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EDITORIAL

A Brief History of *Biochemical Genetics'* 50 Years and a Reflection About Past and Present Research Directions

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Why Biochemical Genetics

Although scientific knowledge, including an inductive–deductive cycle (Woo et al. 2017) is guided by rational guidelines, and was, in some cases, considered to be based on very strict logical paradigms (Persson 2016), aesthetic, emotional and sociological factors clearly affect the decisions of researchers, particularly during their first years of training (King et al. 2015).

Since my biology student days, biochemistry has been one of the most attractive topics. I became fascinated by the different metabolic pathways, including Krebs and Kalvin cycles, the respiratory chain in the mitochondrion and the electron

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transport chain in the chloroplast (Okie et al. 2016). Earlier still, my interest grew in the genetic code, transcription and translation, the evolution of which is still under debate (Koonin and Novozhilov 2017).

Relevant imprints in my training were also the attention given to the coevolution of different genomes, in the so-called eukaryotic cell, where two or three genomes are present, the latter resulting from a long process of evolution of bacteria and algae (Ramanan et al. 2016) and to the viral infection mechanisms, exemplified by the relatively simple model of the bacteriophage. Curiously, phages are presently viewed as having an important role in bacterial ecology and evolution (Obeng et al. 2016). The different metabolic pathways occurring in different types of bacteria and other prokaryotes, such as sulfur bacteria, methane bacteria, cyanobacteria, and heterotrophic bacteria, among many others, also caused an impact on my interest in the field, the genetic basis and evolution of which are still a fascinating subject (Fani and Fondi 2009), as are their possible implications in more global topics, including climate change (Michaud et al. 2017). During my biology studies in the late 1980s, classical experiments with *Drosophila melanogaster* were still common, en route to all the developments that made it a global model organism in genetics (Attrill et al. 2016). Nevertheless, we also addressed more advanced topics, such as bacterial transformation (Johnston et al. 2014), and the estimation of cross-over rates, with relevant effects on genome evolution and speciation (Korunes and Noor 2017).

Since my student time, many and profound changes and innovations have emerged in the area of biochemical genetics, beginning with the possibility of amplifying specific areas of the genome, with the development of Sanger's dideoxy technique, but leading to the emergence of next-generation sequencing (Heather and Chain 2016), a pyrosequencing technique, the possibility of analyzing entire genomes of large samples of human populations (e.g., Gudbjartsson et al. 2015), and eventually to the single molecule sequencing of entire genomes (e.g., VanBuren et al. 2015). At the same time, the possibility of relating genetic variants with the risk of disease development has recently led to an increase in research devoted to genetic epidemiology. Notably, most of the single-nucleotide variants/polymorphisms, suggested by genome-wide association studies, which provide statistical evidence for increased risk of complex diseases, have been mapped to non-coding regions (Zhang and Lupski 2015).

In this context, being a more numerical ecology-oriented researcher, I began to undertake population genetic studies, using dominant markers such as Random Amplified Polymorphic DNA and Inter Simple Sequence Repeats (e.g., Silva et al. 2011) and, a little time afterwards, initiated work with microsatellites, mostly dedicated to conservation genetics (e.g., Silva et al. 2015). Presently, we are undertaking research in the area of metagenomics. Sequence-based metagenomics can provide unprecedented information on the composition, diversity, and functional capacity of microbial communities (see Culligan and Sleator 2016). Within a European team dedicated to the study of soil microbial diversity and its association with permanent grassland management, we aim to link aboveground and belowground processes, as well as external inputs derived from human management, with soil microbial diversity and ecological services (see BIOINVENT project at http://www.biodiversa.org/972).

A Brief History of *Biochemical Genetics*

Biochemical Genetics was initiated in 1967, and has recently completed its 50th anniversary, which is also about my own age. A total of 3547 articles have been published within 55 volumes and 312 issues (http://www.springer.com/10528). I therefore decided to undertake a condensed but, to my view, meaningful analysis of the evolution of the topics covered in the journal since its foundation, the time when I was a biology student and the beginnings of the twenty-first century. To that effect, I have sampled more than 400 papers published around 1967, 1977, 1987, 1997, 2007 and 2017 (Fig. 1).

