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Review Article

Novel Applications of Immuno-bioinformatics in Vaccine and Bio-product Developments at Research Institutes

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ABSTRACT

There are many challenges in the field of public health sciences. Rational decisions are required in order to treat different diseases, gain knowledge and wealth regarding research, and produce biological or synthetic products. Various advances in the basic laboratory science, computer science, and the engineering of biological production processes can help solve the occurring problems. Bioinformatics is defined as a field of science combined of biology, mathematics, physics, chemistry, and computer sciences. Recently, bioinformatics has been extensively used in the designing of the epitope, vaccines, antibodies, adjuvants, diagnostic kits, and therapeutic purposes (e.g., proteins, peptides, or small molecules). Moreover, bioinformatics includes chemoinformatics that has been employed to produce various biological or chemical products to target and combat pathogens. Bioinformatics is involved in other areas of data analysis and prediction, such as structural biology, system biology, phylogeny, population genetics, and next-generation data sequencing. To the best of our knowledge, no published study coherently described the benefits of bioinformatics fields applied for medication development or diagnostic aims in bio-productive and pharmaceutical/vaccine companies. Therefore, in the current review, we attempted to present the available bioinformatics resources, practical experiences, and other findings in the mentioned field along with providing a harmonized and applied model(s). The key points presented in the current review may help to elevate production and reduce the costs for the development of novel vaccines, medicines, and antibodies. In addition, these methods can facilitate the identification of organisms and may guarantee the quality of biological products.

Keywords: Bioinformatics, Biological products, Immunoinformatics, Vaccine

Nouvelles applications de l'immuno-bioinformatique dans le développement de vaccins et de bioproduits dans les instituts de recherche

Résumé: Il existe de nombreux défis dans le domaine des sciences de la santé publique. Des décisions rationnelles sont nécessaires pour traiter différentes maladies, acquérir des connaissances et une richesse en matière de recherche et produire des produits biologiques ou synthétiques. Divers progrès dans les sciences fondamentales de laboratoire, l'informatique et l'ingénierie des processus de production biologique peuvent aider à résoudre les problèmes qui se posent. La bioinformatique est définie comme un domaine scientifique

d'objectifs thérapeutiques (protéines, peptides ou petites molécules, par exemple). De plus, la bioinformatique comprend la chimioinformatique qui a été utilisée pour produire divers produits biologiques ou chimiquescombinant biologie, mathématiques, physique, chimie et informatique. Récemment, la bioinformatique a été largement utilisée dans la conception d'épitopes, de vaccins, d'anticorps, d'adjuvants, de kits de diagnostic et destinés à cibler et à combattre les agents pathogènes. La bioinformatique intervient dans d'autres domaines de l'analyse et de la prévision des données, tels que la biologie structurale, la biologie des systèmes, la phylogénie, la génétique des populations et le séquençage de la prochaine génération (NGS). Au meilleur de nos connaissances, aucune étude publiée ne décrivait de manière cohérente les avantages des domaines de la bioinformatique appliqués au développement de médicaments ou d'outils de diagnostic dans les entreprises de bioproduction de vaccins et dans les sociétés pharmaceutiques. Par conséquent, dans cette revue de la litérature, nous avons tenté de présenter les ressources en bioinformatique disponibles, les expériences pratiques et d'autres résultats dans le domaine mentionné, tout en fournissant un ou plusieurs modèles harmonisés et appliqués. Les points clés présentés dans le présent rapport pourraient contribuer à augmenter la production et à réduire les coûts de développement de nouveaux vaccins, médicaments et anticorps. De plus, ces méthodes peuvent faciliter l'identification des organismes et garantir la qualité des produits biologiques.

Mots-clés: Bioinformatique, Produits biologiques, Immuno-informatique, Vaccin

INTRODUCTION

Nowadays, many challenges have emerged in the field of basic and clinical sciences giving new attitudes toward more targeted strategies to combat and id entify dangerous infectious and non-infectious diseases. Such strategies can lead to the modern designs of vaccines, kits, antibodies, adjuvants (Ranjbar et al., 2015a), or active biological and chemical substances (Leelananda and Lindert, 2016). Conventional vaccines are often characterized by an "isolate, inactivate/attenuated, inject" paradigm of development. Although such vaccines have been successful in most aspects, they have failed for some organism and circumstances (Bragazzi et al., 2018). The mentioned methods ignore both geno-proteomic variability and polymorphism of pathogens and hosts, such as Major Histocompatibility Complex (MHC) genes. There are significant limitations, including inducing inadequate immune protection and inability to develop potent and broad-spectrum immunity against hypervariable viruses, namely Influenza, Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), and Infectious Bronchitis Virus (IBV). Some other organisms with the same problem include malaria caused by plasmodium and tuberculosis agent. In addition, poor knowledge of protective immune responses and interactions involved in the persistence against vaccine antigens are among the other issues (Rappuoli and Aderem, 2011). Furthermore, diverse factors, such as globalization, extensive immigrations, and the rapid growth of population result in the emergence and re-emergence of both old and new infectious agents in animals and human. Consequently, the development of novel vaccine generations is considered as an urgent necessity (Bragazzi et al., 2018). In last decade, bioinformatics has been the most progressive field that is tied up with the present and future achievements in terms of the prevention, control, diagnosis, and treatment of diseases in medical and veterinary science. Bioinformatics is the classification of biological data, quantitative and qualitative analysis along with the improvement of drug/vaccine design based on the gained biological information from macro- and micro-molecules, such as DNA, RNA, and protein. In addition to the above-mentioned points, bioinformatics is more about the computational approaches, specially immunoinformatics, computational vaccinology, and chemoinformatics (Ranjbar et al., 2015a; Leelananda and Lindert, 2016; Diniz and Canduri, 2017; Usha et

