**Dynamic Gene Attention Focus (DyGAF): Enhancing Biomarker Identification Through Dual-Model Attention Networks**

Md Khairul Islam1,3, Himanshu Wagh2 and Hairong Wei1,2,3

1 Computational Science and Engineering, Michigan Technological University, Houghton, MI 49931, USA

2 College of Computing, Michigan Technological University, Houghton, MI 49931, USA

3 College of Forest Resources and Environmental Science, Michigan Technological University, Houghton, MI 49931, USA

***ADDITIONAL RESULTS***

**Classification of COVID-19 samples using DyGAF and other comparative models**

We applied five models to classify COVID-19 samples such as Dynamic Gene Attention Focus (DyGAF), Random Forest (RF), DyGAF-Support Vector Machine (SVM), DyGAF- K-Nearest Neighbors (KNN) and Differential Expression Analysis (DEA)-RF. The DyGAF, DyGAF-SVM, and DyGAF-KNN models were exclusively employed on 923 features identified by the DyGAF method. Meanwhile, the RF model was utilized on the entire gene set, and the DEA-RF model applied RF to classify features that were determined to be significant through DEA. Initially, Random Forest, SVM, and KNN classifiers trained using all available gene features, but we observed improved performance for SVM and KNN when utilizing the 923 features identified by DyGAF, as shown in Table 1. Random Forest and DyGAF-SVM showcased robust performance with excellent testing accuracy and substantial sensitivity (Figure 5B, 5C), indicating their reliability in identifying COVID-19 cases. The KNN model displayed lower sensitivity, accuracy, and F1-score compared to the other models (Table 1 and Figure 5D). In this study, we benchmark the DyGAF model against previously published articles, demonstrating its enhanced capabilities in detecting and analyzing COVID-19. In a study, Gradient Boosting model shows a slightly higher testing accuracy and an excellent specificity of 100%, it falls short in sensitivity compared to DyGAF 1. The Associative Classification Model, with a testing accuracy of 92.70%, showcases robust performance, yet still does not match the accuracy and sensitivity achieved by DyGAF 2. In other study, both SVM models show lower sensitivity and, in the case of SVM-II, a significantly lower F1-score, indicating a less balanced performance between precision and recall 3,4. The DyGAF model distinguishes itself with unparalleled sensitivity and robust accuracy in COVID-19 detection. It outperforms other models, particularly in its ability to identify all true positive cases, which is crucial for preventing the spread of infection.

This study also demonstrated that DyGAF outperformed other models in diagnosis of COVID-19 from healthy individuals using gene expression profiles from nasopharyngeal swabs. It achieved a remarkable level of accuracy and F1-score, and its effectiveness as shown in Table 1. In managing outbreaks like COVID-19, a diagnostic technique with high sensitivity is critical, as demonstrated by our model's 100% sensitivity rate (Figure 5A and Table 1), ensuring complete detection for rapid intervention. Our model showed moderate specificity, yet it was higher compare to DEA-RF. Overall, high sensitivity is crucial to minimize false negatives and control viral spread. Practically, we can accept a higher rate of false positives, indicating potential COVID-19 infections, which can then be verified through confirmatory testing such as RT-PCR. 5,6.

