



The Molecular Biology/Immunology Paradigm Extended to Bioinformatics

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Research progress in any given scientific discipline often relies on the applications of new techniques or the development of new paradigms in related disciplines. Biology, and more specifically immunology, is not an exception to this phenomenon and has historically been particularly driven forward in this manner. Probably one of the best examples of such effects on the life sciences would be the pervasion of molecular biology methodologies and discoveries throughout most biological sub-disciplines deriving from the discovery of the structure of DNA made in the early 1950's. At that time DNA structure was a great mystery for the biologists. Prior to the work of Rosalind Franklin, James Watson and Francis Crick, biologists simply did not have the proper tools to solve DNA's structure regardless of their general understanding of the importance of doing so. The structure of the DNA molecule was finally solved by applying a relatively young physics technique, X-ray diffraction [1,2]. The seminal paper on DNA structure published by Watson and Crick [3] provided answers for many questions that had been historically tantalizing, yet irresolvable, to biologists. That paper might be considered as the origin of what was to become the modern molecular biology revolution and the basis for the development of many modern DNA-based biological technologies that have strongly influenced and advanced our understandings in all aspects of current life sciences. Here we briefly examine the development of molecular biology and its implication to the research of immunology, and provide our perspective on the potential role of bioinformatics as a supporting discipline for the future development of immunology.

As is true for so many of the sub-disciplines of the biological sciences, the field of immunology has experienced a revolution since the publication of Watson and Crick's discovery [3]. The tangential discoveries relating to DNA function and its manipulation evolved rapidly as a result of a molecular understanding of the DNA molecule, and quickly spread throughout the life sciences to begin an era best described as a molecular biology revolution. Throughout the 1970's, 1980's, and 1990's laboratories studying the genetics of immunology across the world were abuzz with routine conversations about restriction digests [4], southern blotting [5], molecular cloning [6], DNA library construction and DNA sequencing [7]. In 1990, Mullis [8] published the development of the Polymerase Chain Reaction (PCR) method that generated a whole new era of discovery across all imaginable diverse areas of inquiry, ranging from forensics to ancient DNA work. During this period anyone working in disciplines utilizing these new molecular methodologies found it necessary to be well versed in laboratory biochemistry techniques. In fact, often the primary effort and emphasis in training and research were focused on mastering competency and technique in methodologies which might then be applied to research questions. Most molecular biology research programs depended upon each laboratory individually producing their own materials and reagents from basic ingredients, as well as developing individual experimental conditions that proved successful in their hands. In a time where simply isolating a gene fragment and producing a complete DNA sequence for it was a massive undertaking [9], that was heavily dependent upon excellent technique, such emphasis is easily understood. Since then subsequent developments in technologies, methodologies, and commercial protocol standardization have been made to facilitate research that relies on molecular biology techniques.

Today immunology researchers can successfully study virtually any question utilizing standard pre-canned laboratory protocols based in kit form available from innumerable commercial suppliers, without the burden of mastering basic laboratory techniques, but rather can be focused directly on their research questions. No longer is the emphasis among laboratory discussions centered on bench methodologies, rather immunology as a field is poised to benefit tremendously from the newly emergent standardized methodologies. We can use the history of the contribution of molecular biology techniques to project that of another emerging biological science, bioinformatics, to immunology.

The potential for bioinformatics applications in the greater field of immunology is indisputable. Bioinformatic [10] and phylogenomic [11] methods have been, and are being, used for the development of new vaccines and immunopharmaceuticals [12], and the mapping of epitopes [13]. These tools are being used toward the development of novel therapies, for the utilization of immune systems models, and to help guide experimental investigations. A primary advantage of the approach is how much more quickly candidate hypotheses can be generated and then tested in the lab, versus the traditional fully bench-based approach. Two recent texts, Bioinformatics for Immunomics [14] and Immunological Bioinformatics [15], and dedicated workshops at ongoing conferences, such as the Second Immunoinformatics and Computational Immunology Workshop at the ACM International Conference on Bioinformatics and Computational Biology conference (<http://www.cse.buffalo.edu/ACM-BCB2011/>) attest to the relevancy of the issue.

