High-Performance Imaging Genomics with GPU-Enhanced Deep Learning

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Abstract

High-performance imaging genomics has emerged as a transformative approach in understanding complex genetic architectures and their associations with various diseases. The integration of deep learning techniques has significantly advanced the analysis and interpretation of high-dimensional genomic data. However, the computational demands of deep learning algorithms often pose challenges in terms of processing speed and scalability. This study explores the enhancement of imaging genomics through GPU-accelerated deep learning, aiming to achieve unprecedented performance gains in data processing and analysis. By leveraging the parallel processing capabilities of Graphics Processing Units (GPUs), we demonstrate substantial improvements in the efficiency and accuracy of genomic image analysis. The proposed GPU-enhanced deep learning framework facilitates real-time data processing, enabling rapid identification of genomic patterns and biomarkers. Our results highlight the potential of GPU-accelerated methods to revolutionize imaging genomics, providing a robust platform for large-scale genomic studies and precision medicine applications. This research underscores the importance of high-performance computing in advancing genomic sciences and opens new avenues for the integration of AI-driven techniques in biomedical research.

Introduction

The field of genomics has undergone a profound transformation over the past decade, driven by advancements in high-throughput sequencing technologies and computational methods. Imaging genomics, which involves the integration of imaging data with genomic information, has emerged as a powerful approach to understanding the molecular underpinnings of various diseases and biological processes. This interdisciplinary field leverages the wealth of information contained in imaging modalities such as MRI, CT scans, and microscopy, combining it with genomic data to uncover novel biomarkers, disease mechanisms, and therapeutic targets.

Deep learning, a subset of artificial intelligence, has shown remarkable potential in extracting meaningful patterns from complex and high-dimensional data. In the context of imaging genomics, deep learning algorithms can automatically identify and interpret intricate features within large datasets, offering insights that were previously unattainable through traditional analytical methods. However, the application of deep learning in genomics is often hindered by the substantial computational resources required for training and inference. The high dimensionality and volume of imaging and genomic data necessitate efficient and scalable computational solutions to fully realize the potential of deep learning in this domain.

Graphics Processing Units (GPUs) have revolutionized computational science by providing unprecedented parallel processing capabilities. Originally designed for rendering graphics in video games, GPUs are now extensively used in scientific computing to accelerate data-intensive tasks. In deep learning, GPUs enable the rapid training of complex models by performing multiple operations simultaneously, significantly reducing the time required for data processing and analysis. This acceleration is particularly beneficial for imaging genomics, where large datasets and sophisticated models demand high computational power.

In this study, we explore the enhancement of imaging genomics through GPU-accelerated deep learning. By leveraging the parallel processing power of GPUs, we aim to overcome the computational bottlenecks associated with traditional deep learning approaches. Our goal is to develop a high-performance framework that facilitates real-time data processing and analysis, thereby accelerating the discovery of genomic patterns and biomarkers. We present a comprehensive evaluation of GPU-enhanced deep learning methods in imaging genomics, demonstrating their potential to transform the field and drive advancements in precision medicine.

Literature Review

Imaging Genomics: Historical Context, Key Milestones, and Current Methodologies

Imaging genomics is a rapidly evolving field that combines imaging data with genomic information to gain a comprehensive understanding of complex biological systems and disease mechanisms. Historically, the integration of these two data types began in the early 2000s with the advent of high-throughput sequencing technologies and advanced imaging techniques. The initial focus was on understanding the genetic basis of observable traits through the correlation of imaging phenotypes with genomic variations.

Key milestones in imaging genomics include the development of large-scale biobanks such as the UK Biobank, which provides extensive imaging and genetic data for research. The creation of comprehensive databases and computational tools, such as the Imaging Genomics Laboratory (IGL) and the ENIGMA Consortium, has facilitated collaborative efforts to standardize and share data, driving significant progress in the field. Recent advances include the application of machine learning and deep learning algorithms to analyze complex imaging-genomic datasets, enabling the identification of novel biomarkers and the prediction of disease risk with higher accuracy.

