

Productivity and Influence in Bioinformatics: A Bibliometric Analysis Using PubMed Central

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Bioinformatics is a fast-growing field based on the optimal use of “big data” gathered in genomic, proteomics, and functional genomics research. In this paper, we conduct a comprehensive and in-depth bibliometric analysis of the field of bioinformatics by extracting citation data from PubMed Central full-text. Citation data for the period 2000 to 2011, comprising 20,869 papers with 546,245 citations, was used to evaluate the productivity and influence of this emerging field. Four measures were used to identify productivity; most productive authors, most productive countries, most productive organizations, and most popular subject terms. Research impact was analyzed based on the measures of most cited papers, most cited authors, emerging stars, and leading organizations. Results show the overall trends between the periods 2000 to 2003 and 2004 to 2007 were dissimilar, while trends between the periods 2004 to 2007 and 2008 to 2011 were similar. In addition, the field of bioinformatics has undergone a significant shift, co-evolving with other biomedical disciplines.

Introduction

The rapid development of powerful computing technology has fueled a global boom in the biomedical industry that has led to the explosive growth of biological information generated by the scientific community. Bioinformatics, a coupling of molecular biology and computing technology, plays an essential role in understanding human diseases by using genomic information to identify new molecular targets for drug discovery. Many universities, government institutions, and pharmaceutical firms have established bioinformatics groups by bringing together computational biologists

and bioinformatics computer scientists. These groups have made great progress in illustrating and clarifying massive amounts of information and thus making bioinformatics an increasingly multidisciplinary field. A deep investigation of this field, including quantitative analysis to identify the disciplines that constitute it, is now of paramount importance.

Peer-reviewed scientific literature is regarded as an excellent means of understanding disciplinary evolution, as it reflects worldwide research activities, encompasses all sectors of employment, and provides the opportunity for bibliometric analysis. As a well-established method to map the structure and development of a given field (McCain, 1990; Ding, 2010; Boyack, Klavans, & Börner, 2005; Ding, Chowdhury, & Foo, 2001), Bansard et al. (2007) define three reasons for the popularity of bibliometric analyses as: (a) the availability of full databases of scientific literature with worldwide electronic access; (b) the availability of efficient tools to perform automatic textual analysis; and (c) the surge in interest in understanding recent research trends to position and evaluate research outcomes both at the institutional and the national level.

Therefore, this study used citations and publications collected from the PubMed Central full-text database to conduct a bibliometric analysis, and to illustrate the development of bioinformatics over the past 10 years. Our analysis focuses on research productivity and influence, which we measure using the most productive and cited papers, authors, organizations, and countries. We also identify and examine emerging researchers and “new stars” in the field and augment our citation analysis by adopting the topic modeling technique.

The rest of this paper is organized as follows: Background gives a brief history of bioinformatics; Related Works reviews related works on bibliometric analysis and its application in bioinformatics; Methods presents the research methods used in this study; Results and Discussion

Received October 23, 2012; revised March 8, 2013; accepted March 8, 2013

© 2013 ASIS&T • Published online 16 October 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/asi.22970

discusses the content analysis by topic modeling, as well as the productivity and impact of bioinformatics; and in the Conclusion we summarize the results and provide implications for future research.

Background

An important landmark of the emerging bioinformatics field was the formal initiation of the Human Genome Project (HGP) in 1990, which sought to sequence and map all human genes—more than 30,000. By 1991, a total of 1,879 human genes had been mapped. In 1993, Genethon, a human genome research center in France, produced a physical map of the human genome, and 3 years later it published the final version of the Human Genetic Map to complete the first phase of the HGP. In 1997, PSI-BLAST (Position-Specific Iterated Basic Local Alignment Search Tool; see Altschul et al., 1997) was invented for investigating sequence similarity. Using this tool, a query protein or nucleotide sequence could be compared to nucleotide or protein sequences in a target database, to identify regions of local alignment and report those alignments with scores above a given score threshold (1 and BLAST chapter). In 2000, a Fly genome was completely sequenced (Adams et al., 2000). In March of the same year, the *Drosophila melanogaster* genome sequencing project was essentially completed. The project planned to map large-insert clones for sequencing, but by the end adopted a Whole Genome Shotgun (WGS) approach marking the first time such an approach was used for sequencing in a multicellular organism. The human genome (3 Giga base pairs) was published in 2001 and HGP was completed in 2003. The draft genome sequence of the brown Norway laboratory rat, *Rattus norvegicus*, was completed by the Rat Genome Sequencing Project Consortium in 2004. Reactome, the knowledge base of biological pathways, was developed in 2005. A major milestone was achieved in September 2008, when the UniProt/Swiss-Prot group completed the manual annotation of the acknowledged full set of human proteins (derived from about 20,000 genes).

Ten years ago, the only way to track genes was to scour large, well-documented, family trees of relatively inbred populations (e.g., Ashkenazi Jews from Europe). Such genealogical searches may survey 11 million nucleotides a day. Today, the field of bioinformatics is burgeoning because of the increased need to create massive databases (e.g., GenBank, EMBL, and DNA Database of Japan) to store and compare the DNA sequence data from HGP and other genome sequencing projects. Bioinformatics has also expanded to include protein structure analysis, gene and protein functional information, data from patients, preclinical and clinical trials, and the metabolic pathways of numerous species.

Because of rapid development over the last 10 years, it is now critical to investigate the current status of bioinformatics, including identifying its major players (e.g., the most

productive and highly cited authors) and new driving forces. This will both explain its historical evolution and shed light on its future direction. Additionally, bioinformatics has triggered innovations across the fields of genomics, computational biology, and bio-imaging. There is thus a need to evaluate its current research performance and landscape, so as to facilitate potential interdisciplinary collaboration in the future.

Related Work

Bibliometrics: Exploring Research Productivity and Scholarly Impact

Bibliometrics is a well-established quantitative approach used to explore research productivity and scholarly impact, which are two interactive and mutually complementary measures of academic performance. It has been widely used for establishing the scholarly performance of authors (e.g., Cronin & Overfelt, 1993; Yan & Ding, 2010), citation patterns of journal articles (Moed, 2005), and the impact of journals (e.g., Garfield, 1955, 2000).

Research productivity is usually described in terms of the quantity of publications produced by individuals and institutions. Ramsden (1994) reported that both internal personal variables (e.g., research talents) and structural variables (e.g., institution management) could impact the level of research productivity. Yan and Sugimoto's (2011) exploration of the social, cognitive, and geographic relationships between institutions, based on their citation and collaboration networks, found that institutional citation behaviors are associated with social, topical, and geographical factors and less dependent on the country boundary or physical distance. He, Ding, and Ni (2011) studied the contextual information of scientific collaboration networks and identified that researchers with a broad range of collaborations tended to have increased productivity.

Scholarly impact is usually defined as the extent to which a researcher's work (e.g., a paper) has been used by other researchers (Bornmann, Mutz, Neuhaus, & Daniel, 2008). Scholar impact can thus be measured by the number of citations made to it by other scholars. As Cronin (1981) stated, "citations are frozen footprints in the landscape of scholarly achievement; footprints which bear witness to the passage of ideas" (p. 16). Nicolaisen (2007) reviewed various theories of citation behavior and citation analysis before introducing the now widespread belief that citing can be regarded as an evolutionary account of science and scholarship and understood in terms of psychology, the normative theory, and the social constructivist theory. In fact, the process of selecting and dressing a work with references is far from random (Cronin, 1981; Small, 2011). There exists a set of norms—Cronin (2004, p. 43) speaks of "the normative ghost in the machine"—and procedural standards to which scientists typically adhere (e.g., Cronin, 1984; Small, 1976). Therefore, citation analysis, as a major

component of bibliometrics, has become an important way to estimate the value, credit, and contribution of any given paper, journal, institution, or individual (Brown & Gardner, 1985). Recently, a few researchers have proposed more refined approaches to measuring scholarly impact. Ding and Cronin (2011) differentiated popularity from prestige by taking the importance of the source of citations into account. Ding (2011) applied weighted PageRank to author citation networks in the information retrieval field. He, Ding, and Yan (2012) proposed a sequence-based mining method to reveal the collaboration patterns for multi-authored papers.

