Diversitas Journal
ISSN 2525-5215
Volume 9, Issue 3 (jul./sep. 2024) p. 1357 - 1368
https://diversitasjournal.com.br/diversitas_journal

The advances and challenges of bioinformatics applied to health: a review

SILVA, Ruana Carolina Cabral da[1]; ALVES, Maria Cidinaria Silva[2]

[1] 0000-0003-0435-1871; Universidade Federal de Ouro Preto. Ouro Preto-MG, Brasil. E-mail: ruana.silva@ufop.edu.br.

[2] 0000-0003-0625-416X; Universidade Federal de Pernambuco, Recife-PE, Brasil. E-mail: cidinaria.alves@ufpe.br.

ABSTRACT

The objective of this review was to discuss recent advancements and challenges encountered in the application of bioinformatics to health issues. To achieve this, a comprehensive literature review was conducted to explore pertinent topics, such as the fundamentals of bioinformatics and its impact on the healthcare sphere, the primary contributions of omics approaches (genomics, proteomics, transcriptomics, among others) to understanding health, as well as the significant role of bioinformatics in biomedical research and clinical practice. It is important to emphasize that bioinformatics, as an interdisciplinary field integrating biology, computer science, and informatics, plays an increasingly crucial role in deciphering complex data associated with human health. The information and findings outlined in this article underscore that bioinformatics remains a fundamental component in improving health and advancing medicine. However, considering the continuous evolution of technologies and tools, fostering collaboration among researchers, healthcare professionals, and industry is pivotal to establish standards and approaches enabling the ethical and effective utilization of this data in clinical practice. This collaboration is essential to develop robust systems, ensure data security, and standardize analysis methods, providing significant benefits for both public and individual health.

RESUMO

O objetivo desta revisão foi discutir os avanços recentes e os desafios enfrentados na aplicação da bioinformática em problemas de saúde. Para tanto, foi conduzida uma revisão bibliográfica abrangente, visando explorar tópicos relevantes, como os fundamentos da bioinformática e seu impacto na esfera da saúde, as principais contribuições das abordagens ômicas (genômica, proteômica, transcriptômica, entre outras) para a compreensão da saúde, bem como o papel importante da bioinformática na pesquisa biomédica e na prática clínica. É importante ressaltar que a bioinformática, como um campo interdisciplinar que integra biologia, computação e informática, desempenha um papel cada vez mais fundamental na decifração de dados complexos associados à saúde humana. As informações e descobertas delineadas neste artigo enfatizam que a bioinformática continua a ser uma peça fundamental na melhoria da saúde e na evolução da medicina. Contudo, considerando a incessante evolução de tecnologias e ferramentas, é fundamental promover colaboração entre pesquisadores, profissionais da saúde e a indústria, a fim de estabelecer padrões e abordagens que permitam a utilização ética e eficaz desses dados na prática clínica. Essa cooperação é essencial para desenvolver sistemas robustos, garantir a segurança dos dados e padronizar métodos de análise, proporcionando benefícios significativos tanto para a saúde pública quanto para a individual.

ARTICLE INFORMATION

Article Process:
Submetido: 12/16/2023
Aprovado: 07/22/2024
Publicação: 08/09/2024

Keywords:
Computational tools, clinical practice, application.

Palavras-Chave:
Ferramentas computacionais, prática clínica, aplicação.

DOI: 10.48017/dj.v9i3.2910

Introduction

Bioinformatics is an interdisciplinary field that combines Biology with Computer Science, Statistics and Information Technology (Hogeweg, 2011). This area aims to understand biological phenomena through the application of computational methods and large-scale data analysis. With recent advances in high-throughput measurement technologies such as next-generation DNA sequencing and mass spectrometry, the amount of biological data generated has increased exponentially (Uesaka et al., 2022). This explosion of data has created an urgent need to adopt bioinformatics approaches to process, store, analyze and interpret this information in an efficient and meaningful way.

Specialized computers and software have become an essential part of the biologist's toolkit, both for routine analysis of DNA or protein sequences and for analyzing meaningful information in huge biological data sets. Since the advent of next generation sequencing (NGS) there has been a new path forward in population genetics, quantitative genetics, molecular systematics, microbial ecology and many other fields of research, including advances in health (Gauthier et al ., 2019).