al., 2017). Computational biology enables us to predict the possibility of improving various properties of available biological products, developing new generations of vaccines, discovering new medications, diagnostic kits, antibodies, and adjuvants, in addition to evaluating allergens and toxic compounds at a lower cost and higher efficiency. The investigation of cancer and autoimmune diseases, modeling of interactions and mechanisms of body function in health and disease states, as well as complex cell cascades are among the bioinformatics applications (McGarvey et al., 2014; Somvanshi and Venkatesh, 2014). Other usages entail designing primers, evaluating highly developed molecular methods, and extensive genetic, demographic, evolutionary, and historiometric studies.

Challenges

In developing countries, bioinformatics approaches are not sufficiently used. It is of remarkable importance for the researchers of all scientific fields, particularly veterinary and medical science to become familiar with the applications of bioinformatics and to use the tools in the best possible way. The goals of many vaccines and sera research institutes are manufacturing vaccines, kits, antibodies, adjuvants, serological and biological products, as well as to detecting animal and human infectious organisms (http://www.rvsri.ir). It should be noted that the costs of bioinformatics science, needed time, side effects, and practical problems, such as culturing highly dangerous or low-growing special organisms need to be reduced. In this regard, the most relevant branches of bioinformatics science that cover the subjects concerning vaccine and sera research in institutes worldwide are immunoinformatic (Sollner et al., 2010; Ranjbar et al., 2015a), chemoinformatics, and general bioinformatics (e.g., working with sequences, databases, or primer/probe design) (Leelananda and Lindert, 2016; Srivastava and Tiwari, 2017). Recently, scientists have so much interest in more rational designed medications, producing novel generations of vaccines, kits, and biological products, and developing new therapeutic methods. To this aim, immunoinformatics and chemoinformatics can be employed as the two main branches of bioinformatics science. Other bioinformatics fields may be the sub-branches of these two main branches. Some sub-branches of immunoinformatics and chemoinformatics encompass structural bioinformatics, next-generation sequencing (NGS) data analysis, RNA-seq, microarray data analysis, phylogenetics, population genetic analyses, system biology, and advanced designing and engineering of protein/peptide/nucleic acid (Figure 1). Knowledge about the possibility of applying bioinformatics in applicable biological research is required for utilizing this science in production institutes. Recently, a few pieces of research without suitable strategically planned connections or interdisciplinary specialists have been performed in developing countries. Moreover, as far as we know, there has not been a published consistency and widespread research concerning the applications of bioinformatics in bio-productive and research institutes in these countries. The present review is based on logic, experience, and studied manuscripts. Consequently, we hope this report is useful for biological scientists in order to create a strategy to form the framework/network of research institutes and universities.

Main Bioinformatics Fields

Figure 1 shows the hierarchies of bioinformatics from simple to advanced levels. Investigations in the various fields of bioinformatics based on complexity and functionality demonstrate that the main corresponding bioinformatics field can be classified into three levels as a pyramid. Immunoinformatics and chemoinformatics might be located at the highest point of the pyramid. Furthermore, antibody and biosensors informatics fields are assumed near the tip of the pyramid, followed by NGS, RNAseq, and microarrays data analysis. The NGS or high-throughput sequencing (HTS), which are new cutting-edge technologies, have expanded and revealed genomics hidden aspects and details of

human, animal, and microorganism characteristics. Current methods have failed to deliver successful vaccine candidates by single-omics to multi-omics technologies. Therefore, the HTS results can provide deep information regarding geno-proteomics for developing, re-designing, and refining potent vaccines against infectious pathogens that are extremely difficult to deal with (Cafardi et al., 2013; Luciani, 2016; Bragazzi et al., 2018). The bottom of the pyramid is a more general area of bioinformatics addressing general bioinformatics and algorithmic/bio-computations bioinformatics. Moreover, the middle of the pyramid belongs to structural bioinformatics, system biology, protein engineering, as well as phylogeny and population genetics analysis. The latter sciences provide a basis for high-level research and design. Details are demonstrated in Figure 1.

Bioinformatics in Bio-research and Production Centers

The next section of the current study addresses the achievements of immunoinformatics that are applicable for vaccine and sera research institutes in details.

1. Immunoinformatics. Immunoinformatics or computational immunology is one of the newest sciences in immunology and microbiology that can accelerate the immuno-biotechnological researches. In recent years, immunoinformatics has been widely considered as a powerful approach to analyze, model, and predict the function of the immune system in both healthy and diseased states (Ranjbar et al., 2015b).