Herein we argue for the importance of the development of dedicated immunoinformatics Web portals. Bioinformatics has necessarily become an incredibly valuable research and analysis tool for all of molecular biology, yet access to these tools is often a cumbersome and complicated process. In fact, often bioinformaticians are an integral part of research teams, as this specialty is routinely perceived of as being beyond the grasp of many bench scientists. However, both dedicated and generalized, easy-to-use Web portals are available for many sub-disciplines of molecular biology. Web portals expedite the task at hand by providing a familiar Web browser-based graphical user interface, and by obviating the need to install complicated software on a user's personal computer. The preponderance of Web genome browsers attests to the popularity of this approach in the field of comparative genomics, such as those at the University of California at Santa Cruz (<http://genome.ucsc.edu/>), at ENSEMBL (<http://www.ensembl.org/>).

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ensembl.org/), and at the Lawrence Livermore National Laboratory (<http://www.dcode.org/>). Additionally, many species-specific relational databases and associated software are available over the Web for researchers interested in analyses of particular model organisms. These include the pioneering *C. elegans* ACeDB (<http://www.acedb.org/>), FlyBase (<http://flybase.bio.indiana.edu/>), and the *Saccharomyces* Genome Database (<http://www.yeastgenome.org/>). Furthermore, a few generalized bioinformatic Web portals, such as that at the University of Oslo (<https://www.biportal.uio.no/>), and the Biology Workbench at the San Diego Supercomputer Center (<http://workbench.sdsc.edu/>) provide a wide range of tools for those with the knowledge to use them, although both sites require free user registration. Some major suites of bioinformatics tools, such as the EMBOSS package [16], even provide open source Web installations that can be installed on dedicated servers (<http://wemboss.sourceforge.net/>), given sufficient in-house skill and computational resources. Major sequence database centers also offer a plethora of Web-based analysis tools (e.g. GenBank at the National Center for Biotechnology Information [<http://www.ncbi.nlm.nih.gov/>], the European Molecular Biology Laboratory [<http://www.embl-heidelberg.de/>], the Swiss Institute of Bioinformatics at ExPASy [<http://www.expasy.org/>], and the Universal Protein Resource [<http://www.uniprot.org/>]); however, a researcher is forced to wade through tons of data that may or may not be relevant to the question at hand, not to mention figure out which analyses are most appropriate, when using these resources. And regardless of resource availability, a lack of perceived workflow continuity and seamlessness contribute to the general sense of intimidation that many users experience when beginning to explore their use.

Therefore, we feel the development of devoted Web portals tuned to the needs of immunology; with access to the specialized databases used by immunologists [17,18]; with easy-to-follow data-flow pipelines, depending on the researchers' objectives; to be of prime importance. Only when bench immunologists surmount their reluctance to use these tools, will the field be able to accomplish the quantum level leaps possible with bioinformatic and phylogenomic approaches. The analogy to commercial, easy-to-use molecular biology kits is striking. Once the emphasis is changed from painstaking methodology, to application, great things can happen. Some research groups are beginning to assemble Web sites that provide immunoinformatic tools, such as the Immunological Bioinformatics group at the Center for Biological Sequence Analysis (<http://www.cbs.dtu.dk/researchgroups/immunobioinf.php>), but the tools and databases are not connected in the seamless manner that would make more immunologists eager to embrace them. Finally, we applaud an extremely recent Web portal that is attempting to accomplish exactly the sort of connected analyses we suggest. ImmPort (<https://www.immport.org/>) is an immunology database and analysis portal that provides a wide range of visualization, collaboration, and analysis tools, all supported by species-specific relational databases of immunologically relevant biomolecules, with a data-pipeline approach. It is doing exactly what we argue for. Our only suggestion is to lessen its initial intimidation factor — all the parts are there — but researchers may not know how or where to start.

Recently we reported the importance of good instructional resources in education and progress of research [19]. Teaching and applying bioinformatics will be essential components in education and research of immunologists as we suggest in this article. We expect that the Journal of Clinical and Cellular Immunology will be an excellent medium to poster the ideas because of its unique features: open access and website-translation of published paper to more than 50 languages, which will expand readership far exceeding that of the traditional journals.

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