Bioinformatics, applied to Health, uses computational methods and data analysis to uncover, interpret and manage important biological information, especially related to human health (Li et al., 2019). Through the integration of genomic data, bioinformatics plays a key role in identifying genetic variants associated with diseases, accurately diagnosing genetic conditions, and personalizing medical treatments based on individual patient characteristics (Sunil Krishnan, Joshi & Kaushik, 2021). In this way, the innovative approach paves the way for the development of personalized therapies, contributing to precision medicine and enhancing the ability to offer more effective and personalized healthcare (Gómez-López et al., 2019).

Given this theme, the aim of this review was to discuss recent advances and challenges faced in the application of bioinformatics to health problems. This study presents a discussion on the fundamentals of bioinformatics and how it applies to the health area, as well as the main contributions of this field of research in genomics, proteomics, transcriptomics and other fields related to Health. Here we present examples of advances through the use of bioinformatics tools in medicine, based on DNA sequencing, as well as the challenges faced in the integration of complex data related to Clinical practice.

Fundamentals of Bioinformatics and its application in Health

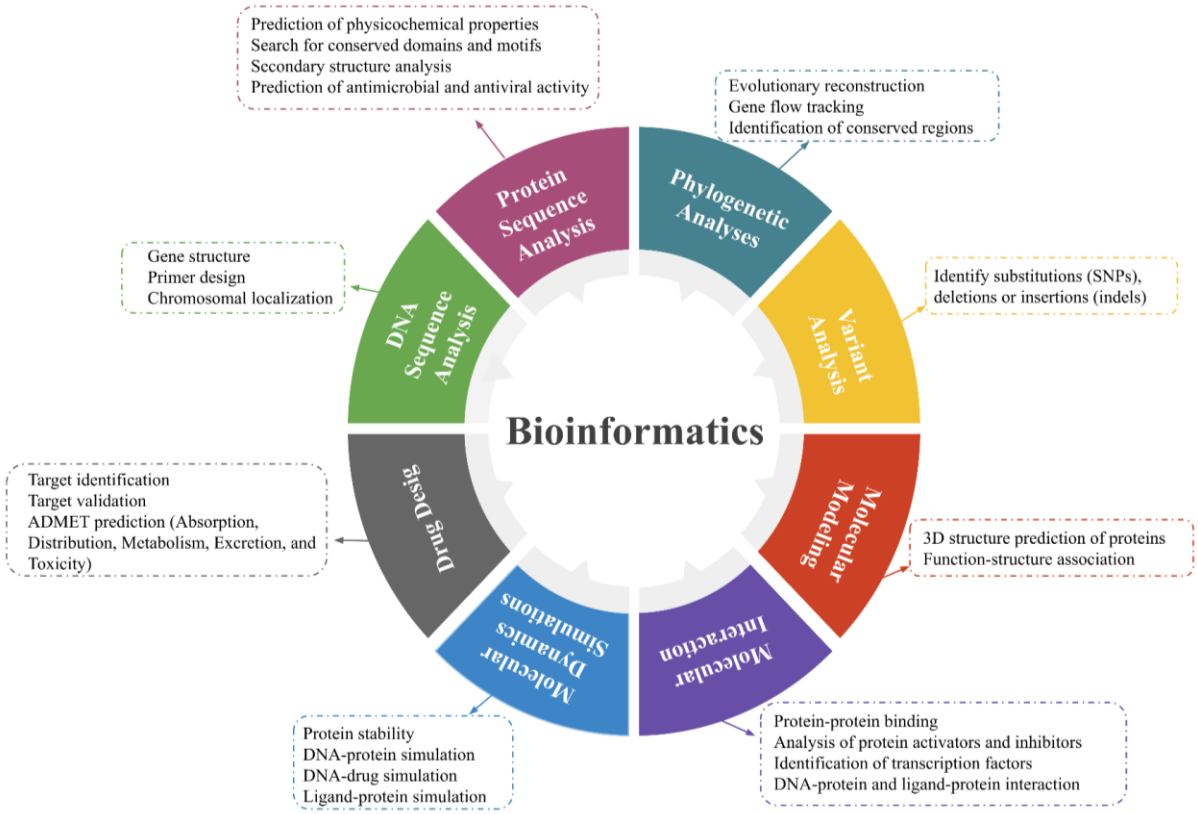
Bioinformatics consists of an interdisciplinary area of science, which encompasses the development of computational approaches and tools with the purpose of facilitating the analysis, interpretation, processing and integration of biological data (Espindola et al., 2010). It is divided into two areas: (1) Classical bioinformatics — addresses issues related to nucleotide

and amino acid sequences; (2) Structural bioinformatics — studies the biological issues of the three-dimensional structure adopted by proteins from the primary structure, using the aid of computational chemistry and molecular modeling (Verli, 2014).