In other words, it can facilitate and speed up the development of new vaccines based on the genomic and proteomic data. Such vaccines, especially those designed against infectious pathogens as an important cause of death worldwide may be strategically important for improving global health. The various applications of immunoinformatics are summarized in Figure 2.

In order to obtain more information about immunological online databases, tools, and resources, readers are referred to the paper published by Hegde et al., 2018. Distinct data sets that can be analyzed by immunoinformatics approaches are presented in Figure 3. Immunoinformatics and some other branches of bioinformatics are mentioned in the pyramid of Figure 1 and could be applied to analyze the mentioned upcoming data. Undoubtedly, many bioinformatics analyses that are required to be used by bio-productive and research institutes can be transferred to the immunoinformatics research area.

Immunoinformatics uses predictive tools for a large number of immuno-biotechnology processes and/or immunomics to make a variety of vaccines, kits, and biological products applicable for the treatment of infectious diseases, allergies, and cancers. The recognition of toxic compound, ease of tissue transplantations, and MHC genotyping can be reached easier by using bioinformatics. In addition, bioinformatics allows better investigation of the functions and interactions of toll-like receptors (TLRs).

This field of work uses all the lower-level knowledge, such as general bioinformatics, structural bioinformatics, phylogeny, population genetics, molecular dynamics, molecular quantum, systemic biology, protein and peptide engineering, viral/bacterial/parasitic bioinformatics, and NGS/RNA-seq/microarray data analysis of immune genes.

Moreover, novel system immunology approaches have reconstructed new attitudes toward vaccines, adjuvants and immune functions or pathways. These attitudes can open the way to find modern approaches for fighting against infectious and non-infectious diseases, which are not treatable by traditional therapeutic practices (Nakaya et al., 2016; Fong et al., 2018).One

1.1 Fields of Interest

A) Vaccine and Kit. A-1. Immunoinformatic in producing classical vaccines

In the case of production, research, and technology, the current applications of bioinformatics could be summarized as follow:

- Epitope prediction, epitope selection, the evaluation of protein/peptides sequences, immunogenicity/ antigenicity, and the prediction of the potential effects of different factors on immunogenicity could be achieved. Furthermore, we can calculate the related immunogenicity and physico-chemical characteristics, such as the prediction of glycosylation, phosphorylation, structural conformations, half-life, and the stability of protein/peptide by these tools (Ranjbar et al., 2013; Ranjbar et al., 2015a; Keyvani et al., 2016).

- Assessing the efficacy spectrum of vaccines in the national and international level by in silico approaches.

- The computational estimation of the annual success rate of vaccines against wild-type strains and pathogens with high mortality rates in a country based on the sequencing of isolates.

- Evaluating the potential applications of the current vaccines and their success rates worldwide by virtual bioinformatics studies.

- Immunogenicity improvement, immunogenicity maturing and elevating the spectrum of current vaccines by protein engineering (Koellhoffer et al., 2014; Hegde et al., 2018), and virtual simulation.

- Enhancing the physico-chemical properties of the existing vaccines, such as increasing solubility, preventing accumulation, raising protein half-life, and promoting temperature stability.

- Predicting the performance of a protein vaccine under various acidic-basic, temperature, and pressure conditions using molecular simulation techniques.

- Selecting the most possible powerful vaccine strain with a broader spectrum and higher immunogenicity as a vaccine candidate strain.

- Cartography for viruses, such as influenza virus (Cai et al., 2011).

- Improving expression, optimization, and functions of therapeutic/diagnostics/vaccine recombinant proteins.

- Investigating or predicting the virulence and immunogenicity of potential isolates virtually for using as vaccines or comparing with other isolates.

- In terms of toxoid vaccines, including Enterotoxaemia and DTP (i.e., Diphtheria, Tetanus, and Pertussis), bioinformatics tools can be utilized to select the immunogenic segments of these proteins. As a result, the costs and side effects of producing toxin proteins are diminished and the production procedure is facilitated in large scale. Moreover, these toxoid vaccines can be used separately after protein/peptide engineering.

Using these methods, several toxins from different organisms or strains could be fused together to make a polyvalent vaccine. These in silico methods reduce the need for bacterial culture, especially for the ones that not grow on common culture media, have a late and hard growing pattern, and are harmful to human.

- Creating and developing a database of vaccine data and other imported vaccines for easier and more comprehensive access to the details of products.

- Quality control and the assessment of safety, potency, and allergenicity. Furthermore, preventing the autoimmunity of vaccines and manufactured products with the nature of a protein/peptide/medicine and the virtual evaluation of products toxicity are among the applications of novel methods (Dimitrov et al., 2013; Ranjbar et al., 2013; McGarvey et al., 2014).

It should be noted that all these areas are applicable for designing and producing a novel generation of vaccines in institutes and laboratories.