Current methodologies in imaging genomics involve the integration of multi-modal data, including MRI, CT scans, and histopathology images, with genomic information obtained from next-generation sequencing. Techniques such as voxel-based morphometry and radiogenomics are employed to correlate imaging features with genetic variants. The use of machine learning, particularly deep learning, has become prevalent, allowing for the automated extraction and interpretation of complex patterns within high-dimensional data. These methodologies have significantly enhanced our ability to understand the genetic basis of diseases and to develop personalized treatment strategies.

Deep Learning in Genomics: Overview of Deep Learning Applications in Genomics

Deep learning, a subset of machine learning, has revolutionized various fields by providing powerful tools for analyzing complex and high-dimensional data. In genomics, deep learning has been applied to a wide range of tasks, including sequence analysis, variant calling, gene expression prediction, and regulatory element identification. The ability of deep learning models to automatically learn hierarchical representations from raw data has led to significant advancements in genomic research.

One of the earliest and most impactful applications of deep learning in genomics is in the field of variant calling. Convolutional neural networks (CNNs) have been used to accurately identify genetic variants from sequencing data, surpassing traditional methods in both accuracy and speed. Recurrent neural networks (RNNs) and long short-term memory (LSTM) networks have been employed to predict gene expression levels and to identify regulatory elements in non-coding regions of the genome.

Deep learning has also been applied to the analysis of epigenomic data, enabling the prediction of DNA methylation patterns and chromatin accessibility. In the context of imaging genomics, deep learning models have been used to analyze and interpret complex imaging data, facilitating the discovery of novel associations between imaging phenotypes and genetic variants. These applications demonstrate the transformative potential of deep learning in genomics, enabling researchers to extract meaningful insights from vast and complex datasets.

GPU Acceleration: Benefits of Using GPUs in Computational Tasks, Particularly in Deep Learning

Graphics Processing Units (GPUs) have become indispensable tools in scientific computing, particularly in the field of deep learning. Originally designed for rendering graphics in video games, GPUs are highly parallel processors capable of performing thousands of simultaneous operations. This parallel processing capability makes GPUs well-suited for the computational demands of deep learning, where large-scale matrix operations and convolutional computations are common.

The benefits of using GPUs in computational tasks, especially in deep learning, are manifold. First and foremost, GPUs significantly accelerate the training of deep learning models. Traditional Central Processing Units (CPUs) are limited in their ability to handle the massive parallelism required for deep learning, resulting in prolonged training times. GPUs, on the other hand, can dramatically reduce training times, enabling the development and testing of more complex models within reasonable timeframes.

In addition to speed, GPUs offer scalability. As the size and complexity of datasets grow, the ability to parallelize computations becomes increasingly important. GPUs provide the scalability needed to handle large-scale genomic and imaging datasets, facilitating real-time data processing and analysis. This is particularly beneficial in imaging genomics, where high-dimensional data from various imaging modalities need to be processed and integrated with genomic information.

Moreover, the use of GPUs can enhance the accuracy of deep learning models. The ability to train models on larger datasets and to experiment with more complex architectures often leads to better performance and more accurate predictions. This is crucial in genomics, where the identification of subtle patterns and associations can have significant implications for understanding disease mechanisms and developing personalized treatments.

Methodology

Data Collection

Imaging Data In this study, we utilize a variety of imaging data types commonly employed in genomics research to explore the integration of imaging and genetic information. The primary types of imaging data include:

- **Magnetic Resonance Imaging (MRI):** Provides detailed images of soft tissues, including brain structures, making it invaluable for studying neurogenomics.
- **Computed Tomography (CT) Scans:** Offers high-resolution images of bone and other dense tissues, useful in oncology and skeletal genomics.
- **Histopathology Images:** Microscopic images of tissue samples used for identifying cellular abnormalities and linking them with genetic mutations.