Bioinformatics associates several areas of knowledge with robust computational tools through analytical programs and targeted systems, which predict biological properties and behaviors, in addition to storing the biological data generated (Araújo et al., 2008; Cattley & Arthur, 2007; Verli, 2014). Its applications cover a wide range of generated data, encompassing analysis for protein function prediction, phylogenetic studies and target identification (Luscombe et al., 2001; Sonam & Singh, 2019). Bioinformatics applications offer valuable insights into the structure, function and evolution of organisms (Figure 1).

Figure 1:

Applications of Bioinformatics in Biological Researchs.



Note: Own Authorship, 2023.

In recent decades, Omics studies have enabled the application of bioinformatics tools in identification of biomarkers, precision medicine and drug interactions, especially in diseases such as cancer (Júnior & Carlos, 2021; Zamora-Obando et al., 2022; Soares et al., 2023). Efforts to identify new therapeutic targets are based on studies that consider pharmacogenetics, proteomics, transcriptomics, personalized medicine, and target regulators such as microRNAs (miRNAs) and transcription factors (TFs) (Zheng et al., 2006; Wang et al. al., 2020).

Main contributions of Omics related to Health

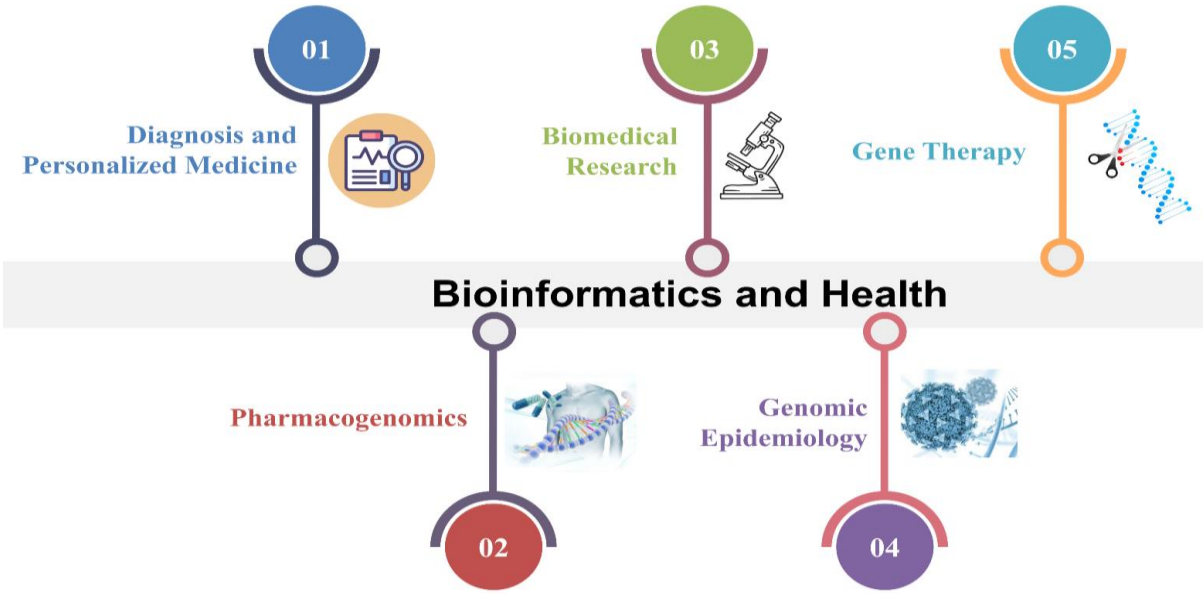
Bioinformatics, associated with Omics, facilitates the identification of biomarkers for early diagnosis, contributes to the development of personalized therapies and boosts research into new medicines. Furthermore, it is essential for understanding genetic variability in populations, helping to predict disease risks and implement preventive strategies (Espindola et al., 2010; Raja et al., 2017).