A.2. Immunoinformatics of Vaccines and/or Vaccinomics: New Vaccine Generations

Recombinant vaccines and/or DNA vaccines can be categorized as polytopic vaccines (other names: polyepitopic, epitopic, or fusion peptides), mosaic vaccines, peptide vaccines (based on the prediction of servers on virtual screening or docking), computationally optimized broadly reactive antigen(s) (COBRA)-based vaccines, and evolutionary vaccine

design system (Ranjbar et al., 2015b; Carter et al., 2017; Krammer, 2017; Wong et al., 2017a).

Using bioinformatics, the new generation of vaccines can be produced with a wide variety of intelligent manipulations. It is possible to utilize computational tools during the designing procedure of vaccines. The steps for rational in silico design (Ranjbar et al., 2015b), especially for polytopic vaccines could be described as follow (example 1):

1. Selecting and retrieving sequences (nucleotide or protein) of vaccine strain(s) from general and specific databases. Studying the variations and virulence of isolates through various bioinformatics tools and specific phylogenetic related analyses.
2. Understanding the genetic polymorphism or allele frequencies of MHC class I and class II in the target population of humans and animals.
3. Predicting the epitopes for cytotoxic and helper T lymphocytes using special immunoinformatics tools with different consensus algorithms and methods. Diverse immunoinformatics tools can be used depending on the type or design of the vaccine and the application of epitopes.
4. Predicting the linear/spatial/discontinues immunogenic regions of proteins for B lymphocytes as humoral immune stimulants. Moreover, the exposure of the protein to humoral immune response and the location of the protein in the organism (i.e., membrane or secreted) should be taken into consideration.
5. Using experimentally pre-approved epitopes and peptides along with specific and general immunoinformatics databases.
6. Predicting post-translational modifications (PTMs), namely glycosylation and phosphorylation followed by the evaluation of spatial structures of immunogens.
7. Joining of epitopes and immunogenetic domains to each other in different patterns to construct novel vaccine structures. Afterwards, assessing the physical properties of the designed structure and simulating the functionality in vitro and in vivo.
8. Final checking of designed vaccine constructs and evaluating the PTMs. Subsequently, optimizing the construct and increasing the expression in different hosts by codon usage and CG percentage optimizing. Inserting restriction sequence sites for restriction enzymes (RE) into the ends of designed gene/primers. Selecting the expression vectors, adding tags, and justifying the start and end codons in addition to the restriction sites for unusual RE to avoid unwanted problems during expression.
9. Adding non-biological and biological adjuvants, such as fimbria, flagella, heat shock protein (HSP), mycobacterium compartments, and toxins. Inserting signaling sequences, enhancement sequences, innate immunity stimulants, and cytokines to the recombinant construct.
10. Improving the designed construct to elevate solubility, temperature stability, and coverage spectrum in silico. Furthermore, to enhance the prevention from protein accumulation, selecting binding carriers, and reducing degradation rate during the time.
11. Selecting new vaccine candidates (e.g., the methods followed for Brucella and Flavivirus) along with discovering and analyzing the vaccine administration routes. Analyzing the intracellular networks in confronting infectious organisms through system biology methods as well as the prediction of a possible immune protein among the proteins of organisms without laboratory work can be valuable.

In terms of designing and engineering diagnostic kit, the stages are very similar to that of designing the lymphocyte-B stimulant vaccine just with a few minor changes.

The Second case of vaccine designing strategy by bioinformatics approaches which will be introduced here is known as COBRA system. This technique enables us to elicit potent, durable, broadly reactive specific antibody responses as a universal vaccine in highly variable viruses, including influenza, HIV, and HCV (Giles and Ross, 2011; Carter et al., 2017; Wong et al., 2017b).

The COBRA antigens are generated by three ways, namely center-of-the-tree (COT), ancestral (i.e., the most recent common ancestor), and consensus (i.e., the most common amino acid found at each position (Giles and Ross, 2011). The COT and ancestral methods predict an actual sequence, which may have existed in the past. On the other hand, the consensus method is related to the sequences present in the circulating isolates (Giles and Ross, 2011). The general steps of COBRA design are summarized her. It should be noted that this is one of the typical professional COBRA designs and may vary to some extent in different studies/cases.

1. Data gathering and categorization based on the year (or season) of collection or outbreak (especially in influenza virus), genotypes (or serotypes), geography of epidemiology, and species from the databases and related laboratory or personal data. Translating the nucleotide sequences to protein sequences if needed. Avoidance from sampling bias should be taken into consideration.

Note that following this step some researchers jump to step 4, especially in case they want to separate and group the sequences according to the year or outbreaks and not based on similarity.

2. Optional step: editing (gaps, short sequences, and missing amino acids) and trimming the sequences followed by removing the signal peptides, transmembrane regions, and cytoplasmic tails to reach ectodomains.

3. Constructing phylogenetic trees and similarity or dissimilarity matrices or using other automated clustering algorithms for the interpretation of tree and matrices characterized by clade/sub-clade groupings and saving these groups in separate datasets. As mentioned previously, in some methods of COBRA design, this step could be step 2 and the final step of design for COT and ancestral. Sometimes phylogenetic method could be used as the first step of design for solving data bias problems.

