Editorial for Infectious Diseases - Drug Targets (in silico issue)

Alexandre De Brevern

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(*in silico* special issue)

Alexandre G. de Brevern

INSERM UMR-S 665, Dynamique des Structures et Interactions des Macromolécules Biologiques (DSIMB), Université Paris Diderot – Paris 7, Institut National de la Transfusion Sanguine (INTS), 6, rue Alexandre Cabanel, 75739 Paris 15, France.

Coming from Crimea, the *Black Death* spread to Western Europe and North Africa during the 1340s. From 1346 to 1352, the plague killed an estimated 25-40% of Europeans of all age-groups [1] , *i.e*. 30 to 60% of Europe population. One of the earliest and most widely accepted explanations was that God was punishing humanity for their sins. One remedy for the curse was to do penitence. Thus in 1348 there rapidly arose a mass movement of flagellation [2]. In fact flagellation could not really help against such threat. The *Black Death* or *Bubonic plague* is caused by *Yersinia pestis*, a Eubacteria discovered in 1894 by Alexandre Yersin. It is transmitted by the bite of the flea *Xenopsylla cheopsis*. This flea lives by feeding the blood of many species besides man but its most preferred relationship is with the black rat (*Rattus rattus*). Fossilized remains of the plague flea have been found in large numbers in Amarna, Egypt [3, 4] about 1350 BC, and thus could be directly linked to the events described in the Book of *Samuel* [5, 6]. During the epidemic of Bubonic plague in London in 1665-1666, the known treatments were made use of, *e.g*. the so-famous Theriac or Venice Treacle which is used from the time of ancient Rome as a remedy against poison [7]. Since then, more specialized and novel treatments have been developed. However, since the characterization of *Yersinia pestis*, numerous drugs have been developed against it, *e.g*. gentamicin or doxycycline [8].. These researches had been carried out using more elaborated biochemical, biophysical and biological approaches.

However, with the explosion of genomic sequencing -815 complete genomes are made available for the scientific community (as of January 2009) [9]- complementing the

experimental information with the increasing power of computational facilities has given new opportunities to fight against infectious diseases and to identify pertinent drug targets with novel methodologies. The *in silico* approaches have been playing a prominent role in this research area during the last decade. This special issue presents the various views about the different *in silico* approaches by some of the best international research teams. Pr. Sowdhamini's group has compared different genomes from a group of enterobacteric pathogens known to share similar genomic content but having diverse host specificities and distinct disease symptoms [10]. The detailed cross-genome analysis of these subspecies provides an understanding of the diversity and unique attributes defined in the individual *Salmonella enterica* genomes. Pr. Srinivasan's group develops new approaches dedicated to *Plasmodium falciparum analysis*, the most important causative agent of malaria [11]. The latter has a very specific genome and thus needs to be studied thoroughly and specifically. They present examples of protein-protein interactions across human and *P. falciparum*, potentially happening during pathogenesis. Pr. Deléage's work deals with Hepatitis C Virus (HCV). They have developed the European Hepatitis C Virus Database (euHCVdb, http://euhcvdb.ibcp.fr/), a collection of relevant structural models that can help in drug design , with strategies for combating resistance to drug treatment and to have a better understanding structural biology of the HCV [12]. They present some examples of the use of the database.

Within this new research field, an important axis of research concerns the transmembrane proteins, they represent about ~25% of proteins coded by genomes. Moreover, they serve as targets for about 2/3rd of the marketed drugs out of which 50% specifically target a GPCR [13]. As these proteins are embedded in a lipid membrane that constitutes a very specific environment, they represent only about ~1% of all the available structures, owing to the difficulties associated with their crystallization [14]. . Thus alternative approaches are required to obtain structural information. Consequently methods aiming at constructing 3D structural models are becoming an important area of research, for understanding biological mechanisms and interactions [15]. Wang and Duan summarizes the recent computational researches done on CC-chemokine receptor 5 (CCR5), an essential co-receptor for HIV entry into the cells and show how the recently solved GPCR structures would provide new insights into the modeling of CCR5-inhibitor binding [16]. Pr. Etchebest's group work focus on an unorthodox chemokine receptor, named DARC, which binds chemokines of both CC and CXC classes and do not couple to G proteins and activate their signaling pathways. DARC had also been associated to cancer progression, numerous inflammatory diseases, and possibly

to AIDS. We show our recent development of the construction and analyzes of structural models of DARC [17]. We underline the difficulty to propose pertinent structural models of transmembrane protein using comparative modeling process, and also highlight the use of other dedicated approaches like the analysis using Protein Blocks [18-20]. Finally, we present the recent development of protein – protein docking carried out between DARC structural models and CXCL-8 structures using an innovative hierarchal search procedure, based on both rigid and flexible docking [21].