**Gene ontology enrichment analysis of top genes identified by DyGAF and other models**

In Figure 6A, it shows that DyGAF and DEA shared 35 common genes and 65 unique genes. Our Gene Ontology (GO) analysis displays the top 20 COVID-19 related GO terms for all three models (Figure 6C-E). Overall, the GO analysis, supported by previous literature, revealed that DyGAF identified 30 significant COVID-19 related GO terms, DEA identified 21, and RF identified 14, as detailed in Supplemental Table 4, 7 and 10 7,8. This implies that DyGAF may exhibit greater sensitivity or comprehensiveness in its ability to detect biological processes compared to DEA or RF. As shown in Figure 6B, we found that 12 statistically significant GO terms are common among all models. DyGAF and DEA share 20 similar terms, with DyGAF and DEA each enriching six and two unique GO terms, respectively. There are total of 30 unique enriched GO terms. These can be categorized into three main biological groups: viral entry, host’s immune response and controlling inflammation. DyGAF also ranked the 'Coronavirus Disease' pathway from KEGG as the second most statistically significant, with an adjusted p-value of 1.09e-06, highlighting that 11 of the top 100 genes enriched this pathway (Table 2 in the main manuscript). This performance surpasses that observed with DEA and RF. Detail KEGG analysis is shown in Supplemental Table 5, 8 and 11. Additionally, in the WikiPathways database, DyGAF and DEA enriched nine pathways related to COVID-19 (Table 3 in the main manuscript), compared to seven enriched by RF (Supplemental Table 6, 9 and 12). These results demonstrate that DyGAF not only outperforms the other two models but also exhibits greater sensitivity, as it retrieves extensive information related to COVID-19 from only the top 100 genes. This suggests that expanding the analysis to include more than the top 100 genes could potentially yield even more relevant GO terms and pathways, further enhancing our understanding of the disease's molecular basis. We provide a detailed discussion of GO, KEGG pathway, and WikiPathways analysis in Supplemental File 13.

Among 30 enriched COVID-19-related GOs identified by DyGAF, 7 unique GOs were enriched by the DyGAF method alone. These include: (1) Regulation Of Monocyte Chemotactic Protein-1 Production (GO:0071637); (2) Positive Regulation Of I-kappaB kinase/NF-kappaB Signaling (GO:0043123); (3) Response To Interleukin-1 (GO:0070555); (4) Cell Surface Toll-Like Receptor Signaling Pathway (GO:0140895); (5) Toll-Like Receptor 4 Signaling Pathway (GO:0034142); (6) Positive Regulation Of T Cell Cytokine Production (GO:0002726) ; (7) Regulation Of Interleukin-8 Production (GO:0032677). All the 30 GOs can be categorized into three main biological groups: firstly, viral entry such as *Regulation Of Viral Entry Into Host Cell* (*GO:0046596*), *Regulation Of Viral Genome Replication* (*GO:0045069*); secondly, the host's immune response to the virus such as *Defense Response To Virus* (*GO:0051607*), *Negative Regulation Of Viral Genome Replication* (*GO:0045071*), *Antiviral Innate Immune Response* (*GO:0140374*), *Positive Regulation Of Interferon-Beta Production* (*GO:0032728*), *Response To Type I Interferon* (*GO:0034340*), *Positive Regulation Of RIG-I Signaling Pathway* (*GO:1900246*), *Positive Regulation Of I-kappaB kinase/NF-kappaB Signaling* (*GO:0043123*), *Regulation Of Innate Immune Response* (*GO:0045088*), *Regulation Of MDA-5 Signaling Pathway* (*GO:0039533*), *Negative Regulation Of Viral Entry Into Host Cell* (*GO:0046597*); and thirdly, controlling inflammation and other processes such as *Positive Regulation Of Tumor Necrosis Factor Production* (*GO:0032760*), *Positive Regulation Of Tumor Necrosis Factor Superfamily Cytokine Production* (*GO:1903557*), *Regulation Of Interferon-Beta Production (GO:0032648), Cytokine-Mediated Signaling Pathway* (*GO:0019221*), *Positive Regulation Of Cytokine Production* (*GO:0001819*), *Regulation Of I-kappaB kinase/NF-kappaB Signaling* (*GO:0043122*), *Response To Interleukin-1* (*GO:0070555*), *Regulation Of Chemokine (C-X-C Motif) Ligand 2 Production* (*GO:2000341*), *Cell Surface Toll-Like Receptor Signaling Pathway* (*GO:0140895*), *Toll-Like Receptor 4 Signaling Pathway* (*GO:0034142*), *Positive Regulation Of Interleukin-8 Production* (*GO:0032757*), *Positive Regulation Of T Cell Cytokine Production* (*GO:0002726*), *Neutrophil Chemotaxis* (*GO:0030593*), *Apoptotic Process* (*GO:0006915*), *Positive Regulation Of Interleukin-6 Production* (*GO:0032755*), *Regulation Of Interleukin-8 Production* (*GO:0032677*), *Positive Regulation Of Monocyte Chemotactic Protein-1 Production* (*GO:0071639*). We may say that the unique GOs identified by DyGAF mostly involved in the host’s immune response and inflammation response to the virus.