4. Alignments for each dataset and achieving consensus sequences by applying different criteria in alignment, such as amino acid tolerable substations and threshold frequency for inclusion in the consensus sequence(s).

5. The alignment of consensus sequences with each other to achieve secondary, tertiary, and so on (if needed) consensus sequences. This may be known as the first consensus layer, second consensus layer, third consensus layer, and final consensus.

6. The insightful engineering of selected secondary or tertiary consensus sequences to achieve more broadly covering strains.

7. Modeling the tertiary structure of candidate(s) consensus engineered sequence(s) and checking and validating of the structure.

8. Optional step: the engineering of physico-chemical properties.

9. Blasting against the database of sequences for comparing the similarity to previously reported sequences or to find whether it is a unique sequence not isolated from the environment.

10. Reverse translation and optimization to nucleotide sequence for cloning and expression.

B- Immunoinformatics in the Engineering of Antibodies (Informatics of Antibodies). There are several antibodies of animal origin or synthetic repertoires that are used for the diagnosis and treatment of diseases in clinics and to a greater extent in research (Baran et al., 2017). Therefore, the designing and engineering of antibodies could help maintain human and animal health in a suitable status and assists to fight against infectious and non-infectious diseases. In addition, it can overcome laboratory and facility limitations and earn economical profits (Baran et al., 2017).

Recently, NGS of antibody display repertoires has been used to assess library diversity, clonal enrichment, and affinity maturation. The NGS paves the way to understand the special characteristics of antibodies. Bioinformatics allows refining and improving the

current production of antibodies in institutes and the production of new antibodies applicable in therapeutics serum preparation, serum purification, and kit manufacturing.

Here we present some applications of bioinformatics in antibody designing and engineering:

- Concerning current traditional antibodies, the protein sequencing can be performed leading to the determination of antibodies structures and structural optimization to produce the best possible production.
- Numbering schemes, the analysis of antigenic protein areas in antibody sequences/structures, in addition to defining complementarity-determining regions and scaffold regions to document the type of antibodies produced by an institution against infectious diseases can ultimately reduce costs and time remarkably.

Increasing the affinity of an antibody to antigen targets is achieved through artificial intelligence, efficient mutations in the loops, modeling, optimization, docking, and ultimately molecular dynamics (Rashidieh et al., 2015; Farhadi et al., 2017; Tiller et al., 2017; Vivcharuk et al., 2017). These in silico predictions can elevate efficiency, neutralization effects, sensitivity, and accuracy.

- Solving the structural defects by the special engineering of antibodies in terms of solubility, aggregation, and formation of antibody mass.
- Screening the antibodies of institutes/companies against the peptides/proteins of scorpion and snake venom or infectious organisms toxins to determine the specific neutralizing function of the antibody.
- In silico humanizing or the animalization of antibodies in order to reduce the unwanted immunological reactions after injection.
- Solving the complications of cross-reactive antibodies (i.e., the antibodies that react with a variety of similar proteins) in diagnostics kits. Antibodies can be specialized for an organism or a peptide or get manipulated to omit the cross-reactivity.
- Obviously, the results of virtual design and engineering of antibodies or the optimization of antibodies carried out by bioinformatics can be used in enzyme-linked immunosorbent assay kits and rapid test designs.

C- New Adjuvants with Improved Characteristics and Interactions. In modern vaccinology and immunization, attentions gradually turned from focusing only on the antigen-specific receptors of T and B cells to the simultaneous stimulation of a set of non-polymorphic germline-encoded receptors known as pattern recognition receptors (PRRs) and molecules (cytokines) that play important roles in innate immunity (Suresh and Mosser, 2013; Toussi and Massari, 2014). The mentioned receptors and molecules are responsible for the primary defenses against invading microorganisms. Nowadays, a variety of these immunostimulatory molecules are designed and formulated as bio-adjuvants in combination with poor immunogenic DNA and subunit vaccines to enhance immune responses against a target antigen or pathogen (Wiley and Raman, 2017). The benefits of bio-adjuvants include the inducing innate immune system (more signaling, cytokine secretion, receptor expressions, and proliferation), decreasing vaccine costs due to higher antigenicity and lower dose usage, better antigenic distribution and release, *immunomodulatory* effects, the stimulation of more specific antibody secretion and response, better stimulation of B and T cells and longer immune response memory (Christensen, 2016). Computationally designed (bio-) adjuvants in most cases were related to the engineering or modification of the TLRs (e.g., TLR4, TLR5, TLR7, and TLR9) (Suresh and Mosser, 2013; Toussi and Massari, 2014; Farhadi et al., 2016) or the agonists of TLRs and their biological pathways. These agonists entail pathogen-associated molecular patterns (PAMPs) and non-pathogen, such as cytokines, interleukins, interferons, lymphokines, and tachykinin family (interleukin inductor, namely hemokinin-1 and Mx proteins, and tumor necrosis factor) (Suresh and Mosser, 2013; Toussi and Massari, 2014; Shahsavandi et al., 2015; Nakaya et al., 2016).