Dealing with *Plasmodium falciparum*, Pr. Louw and co-workers describes the peculiarities of malaria proteins and various *in silico* strategies to select and allow descriptions of the molecular structures of potential drug target candidates. They also present the subsequent rational approaches that can be used for *drug design*. The uniqueness of this organism makes the *in silico* approaches for the specific design of an inhibitor drugs invaluable and as an economic and rational alternative to chemical library screening [22]. Following the same approach, Murphy and Brown focus on another major global healthcare problem: the resurgence of drug resistant *Mycobacterium tuberculosis*. The identification of genes essential for the bacterium in its dormancy phase infections, is a key strategy in the development of new anti-*Mycobacterium tuberculosis* therapeutics. They present the applications of advanced computational analyses to predict potential drug targets and also highlight the difficulties associated with translating *in silico* predictions to effective clinical therapies [23]. Dr. Watowich's group works on the Dengue virus, one of the most important global pathogens which represent a global pandemic. The resurgence of Dengue virus since the 70's has occurred after the cessation of mosquito control measures. The authors summarize the biology of this *Flaviviridae* and especially its different proteins. They highlight the possibility of utilizing Dengue virus nonstructural proteins as potential drug targets and also give an extensive overview of computational methods for drug discovery like docking, HTS or ligand compound database [24].

To conclude this special issue, we present three papers that deal with impressive novel methodological developments. The first one is by Dr. Doppelt-Azeroual and co-workers. As protein structures are directly associated with their functions that often involves the binding of other proteins, ligands, nucleic acids or other compounds, the knowledge of 3D structures can explain biological mechanisms and help to design drugs. They have developed MED-SuMo [25], an efficient method that can compare and detect binding sites. This tool can locate similar regions on macromolecular surfaces, associated to a defined chemical function. In this

review, they present the recent improvements in MED-SuMo and its interest in several applications in biology, *e.g.*, structural superimposition, pocket profiling, drug repurposing and an automated function binding sites classification. A new protocol combines a fragment-based approach and local similarities of protein surfaces [26]. Another one deals with the use of powerful Grid computing in the life science domain. Grid computing is an exciting new technology promising to revolutionize many services already offered by the internet. Grids are defined as a fully distributed, dynamically reconfigurable, scalable and autonomous infrastructure to provide location independent, pervasive, reliable, secure and efficient access to a coordinated set of services encapsulating and virtualizing resource [27]. Dr. Breton and collaborators have explored some innovative *in silico* approaches to better tackle avian flu, taking advantage of the very large computing resources available on international grid infrastructures. Grids are used to study the impact of mutations on the effectiveness of existing drugs against H5N1 and to find potential new leads active on mutated strains [28]. The third one concludes this issue by presenting the difficult problem of text mining. As nowadays, the number of publications has increased tremendously, it has a crucial issue. The solution proposed by Vellay and collaborators are implemented inside Pipeline Pilot [29]. This is a famous application designed to manipulate and analyze huge quantities of data in real time. This approach, known as "data pipelining", uses a data flow framework to describe the processing of data [30]. After presenting the core of the Bibliography Platform protocol, the authors gives a pertinent example of the relevance of their approach. In the context of the neglected disease *Leishmaniasis*, this interface presents an overview allowing a fast understanding of the topic, an appreciation of its growing trend, and an instant identification of the most prolific authors and most popular journals in the disease area [31].

The quality of articles in this special issue depends on the authors who have clearly done a terrific job, and also on those individuals who lend their expertise to review manuscripts. On behalf of myself and the authors of papers published in this issue, I express my sincere thanks and appreciation to the individuals who generously gave their time to review one or more manuscripts. I would also like to thanks people of my team, especially Catherine Etchebest, Agnel Praveen Joseph and Aurélie Bornot for their help.

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