Among Omics studies, genomics is used to discover new genes or susceptibility loci associated with different characteristics (Bertrand et al., 2015; Tsoi et al., 2015). Proteomics deals with the structure, function and modification of proteins expressed in a biological system, especially post-transcriptional modifications such as phosphorylation, methylation and acetylation, which impact transcription and translation of the genome in different proteomes (James, 1997; Khoury et al ., 2011). The epigenomic study aims to characterize the epigenetic modifications of the genome to understand the regulations of gene expression, while metabolomics identifies the metabolites present in the cell and tissue, revealing the fluctuation of these metabolites in different conditions (Nicholson et al., 1999). Transcriptomics allows the comprehensive assessment of gene expression patterns in cells and tissues, studying the complete set of RNA transcriptomes (Mortazavi et al., 2008).

Omics often generates data at high speed, with high throughput and massive outputs, making them highly dependent on computational tools and bioinformatics (Mosa et al., 2017). A major challenge is the integration of data generated by different Omics to generate meaningful information. Understanding the biological system can have significant impact in areas such as disease prevention, diagnosis, and treatment strategies (Figure 2) (Guido et al., 2010).

Figure 2:

Bioinformatics applications in Health.



Note: Own Authorship, 2023.

In diagnosis and personalized medicine, the analysis of genomic data stands out to identify genetic diseases and guide the development of personalized treatments based on the individual genetic profile (Pantoja et al., 2022). In pharmacogenomics, the influence of genetic variations on the response to medications is examined, optimizing drug prescriptions to minimize side effects and maximize effectiveness (Stein et al., 2020). Furthermore, in biomedical research, it is important to identify therapeutic targets, study biological pathways and analyze gene expression to understand molecular bases of pathological conditions (Silva & Cavalcante, 2021).

In genomic epidemiology, it tracks genetic patterns in populations to understand genetic predisposition to disease and the evolution of pathogens (Zhu et al., 2021). In gene therapy, it contributes to the development of therapeutic strategies, based on genetic manipulation to treat hereditary diseases (Bulaklak & Gersbach, 2020).

Bioinformatics in Biomedical research and Clinical practice

In healthcare, Bioinformatics is fundamental for the analysis of clinical data, being used to identify genetic predispositions to hereditary diseases, thus directing personalized therapies (Kanzi et al., 2020). These studies have seen major advances in NGS technology, using sequencing data to develop workflows and/or tools that are applied in clinical diagnostics to identify genetic mutations associated with diseases, through the detection of variants (Haworth, Savage & Lench, 2016; Al Kawam et al., 2017).

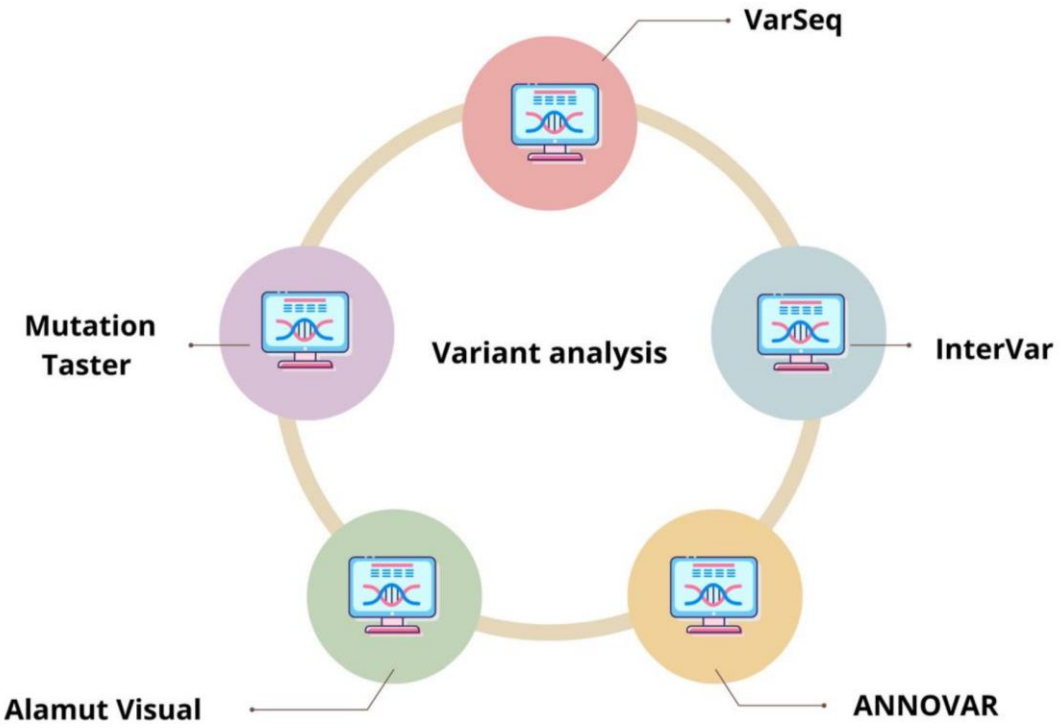
Also noteworthy is the use of molecular modeling that helps predict the three-dimensional structure of proteins based on the amino acid sequence. This is useful for understanding the function of proteins and designing targeted drugs (Orlov et al., 2021). In this context, the important role of drug design and understanding drug-protein interactions stands out, leading to a better understanding of the side effects and efficacy of these drugs (Orlov et al., 2021). For these cases, molecular docking is used, which can predict how molecules interact with each other (Takaya et al., 2008).