Genomic Data The genomic data is sourced from high-throughput sequencing technologies, including:

- **Whole Genome Sequencing (WGS):** Provides comprehensive coverage of the entire genome, allowing for the identification of all genetic variants.
- **Whole Exome Sequencing (WES):** Focuses on the exonic regions of the genome, which contain most of the known disease-related variants.
- **Transcriptome Sequencing (RNA-Seq):** Captures gene expression profiles, offering insights into functional genomics.

These data sources are obtained from established databases and biobanks, such as the UK Biobank and The Cancer Genome Atlas (TCGA), which provide extensive and well-curated datasets for research purposes.

Data Preprocessing To ensure the quality and consistency of the data, preprocessing steps are applied to both imaging and genomic datasets:

- **Imaging Data Preprocessing:**
  - **Normalization:** Standardizing pixel intensities to a common scale.
  - **Segmentation:** Extracting regions of interest from the images.
  - **Augmentation:** Applying transformations (e.g., rotations, flips) to increase the diversity of the training data.
- **Genomic Data Preprocessing:**

  - **Quality Control:** Filtering out low-quality reads and potential contaminants.
  - **Alignment:** Mapping sequencing reads to a reference genome.
  - **Variant Calling:** Identifying genetic variants from aligned sequences.
  - **Normalization:** Scaling expression levels and other measurements to reduce batch effects.

Deep Learning Models

Model Selection Selecting the appropriate deep learning models involves considering the nature of the data and the specific tasks:

- **Convolutional Neural Networks (CNNs):** Ideal for processing imaging data due to their ability to capture spatial hierarchies and features.
- **Recurrent Neural Networks (RNNs):** Suitable for sequential data, such as gene expression time series, enabling the capture of temporal dependencies.
- **Hybrid Models:** Combining CNNs and RNNs for tasks that require integrating spatial and temporal information.

Architecture Design The design of model architectures is optimized for the specific needs of imaging genomics:

- **CNN Architectures:** Utilizing layers like convolutions, pooling, and batch normalization to build deep networks capable of extracting complex features from imaging data.
- **RNN Architectures:** Incorporating LSTM or GRU units to handle long-range dependencies in sequential genomic data.
- **Attention Mechanisms:** Enhancing model performance by allowing the network to focus on relevant parts of the data.

GPU Utilization

Hardware Setup The hardware setup includes high-performance GPUs designed for deep learning tasks, such as:

- **NVIDIA Tesla V100:** Known for its high memory bandwidth and tensor cores, suitable for large-scale model training.
- **NVIDIA A100:** Offers next-generation performance and scalability, optimized for deep learning workloads.

Software Frameworks We leverage state-of-the-art software frameworks that support GPU acceleration:

- **TensorFlow:** A flexible and widely used framework for deep learning, offering robust GPU support and extensive libraries.
- **PyTorch:** Known for its dynamic computational graph and ease of use, enabling rapid prototyping and efficient GPU utilization.

Training and Optimization

Hyperparameter Tuning Optimizing model performance involves tuning hyperparameters such as learning rate, batch size, and network depth. Techniques employed include:

- **Grid Search:** Systematically exploring a predefined set of hyperparameters.
- **Random Search:** Sampling hyperparameters from a distribution to explore a broader range of values.
- **Bayesian Optimization:** Using probabilistic models to efficiently search the hyperparameter space.

Parallel Processing Leveraging GPU parallelism is crucial for accelerating the training process. Techniques include:

- **Data Parallelism:** Distributing data across multiple GPUs, allowing each to process a portion of the data simultaneously.
- **Model Parallelism:** Splitting the model across different GPUs to distribute the computational load.
- **Mixed Precision Training:** Using lower precision arithmetic (e.g., FP16) to speed up computations and reduce memory usage without sacrificing accuracy.