Bibliometric Analyses in Bioinformatics

Several bioinformatics researchers have applied bibliometric analyses to understand the development of the field. Patra and Mishra (2006) analyzed the growth of the scientific literature in bioinformatics collected from NCBI PubMed using standard bibliometric techniques (e.g., Bradford's law of scattering and Lotka's law). Their study identified core primary journals, productivity patterns of authors and their institutions, publication types, languages used, and countries of publication and concluded that bioinformatics is a relatively new area and still does not have any specific scientific community behind it. Janssens, Glänzel, and De Moor (2007) and Glänzel, Janssens, and Thijs (2009) analyzed the core bioinformatics literature by incorporating text mining and citation-based techniques. The primary focus of their study was to improve the classification of literature based on a combination of linguistic and bibliometric tools.

Manoharan, Kanagavel, Muthuchidambaram, and Kumaravel (2011) conducted a bibliometric analysis of the corpus of bioinformatic literature covered by the Thomson Reuters Web of Science database for the period 2000 to 2010, aiming to evaluate the publication frequency, country, individual productivity, and collaboration in the field. Their overall conclusion was that bioinformatics may risk becoming a purely scholarly and unevenly distributed discipline, because only a few countries (e.g., India and China) produce the majority of the publications. Using the same database (Web of Science), Huang, Andrews, and Tang (2012) analyzed the citation patterns in bioinformatics journals (instead of the citation patterns of individual articles) and their corresponding knowledge subfields by normalizing the journal impact factor available in *Journal Citation Reports (JCR)*. Their results showed that bioinformatics journal citations were field-dependent, with scattered patterns in article life span and citing propensity. However, both studies were limited by their data source—only the Web of Science—which is biased towards certain domains, languages, and regions, and by their focus on merely journal-level citation patterns.

Seeking to derive potential and beneficial collaboration, Bansard et al. (2007) analyzed the bioinformatic and medical informatic literature to identify present links and

potential synergies shared between the two research fields. Their bibliometric analysis used the most significant words and groups of words from the documents to find that bioinformatics and medical informatics were still relatively separate fields, despite both having undergone fast changes and the use by both of advanced computer techniques to process massive biological data. The major limit of their study was their complete dependence on “words” or “word co-occurrences,” which should be estimated together with other normalization techniques to decrease contextual errors. In summary, bibliometric analysis has been used to map the research trends of bioinformatics (e.g., Manoharan et al., 2011; Patra & Mishra, 2006), to compare bioinformatics research in different countries (e.g., Guan & Gao, 2008; Manoharan et al., 2011), and to identify key words, scholars' prominence, and research collaboration (e.g., Glänzel, Thijs, Schubert, & Debackere, 2009; Patra & Mishra, 2006). However, as a relatively young field, further study is still needed to identify and define bioinformatics, especially its impact and productivity.

Methods

As bioinformatics is a highly interdisciplinary field, journals that contribute to bioinformatics tend to be cross-disciplinary. The bioinformatics journals in this study were therefore selected from diverse sources. The selection criteria were originally provided by Huang et al. (2012). We used most of the journals in their study and added a few more sources. Our additional sources were compiled from the following: (a) the International Society of Computational Biology (<http://www.iscb.org/iscb-publications-journals>); (b) the bioinformatics journal list on Wikipedia (http://en.wikipedia.org/wiki/List_of_bioinformatics_journals); and (c) the Mathematical and Computational Biology section of the Web of Science's *Science Journal Citation Reports (SJCR)*. From these sources we compiled a comprehensive list of 48 bioinformatics journals found in PubMed Central (Table 1). The choice of PubMed Central instead of Web of Science, which has been used in previous studies, was influenced by the fact that only 34 (72%), of the 48 journals were indexed in the Web of Science. All full-text articles pertinent to bioinformatics in the 48 journals were collected, which totaled 20,869 papers. However, some journals did not have many full-text articles, which has slightly limited this study.

To extract elements of interest, such as title, abstract, and references from the full text, we developed a SAX XML parser in Java. Based on an event-driven sequential access model, this was effective at processing the large data set due to its low memory requirements. To recognize data elements, we used Journal Publishing DTD made by the NLM (National Library of Medicine) available at <http://dtd.nlm.nih.gov/publishing/w3c-schema.html>. The extracted elements were stored in a relational citation database we built for further analysis. Figure 1 shows the database schema for this citation database.

TABLE 1. Journals selected and the number of papers included.

Journal	No. Paper	Journal	No. Paper
BMC Bioinformatics	3982	Source Code for Biology and Medicine	53
BMC Genomics	3203	Advanced Bioinformatics	42
PLoS Biology	2648	BioData Mining	32
Genome Biology	2321	Journal of Computational Neuroscience	26
PLoS Genetics	1876	Journal of Proteome Research	23
PLoS Computational Biology	1613	Journal of Biomedical Semantics	18
BMC Research Notes	744	Journal of Computer-Aided Molecular Design	18
Bioinformatics	705	Genome Integration	16
Molecular Systems Biology	485	Journal of Molecular Modeling	12
BMC Systems Biology	480	Bulletin of Mathematical Biology	11
Comparative and Functional Genomics	478	Pharmacogenetics and Genomics	9
Bioinformation	398	Statistical Methods in Medical Research	9
Theoretical Biology and Medical Modeling	256	Neuroinformatics	6
Human Molecular Genetics	223	Genomics	5
The EMBO Journal	215	Protein Science	5
Cancer Informatics	168	Physiological Genomics	4
Genome Medicine	134	Trends in Genetics	4
Evolutionary Bioinformatics	121	Journal of Proteomics	3
Biochemistry	115	Proteomics	3
Algorithms for Molecular Biology	110	Trends in Biochemical Sciences	3
EURASIP Journal on Bioinformatics and Systems Biology	86	Journal of Biotechnology	2
Journal of Molecular Biology	81	Trends in Biotechnology	2
Molecular & Cellular Proteomics	64	Briefings in Functional Genomics & Proteomics	1
Mammalian Genome	55	Journal of Theoretical Biology	1

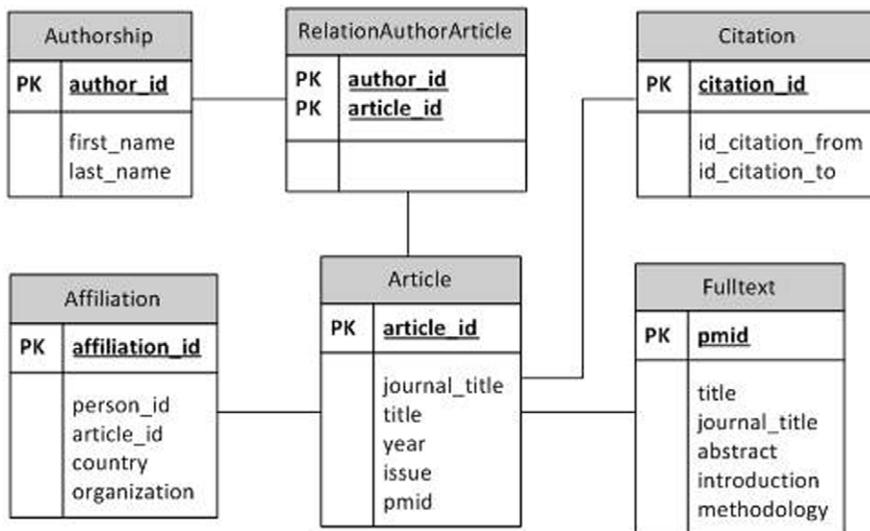


FIG. 1. Database schema for a custom-made database.

One of the challenges in building such a citation database was the need to detect duplicate citations, which was made even more difficult by the use of different citation styles in the reference sections of the full-text articles. PubMed Central XML data helped detect duplicate records by providing different XML tags to citation elements (e.g., author name, journal title, publication year, etc.) in the reference section. However, these tags could not cover all citations. To improve the accuracy of spotting citations, we employed the

edit distance technique, SoftTFIDF, to compare two entities in terms of string similarity (Cohen, Ravikumar, & Fienberg, 2003). Cohen et al. reported that SoftTFIDF outperformed other compared edit distance techniques with 0.91 average precision using the UTA data set, and 0.914 average precision using the CoraATDV data set. A pilot test, conducted with our data set, achieved a 0.92 average precision. After populating the extracted citation data into the tables, we had the following number of instances: Affiliation: 60,263;

Articles: 20,869; Authors: 445,034; Citation: 546,245; RelationAuthorArticle: 2,264,079. The RelationAuthorArticle table paired each author to the paper the author (co)authors on it.