There are different Bioinformatics tools that can be applied in Health, mainly in the analysis of variants, including: VarSeq (https://www.goldenhelix.com/products/VarSeq/), InterVar (https://wintervar.wglab.org/), ANNOVAR (https://annovar.openbioinformatics.org/en/latest/), Alamut Visual (https://www.sophiagenetics.com/platform/alamut-visual-plus/), Mutation Taster (https://www.mutationtaster.org/) etc.

Developed by Golden Helix, VarSeq is a genomic analysis platform that helps interpret variants for genetic diseases. InterVar is a tool used to interpret genetic variants, mainly in cases of rare and hereditary diseases. ANNOVAR is widely used software to annotate genetic variants with information from various public databases, helping with the interpretation of variants. Alamut Visual is variant interpretation software used by clinical geneticists for analysis and annotation of genetic variants. Mutation Taster is an online tool that helps predict functional effects of sequence variants (Figure 3).

Figure 3.

Bioinformatics tools to analyse variants applied to Health



Note: Own Authorship, 2023.

However, it is important to highlight that the integration of complex data generated by various Bioinformatics techniques into clinical practice faces a number of challenges (Al Kawam et al., 2017). One of the main obstacles is the heterogeneity and scale of the data. Different Bioinformatics techniques produce data sets that vary in terms of format, structure and size, making joint integration and analysis a complex task (Merelli et al., 2014).

Furthermore, data quality and standardization pose significant challenges. The accuracy of data from different sources and techniques may vary, and the lack of standardization in collection, storage and analysis methods can generate inconsistencies,

hindering the correct interpretation of results (Fernald et al., 2011). The ethical and legal dimension, related to privacy and patients' consent to the use of genomic data in clinical practice, is also a fundamental concern that must be addressed (Thompson, Drew & Thomas, 2012).

The complexity of bioinformatics data requires a robust storage, processing and analysis infrastructure, which requires significant investments in computational resources and specialized personnel. Furthermore, training health professionals to properly interpret and use the information generated by these techniques is important, but represents a considerable challenge due to their complexity and constant evolution (Mulder et al., 2017).

Overcoming these challenges requires collaborative efforts between researchers, healthcare professionals, regulators and industry to develop standards, tools and approaches that enable the effective and ethical use of these data to improve healthcare.

Final considerations

The present study explored the relevance of Bioinformatics in clinical data analysis, highlighting its fundamental role in identifying genetic predispositions, drug discovery and developing personalized therapies.

However, the integration of complex data generated by diverse Bioinformatics techniques into clinical practice presents significant challenges, from data heterogeneity to ethical issues related to patient privacy. The need for a robust infrastructure, investments in computing resources and continuous training of healthcare professionals are crucial aspects to be considered.

The study also highlighted that Bioinformatics continues to play a central role in improving health and advancing medicine. The constant evolution of technologies and tools will require collaborative efforts between researchers, healthcare professionals and industry to develop standards and approaches that enable the ethical and effective use of these data in clinical practice.

It is also necessary to renew data standardization, improve integration and analysis techniques, in addition to developing more accessible and user-friendly tools for healthcare professionals. By addressing these challenges, we will be able to fully explore the potential of Bioinformatics to benefit global health and drive significant advances in personalized Medicine.

REFERÊNCIAS

Al Kawam, A., Sen, A., Datta, A., & Dickey, N. (2018). Understanding the Bioinformatics Challenges of Integrating Genomics into Healthcare. *IEEE Journal of Biomedical and Health Informatics*, *22*(5), 1672–1683. https://doi.org/10.1109/JBHI.2017.2778263

Araújo, N.D., Farias, R.P., Pereira, P.B., Figueirêdo, F.M., Morais, A.M.B., Saldanha, L.C. & Gabriel, J.E.A. (2008). Era da Bioinformática: seu potencial e suas implicações para as ciências da saúde. Estudos de Biologia, v. 30, n. 70/72, 27:143-8.