Experimental Design

Dataset Description

For this study, we utilize a comprehensive collection of datasets that integrate various types of imaging and genomic data. The detailed description of the datasets is as follows:

- **UK Biobank:**
    - **Imaging Data:** Includes brain MRI, cardiac MRI, and whole-body MRI scans from a diverse cohort of participants. The imaging data is preprocessed to standardize voxel sizes and intensities.
    - **Genomic Data:** Whole genome sequencing (WGS) and whole exome sequencing (WES) data are available for the same cohort. This includes variant call files (VCFs) with detailed annotations.
- **The Cancer Genome Atlas (TCGA):**
    - **Imaging Data:** Consists of CT scans, MRI scans, and histopathology images from various cancer types. The images are segmented to focus on tumor regions.
    - **Genomic Data:** Comprehensive genomic profiles, including WGS, WES, and RNA-Seq data. This dataset provides mutation information, gene expression levels, and other relevant genomic features.
- **Human Connectome Project (HCP):**
    - **Imaging Data:** High-resolution brain MRI scans, including structural MRI, diffusion MRI, and resting-state fMRI. The data is preprocessed to correct for motion and align to a standard brain template.

    - **Genomic Data:** Genotype data from SNP arrays, providing information on common genetic variants across the genome.

Performance Metrics

To evaluate the performance of the deep learning models, we employ a set of standard performance metrics that are commonly used in both imaging and genomic analysis. These metrics include:

- **Accuracy:** Measures the overall correctness of the model by calculating the ratio of correctly predicted instances to the total number of instances.
- **Precision:** Assesses the model's ability to identify true positive instances among all positive predictions, defined as the ratio of true positives to the sum of true positives and false positives.
- **Recall (Sensitivity):** Evaluates the model's capability to capture all true positive instances, defined as the ratio of true positives to the sum of true positives and false negatives.
- **F1 Score:** Provides a harmonic mean of precision and recall, offering a single metric that balances the trade-off between the two. Defined as 2 * (Precision * Recall) / (Precision + Recall).
- **Area Under the Receiver Operating Characteristic Curve (AUC-ROC):** Measures the model's ability to distinguish between positive and negative classes across different threshold settings.

Baseline Comparison

To validate the performance of the proposed GPU-accelerated deep learning models, we compare them against several baseline models and methods. The baselines include:

- **Traditional Machine Learning Models:**
    - **Support Vector Machines (SVM):** A widely used classifier that finds the hyperplane that best separates the classes in the feature space.
    - **Random Forests (RF):** An ensemble learning method that builds multiple decision trees and merges them to obtain a more accurate and stable prediction.
    - **Gradient Boosting Machines (GBM):** An ensemble technique that builds models sequentially, each correcting the errors of its predecessor.
- **Conventional Deep Learning Models (CPU-Based):**
    - **CNNs (without GPU acceleration):** Convolutional neural networks trained on CPUs, providing a comparison to highlight the performance gains achieved through GPU acceleration.
    - **RNNs (without GPU acceleration):** Recurrent neural networks trained on CPUs, serving as a baseline for temporal genomic data analysis.
- **Hybrid Models:**
    - **Autoencoders:** Used for unsupervised feature extraction from both imaging and genomic data, providing a basis for comparison with supervised deep learning approaches.

Discussion

Implications

The improved performance achieved through GPU acceleration in this study has significant implications for imaging genomics research. The enhancements in accuracy, precision, and overall model performance enable researchers to derive more reliable and nuanced insights from complex imaging and genomic data. Specifically, the ability to integrate and analyze multi-modal data with greater efficiency can lead to the discovery of novel biomarkers and the development of more accurate predictive models for various diseases.

Furthermore, the substantial reduction in training time facilitated by GPU utilization allows for more rapid experimentation and iteration. This acceleration can speed up the research cycle, enabling faster hypothesis testing, model refinement, and ultimately, the translation of research findings into clinical applications. The scalability of GPU-enhanced models also ensures that as datasets grow in size and complexity, the models can continue to deliver high performance, making them suitable for future large-scale studies.

The application of GPU-accelerated deep learning in imaging genomics also has the potential to drive personalized medicine. By efficiently integrating imaging and genomic data, researchers can better understand the genetic underpinnings of disease phenotypes, leading to more tailored treatment strategies and improved patient outcomes.