A major source of error in processing the PubMed Central citation data was related to disambiguation of author names. The problem was exacerbated when the first name was only initialized in the reference section. To solve this problem, we developed an automatic procedure that linked PubMed Central papers to PubMed papers through the PubMed E-Utils APIs (<http://www.ncbi.nlm.nih.gov/books/NBK25500/>) to obtain the full first name and the author affiliation information. Due to the low matching rate between the PubMed Central ID and the PubMed ID, we searched PubMed with paper titles including ambiguous author names. Still, a lot of affiliation information was difficult to extract; therefore, we manually checked the top 200 most productive authors and most highly cited authors. We found seven ambiguous authors from the most productive authors list and nine from the most highly cited authors list. We suggest that more comprehensive methods should be applied to disambiguate author names (Tang, Fong, Wang, & Zhang, 2012). Because of this, out of 20,869 papers with 546,245 citations, only 310,002 (57%) citations came from the PubMed database.

As major progress within this field began in early 2000, when it acquired significant funding from the European Commission and the U.S.A., we chose to portray details of this important phase and better outline the field's dynamic changes, by dividing the period 2000 to 2011 into three phases; 2000 to 2003, 2004 to 2007, and 2008 to 2011. This resulted in 132,051 citations for the period 2000 to 2003, 180,570 for the period 2004 to 2007, and 64,064 for the period 2008 to 2010. It should be noted that there were 169,560 citations published before 2000.

We divided the time span into three phases for the following reasons: (a) in order to do meaningful topic modeling, we needed to guarantee a certain number of articles per period (dividing it into finer-grained levels would have deteriorated the quality of topic modeling); (b) the number of publications per year varied, which could have led to potential bias in the results analysis; and (c) within bioinformatics some noticeable trends are associated with these three phrases (i.e., during the period 2000 to 2003, the major of topic was the protein study, while during the period 2004 to 2007, topics diversified to include sequence and structure analysis of genes, brain, cancer, virus, etc.).

To identify author productivity and impact, we divided authors into two categories; first author and second author. The first author category included authors who were indicated as the first author, while the second author category included the remaining set of coauthors. Author order is usually tightly connected to contribution, as first authors tend to be those who contributed the most to the paper and are often the corresponding author. By example, tenure promotion at major universities in the U.S.A. recognize author

order as one of the most important indicators for measuring faculty member contribution. While it varies from discipline to discipline and from country to country, from the authors' own experience, the most significant contribution still comes from the first author in the bioinformatics domain. According to Sekercioglu (2008), author order is of particular importance in bioinformatics.

We applied a topic modeling technique to analyze research productivity and author/country impact associated with the identified topics. Topic modeling has often been used to identify topics from large-scale document collections. In the model, a topic represents an underlying semantic theme, approximated as an organization of words, and operationalized as a probability distribution over terms in a vocabulary (Blei, Ng, & Jordan, 2003). The topic modeling technique used in this paper is Dirichlet-multinomial regression (DMR) proposed by Mimno and McCallum (2008), which is an extension of the latent Dirichlet Allocation (LDA) proposed by Blei et al. (2003). It allows conditioning on arbitrary document features by including a long-linear prior on document-topic distributions that is a function of the features of the document, such as author, publication venue, references, and dates. By applying the topic modeling technique to the bioinformatics journals we collected, we could examine which leading countries or authors have strengths in each topic.

We also conducted coauthorship analysis to understand scientific collaboration patterns and the status of bioinformatics researchers. Studies of coauthorship networks have relied on topological features, including centrality, largest component, diameter, clustering coefficient, average separation, average number of collaborator, etc. (Yang, Tang, & Song, 2013).

Topic modeling was also used to spot thematic development in bioinformatics over time, as defined by our three time periods. We used the MALLET package (McCallum, 2002) as a basis for our system and extended the DMR topic modeling algorithm implemented in MALLET to suit our needs. MALLET was applied on each period of interest to find the top topic groups. We used 1,000 iterations with stop word removal.

Results and Discussion

Content Analysis by Topic Modeling

By and large, there are two major subfields in bioinformatics: computational bioinformatics and application bioinformatics (Baldi & Brunak, 2001). Computational bioinformatics uses computational work, including algorithm, software development, database construction, and curation, to develop applications that are aimed at addressing certain problems in biology. Applications of bioinformatics can be categorized into three groups: sequence, function, and structure analysis. Sequence analysis covers various types of sequence information on genes and proteins. Function

TABLE 2. DMR-based topic modeling results for the period of 2000 and 2003.

Topic 1: Cell cloning	Topic 2: Protein sequence	Topic 3: Ontology	Topic 4: Protein prediction	Topic 5: Protein analysis
cell cloning genes expression development mapping	sequences region alignment protein algorithm method	data information database ontology biological tools	model measures predictions protein experiments parameters	proteins conserved domain function family analysis
Topic 6: Gene study	Topic 7: DNA binding	Topic 8: Yeast network	Topic 9: Gene expression	Topic 10: RNA/DNA
genes study identified gene mutations tmc	dna sites binding transcription regulatory motifs	yeast protein networks analysis coli mass	expression data gene microarray genes analysis	amplification rna dna rna gene protocol
Topic 11: BTBD/Receptor	Topic 12: Protein/arabidopsis	Topic 13: Tuberculosis/Genomics	Topic 14: Chromosome/Mutations	Topic 15: Genomics
receptor channel btbd binding mhc olfactory	proteins arabidopsis plant membrane family plants	tuberculosis functional comparative current awareness genomics	chromosome mutations biology genotyping human snp	genomics cdca gene expression genome sequence

analysis examines the function expressed within the sequences and predicts the functional interaction between various proteins or genes. Structure analysis predicts the structure and possible roles for the structure of proteins or RNA. We used this general taxonomy of the bioinformatics field to analyze the results of topic modeling (Tables 2–4).

During the period 2000 to 2003, the major topic is protein study (topic 2, topic 4, topic 5, and topic 12) with particular interest in those topics relate to the functional analysis of proteins—a core component of application bioinformatics.

Topics during the period 2004 to 2007 are more diverse and include sequence and structure analysis of genes, brain, cancer, virus, etc. In addition, two topics directly relate to computation bioinformatics (topic 3 and topic 12), which is different from the first period.

During the period 2008 to 2011, topics continue to be diverse and similar to the second period. However, new topics like mutation and RNA emerge during this period.

Topics over the entire time period 2000 to 2011 follow patterns similar to the second and the third periods due to the bulk of data sets coming from those two periods and the sensitivity of topic modeling to the size of data sets. Table 5 shows all 15 topics, which include protein binding, algorithm/method, cell/model, network/interaction, genome sequence, immune/virus, gene expression, genetic/evolution, database/software, gene transcription, DNA/chromosome, ontology/mining, gene/genomics, and cancer/cell.

Productivity

Productive authors. Appendix A1 shows the top 15 most productive authors in bioinformatics based on PubMed Central data. Over the entire period 2000 to 2011, the most productive author is Michael L. Gross, who published 124 papers in the period 2004 to 2007. In terms of consistent productivity, G.A. Petsko leads, by ranking first or second in all three periods: 2000 to 2003, 2004 to 2007, and 2008 to 2011. R. Robinson is also a highly productive researcher, ranking third in the period 2004 to 2007, and first in the period 2008 to 2011.

In the second author category, P.O. Brown ranks fourth in the period 2000 to 2003 and third in the period 2004 to 2007. M. Gerstein ranks fourteenth in the period 2000 to 2003, eleventh in the period 2004 to 2007, and fifth in the period 2008 to 2011, which shows his steady production in the field of bioinformatics over the entire period. Among the top 15 productive authors from 2000 to 2003, no author, except G.A. Petsko, M. Gerstein, and P.O. Brown, is included in the productive author lists for the other two periods. P.E. Bourne emerges in the second period, 2004 to 2007, where he ranks seventh in the first author category and fourth in the second author category. He also ranks first in the second author category for the period 2008 to 2011. In addition, the following authors are productive in the first author category for the last two periods, 2004 to 2007 and 2008 to 2011: L. Gross (first and sixth), R. Robinson (third and first), M. Hoff

TABLE 3. DMR-based topic modeling results for the period of 2004 and 2007.