Bertrand, D., Chng, K. R., Sherbaf, F. G., Kiesel, A., Chia, B. K. H., Sia, Y. Y., Huang, S. K., Hoon, D. S. B., Liu, E. T., Hillmer, A., & Nagarajan, N. (2015). Patient-specific driver gene prediction and risk assessment through integrated network analysis of cancer omics profiles. *Nucleic Acids Research*, *43*(7), e44. https://doi.org/10.1093/nar/gku1393

Bulaklak, K., & Gersbach, C. A. (2020). The once and future gene therapy. *Nature Communications*, *11*(1), Artigo 1. https://doi.org/10.1038/s41467-020-19505-2

Cattley, S., & Arthur, J. W. (2007). BioManager: The use of a bioinformatics web application as a teaching tool in undergraduate bioinformatics training. *Briefings in Bioinformatics*, *8*(6), 457–465. https://doi.org/10.1093/bib/bbm039

Espindola, F. S., Calábria, L. K., Rezende, A. A. A. de, Pereira, B. B., Santana, F. A., Amaral, I. M. R., Lobato, J., França, J. L., Mario, J. L., Figueiredo, L. B., Santos, L. P. dos, Gouveia, N. M. de, Nascimento, R., Teixeira, R. R., Reis, T. A. dos, & Araújo, T. G. de. (2010). Recursos de bioinformática aplicados às ciências ômicas como genômica, transcriptômica, proteômica, interatômica e metabolômica. *Bioscience Journal*, *26*(3), Artigo 3.

Fernald, G. H., Capriotti, E., Daneshjou, R., Karczewski, K. J., & Altman, R. B. (2011). Bioinformatics challenges for personalized medicine. *Bioinformatics (Oxford, England)*, *27*(13), 1741–1748. https://doi.org/10.1093/bioinformatics/btr295

Gauthier, J., Vincent, A. T., Charette, S. J., & Derome, N. (2019). A brief history of bioinformatics. *Briefings in Bioinformatics*, *20*(6), 1981–1996. https://doi.org/10.1093/bib/bby063

Gómez-López, G., Dopazo, J., Cigudosa, J. C., Valencia, A., & Al-Shahrour, F. (2019). Precision medicine needs pioneering clinical bioinformaticians. *Briefings in Bioinformatics*, *20*(3), 752–766. https://doi.org/10.1093/bib/bbx144

Guido, R. V. C., Andricopulo, A. D., & Oliva, G. (2010). Planejamento de fármacos, biotecnologia e química medicinal: Aplicações em doenças infecciosas. *Estudos Avançados*, *24*, 81–98. https://doi.org/10.1590/S0103-40142010000300006

Haworth, A., Savage, H., & Lench, N. (2016). Chapter 4—Diagnostic Genomics and Clinical Bioinformatics. Em D. Kumar & S. Antonarakis (Orgs.), *Medical and Health Genomics* (p. 37–50). Academic Press. https://doi.org/10.1016/B978-0-12-420196-5.00004-6

Hogeweg, P. (2011). The Roots of Bioinformatics in Theoretical Biology. *PLOS Computational Biology*, *7*(3), e1002021. https://doi.org/10.1371/journal.pcbi.1002021

James, P. (1997). Protein identification in the post-genome era: The rapid rise of proteomics. *Quarterly Reviews of Biophysics*, *30*(4), 279–331. https://doi.org/10.1017/S0033583597003399

Júnior, L., & Carlos, L. (2021). A era da medicina de precisão e o impacto na enfermagem: Mudanças de paradigmas? Revista Brasileira de Enfermagem, 74, e740501. https://doi.org/10.1590/0034-7167.2021740501

Kanzi, A. M., San, J. E., Chimukangara, B., Wilkinson, E., Fish, M., Ramsuran, V., & de Oliveira, T. (2020). Next Generation Sequencing and Bioinformatics Analysis of Family Genetic Inheritance. *Frontiers in Genetics*, *11*, 544162. https://doi.org/10.3389/fgene.2020.544162

Khoury, G. A., Baliban, R. C., & Floudas, C. A. (2011). Proteome-wide post-translational modification statistics: Frequency analysis and curation of the swiss-prot database. *Scientific Reports*, *1*(1), Artigo 1. https://doi.org/10.1038/srep00090

Li, Y., Huang, C., Ding, L., Li, Z., Pan, Y., & Gao, X. (2019). *Deep learning in bioinformatics: Introduction, application, and perspective in big data era* (arXiv:1903.00342). arXiv. https://doi.org/10.48550/arXiv.1903.00342

Luscombe, N. M.; Greenbaum, D.; Gerstein, M. Review What is bioinformatics? An introduction and overview. Gene Expression, v. 40, n. 5, p. 83-100, jan. 2001.