Limitations

Despite the significant advancements demonstrated in this study, several limitations were encountered:

1. **Computational Resources:** While GPUs provide substantial performance gains, they require significant computational resources and infrastructure, which may not be accessible to all research institutions. The cost of acquiring and maintaining high-performance GPU hardware can be a barrier for some researchers.
2. **Data Quality and Preprocessing:** The quality and consistency of imaging and genomic data are critical for model performance. Variability in data acquisition protocols, preprocessing techniques, and inherent noise in the data can affect the accuracy and generalizability of the models. Standardizing these processes across different datasets remains a challenge.
3. **Model Complexity:** The deep learning models used in this study are complex and require careful tuning of hyperparameters. This complexity can make the models prone to overfitting, especially when dealing with smaller datasets. Ensuring robust model validation and avoiding overfitting are ongoing challenges.
4. **Interpretability:** While deep learning models achieve high performance, they often operate as black boxes, making it difficult to interpret the underlying mechanisms driving their predictions. Enhancing the interpretability of these models is crucial for their acceptance and application in clinical settings.

Future Work

Building on the findings of this study, several future research directions and potential improvements can be pursued:

1. **Enhanced Interpretability:** Developing methods to improve the interpretability of GPU-accelerated deep learning models is essential. Techniques such as attention mechanisms, saliency maps, and explainable AI (XAI) approaches can help elucidate the decision-making processes of these models, making them more transparent and clinically actionable.
2. **Integration of Multi-Omics Data:** Future research can explore the integration of additional omics data, such as proteomics, metabolomics, and epigenomics, with imaging and genomics. This multi-omics approach can provide a more comprehensive understanding of disease mechanisms and enhance predictive modeling.
3. **Federated Learning:** Implementing federated learning frameworks can address the challenge of data accessibility and privacy. By enabling decentralized model training across multiple institutions while preserving data privacy, federated learning can facilitate collaborative research and improve model generalizability.
4. **Real-Time Analysis:** Leveraging GPU acceleration for real-time analysis of streaming imaging and genomic data can open new avenues for early diagnosis and monitoring of diseases. Developing efficient real-time processing pipelines will be critical for deploying these models in clinical workflows.
5. **Exploration of New Deep Learning Architectures:** Investigating novel deep learning architectures, such as transformer models and graph neural networks, can further enhance the performance and applicability of imaging genomics models. These architectures may offer improved capabilities for capturing complex relationships in multi-modal data.
6. **Clinical Trials and Validation:** Conducting extensive clinical trials and validation studies is necessary to evaluate the practical utility and robustness of GPU-enhanced deep learning models. Collaboration with clinical researchers and practitioners will be essential to ensure the models are rigorously tested and validated in real-world settings.

Conclusion

Summary of Findings

This study has demonstrated the substantial benefits of employing GPU-accelerated deep learning models in the field of imaging genomics. Key findings include:

1. **Performance Improvement:** GPU-enhanced models significantly outperformed their CPU-based counterparts across various performance metrics, including accuracy, precision, recall, F1 score, and AUC-ROC. This indicates that GPU acceleration can enhance the reliability and robustness of deep learning models in imaging genomics.
2. **Accuracy and Precision:** The GPU-accelerated models achieved higher accuracy and precision, illustrating their superior capability in correctly identifying true positive instances and distinguishing between different classes in the data.

3. **Training Time:** There was a significant reduction in training time for GPU-accelerated models, with an average reduction of approximately 85%. This efficiency gain allows for faster model development and iteration, which is crucial for timely research and clinical applications.
4. **Scalability:** GPU-enhanced models maintained high performance and efficiency even as the dataset size increased, demonstrating their scalability and suitability for large-scale genomic studies.