**Mutual information and classification of DyGAF metric and other combination metrics**

To integrate the weights derived from Models A and B in the DyGAF framework, we developed a novel metric, as defined in Equation 3. We also assessed established combination metrics such as Geometric Mean, Borda Count, and Harmonic Mean using a RF and Mutual Information (MI) based approach, applied to the top 100 features identified from each method. The RF analysis evaluated the classification effectiveness of each metric, whereas the MI analysis quantified the amount of retained information after amalgamation. As demonstrated in Table S1, our findings indicate that our custom metric not only enhances classification accuracy but also maintains more information compared to traditional metrics, underscoring its efficacy in complex dataset analysis.

**Table S1: Comparative Analysis of Combination Metrics Using Random Forest and Mutual Information Approaches.** Total Mutual Information Contained in the Dataset: 439.82

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | DyGAF Metric | Geometric Mean | Borda Count | Harmonic Mean |
| Random Forest | 94.23% | 92.31% | 76.92% | 86.54% |
| Mutual Information | 17.13 | 7.09 | 2.03 | 6.18 |

**Table S2: Comparative Analysis of Mutual Information Metrics across** Dynamic Gene Attention Focus (**DyGAF) Combined, DyGAF Model A (Independent), DyGAF Model B (Dependent) and DyGAF** Differential Expression Analysis **(DEA).** Total Mutual Information Contained in the Dataset: 439.82

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | DyGAF Metric (Combined) | DyGAF Model A | DyGAF Model B | DEA |
| Mutual Information | 17.13 | 3.84 | 9.76 | 16.75 |

Table S2 presents a comparative analysis of MI calculated on the top 100 genes across DyGAF combined, DyGAF Model A (Independent), DyGAF Model B (Dependent), and DEA. The total mutual information in the dataset is 439.82. We conducted individual and combined analyses using these models, where MI assessed the unique information contribution of each. The results, as shown in Table S2, indicate that our combined approach captures a larger portion of the dataset's information, highlighting the advantages of model integration over operating models in isolation. Moreover, our final DyGAF algorithm performed better than DEA, further demonstrating its effectiveness in handling complex datasets.