Merelli, I., Pérez-Sánchez, H., Gesing, S., & D'Agostino, D. (2014). Managing, analysing, and integrating big data in medical bioinformatics: Open problems and future perspectives. *BioMed Research International*, *2014*, 134023. https://doi.org/10.1155/2014/134023

Mortazavi, A., Williams, B. A., McCue, K., Schaeffer, L., & Wold, B. (2008). Mapping and quantifying mammalian transcriptomes by RNA-Seq. *Nature Methods*, *5*(7), Artigo 7. https://doi.org/10.1038/nmeth.1226

Mosa, K. A., Ismail, A., & Helmy, M. (2017). Omics and System Biology Approaches in Plant Stress Research. Em K. A. Mosa, A. Ismail, & M. Helmy (Orgs.), *Plant Stress Tolerance: An Integrated Omics Approach* (p. 21–34). Springer International Publishing. https://doi.org/10.1007/978-3-319-59379-1_2

Mulder, N. J., Adebiyi, E., Adebiyi, M., Adeyemi, S., Ahmed, A., Ahmed, R., Akanle, B., Alibi, M., Armstrong, D. L., Aron, S., Ashano, E., Baichoo, S., Benkahla, A., Brown, D. K., Chimusa, E. R., Fadlelmola, F. M., Falola, D., Fatumo, S., Ghedira, K., … H3ABioNet Consortium, as members of the H3Africa Consortium. (2017). Development of Bioinformatics Infrastructure for Genomics Research. *Global Heart*, *12*(2), 91–98. https://doi.org/10.1016/j.gheart.2017.01.005

Nicholson, J. K., Lindon, J. C., & Holmes, E. (1999). "Metabonomics": Understanding the metabolic responses of living systems to pathophysiological stimuli via multivariate statistical analysis of biological NMR spectroscopic data. *Xenobiotica*, *29*(11), 1181–1189. https://doi.org/10.1080/004982599238047

Orlov, Y. L., Anashkina, A. A., Klimontov, V. V., & Baranova, A. V. (2021). Medical Genetics, Genomics and Bioinformatics Aid in Understanding Molecular Mechanisms of Human Diseases. *International Journal of Molecular Sciences*, *22*(18), 9962. https://doi.org/10.3390/ijms22189962

Pantoja, R. E. de L., Monteiro, M. C. C., Nascimento, B. dos S., Mota, D. A. da, Balla, I. L., Rocha, I. M. da, Cruz, K. R. M., Fernandes, L. B., Gomes, M. P. de O. M., Espinheiro, R. de F., Araújo, S. A. N., Silva, S. F. da, & Gomes, M. F. (2022). A aplicação do mapeamento genético na identificação dos polimorfismos do câncer de mama e o direcionamento da terapia alvo. *Research, Society and Development*, *11*(10), Artigo 10. https://doi.org/10.33448/rsd-v11i10.32762

Raja, K., Patrick, M., Gao, Y., Madu, D., Yang, Y., & Tsoi, L. C. (2017). A Review of Recent Advancement in Integrating Omics Data with Literature Mining towards Biomedical Discoveries. *International Journal of Genomics*, *2017*, e6213474. https://doi.org/10.1155/2017/6213474

Silva, R. A. dos S. Q., & Cavalcante, G. M. (2021). Potenciais alvos terapêuticos para Covid-19: Uma revisão integrativa. *Jornal de Ciências da Saúde do Hospital Universitário da Universidade Federal do Piauí*, *4*(2), Artigo 2. https://doi.org/10.26694/jcshuufpi.v4i2.986

Soares, J. A., Borges, E. F., Terrinha, D. S., Carmo, V. L. do, Valle, P. D. R. do, Cruz, R. M. S., Oliveira, V. P. O. P., & Martins, A. A. S. (2023). Genoma Humano: 20 anos do sequenciamento que revolucionou a ciência. Brazilian Journal of Implantology and Health Sciences, 5(3), Artigo 3. https://doi.org/10.36557/2674-8169.2023v5n3p1168-1189

Sonam, S.; Singh, K. S. Bioinformatics: Concepts and Applications. In: Advances in Horticultural Crop Management and Value Addition. India: Laxmi Publications Pvt Ltda, p. 127-132, 2019.