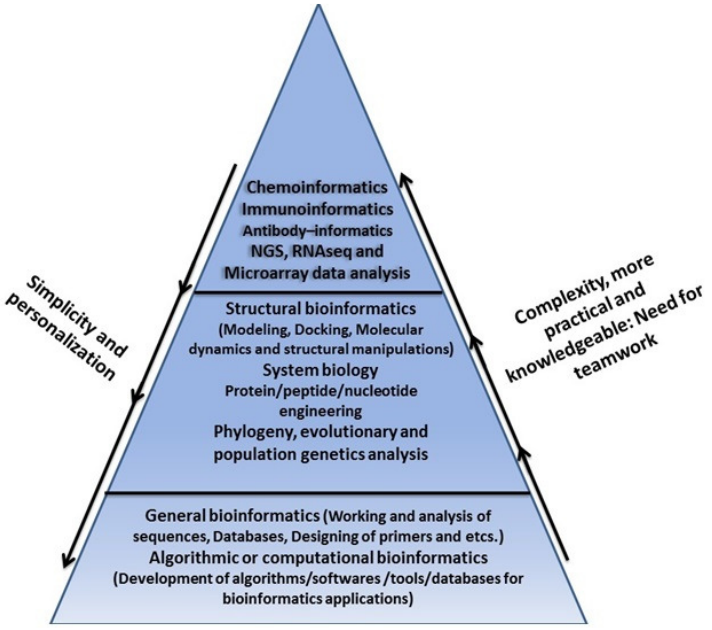

Figure 1. Levels defined for the study and application of bioinformatics in the bio-research and -production centers

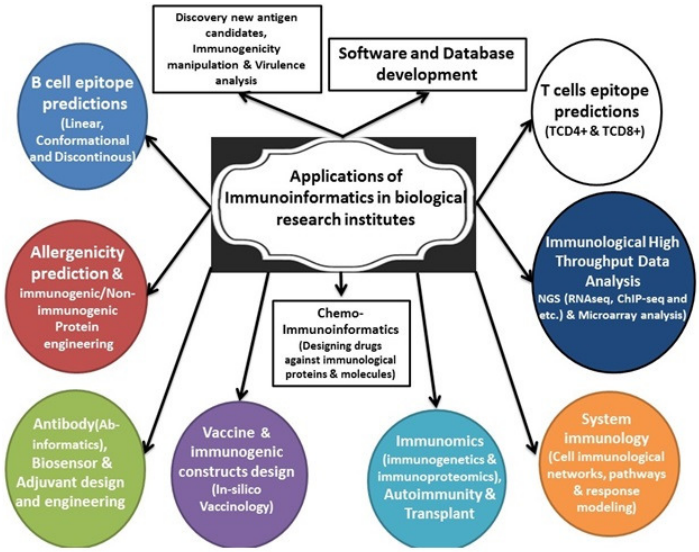

Figure 2. Different applications of computational immunology (immunoinformatics)

Moreover, the characterization and development of the models for network interactions, as well as the gene regulation of TLRs and the corresponding cytokines in the body against PAMPs are among the progressive and attractive fields of immunoinformatics (Castiglione et al., 2016; Paricharak et al., 2018). The correct selection of an innate immune stimulator adjuvant and delivery system is the second major challenge in terms of epitopes and other types of vaccines designed by immunoinformatics.

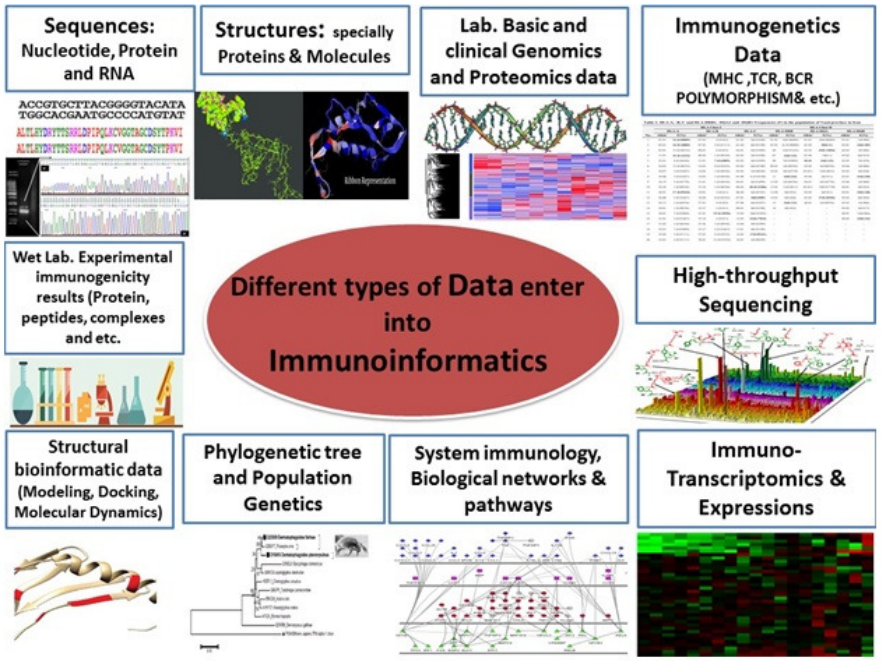

Figure 3. Different types of data that can be used as input for analysis via immunoinformatics. Data from various sources can be introduced to immunoinformatics-based tools to be analyzed and interpreted