The first two decades of *Biochemical Genetics* were clearly dominated by research addressing proteins, in particular enzymes, and more specifically isozymes or allozymes. The study of isozymes contributed to our understanding of the variation of enzymatic activity in different organs and along successive stages of ontogenetic development. It was also used to develop population genetic markers, providing considerable insight into genetic diversity, population genetic structure, gene flow, and differentiation between populations of the same species and of closely related taxa. These studies mostly included electrophoretic techniques, but also less

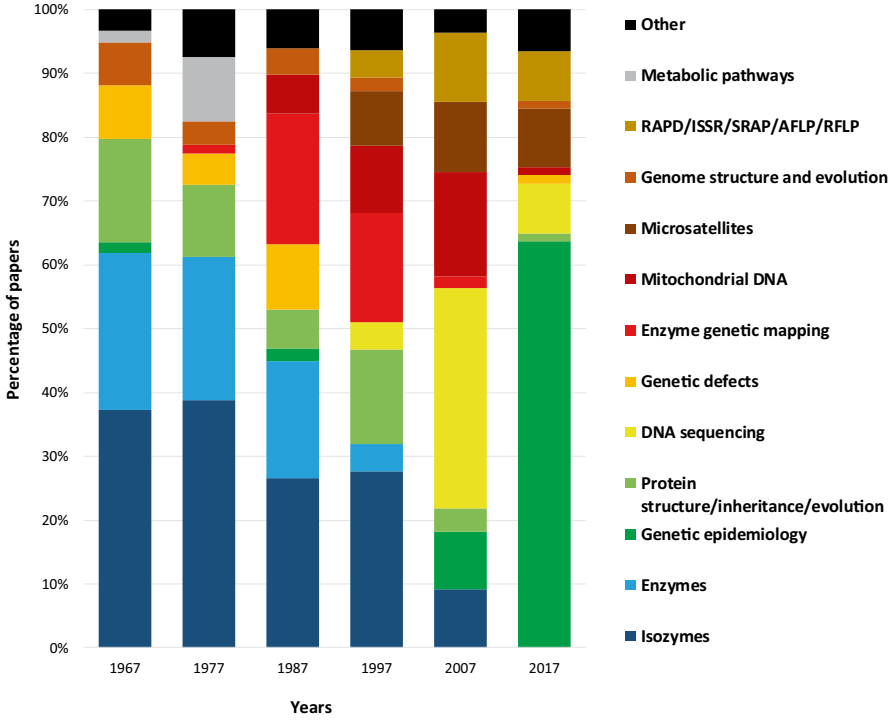

Fig. 1 Research topics addressed in *Biochemical Genetics*, based on a systematic review of a sample of 426 papers published around (i.e., within a 3-year interval) 1967, 1977, 1987, 1997, 2007 and 2017. Topics that were addressed less than 1% of the time have been merged as *Other*

conventional approaches, such as cell hybridization, in order to gain understanding about the inheritance mechanisms of enzymatic systems.

Aspects linked to the determination of protein structure, inheritance and evolution were also addressed, mostly devoted to blood proteins in animals but also to seed proteins in plants. Moreover, genetic mapping of enzymes, in order to find the location of the respective genes in chromosomes and the relative position of the areas coding for different enzymes, was particularly addressed in the 1980s and 1990s.

Genetic defects, including pathological conditions associated with deleterious changes in protein structure were also investigated, although not constituting a main topic.

Mitochondrial DNA began to be mentioned in the 1980s and continued to be so, well into the beginnings of the twentieth century, with applications in phylogeny and philogeography, particularly of animal taxa. This was accompanied by a marked increase in the application of DNA sequencing techniques, used to understand gene structure but also to define regions to be used as genetic markers.

