cell fate commitment</td>
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<td></td>
<td></td>
<td>GO:010002 cardioblast differentiation</td>
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<td></td>
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<td>GO:0035051 cardiac cell differentiation</td>
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<td></td>
<td></td>
<td>GO:0007369 gastrulation</td>
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<td></td>
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<td>GO:0007507 heart development</td>
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<td></td>
<td></td>
<td>GO:0006928 cellular component movement</td>
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<tr>
<td></td>
<td></td>
<td>GO:0045892 negative regulation of transcription, DNA-dependent</td>
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<tr>
<td></td>
<td></td>
<td>GO:0051253 negative regulation of RNA metabolic process</td>
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<tr>
<td></td>
<td></td>
<td>GO:0007507 heart development</td>
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<td></td>
<td></td>
<td>GO:0048565 gut development</td>
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<td>GO:0007507 heart development</td>
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<td>GO:0007350 blastoderm segmentalization</td>
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FFL and FBL denote feed-forward loop and feedback loop, respectively, and the order of triple genes X, Y, and Z is shown in Fig. 3A.
specific developmental processes such as organ development or differentiation. For example, triple genes, even-skipped (eve), tin, and abdominal-A (abd-A), are involved in the muscle organ development (GO: 0007517) at the end of stage 13 [29]. At this stage, differentiation is pivotal and the triple genes are specifically related to cardiac cell differentiation (GO: 0035051). The expression of tin in cardioblasts is indispensable for cardiomyocyte differentiation [30]. At stages 13 and 14, the triple genes decapentaplegic (dpp), Ultrabithorax (Ubx), and Antennapedia (Antp) are associated with the gut development (GO: 0048565), which begins after segmentation genes have determined the future body plan [31]. It is known that dpp expresses during the hindgut formation in gut development and that this happens at stage 14 [32].

We have further incorporated the spatial information from the Berkeley Drosophila Genome Project (BDGP) [33] into our network motif analysis since the spatial expression patterns are essential for understanding developmental processes [34]. In Table 2, we have summarized the body parts where related triple genes are commonly expressed, implying that the triple genes are involved in the regulation of nervous system development in the ventral ectoderm [27]. Hence, we infer that the triple genes are involved in the regulation of nervous system development in the ventral nerve cord. Together, these results show that the temporal sequence of network motifs can be used to describe the pivotal developmental events. Note, however, that our method still has a limitation and cannot describe all the details of biological processes. So, the previous examples might also endure such a limitation and the real stories behind the examples shown can be a bit more complex.

In the above, we found that rather diverse network motifs are identified at late stages. Why do diverse network motifs including feedback loops appear at late stages? There have been several studies showing that feedback regulation plays an important role at a specific stage of development [35–37]. From GO analysis, we found that the network motifs involved in cell fate determination are more related to feedback loops (ten cases) than to feed-forward loop (three cases). Cell fate commitment in D. melanogaster consists of two steps: specification and determination [23]. In the early embryo stages, the cell fate depends on cues provided by gradients of specific proteins. Specification of cell fate is flexible and can still be changed in response to signals from other cells. However, determination of cell fate is an irreversible process. The transition from specification to determination is mediated by the segmentation genes. Once determination has taken place, the segmentation genes will become committed to down a specific pathway regardless of the differentiating cells environment. So, feedback loops at late stages might be more related to cell fate determination rather than specification.

This is also well supported by other recent studies: Seo et al. [18] showed that hub genes with positive feedback loops function as important developmental switches to determine developmental fates. Mitrophanov and Groisman [38] showed that the bistability of a feedback loop is used by eukaryotes as a cell fate determination mechanism. Loewer and Lahav [39] showed that external positive feedback loops affect cell fate decision in a population of cells. Taken together, we conclude that the appearance of various network motifs including feedback loops might be caused by increasing the complexity of the embryo and the variety of cell types at late stages.

### Dynamic roles of the identified network motifs

Since the GRN that we obtained from the TRANSFAC database does not contain any information on the sign of regulatory interactions, we could consider only the direction of regulation when we identified network motifs (Figs. 1 and 2; Tables 1 and 2). However, we took account of the regulatory interaction sign when we investigated the dynamical role of a particular network motif in Figs. 3 and 4, where we assumed only positive regulation sign since it is known that positive feedback loops are predominant throughout development in a number of cases [2]. Then, we further generalized this result by considering various combinations of interaction signs in Fig. 5.