Topic 1:	Topic 2:	Topic 3:	Topic 4:	Topic 5:
Protein structure	Brain	Ontology	Immune/Virus	Gene
protein structure family binding peptide method	brain neurons circadian activity cortex neural	gene annotation ontology functional terms biological	immune infection virus host viral hiv	gene genomics cell sequence genome est
Topic 6:	Topic 7:	Topic 8:	Topic 9:	Topic 10:
Network pathway	Gene expression	DNA/Chromosome	Cancer research	Gene transcription
network pathway interactions metabolic yeast protein	data gene expression microarray analysis profile	dna chromosome microarray methylation chromatin hybridization	mass research biology spectrometry cancer new	transcription genes sites binding motifs regulatory
Topic 11:	Topic 12:	Topic 13:	Topic 14:	Topic 15:
Gene evolution	Database/Software	Gene/Genome	Cell/Model	SNP/Disease
evolution species gene phylogenetic duplication human	data database analysis software tool information	genome genes genomes bacterial sequences bacteria	model cell development system stem signaling	genetic snps disease polymorphisms variation association

TABLE 4. DMR-based topic modeling results for the period of 2008 and 2011.

Topic 1:	Topic 2:	Topic 3:	Topic 4:	Topic 5:
Ontology/Mining	Gene sequence	Gene/Protein	DNA/Chromosome	HIV/Virus
information research ontology biomedical terms system	gene sequence marker splicing genome analysis	genes proteins plant identified analysis expressed	dna methylation chromatin cells histone chromosome	patients Study Hiv clinical virus health
Topic 6:	Topic 7:	Topic 8:	Topic 9:	Topic 10:
Mutation	Protein binding	Cancer	Network pathway	SNP/Disease
mutations mice disease mutation protein muscle	protein binding Molecular Structure Sequence Prediction	cells cancer profile tumor human breast	network pathway modules interaction protein biological	genetic association snps disease studies polymorphisms
Topic 11:	Topic 12:	Topic 13:	Topic 14:	Topic 15:
Algorithm/Database	Neuron/Dynamics	Metabolism	RNA	Cell signaling
data method algorithm database software tool	model neuron dynamics system time cell	metabolic metabolism growth coli bacteria response	rna binding sites transcription mirnas regulatory	cell signaling receptor protein kinase development

TABLE 5. Overall topic modeling results for the period of 2000 and 2011.

Topic 1: Protein binding	Topic 2: Algorithm/Method	Topic 3: Cell/Model	Topic 4: Network/Interaction	Topic 5: Genome sequence
protein binding receptor sequence structure domain	data method methods algorithm model approach	model cell cells system dynamics time	network interactions pathway gene interaction biological	genome genomic sequence dna plant species
Topic 6: Immune/Virus	Topic 7: Gene expression	Topic 8: Generic/Evolution	Topic 9: Database/Software	Topic 10: Gene transcription
infection host strains immune virus resistance	expression gene genes microarray data analysis	evolution selection evolutionary species genetic variation	data database analysis information software tool	gene transcription response sites stress metabolism
Topic 11: DNA/Chromosome	Topic 12: Ontology/Mining	Topic 13: Disease/SNP	Topic 14: Gene/Genomics	Topic 15: Cancer/Cell
dna cells chromatin histone chromosome replication	research biology information biomedical text ontology	genetic disease association snps studies study	genes genome gene genomes species sequence	cancer cell genes tumor expression cells

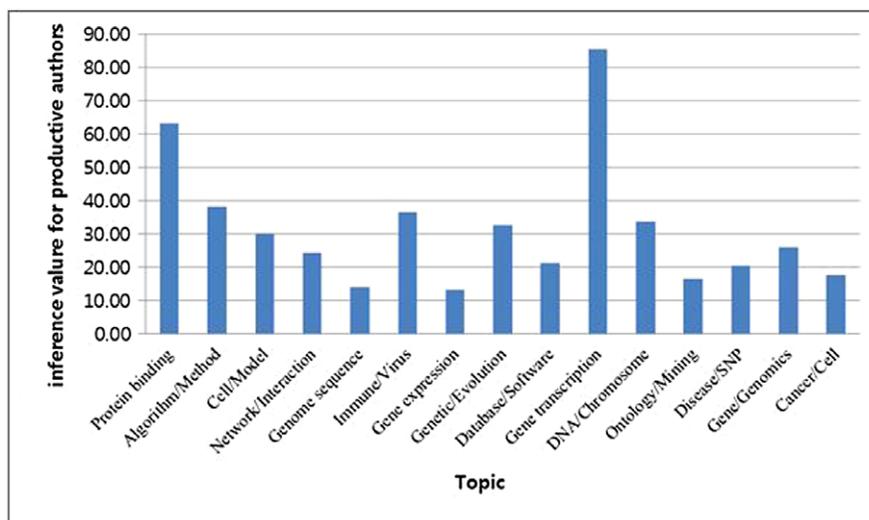


FIG. 2. Inference value for the most productive authors. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(fourth and ninth), and R. Jones (seventh and seventh). The list of productive authors for the three consecutive periods reveals that just a few researchers were steadily productive and that highly productive new authors have emerged since 2004.

As we are interested in identifying the topical areas productive authors publish in, we analyzed papers published by the top 10 most productive authors in the first

author category over the period 2000 to 2011 using the DMR topic modeling technique to infer the topic distribution of these papers. Figure 2 shows the results of this topic inference for 15 topics. The topic inference was calculated without partitioning the time period to find the general focus of most productive authors up to rank 10 (total 22 authors) on the identified subject areas.

TABLE 6. Top 20 most productive countries.

R	2000–2003		2004–2007		2008–2011	
	Country	No.	Country	No.	Country	No.
1	USA	1090	USA	9314	USA	15683
2	UK	305	UK	1690	UK	3593
3	Germany	114	Germany	1176	Germany	2445
4	Canada	82	France	816	France	1857
5	France	75	Canada	707	Canada	1347
6	Australia	38	Japan	588	China	1153
7	Spain	36	Italy	427	Japan	1145
8	Italy	30	China	385	Italy	895
9	Japan	30	The Netherlands	370	Spain	866
10	Switzerland	27	Australia	334	Australia	833
11	Sweden	25	Spain	318	The Netherlands	832
12	The Netherlands	19	Switzerland	303	Switzerland	622
13	Belgium	18	Sweden	267	Sweden	567
14	Norway	17	Israel	252	India	485
15	Denmark	14	India	247	Israel	459
16	Poland	11	Taiwan	195	Taiwan	427
17	India	10	Singapore	162	Belgium	355
18	Finland	9	Finland	152	Korea	343
19	Ireland		Denmark	146	Singapore	333
20	Israel		Korea	144	Finland	303
	Russia					

The average topic inference is 31.49 with a standard deviation of 18.9. Among the 15 topics, two topics exceed the standard deviation. The first topic is related to protein binding and the second is about gene transcription. This implies that the top 10 most productive authors focused on those two topical areas more than other topics.

Productive countries. Table 6 shows the top 20 most productive countries. Over the entire period the U.S.A., U.K., and Germany rank first, second, and third, respectively. Canada and France rank fourth and fifth. Denmark is included in the top 20 most productive countries in the first two periods, but not in the third period, 2008 to 2011. Belgium is included in the first and the last periods, but not in the period 2004 to 2007. Countries included in the top 20 for the period 2000 to 2003, but excluded in the last two periods include Norway, Poland, Ireland, and Russia. Since 2004, China, Taiwan, Singapore, and Korea are among the top 20 productive countries. This indicates that Asian countries have begun to stand out in the field of bioinformatics. Among Asian countries, Japan is the only one included among top 20 countries for all three periods. Other countries shown in Table 6 are included in the top 20 but with various rankings in the three periods.

To generate topic models with the condition on countries (Figure 3), we selected the top five countries for analysis, the U.S.A., U.K., Germany, Canada, and France, based on consistent ranks within the top 10 during the period of 2000 to 2011. The topic modeling results confirm that the U.S.A. is the leading country. For the period 2000 to 2003, the top five countries have a strong topical relationship with gene expression and genomics, with all five countries exceeding the

inference average. For the period 2004 to 2007, the top five countries have strong research interests in four topics: gene, gene transcription, gene evolution, and cell/model. In the period 2008 to 2011, topical interests shift to gene sequence, HIV/virus, metabolism, and algorithm/database. Topic modeling with the condition of a country reveals that the early interests of the top five countries are in gene-centric research, but that recently their interests have expanded to include disease research and computational tools.

Productive organizations. Table 7 shows the leading organizations in the field of bioinformatics. Brandeis University ranks first in the period 2000 to 2003, and twentieth in the period 2004 to 2007, but is not included in the period 2008 to 2011. The University of California, Berkeley ranks second for the period 2000 to 2003, seventh for the period 2004 to 2007, and fourteenth for the period 2008 to 2011. Stanford University ranks third in the period 2000 to 2003, and first since 2004. Harvard University ranks sixth in the period 2000 to 2003, second in the period 2004 to 2008, and third in the period 2009 to 2011. The University of Washington ranks fifth in the first two periods and second in the period 2008 to 2011. Two institutions have steadily increasing rankings over the three time periods: the University of Cambridge (eleventh, eighth, and fifth), and University College London (seventeenth, eleventh, and tenth). The University of Oxford is not included in the period 2000 to 2003, but ranks tenth in the period 2004 to 2008, and sixth in the period 2009 to 2011.