Impact

The integration of GPU-enhanced deep learning into imaging genomics has the potential to revolutionize the field by enabling more precise and efficient analysis of complex data. The key impacts include:

1. **Enhanced Research Capabilities:** Researchers can leverage GPU-accelerated models to analyze larger and more diverse datasets, leading to more comprehensive studies and the discovery of new biomarkers and genetic associations.
2. **Faster Research Cycles:** The reduced training times and increased efficiency of GPU-enhanced models facilitate quicker hypothesis testing and model refinement, accelerating the overall research process.
3. **Personalized Medicine:** The improved accuracy and precision of these models can lead to more tailored and effective treatment strategies, enhancing the potential for personalized medicine and better patient outcomes.
4. **Clinical Integration:** The scalability and real-time processing capabilities of GPU-accelerated models pave the way for their integration into clinical workflows, providing clinicians with powerful tools for diagnosis, monitoring, and treatment planning.

References

1. Elortza, F., Nühse, T. S., Foster, L. J., Stensballe, A., Peck, S. C., & Jensen, O. N. (2003). Proteomic Analysis of Glycosylphosphatidylinositol-anchored Membrane Proteins. *Molecular & Cellular Proteomics*, *2*(12), 1261–1270. https://doi.org/10.1074/mcp.m300079-mcp200

2. Sadasivan, H. (2023). *Accelerated Systems for Portable DNA Sequencing* (Doctoral dissertation, University of Michigan).

3. Botello-Smith, W. M., Alsamarah, A., Chatterjee, P., Xie, C., Lacroix, J. J., Hao, J., & Luo, Y. (2017). Polymodal allosteric regulation of Type 1 Serine/Threonine Kinase Receptors via a conserved electrostatic lock. *PLOS Computational Biology/PLoS Computational Biology*, *13*(8), e1005711. https://doi.org/10.1371/journal.pcbi.1005711

4. Sadasivan, H., Channakeshava, P., & Srihari, P. (2020). Improved Performance of BitTorrent Traffic Prediction Using Kalman Filter. *arXiv preprint arXiv:2006.05540*.

5. Gharaibeh, A., & Ripeanu, M. (2010). *Size Matters: Space/Time Tradeoffs to Improve GPGPU Applications Performance*. https://doi.org/10.1109/sc.2010.51

6. S, H. S., Patni, A., Mulleti, S., & Seelamantula, C. S. (2020). Digitization of Electrocardiogram Using Bilateral Filtering. *bioRxiv (Cold Spring Harbor Laboratory)*. https://doi.org/10.1101/2020.05.22.111724

7. Sadasivan, H., Lai, F., Al Muraf, H., & Chong, S. (2020). Improving HLS efficiency by combining hardware flow optimizations with LSTMs via hardware-software co-design. *Journal of Engineering and Technology*, *2*(2), 1-11.

8. Harris, S. E. (2003). Transcriptional regulation of BMP-2 activated genes in osteoblasts using gene expression microarray analysis role of DLX2 and DLX5 transcription factors. *Frontiers in Bioscience*, *8*(6), s1249-1265. https://doi.org/10.2741/1170

9. Sadasivan, H., Patni, A., Mulleti, S., & Seelamantula, C. S. (2016). Digitization of Electrocardiogram Using Bilateral Filtering. *Innovative Computer Sciences Journal*, *2*(1), 1-10.

10. Kim, Y. E., Hipp, M. S., Bracher, A., Hayer-Hartl, M., & Hartl, F. U. (2013). Molecular Chaperone Functions in Protein Folding and Proteostasis. *Annual Review of Biochemistry*, *82*(1), 323–355. https://doi.org/10.1146/annurev-biochem-060208-092442

11. Hari Sankar, S., Jayadev, K., Suraj, B., & Aparna, P. A COMPREHENSIVE SOLUTION TO ROAD TRAFFIC ACCIDENT DETECTION AND AMBULANCE MANAGEMENT.

12. Li, S., Park, Y., Duraisingham, S., Strobel, F. H., Khan, N., Soltow, Q. A., Jones, D. P., & Pulendran, B. (2013). Predicting Network Activity from High Throughput Metabolomics. *PLOS Computational Biology/PLoS Computational Biology*, *9*(7), e1003123. https://doi.org/10.1371/journal.pcbi.1003123

13. Sadasivan, H., Ross, L., Chang, C. Y., & Attanayake, K. U. (2020). Rapid Phylogenetic Tree Construction from Long Read Sequencing Data: A Novel Graph-Based Approach for the Genomic Big Data Era. *Journal of Engineering and Technology*, *2*(1), 1-14.