The four network motifs identified using both approaches are ID 4, 5, 6, and 10. The functional roles of these motifs have been elucidated previously [40, 41]. Motif ID 4 (feed-forward loop) is composed of three transcription factors, X, Y, and Z, where X regulates Y and Z, and Z also regulates Y. This motif performs signal-processing tasks such as persistence detection, pulse generation, and acceleration of responses [42]. As seen in Fig. 2B and C, motif ID 4 was found ubiquitously across the developmental stages. This means that ID 4 is required at overall stages of embryogenesis, which is supported by the

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<th>BDGP term</th>
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<tr>
<td>FFL</td>
<td>zen2, en, Ubx</td>
<td>Dorsal ectoderm anlage in statu nascendi</td>
</tr>
<tr>
<td></td>
<td>Kr, en, Ubx</td>
<td>Ventral ectoderm anlage in statu nascendi</td>
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<tr>
<td></td>
<td>Antp, en, Ubx</td>
<td>Dorsal/ventral ectoderm anlage in statu nascendi</td>
</tr>
<tr>
<td>FBL</td>
<td>Antp, Ubx, en</td>
<td>Ventral nerve cord</td>
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fact that Kr, eve, and abd-A, frequently found in motif ID 4, are known to be responsible for the overall embryonic process [43–45]. Motif ID 5 is found predominantly in developmental GRNs [18]. Motif ID 6 is a structure in which a target gene is regulated by a two-node feedback whose functions are well known [12, 42, 46]. For example, the motif plays important roles in maintaining cellular homeostasis, producing sustained oscillations, and making critical decisions such as cell fate [46].

Motif ID 10, which contains various other motifs such as ID 1, 2, 3, 4, 5, 7, and 9, is also found frequently (Fig. 2C), but it has not been fully explored yet. So we investigated its detailed dynamical properties. To do this, we constructed and simulated a mathematical model using MATLAB and considered three different types of stimuli (Fig. 3, black lines): a noise-free on-step stimulus; a noise-free on- and off-step stimulus; a noisy on- and off-step stimulus. In order to further investigate the dynamics of ID 10, we considered a single feedback loop and a simple regulation for comparison (Fig. 3A). We discovered three fundamental characteristics from the simulations. First, the nested feedback loops can enhance signal amplification (Fig. 3B). When high signal amplification is applied to a system, it can easily determine whether the signal is correct or not. The system can correctly communicate the signal. Second, the nested feedback loops can have a slow response time (Fig. 3C), which can be useful in making important decisions such as cell fate determination. Third, the nested feedback loops can be robust against noisy external stimuli compared with the single feedback loop and simple regulation (Fig. 3D). As it is necessary for developmental networks to be stable and robust against both noise and small perturbations [47], we conclude that the nested feedback loop plays an important role in the elaborate regulation of the developmental processes of D. melanogaster.

In order to further understand the roles of the ID 10, we compared the dynamics of the coupled feedback loops (ID 8 in Fig. 4) and the nested feedback loops (ID 10 in Fig. 4). Even though both network structures are topologically similar except for one link [the links Y → X (ID 8) and Y → Z (ID 10) in Fig. 4], the two motifs showed very different dynamical characteristics. For example, when we increased the link strength (S) above some level (S > 5 in this model), the simulation results showed that ID 8 (magenta line) responded to a smaller stimulus. Hence we can conclude that ID 10 (blue line) is more stable and robust against noise than ID 8. Since there are numerous noise sources in many biological systems, ID 10 can perform its roles decisively. From these simulation results, we conclude that the nested feedback structure is more robust against noise than the coupled feedback structure.

In order to further investigate the effect of coupling feedback and feed-forward loop in ID 10 (nested feedback loops), we have compared it with both a single feedback loop and a single feed-forward loop with different combinations of
activation and inhibition links (Fig. 5). The simulation results showed that type 1 (coherent feed-forward loop, positive feedback loops) and type 2 (incoherent feed-forward loop, negative feedback loops) network motifs, which are homogeneous couplings in terms of the response speed, induce a slower response (Fig. 5A). We also found that type 3 (incoherent feed-forward loop, positive feedback loops) and type 4 (coherent feed-forward loop, negative feedback loops) network motifs, which are heterogeneous couplings in terms of the response speed, regulate the response speed depending on regulatory conditions (Fig. 5B). Together, these results imply that homogeneous coupling preserves and enhances the original dynamic properties, whereas heterogeneous coupling introduces a new property required to adapt to given regulatory conditions.