At the same time, there was a marked increase in the number of studies devoted to the use of a wide array of dominant genetic markers, based on random or specific nuclear, mitochondrial or chloroplast DNA regions, such as Random Amplified Polymorphic DNA, Inter Simple Sequence Repeats, Amplified Fragment Length Polymorphism and Restriction Fragment Length Polymorphism, which were progressively replaced by the use of codominant microsatellites, although both types of markers coexisted in *Biochemical Genetics*. Those developments caused an explosion in the number of studies dedicated to population genetics.

It is clear from Fig. 1 that a reversal has occurred in *Biochemical Genetics*, from research mostly dedicated to enzymes/proteins to investigations focusing on different aspects of nucleic acid structure and sequencing.

The recent surge in the publication of articles devoted to genetic epidemiology is most likely explained by the emergence of techniques allowing the identification of thousands of single-nucleotide variants/polymorphisms, and to proceed to their relatively easy amplification, with many teams searching for connections between genetic variants in human genes and the development of a wide variety of diseases and pathologies. A wider analysis and future monitoring will be needed to better understand if this peak resulted from a sporadic episode, ensuing from the coincidence of a high number of submissions within the same topic, or if this represents a more stable and continuing trend.

Present and Future Challenges

With the constant increase in the number of journals and the expansion of the genetic research to larger areas of the planet, the increase in the number of published papers has been enormous (about 20,700 items in 1967/68 to 817,000 items in 2017/08, according to a "genetics" search in Google Scholar), even if possible differences between search engines and along time are taken into account (de Winter et al. 2014). A large effort is needed to maintain high standards in the areas of ethical conduct and to ensure the publication of original and innovative research results.

This will be even more emphasized in the future due to the high level of competition for funding and publication space (e.g., Tijdink et al. 2014; van Wesel 2016; Waaijer et al. 2017) in a very disputed topic, including research devoted to cornerstone areas such as genome structure and evolution, medical applications, the evaluation of genetic resources, and the continuous emergence of new developments such as the sequencing of the minute amounts of DNA and RNA present in a single cell, offering a window into the extent and nature of genomic and transcriptomic heterogeneity which occurs in both normal development and disease (Macaulay and Voet 2014).

Regarding those areas that have dominated the published topics, we will have to gradually increase the quality and scientific consistency and innovation, and avoid the frequent publication of extremely descriptive reports that provide a limited contribution to the advancement of this broad research field. As an example, papers in population genetics will have to ensure robust sampling, the preferential use of codominant markers, and novel approaches to the development of new tools linking population genetics and genomics (Paradis et al. 2017). Deposition of sequences and of genetic data on devoted platforms will have to become a common practice for our authors. In the area of genetic epidemiology, we often receive manuscripts based on the evaluation of relatively small samples, and using a limited number of genetic markers, applied to diseases that are mostly polygenic and multifactorial in their natural history. Therefore, although there is presently an explosion of papers in this area, special caution will be needed to avoid the publication of potentially irrelevant research which does not follow an appropriate procedure for genetic marker selection and application (see Elands et al. 2017). Meanwhile, other fast-growing areas are becoming more relevant and will have to deserve our full attention, since they will most likely affect not only the core knowledge of biochemical genetics but also provide many future applications, as in the case of genome editing (see, for example, the article collection at https://www.nature.com/collections/rpdbdzpccx).

In this context, *Biochemical Genetics*, as a generalist journal, will search for a more balanced distribution of the published papers within the different fields covered by the present aims and scope, including basic and applied research in areas such as genomics, proteomics, population genetics, phylogenetics, metagenomics, genetic markers of diseases, gene technology and therapy, among others. We will give preference to manuscripts addressing and testing clear scientific hypotheses, directed to a broad scientific audience, and which will potentially contribute for the advancement of the knowledge in the field, through the use of sound sampling or experimental designs, reliable analytical methodologies, and robust statistical analyses, including meta-analyses.

Above all, we expect to continue to participate in the development of this fascinating field of human knowledge, dedicated to the understanding of the structure, function and evolution of the biochemical machinery that codes and translates into life itself, and which will not cease to cause awe and excitement in the next generations of biologists, biochemists and geneticists.

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