Stein, R., Beuren, T., Cela, L. R., & Ferrari, F. (2020). Farmacogenômica e Doença Cardiovascular: Onde Estamos e Para Onde Vamos. *Arquivos Brasileiros de Cardiologia*, *115*, 690–700. https://doi.org/10.36660/abc.20200151

Sunil Krishnan, G., Joshi, A., & Kaushik, V. (2021). Bioinformatics in Personalized Medicine. Em V. Singh & A. Kumar (Orgs.), *Advances in Bioinformatics* (p. 303–315). Springer. https://doi.org/10.1007/978-981-33-6191-1_15

Takaya, D., Takeda-Shitaka, M., Terashi, G., Kanou, K., Iwadate, M., & Umeyama, H. (2008). Bioinformatics based Ligand-Docking and in-silico screening. *Chemical & Pharmaceutical Bulletin*, *56*(5), 742–744. https://doi.org/10.1248/cpb.56.742

Thompson, R., Drew, C. J. G., & Thomas, R. H. (2012). Next generation sequencing in the clinical domain: Clinical advantages, practical, and ethical challenges. *Advances in Protein Chemistry and Structural Biology*, *89*, 27–63. https://doi.org/10.1016/B978-0-12-394287-6.00002-1

Tsoi, L. C., Spain, S. L., Ellinghaus, E., Stuart, P. E., Capon, F., Knight, J., Tejasvi, T., Kang, H. M., Allen, M. H., Lambert, S., Stoll, S. W., Weidinger, S., Gudjonsson, J. E., Koks, S., Kingo, K., Esko, T., Das, S., Metspalu, A., Weichenthal, M., … Elder, J. T. (2015). Enhanced meta-analysis and replication studies identify five new psoriasis susceptibility loci. *Nature Communications*, *6*(1), Artigo 1. https://doi.org/10.1038/ncomms8001

Uesaka, K., Oka, H., Kato, R., Kanie, K., Kojima, T., Tsugawa, H., Toda, Y., & Horinouchi, T. (2022). Bioinformatics in bioscience and bioengineering: Recent advances, applications, and perspectives. *Journal of Bioscience and Bioengineering*, *134*(5), 363–373. https://doi.org/10.1016/j.jbiosc.2022.08.004

Verli, H. (2014). *Bioinformática: Da biologia à flexibilidade molecular*. Sociedade Brasileira de Bioquímica e Biologia Molecular. https://lume.ufrgs.br/handle/10183/166105

Wang, Y., Zhang, S., Li, F., Zhou, Y., Zhang, Y., Wang, Z., Zhang, R., Zhu, J., Ren, Y., Tan, Y., Qin, C., Li, Y., Li, X., Chen, Y., & Zhu, F. (2020). Therapeutic target database 2020: Enriched resource for facilitating research and early development of targeted therapeutics. *Nucleic Acids Research*, *48*(D1), D1031–D1041. https://doi.org/10.1093/nar/gkz981

Zamora-Obando, H. R., Godoy, A. T., Amaral, A. G., Mesquita, A. de S., Simões, B. E. S., Reis, H. O., Rocha, I., Dallaqua, M., Baptistão, M., Fernandes, M. C. V., Lima, M. F., & Simionato, A. V. C. (2022). Biomarcadores Moleculares De Doenças Humanas: Conceitos Fundamentais, Modelos De Estudo E Aplicações Clínicas. Química Nova, 45, 1098–1113. https://doi.org/10.21577/0100-4042.20170905

Zheng, C. J., Han, L. Y., Yap, C. W., Ji, Z. L., Cao, Z. W., & Chen, Y. Z. (2006). Therapeutic Targets: Progress of Their Exploration and Investigation of Their Characteristics. *Pharmacological Reviews*, *58*(2), 259–279. https://doi.org/10.1124/pr.58.2.4

Zhu, Y., Mo, M., Wei, Y., Wu, J., Pan, J., Freedland, S. J., Zheng, Y., & Ye, D. (2021). Epidemiology and genomics of prostate cancer in Asian men. *Nature Reviews Urology*, *18*(5), Artigo 5. https://doi.org/10.1038/s41585-021-00442-8