Popular subject terms. Subjects assigned to journals in our data collection are listed in Table 8. These subjects are

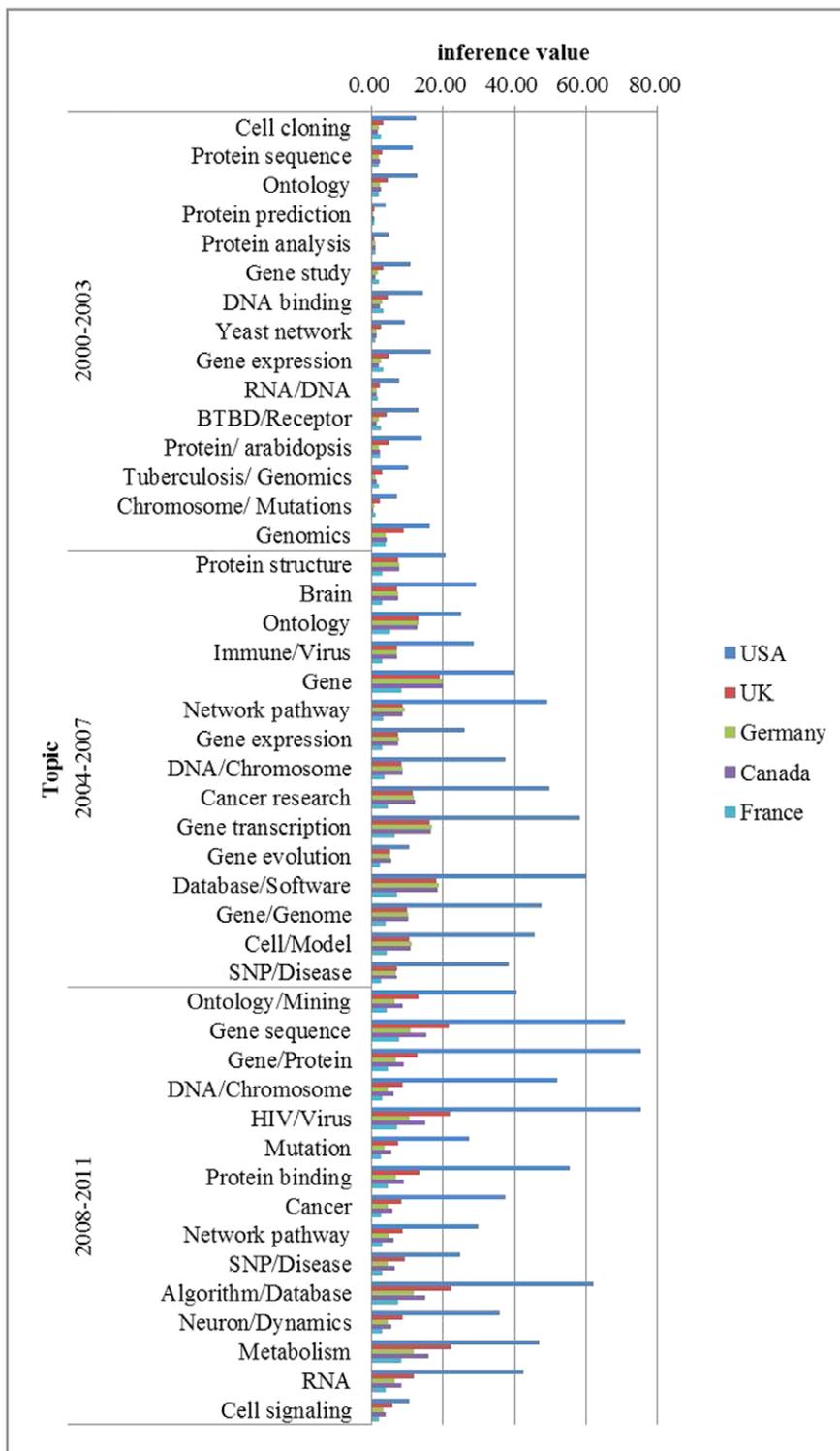


FIG. 3. Topic distribution of the top countries over the period 2000 and 2011. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

automatically assigned to journals based on the subject heading(s) provided by the Stanford Lane Medical Library. We created an HTML parser class that connected to the Stanford Lane Medical Library to query the search engine

with the journal title, and parse the extracted subject heading(s) for the corresponding journal. Table 8 show that molecular biology and medical informatics are the top two subjects, followed by genetics, biology, and biochemistry.

TABLE 7. Top 20 most productive organizations.

R	2000–2003		2004–2007		2008–2011	
	Organization	No.	Organization	No.	Organization	No.
1	Brandeis University	47	Stanford University	315	Stanford University	514
2	University of California, Berkeley	44	Harvard University	283	University of Washington	506
3	Stanford University	43	University of California, San Diego	206	Harvard University	481
4	National Center for Biotechnology Information	29	University of California, San Francisco	188	University of California, San Diego	347
5	University of Washington	27	University of Washington	223	University of Cambridge	307
6	Harvard University		Yale University	165	University of Oxford	281
7	University of Toronto	23	University of California, Berkeley	159	University of California, San Francisco	277
8	University of California, San Francisco		University of Cambridge	154	University of Toronto	259
9	University of Texas at Austin		University of California, Los Angeles	138	Duke University	243
10	Yale University	21	University of Oxford	138	University College London	226
11	University of Cambridge	19	University College London	117	University of California	221
12	European Bioinformatics Institute	14	University of Michigan	116	Yale University	219
13	Duke University		University of Minnesota	114	University of Michigan	205
14	University of Edinburgh	13	Duke University	109	University of California, Berkeley	204
15	Columbia University	12	Princeton University	107	University of California, Los Angeles	200
16	Wellcome Trust Sanger Institute		University of California	106	University of Chicago	190
17	University College London		University of Toronto	105	Princeton University	187
18	New York University		Columbia University	103	University of California, Davis	185
19	Institute for Genomic Research	11	University of Pennsylvania	92	CNRGV	177
20	The Rockefeller University University of Michigan		Brandeis University	91	University of North Carolina	174

TABLE 8. Subject terms of journals.

Subject Term	Count
Molecular Biology	11
Medical Informatics	10
Genetics	9
Biology	7
Biochemistry	5
Biomedical Engineering	3
Biotechnology	2
Medicine	2
Neurology	2
A publication of protein society*	1
Computers	1
EURASIP journal on bioinformatics and systems biology*	1
Functional Genomics	1
Genetics, Medical	1
Journal of theoretical biology	1
Molecular cellular proteomics*	1
Oncology	1
protein science	1
Proteomics	1
Technology	1
The EMBO journal*	1
The pharmacogenomics journal*	1
Theoretical biology medical modeling*	1
Trends in genetics*	1

Note. *Journal title.

Influence

Influential papers. Table 9 shows the top three most cited papers in the field of bioinformatics. We present the rest of the top 20 most highly cited papers in Appendix A2. Among

the papers published in the period 2000 to 2003, the most cited paper is “Gene ontology: tool for the unification of biology,” which was published in *Nature Genetics* and written by the Gene Ontology Consortium consisting of 20 bioinformatics researchers. Eight authors among the 20 are included in the top 20 most highly cited authors for the same period (D. Botstein, G. Rubin, G. Sherlock, M. Ashburner, J. Cherry, C. Ball, J. Matese, H. Butler). The second most cited paper for this period is “Initial sequencing and analysis of the human genome” published in *Nature*. The authors of this paper consist of 249 researchers from 48 organizations. The third most cited paper for this period is “Significance analysis of microarrays applied to the ionizing radiation response” written by V. Tusher, R. Tibshirani, and G. Chu, all of whom are affiliated with Stanford University. R. Tibshirani also ranks twelfth in the highly cited author list for the same period.

In the period 2004 to 2007, the most cited paper is “Bioconductor: open software development for computational biology and bioinformatics” written by 25 authors from 19 organizations. The first author of this paper is R. Gentleman of the Dana-Farber Cancer Institute. Among the 25 authors for this article, 4 are also included in the highly cited author list for the same period. The second most cited paper for this period is “R: A language and environment for statistical computing” and the third is “Transcriptional regulatory code of a eukaryotic genome” written by 20 authors from four organizations.