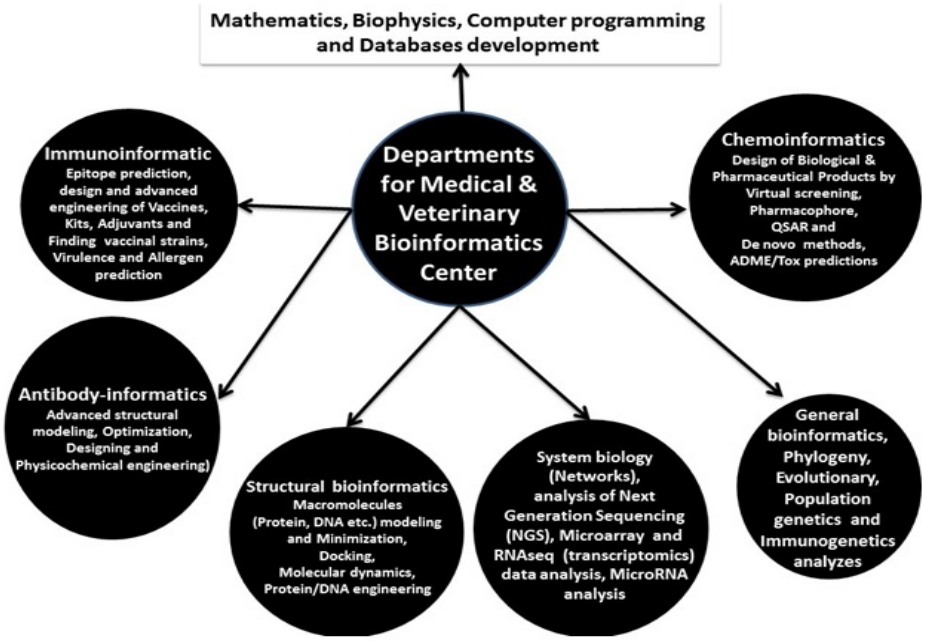

Figure 4. Proposed departments and their responsibilities for typical bio-production and research institutes

It should be noted that most of the chemical adjuvants have shown some degrees of toxicity and side effects for human and animals. The function and interactions of biologic protein-based adjuvants, such as parts of toxins and bacterial cells, fimbria, flagellum, and HSP could be clarified by modeling, truncating, modifying,

or tagging using bioinformatics methods to simulate their activity under different in vivo conditions.

These pre-production issues significantly diminish the costs, errors, time, and in some cases the need for laboratory and experimental work. In addition, it is possible to manipulate or fragment the adjuvant and harvest the desired areas of response with body receptors via bioinformatics. Furthermore, this product or a selected piece of that is used to attach vaccine constructs and proteins for higher immune response reducing the cost and side effects, as well as the volume of vaccine injection. It is possible to select new adjuvant candidate among a large number of adjuvants through modeling and docking methods with TLRs and nucleotide-binding oligomerization domain-like (NOD-like) receptors and eliminating additional pieces. Moreover, one can predict the adjuvant strength of different biological materials before they are used together. Non-biological adjuvants, including aluminum salts, oily compounds, and new chemical candidates could be evaluated by docking and dynamic simulation techniques prior to constructing and evaluating in the laboratory.

D- Immunoinformatics Evaluation of Allergenicity, Safety, and Toxicity of Vaccine and Biological Products. This area is systematically related to the duties of the quality assurance department. With the current potentials of bioinformatics, the allergenicity, safety, and toxicology assessments of vaccines and chemical/biological products with protein and non-protein nature could be predicted with high precision before clinical trials. Therefore, some vaccines with definite toxic effect will be eliminated from production. However, these vaccines could be upgraded concerning the potential hazards before manufacturing. In addition to checking the allergenicity of proteins as a vaccine, it is possible to predict recombinant food proteins or proteins obtained from various sources of hygiene. Moreover, bioinformatics tools can identify the allergen proteins of infectious organisms, which may not be used in the vaccine. In addition, it is possible to evaluate the toxicity of materials virtually before being used and grouped.

E. Characterizing the Allele Frequency of MHC Class I and Class II in Humans and Animals. The population genetics and immunogenetics analysis of MHC sequence/traits and other genes in hosts or organisms could be applied to determine the reason for the difference in the level of the immune response or lack of response (non-responder human or animals) to the infectious diseases and vaccines (Nikbin et al., 2017). Recognizing the alleles and populations susceptible or resistant to diseases, populations with vaccine priority, designing vaccines according to the target susceptible or frequent population genetics/alleles (personalized medicine or herd medicine in animal breeding), and maximizing the immune responses and protections (considering host-pathogen interactions) are among the novel approaches in the recent researches. In other words, in personalized medicine, the personal-genomics data of immunological and non-immunological related genes derived from sequencing may prepare a link between genotype and phenotype leading to an insight into the treatment of the disease or the refinement of vaccination strategies (Fernald et al., 2011). In the field of pharmacogenomics, there is a relationship between genotype and specific disease treatment. In traditional medicine, only pathological conditions and clinical observations are considered for the evaluation and adjustment of the treatment process. Consequently, bioinformatics usage can ultimately reduce the costs, duration of treatment, and side effects for the patients. Furthermore, vaccinations may result in poor success in some vaccinated human and animal populations. Following the establishment of the link between the genetic and immune responses of human and livestock, the protective vaccine response can be modified by changing the vaccine contents for the special populations.