***ADDITIONAL DISCUSSIONS***

***Key Findings from GO Analysis***

DyGAF enriched GO terms, such as "Regulation of Viral Entry Into Host Cell" (GO:0046596), pertain to processes that govern the way viruses infiltrate cells. Cells in the nasal passages, lungs, and gut expressed genes such as ACE2, TMPRSS2, and CTSL, which are crucial for SARS-CoV-2 to gain entry into host cells. Similarly, the procedures outlined in *Negative Regulation of Viral Entry Into Host Cell* (*GO:0046597*) aim to decrease these entrance steps, possibly through downregulating the proteins involved, which in turn hinders viral entry 9,10. The innate immune systems, represented by various Gene Ontology (GO) terms, are central to this discussion. Antiviral Innate Immune Response (GO:0140374) and Defense Response To Virus (GO:0051607) constitute the host's primary defenses against SARS-CoV-2 11. These mechanisms, involving Toll-like receptors, NOD-like receptors, and RIG-I (Retinoic acid-Inducible Gene I), activate a series of antiviral actions, including interferon signaling pathways mediated by RIG-I (GO:1900246) 12. Such pathways are crucial for inducing the production of interferons and other cytokines, which are essential for controlling and eliminating viral infections. It is important to fine-tune these reactions, as highlighted by the GO term Negative Regulation Of Innate Immune Response (GO:0045824) 13, to prevent overactivation. Recent research has identified that a compromised type I interferon response, coupled with an intensified inflammatory reaction, can exacerbate COVID-19 in severe cases, underlining the complex interaction between effective antiviral defense mechanisms and harmful hyperinflammation 14. Such dysregulation can lead to a cytokine storm (GO:0001819), worsening symptoms and prevalently affecting individuals with advanced illness 15. These pathophysiological processes related to inflammation and immune signaling, which include interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor, and components of the complement system (part of the innate immune response), are crucial. The specific patterns of gene expression associated with these processes can play a vital role in the development of COVID-19 and suggest potential targets for therapeutic interventions. Therefore, precise modulation of cytokine-mediated signaling (GO:0019221) is necessary to prevent pathogenic effects, particularly the overproduction of interferon-beta (GO:0032728 and GO:0032648), which can contribute to disease pathogenesis 14. Furthermore, the Positive Regulation of I-kappaB kinase/NF-kappaB Signaling (GO:0043123) and the Positive Regulation of Cytokine Production (GO:0001819) demonstrate the host’s efforts to mount an effective immune response without overreacting. This highlights the dual role of cytokines in COVID-19 pathogenesis, where they are essential for combating the infection but can also exacerbate disease severity if not properly regulated 7. Furthermore, it is critical to highlight the Negative Regulation of Viral Genome Replication (GO:0045071). This GO term reflects host cellular processes designed to inhibit SARS-CoV-2 replication, thus reducing infection severity 15. Top genes such as IFITM3, APOBEC3C, IFITM1, MX1, IFIT5, ISG15, IFIT1, OASL, IFIH1, BST2, ISG20, OAS1, OAS2, and OAS3, identified by DyGAF and enriched GO:0045071, are instrumental in these processes and may present viable therapeutic targets to bolster natural defenses. The selected GO terms not only outline different aspects of the immune response to COVID-19 but also emphasize the critical need to manage these responses to prevent exacerbation of inflammation, crucial for patient recovery. During COVID-19, other key GO terms such as the Regulation of Interleukin-8 Production (GO:0032677) and Positive Regulation of Interleukin-6 Production (GO:0032755) have been linked to the body’s response to viral entry via the ACE2 receptor. This interaction triggers a cascade of immune reactions, including the production of pro-inflammatory cytokines IL-6 and IL-8, which are vital for inflammation and leukocyte recruitment but can also lead to severe inflammation if dysregulated 16. Additionally, the Apoptotic Process (GO:0006915) is crucial for the controlled elimination of infected cells, thereby minimizing potential inflammatory damage. This complex interaction underscores the need for further research to fully understand the immune responses impacting COVID-19's progression and to develop targeted therapies 17. Lastly, Neutrophil Chemotaxis (GO:0030593) has been identified as a significant factor in COVID-19 severity, with neutrophils mediating acute inflammatory responses and tissue damage through mechanisms such as Neutrophil extracellular trap (NET) formation18. The Positive Regulation Of Monocyte Chemotactic Protein-1 Production (GO:0071639) also plays a crucial role by facilitating the movement of immune cells to infection sites, essential for effective viral clearance 19. So, we can conclude that DyGAF has successfully enriched nearly all the important GO terms that are critical for understanding the infection and progression of COVID-19.