During the period 2008 to 2011, the most cited paper is “The Pfam protein families database” written by 13 authors from three organizations. The first author of this paper is A.

TABLE 9. Top 3 most cited papers.

R	2000–2003			2004–2007			2008–2011		
	Paper	Journal	No. Cited	Paper	Journal	No. Cited	Paper	Journal	No. Cited
1	Gene ontology: tool for the unification of biology. The Gene Ontology Consortium	Nat Genet	948	Bioconductor: open software development for computational biology and bioinformatics	Genome Biol	395	The Pfam protein families database	Nucleic Acids Res	112
2	Initial sequencing and analysis of the human genome	Nature	465	R: A language and environment for statistical computing	R: A language and environment for statistical computing	304	KEGG for linking genomes to life and the environment	Nucleic Acids Res	104
3	Significance analysis of microarrays applied to the ionizing radiation response	Proc Natl Acad Sci USA	349	Transcriptional regulatory code of a eukaryotic genome	Nature	234	Mapping short DNA sequencing reads and calling variants using mapping quality scores	Genome Res.	91

Bateman, and among the other 13 authors R. Durbin ranks ninth on the top 20 highly cited authors list for the period 2004 to 2007, and first for the period 2008 to 2011. The second most cited paper for this period is “KEGG for linking genomes to life and the environment” written by 11 authors from three Japanese organizations. The third most cited paper for this period is “Mapping short DNA sequencing reads and calling variants using mapping quality scores” written by H. Li, J Ruan (ninth among highly cited authors for the same period), and R. Durbin (first among highly cited authors for the same period).

Figure 4 shows the topics most associated with influential papers. By building three topic models with DMR for three data sets (2000 to 2003, 2004 to 2007, and 2008 to 2011) we are able to select the top 100 most cited papers not part of the data sets used for the topic model, infer topic distribution of each highly cited paper, and sum up an inferred topic value of the highly cited paper. During the period 2000 to 2003, the average inference value is 6.67 with a standard deviation of 9.099. These statistics imply that influential papers have a significant thematic relationship with topics such as gene expression (26.21) and genomics (30.17). During the period 2004 to 2007, we observe the topical extension of influential papers with an average influence value of 8.6 and a standard deviation of 7.75. Influential papers during this period focus on protein structure (19.08), brain (18.18), gene evolution (24.44), and cell/model (21.91). This trend continues in the third period, with an average influence value of 9.29 and a standard deviation of 9.33. Most influential papers during this period focus on the topics of gene sequence (22.79), DNA/chromosome (23.93), SNP/disease (20.48), neuron/dynamics (19.87), and cell signaling (24.01). The diversification of topics starting from the second period is also observed in the thematic focus of the most productive authors, as analyzed in the earlier section.

Influential authors. Appendix A3 shows the top 20 most highly cited authors based on 546,245 citations from PubMed Central. In all three periods, M. Gerstein, a professor in computational biology and bioinformatics at Yale University, is both the most highly cited and productive author in the first author category. D. Botstein, a professor in molecular biology at Princeton University, is the most cited author in the second author category for the period 2000 to 2003. He and his group have excelled in research in cellular growth rate in controlled circumstances. E. Lander is the most cited author, as second author, for the period 2004 to 2007 and ranks third in the second author category and eighteenth in the first author category for the period 2000 to 2003. He is a professor of biology at the Massachusetts Institute of Technology, an expert in genomics, and a collaborator with D. Botstein.

J. Storey is the second most cited author, as first author, for the period 2000 to 2003. He is a professor of molecular biology at Princeton University and, with his research group, is actively involved in genomics. T. Speed is ranked third in the first author category, as well as fifteenth in the second

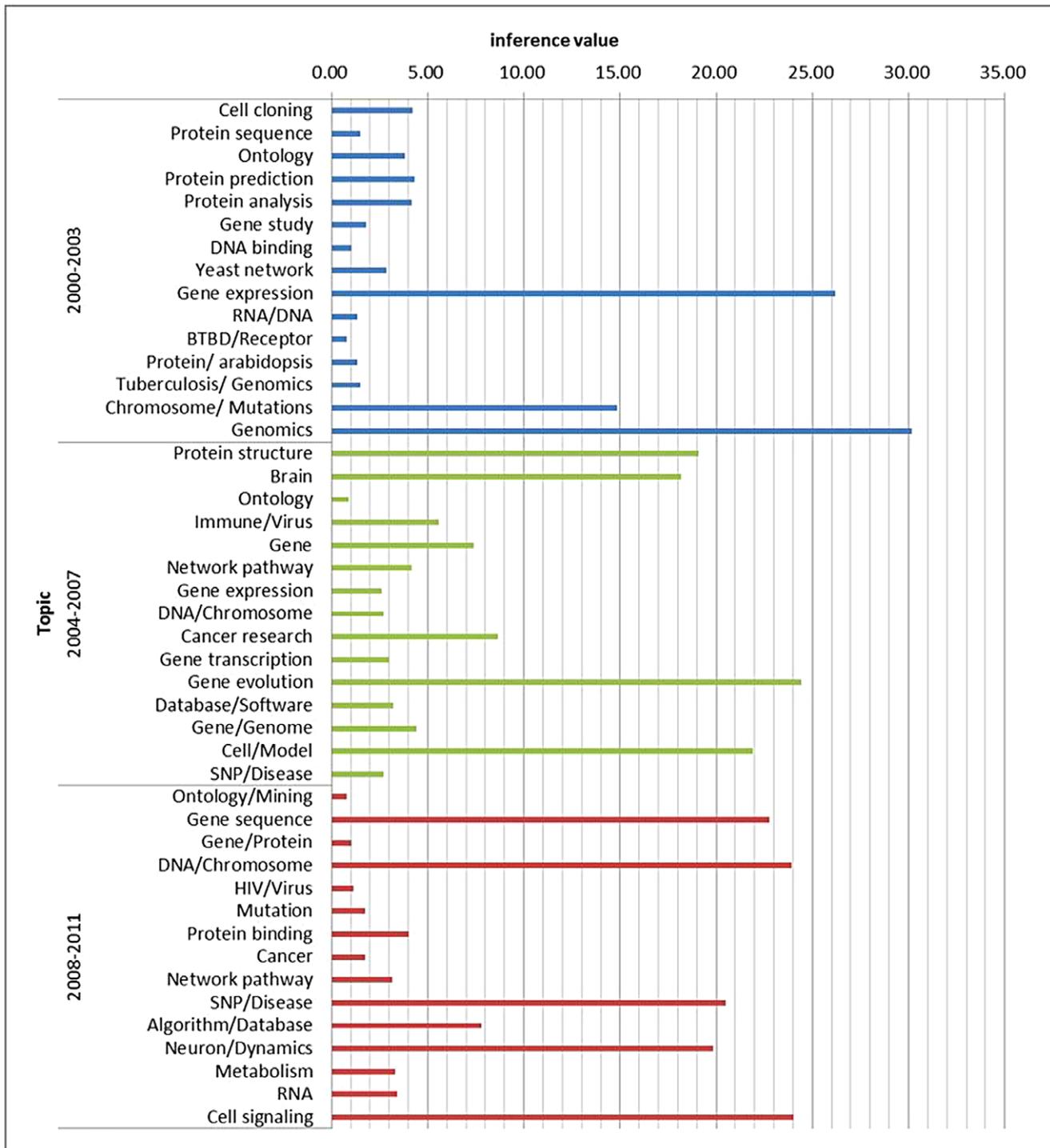


FIG. 4. Topic distribution of papers of highly cited authors. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

author category for the period 2000 to 2003. He is an Australian statistician who is well known for his contributions to the analysis of variance and bioinformatics. P. Bork is the second most cited author, as second author, in two consecutive periods (2004 to 2007 and 2008 to 2011). He is the head of the division of bioinformatics at EMBL Heidelberg.

There are a couple of authors who have become more influential in the last two periods: R. Durbin, Joint Head of Human Genetics at the Wellcome Trust Sanger Institute and leader of the Genome Informatics group, ranks ninth in the second author category for the period 2004 to 2007, and first for the period 2008 to 2011, and D. Smith, professor of molecular & integrative physiology at the University of

TABLE 10. Leading journals or conferences.