Concluding remarks

Biological networks are highly dynamic [17], and regulate temporally varying processes through complex GRNs. Constituent genes of GRNs have recently been identified using high-throughput measurements [19]. A key challenge in this field is to unravel how the numerous genes are temporally activated within the networks in order to accomplish specific functions such as differentiation, proliferation, and apoptosis. Network motifs are the sub-graphs that recur within a network much more often than expected in random networks. So, it is now widely accepted that such network motifs cannot occur by chance but must have evolved by selective pressure and serve some crucial functions [42, 48]. In this regard, each network motif can be considered as a significantly functioning module that has its own particular information-processing function [49]. Analysis of the network motifs often helps to obtain valuable insights regarding the principles governing the architecture of the complex developmental networks. However, previous approaches using static networks cannot explain more detailed features of the dynamically changing regulatory networks.

To overcome this limitation, we applied the temporal sequence of network motifs approach to the developmental network of D. melanogaster and identified the temporal sequence of network motifs that differs from the static network motifs. Furthermore, we showed that the proposed method can be used to investigate some important biological roles of networks. We found that the observed network motifs change over time, diverse network motifs including feedback loops appear at late stages, and the network motifs with feedback loops are more robust. The dynamical behaviors of both feed-forward and feedback loops have been considered in detail [50], and there have been a number of studies on coupled feedback motifs [46]. However, to the best of our knowledge, there has been no computational investigation on nested feedback loops. Through a simulation study, we showed that nested feedback loops are more robust against noise than not only a single feedback loop but also coupled feedback loops. We found that the nested feedback loops enable robustness by...
effectively dealing with external noise. This result implies that the combination of the feed-forward loop and feedback loops can induce an emergent property. Furthermore, we found that either such original dynamics is enhanced or a new property required for adaptation is introduced, depending on the way of coupling between feedback and feed-forward loops by considering different combinations of interaction signs in this motif.

There are still many important issues to be addressed. For example, the incorrect interactions of networks and the false selection of DEG deleteriously affect the analysis results of the proposed method, and are thereby two general limitations of network motif approaches. Nonetheless, our findings can provide a reasonable clue to describing how developmental programs have been evolved to attain robustness so that sequential developmental processes can be performed appropriately. Hence, the proposed method seems to be relevant for analysis of organizing principles of networks whose structures change temporally, such as developmental networks.

Methods

Network reconstruction at each time point and gene expression time-course data

The transcriptional regulation information of D. melanogaster from the TRANSFAC database [51, 52] (version 11.4) was used. The GRN consists of 245 nodes and 350 links. We utilized the Gene Expression Omnibus database to obtain microarray experimental data with the accession number GSE6186 [19]. This dataset contains almost all the genes (~14,000) expressed over the time course (from 1 to 15 hours) of D. melanogaster embryogenesis. The reference sample [1], described by Arbeitman et al., was made from pooled samples from all stages of the Drosophila life cycle and therefore should represent a median level of expression for all genes in the genome. Using normalized values, we selected DEG at each time point using a 0.5-fold cut-off criterion. Although the fold-change method is regarded as an early method for the identification of DEGs, it is a useful approach in single-slide microarray experiments [53, 54]. If there is evidence that two DEG interact with each other, an interaction edge is assigned between the two genes.

Identification of network motifs

Motif analysis and visualization were performed using MAVisto [55]. Statistical significance of each sub-graph was evaluated based on the probability (p-value), which represents the significance compared to randomized cases. The transcription network was scanned for three-node motifs, it is a useful approach in single-slide microarray experiments [53, 54]. If there is evidence that two DEG interact with each other, an interaction edge is assigned between the two genes.

Gene ontology classification and analysis

Gene ontology annotation provides an indication of the trait of a group of genes and is a useful tool for both small- and large-scale analyses of genes. GO functional annotations in this study were obtained from the GO database [56]. We evaluated the statistical significance of the overlap between selected genes (co-expression or overrepresentation) through GO terms enrichment using AmiGO [57]. FlyBase [58], a D. melanogaster gene database, was used as a database filter in the GO analysis.

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References

Prospects & Overviews

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