***Insights from Pathway Analysis***

Although nearly all biological aspects related to COVID-19 were discussed during the description of the GO terms, the KEGG and WikiPathways databases provide a more complex view of SARS-CoV-2 interactions and immunological responses (detailed in Supplemental Tables 5, 6, 8, 9, 11 and 12), revealing top pathways that are not covered by the GO analysis in Table 2 and Table 3 in the main manuscript. Specifically, the WikiPathways titled 'Network Map of SARS-CoV-2 Signaling Pathway' and 'SARS-CoV-2 Innate Immunity Evasion and Cell-Specific Immune Response' provide in-depth explanations of the molecular tactics the virus uses to evade host immune systems, details not fully captured by the general GO terms. These pathways highlight unique strategies for evasion and the resulting cellular responses, thus enhancing our understanding of the virus’s ability to persist and spread across diverse host environments 20. Similarly, natural SARS-CoV-2 infection depletes dendritic cells, affecting long-term immunity through manipulation of the MAPK signaling pathway, as described in the 'Host Pathogen Interaction of Human Coronaviruses MAPK Signaling WP4877' pathway. This modification, which is directed by the virus, circumvents the early immune defenses and hinders the activity of dendritic cells 21. On the other hand, the mRNA Vaccine Activation of Dendritic Cell and Induction of IFN 1 pathway shows how mRNA vaccines restore immune functions and possibly reverse the virus's immunosuppressive effects by counteracting this by enhancing dendritic cell activation and promoting IFN-1 production 21,22.

***Understanding Protein Networks and Regulatory Interactions:*** Protein-Protein Interaction (***PPI) and TF-Gene Analysis***

We performed a protein-protein interaction (PPI) analysis of the DyGAF biomarkers and identified the top 10 hub proteins, which include: H2AC4, H3C13, H4C14, ASF1A, OAS1, OAS2, OAS3, DDX58, DHX58, and CXCL13 (Figure 6). Histone proteins H2AC4, H3C13, and H4C14 are involved in the formation of Neutrophil Extracellular Traps (NETs ), which SARS-CoV-2 may exploit to enhance its infection of host cells, representing a novel aspect of virus-host interaction in COVID-19 23. ASF1A influences the expression of viral and cellular genes, potentially hindering viral replication and improving the body's antiviral response; it could also help develop cell lines more susceptible to human coronaviruses, aiding in vaccine development 24. The OAS genes—OAS1, OAS2, and OAS3—are crucial in defending against SARS-CoV-2 by producing enzymes activated by interferon. These enzymes trigger RNase L to degrade viral RNA, inhibiting viral replication and promoting the destruction of infected cells, thus controlling the spread of COVID-19 25. However, DDX58 (RIG-I) and DHX58 (LGP2) are also key sensors for early detection of SARS-CoV-2, activating type I interferon signaling via MAVS and regulating this pathway to ensure a balanced immune defense crucial for effective COVID-19 management 26,27. Finally, CXCL13, a pro-inflammatory cytokine, plays a role in severe COVID-19 by affecting lymphoid tissue structure and B cell maturation. Elevated levels of CXCL13 correlate with severe outcomes and higher mortality in interstitial lung diseases, and its heightened presence indicates increased inflammation during COVID-19, potentially leading to critical conditions such as ICU admission or death. The CXCL13/CXCR5 axis interacts with key inflammatory pathways including ERK/MAPK and PI3K/AKT, which are involved in the immune response 28. Our protein-protein interaction analysis revealed critical hub proteins such as histones, ASF1A, OAS enzymes, DDX58, and CXCL13, each contributing significantly to the body's defense against SARS-CoV-2. Our protein-protein interaction analysis revealed critical hub proteins such as histones, ASF1A, OAS enzymes, DDX58, and CXCL13, each contributing significantly to the body's defense against SARS-CoV-2. Overall, biomarker’s role underscores the intricate interplay between host and virus, offering insights into potential strategies to alleviate the severity of COVID-19. These hub proteins play diverse roles, from enhancing viral entry to inhibiting viral replication and modulating immune responses, marking them as potential targets for therapy. This demonstrates DyGAF's superior performance compared to other methods.

Then, we utilized NetworkAnalyst to construct a TF-gene network that elucidates the interactions between TFs and their corresponding target genes depicted in Figure 8. It's a valuable tool for understanding how cells respond to viruses like COVID-19, helping identify new therapeutic targets and mechanisms. Our analysis encompasses of GO and pathways along with PPI, hub proteins, and TF-gene networks, demonstrating how DyGAF more efficient in identifying biomarker genes and elucidating their biological relevance compared to other models.

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