R	2000–2003		2004–2007		2008–2011	
	Journal	No.	Journal	No.	Journal	No.
1	Proc. Natl. Acad. Sci. U.S.A	12796	Nucleic Acids Res	14784	Nucleic Acids Res	3701
2	Nature	11718	Bioinformatics	12766	Nature	2684
3	Nucleic Acids Res	10438	Proc. Natl. Acad. Sci. U.S.A	12718	Proc. Natl. Acad. Sci. U.S.A	2425
4	Science	10174	Nature	10891	Bioinformatics	2220
5	Bioinformatics	8433	Science	8647	BMC Bioinformatics	1866
6	Genome Res	6955	BMC Bioinformatics	7260	Science	1861
7	Nat Genet	5816	Genome Res	5903	Nat Genet	1486
8	J Biol Chem	5266	Cell	5412	Genome Res	1442
9	Cell	3835	Nat Genet	5192	BMC Genomics	1377
10	Journal of Molecular Biology	3689	J Biol Chem	4671	PLoS One	1275
11	Genome Biology	3145	Genome Biology	4299	Cell	1194
12	Genetics	2477	PLoS Biology	3219	PLoS Genetics	1131
13	The EMBO Journal	2169	Genetics	2804	PLoS Computational Biology	934
14	Genes Dev	2112	Journal of Molecular Biology	2468	Genome Biology	818
15	Mol Cell Biol	1972	Mol Biol Evol	2426	J Biol Chem	772
16	Curr Biol	1935	BMC Genomics	2417	PLoS Biology	669
17	Trends in Genetics	1837	Genes Dev	2196	Nat Biotechnol	579
18	Mol Biol Evol	1730	Nat Rev Genet	2182	Nat Rev Genet	557
19	Mol Cell	1691	Mol Cell	2029	Nat Methods	553
20	J Bacteriol	1675	Mol Cell Biol	1992	Mol Cell	494

Michigan and co-director of the A. A. Taubman Consortium for Stem Cell Therapies, ranks third in the first author category for the period 2004 to 2007, and eighth for the period 2008 to 2011.

Emerging Stars. Appendix A4 shows the top 20 emerging researchers for the periods 2004 to 2007 and 2008 to 2011, using a set notation of A–B for selecting emerging authors. In other words, the top 20 authors in Appendix A4 are selected when they do not appear in the previous period. For example, L. Shi does not appear in the period 2000 to 2003, but for the period 2004 to 2007 receives 77 citations. He is affiliated with the U.S. Food and Drug Administration and is involved in MicroArray Quality Control (MAQC). Other emerging authors during this time period include: H. Mermjakob, S. Toy, F. Spencer, and G. Smyth. For the period 2008 to 2011, D. Goldstein, S. Guo, and W. Baumgartner look to be emerging researchers, but it is too early to evaluate their influence.

Influential journals or conferences. Table 10 illustrates the leading journals or conferences in bioinformatics. Analysis of a journal's citation count reveals that throughout the three time periods journals such as the *Proceedings of the National Academy of Sciences* (Proc Natl Acad Sci USA), *Nucleic Acids Research* (Nucleic Acids Res), *Nature*, *Bioinformatics*, and *Science* rank as the top five leading journals in bioinformatics.

BMC Bioinformatics ranks sixth for the period 2004 to 2007, and fifth for the period 2008 to 2011. Among the top 20 journals, 11 journals are included in the top 20 for the entire period 2000 to 2011. The *EMBO Journal*, *Current*

Biology (Curr Biol), *Trends in Genetics*, and *Journal of Bacteriology* (J Bacteriol), which are in the top 20 for the period 2000 to 2003, are not included among the top 20 journals past 2004. Journals such as the *Journal of Molecular Biology*, *Genetic*, *Genes & Development* (Genes Dev), *Molecular and Cellular Biology* (Mol Cell Biol), *Molecular Biology and Evolution* (Mol Biol Evol) are included in the top 20 for the period 2004 to 2007, but their overall rankings decrease over time.

New journals emerging in the period 2004 to 2007, are *BMC Bioinformatics*, *PLoS Biology*, *BMC Genomics*, and *Nature Reviews Genetics* (Nat Rev Genet). The rankings of these journals also increase during the period 2008 to 2011. New journals such as *PLoS One*, *PLoS Genetics*, *PLoS Computational Biology*, *Nature Biotechnology* (Nat Biotechnol), and *Nature Methods* (Nat Methods) are also included in the top 20 leading journals for the period 2008 to 2011.

Coauthorship Analysis

In this section we attempt to understand the knowledge structure of the field of bioinformatics using coauthorship analysis of the 2,088,356 coauthor pairs. Since this network is too big to either analyze or visualize, we focus our analysis on authors collaborating with more than 30 colleagues, which consists of 13,952 pairs. We identify 15 communities of coauthor networks using the modularity algorithm widely used in social network analysis. We use modality to examine how strongly the groups of the coauthor networks are structured. Networks with high modularity tend to show a dense connection between the nodes within groups,

TABLE 11. Community statistics by modularity.

Community	Topic	Size	%	Top Ranked Author	Degree	Closeness Centrality
1	Genomics	653	7.13	N.G.Martin	117	0.31
				N.Chatterjee	104	0.32
				K.V.Shianna	91	0.27
2	Genomics	2151	23.5	Y.Li	351	0.38
				L.Shi	114	0.31
3	Protein and RNA Sequences	498	5.44	R.D.Finn	70	0.26
				A.Bateman	65	0.25
				E.W.Deutsch	55	0.23
4	Software	216	2.36	J.Anderson	138	0.25
				C.Nguyen	131	0.25
				C.Gonzalez	128	0.25
5	Biomedical Text Mining	271	2.96	W.J. Wilbur	6	0.25
				A. Valencia	5	0.25
				C. Blachke	5	0.23
6	Gene regulation/ Sequence	907	9.91	J.Aerts	125	0.27
				M.A.Quail	96	0.26
				P.J.deJong	82	0.29
7	Functional Genomics	538	5.88	M.Nakao	209	0.29
				P.Carninci	201	0.30
				Y.Hayashizaki	170	0.30
8	Molecular Biology	281	3.07	A.Poustka	321	0.30
				R.Holt	215	0.29
				A.Prasad	205	0.28
9	Computational Biology	1118	12.21	S.L.Salzberg	149	0.29
				J.A.Eisen	139	0.29
				P.Flicek	105	0.27
10	Algorithm	128	1.4	M.Vidal	61	0.25
11	Genetics	1269	13.86	A.Oliveira	60	0.20
				A.G.Uitterlinden	305	0.31
				H.Wichmann	256	0.31
12	System Biology	50	0.55	T.D.Spector	244	0.31
				A.A.Sharov	53	0.27
				Y.Piao	49	0.27
13	Computational Biology	114	1.25	D.L.Longo	5	0.27
				A.Helgason	77	0.26
				G.Hallmans	76	0.28
14	Evolutionary Genomics	542	5.92	U.Styrkarsdottir	68	0.30
				V.Barbe	114	0.25
				J.Johnson	94	0.30
15	Functional Genomics	417	4.56	P.Wincker	89	0.27
				S.J.Chanock	319	0.32
				D.J.Hunter	299	0.33

whereas networks with slow modularity show sparse connections between nodes in different groups (Newman, 2006). To calculate modularity, we use an open source visualization program called JUNG (<http://jung.sourceforge.net/>). Table 11 shows the characteristics of these communities. The biggest community has a general research interest of genomics and includes 2,151 authors, which is about 23.5% of authors on the coauthor network. The second biggest community has 1,269 authors, with top ranked authors A.G. Uitterlinden, H. Wichmann, and T.D. Spector (0.3095, 0.3084, 0.3084, respectively), and a general research interest in genetics. The third biggest community has 1,118 authors, with top ranked authors S.L. Salzberg, J.A. Eisen, and P. Flicek (0.2873, 0.2946, 0.2723,

respectively) and a general research interest of computational biology. The top ranked authors in terms of closeness centrality are Y. Li (0.38) in community 2, D.J.Huter (0.33) in community 15, N. Chatterjee (0.32) in community 1, and S.J.Chanock (0.32) in community 15.

By visualizing the coauthorship network, we are able to map the topology of the bioinformatics field (Figure 5). Figure 5 illustrates that the major driving force of bioinformatics research is genomics related. The neighboring fields of genomics are gene regulation and sequence, protein and RNA sequence, system biology, and genetics. Figure 5 also denotes that the computational side of the field, such as software and algorithms, is located a distance from the main driving force.