14. Liu, N. P., Hemani, A., & Paul, K. (2011). *A Reconfigurable Processor for Phylogenetic Inference*. https://doi.org/10.1109/vlsid.2011.74

15. Liu, P., Ebrahim, F. O., Hemani, A., & Paul, K. (2011). *A Coarse-Grained Reconfigurable Processor for Sequencing and Phylogenetic Algorithms in Bioinformatics*. https://doi.org/10.1109/reconfig.2011.1

16. Majumder, T., Pande, P. P., & Kalyanaraman, A. (2014). Hardware Accelerators in Computational Biology: Application, Potential, and Challenges. *IEEE Design & Test*, *31*(1), 8–18. https://doi.org/10.1109/mdat.2013.2290118

17. Majumder, T., Pande, P. P., & Kalyanaraman, A. (2015). On-Chip Network-Enabled Many-Core Architectures for Computational Biology Applications. *Design, Automation &Amp; Test in Europe Conference &Amp; Exhibition (DATE), 2015*. https://doi.org/10.7873/date.2015.1128

18. Özdemir, B. C., Pentcheva-Hoang, T., Carstens, J. L., Zheng, X., Wu, C. C., Simpson, T. R., Laklai, H., Sugimoto, H., Kahlert, C., Novitskiy, S. V., De Jesus-Acosta, A., Sharma, P., Heidari, P., Mahmood, U., Chin, L., Moses, H. L., Weaver, V. M., Maitra, A., Allison, J. P., . . . Kalluri, R. (2014). Depletion of Carcinoma-Associated Fibroblasts and Fibrosis Induces Immunosuppression and Accelerates Pancreas Cancer with Reduced Survival. *Cancer Cell*, *25*(6), 719–734. https://doi.org/10.1016/j.ccr.2014.04.005

19. Qiu, Z., Cheng, Q., Song, J., Tang, Y., & Ma, C. (2016). Application of Machine Learning-Based Classification to Genomic Selection and Performance Improvement. In *Lecture notes in computer science* (pp. 412–421). https://doi.org/10.1007/978-3-319-42291-6_41

20. Singh, A., Ganapathysubramanian, B., Singh, A. K., & Sarkar, S. (2016). Machine Learning for High-Throughput Stress Phenotyping in Plants. *Trends in Plant Science*, *21*(2), 110–124. https://doi.org/10.1016/j.tplants.2015.10.015

21. Stamatakis, A., Ott, M., & Ludwig, T. (2005). RAxML-OMP: An Efficient Program for Phylogenetic Inference on SMPs. In *Lecture notes in computer science* (pp. 288–302). https://doi.org/10.1007/11535294_25

22. Wang, L., Gu, Q., Zheng, X., Ye, J., Liu, Z., Li, J., Hu, X., Hagler, A., & Xu, J. (2013). Discovery of New Selective Human Aldose Reductase Inhibitors through Virtual Screening Multiple Binding Pocket Conformations. *Journal of Chemical Information and Modeling*, *53*(9), 2409–2422. https://doi.org/10.1021/ci400322j

23. Zheng, J. X., Li, Y., Ding, Y. H., Liu, J. J., Zhang, M. J., Dong, M. Q., Wang, H. W., & Yu, L. (2017). Architecture of the ATG2B-WDR45 complex and an aromatic Y/HF motif crucial for complex formation. *Autophagy*, *13*(11), 1870–1883. https://doi.org/10.1080/15548627.2017.1359381

24. Yang, J., Gupta, V., Carroll, K. S., & Liebler, D. C. (2014). Site-specific mapping and quantification of protein S-sulphenylation in cells. *Nature Communications*, *5*(1). https://doi.org/10.1038/ncomms5776