2. General Bioinformatics. The characterization of protein and nucleotide sequences, alignment methods, BLAST search, use of primary and secondary

databases, designing, and checking primers or probes for different PCR and real-time protocols are among the issues addressed in general bioinformatics. The mentioned applications are important in the diagnostic procedures, production departments, molecular-epidemiological studies, and genetic investigations (genotyping). Furthermore, this science is considered as basic studies for genomic and proteomic identification and the characterization of infectious pathogens in the production of vaccines and kits. This is obtained by protein or nucleotide sequencing, alignment, and blast results for the concepts defined in parts A.1 and A.2.

3. Phylogeny and Evolutionary Studies for Vaccine and Quitting Purposes. The basic epidemiological studies of genotypes, characterizing similarities, specifying and analyzing the root of isolates obtained from viral (Dadmanesh et al., 2015), bacterial, and parasitic infectious agents of clinical samples are useful for further investigations. In addition, the data in databases regarding the evaluation of genetic properties, mutations, changes (Malekan et al., 2016), evolution, phylogenic clusters, and implications help for future decisions. The interpretation of situations is crucial for vaccine production institutes or companies. Furthermore, the information obtained by these methods is of value for further planning concerning the need for vaccination, selection of vaccine strains, or proteins especially in COBRA system, and the prediction of vaccine coverage around the region and world.

4. Chemoinformatics. Chemoinformatics is a branch of bioinformatics in which chemical reagents, products (non-protein, nucleic acid, and small molecules), and non-biological (chemical) adjuvants are investigated (Leelananda and Lindert, 2016; Ranjbar et al., 2016a; Usha et al., 2017). The major components of chemoinformatics involve the modification, designing, discovery, and screening of new medications. Moreover, the medicines are optimized for diverse infectious and non-infectious diseases from different sources using virtual screening methods, quantitative structure-activity relationship (QSAR), pharmacophore, and fragment-based design. Non-vaccine products, kits, and antibodies can be categorized in this area (Leelananda and Lindert, 2016). Toxicity test and drug-likeness tests may be carried out utilizing the chemoinformatics tools (Leelananda and Lindert, 2016; Ranjbar et al., 2016b; Srivastava and Tiwari, 2017).

5. Supporting Bio-production and Research Institutes. Undoubtedly, a successful and strong bioinformatics center can meet the requirements of a large research institute with biological and pharmaceutical products. In this regard, the structure demonstrated in Figure 4 is proposed as the most up-to-date and ideal model with seven departments (workrooms) and the responsibilities of all department are mentioned separately.

DISCUSSION

Bioinformatics science is undergoing progress and development with unprecedented advances in computer technology. As a result, researchers in the field of biology, especially the design and manufacture of medicines, vaccines, biological products, diagnosis, and industry should be up-to-date in terms of this field. Moreover, their knowledge of bioinformatics should be expanded day by day and they should use this science in a powerful manner for manufacturing. Obviously, the long-term usage of the undeveloped methods in designing and production will cause inability to compete with foreign products in undeveloped countries and will not be possible to reduce the critical problems, costs, and time of production processes. Consequently, the system will not have good performance and efficiency. Furthermore, the emerging of CRISPER-CAS, deep sequencing as an NGS, RNA-seq, and microarray with the advantage of rapid growing genomic and proteomic datasets and complex bioinformatics computation in their output results process have led to a more sophisticated and wider view in applications of this science in vaccinology. In addition, the fast raising and accumulation of genomic and proteomic sequencing data have created new opportunities and challenges for the growth of science

parts, such as personalized medicine by bioinformatic potentials in the diverse fields of providing databases, tools, and analytic programs (Fernald et al., 2011). Personalized medicine can be widely defined as an ultra-structured and high-quality model for healthcare that is predictive, personal, preventive, and collaborative (Overby and Tarczy-Hornoch, 2013). Some important goals of personalized medicine achieved by bioinformatics encompass: 1) processing and analysis of the results of increasing voluminous biomedical (genomic or proteomic) data obtained by high-throughput experimental technologies, 2) interpreting the functional and structural effects of genomic or proteomic variations, 3) the integrating and refinements of systems data, 4) defining the relationship between complex genetic data and corresponding phenotypes, and 5) providing a basis for the translation of findings into real medical practice and clinics. Therefore, the development of biology in a steady and rapid state is not possible without the use of bioinformatics. In the present study, we tried to discuss rationally and realistically the different dimensions of this science for use in the various parts of a large research and bio-production institutes.

Ethics

We hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest

The authors declare that they have no conflict of interest.

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