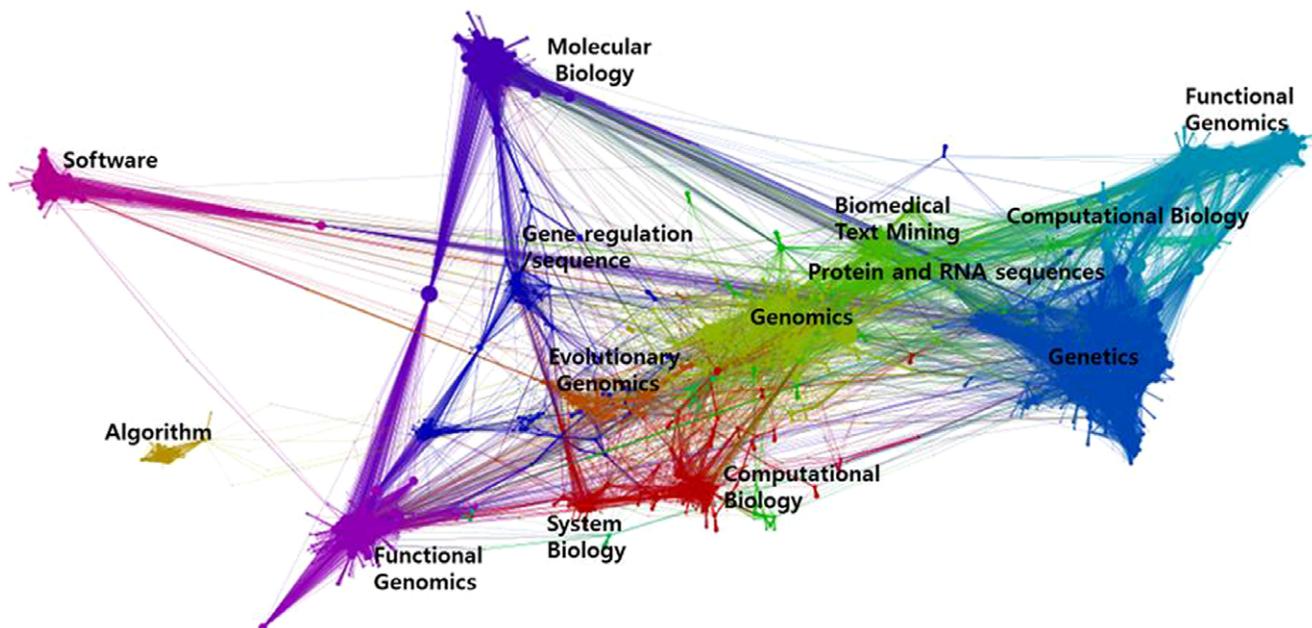


FIG. 5. Visualization of author collaboration map in bioinformatics. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Conclusion

In this study we conducted a bibliometric analysis of the bioinformatics field using PubMed Central data. Citations were extracted from full-text articles for the period 2000 to 2011, which were included in the PubMed Central collections. Both productivity and impact of the bioinformatic community were analyzed, notably for three periods within the last decade: 2000 to 2003, 2004 to 2007, and 2008 to 2011. For productivity, four measures were used: most productive authors, most productive countries, most productive organizations, and most popular subject terms. The most productive first authors were Michael L. Gross, G.A. Petsko, and R. Robinson. In the second author category, E.V. Koonin, Y. Hayashizaki, and P.E. Bourne were the emerging productive authors. The most productive countries were the U.S.A., the U.K., and Germany. The most productive organizations were Stanford University, Harvard University, the University of California, San Diego, and the University of Washington. The most popular subject terms were molecular biology, medical informatics, genetics, and biology.

Research impact was analyzed based on citation counting. To measure influence, we looked at the following aspects: most cited papers, most cited authors, emerging stars, and leading organizations. For most cited papers, in the entire period 2000 to 2011, we identified the following four: “Gene ontology: tool for the unification of biology,” “Initial sequencing and analysis of the human genome,” “Bioconductor: open software development for computational biology and bioinformatics,” and “R: A language and environment for statistical computing.” M. Gerstein, D. Botstein, and

E. Lander were ranked as the top three authors. Upon observing that a few productive authors (G.A. Petsko and J. Wixon) in the period 2000 to 2003 were not included in the influential authors, we further examined those authors and realized that their papers were not research-oriented papers, but one-page-long essays or review papers. This implies that productivity should be considered along with the impact measure to evaluate an author’s research performance. With regard to emerging influential authors, L. Shi, H. Hermsjakob, and S. Roy were identified for the period 2004 to 2007 and D. Goldstein, S. Guo, and W. Baumgartner for the period 2008 to 2011. The highly cited journals and conferences were Proc Natl Acad Sci USA, Nucleic Acids Res, *Nature*, *Bioinformatics*, and *Science*.

The results of productivity and influence analyses indicate that the field of bioinformatics has undergone a significant shift and is now co-evolving with other biomedical disciplines and that the topical focus has shifted over time. We observed that the growth of computational approaches has facilitated the proliferation of biological databases and methods within various biomedical disciplines, which has become an early driving force for the development of bioinformatics. We found that the use of computational methods became prevalent across biomedical disciplines in the period 2000 to 2003, while the use and application of biological databases have been rapidly increasing since 2004. In addition, we observed that the field of bioinformatics contributed to the wide adoption of molecular sequence databases in biomedicine, and that microarray analysis and biological network modeling became two major new topics emerging in the bioinformatics community.

Overall, trends for the periods 2000 to 2003 and 2004 to 2007 were dissimilar, while trends between the periods 2004 to 2007 and 2008 to 2011 were similar. This coincides with the exponential publication growth since 2004. In the collection of test data, the rate of publication increased 114% for the period 2003 to 2004 (499 publications in 2003 and 1,068 in 2004). Since then, the rate of increase has been more than 50%. Except for three authors, the top 15 authors for the period 2000 to 2003 did not appear in the period 2004 to 2011. Among the top 20 countries for the period 2000 to 2003, four were not included in the top 20 for the period 2004 to 2011. Among leading organizations for the period 2000 to 2003, eight organizations were not included for the period 2004 to 2011.

Our future research will include comparing results reported in this paper with citation analysis of Web of Science data to investigate how the field of bioinformatics is represented by PubMed Central. We will also use social network analysis to detect research groups or communities in this field. In addition, a follow-up study will be conducted to identify the knowledge diffusion and transfer patterns in this field using content-based citation analysis. We also intend to explore more comprehensive methods to disambiguate author names such as a probabilistic method proposed by Tang et al. (2012).

Acknowledgments

This work was supported by National Research Foundation of Korea Grant funded by the Korean Government (NRF-2012-2012S1A3A2033291) and by the National Research Foundation of Korea (NRF) grant funded by the Korean Government (No. 2012033242).

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Appendix A1. Top 15 most productive authors.

R	2000–2003		2004–2007		2008–2011	
	First author	Second author	First author	Second author	First author	Second author
1	G.A. Petsko 42	E.V. Koonin 11	L. Gross 124	Y. Hayashizaki 23	R. Robinson 28	P.E. Bourne 17
2	J. Wixon 13	L. Aravind 10	G.A. Petsko 49	P. Carninci 21	G.A. Petsko 23	J. Feng 17
3	V. Anantharaman 5	A. Valencia 8	R. Robinson 39	P.O. Brown 17	C. Sedwick 21	L. Peltonen 17
4	S. Brenner 5	P.O. Brown 7	M. Hoff 19	P.E. Bourne 14	J. Gitschier 16	J. Nielsen 16
5	C. Blaschke 5	R. Apweiler 5	F. Chanut 17	M.B. Eisen 14	R. Meadows 14	M.B. Gerstein 16
6	C.A. Semple 4	C.A. Ouzounis 5	H. Parthasarathy 10	D.R. Flower 13	L. Gross 13	B.Ø. Palsson 16
7	S. Oliver 4	L. Wang 5	P.E. Bourne 9	N. Barkai 12	R. Jones 10	Y. Hayashizaki 16
8	L.M. Iyer 4	J. Hinds 4	R. Jones 9	Y. Li 12	D.G. Nathan 10	C.M. van Duijn 15
9	K.C. Woodwark 4	I.B. Rogozin 4	M. Inman 9	S. Pääbo 10	M. Hoff 9	P. Wincker 15
10	L. Aravind 3	G.M. Rubin 4	J. Gitschier 8	M. Tomita 10	J. Bohlin 7	T.D. Spector 15
11	G. Xie 3	K. Hashimoto 4	P.D. Taylor 8	S.L. Salzberg 9	K. Heller 7	
12	K.S. Makarova 3	Y.I. Wolf 4	H. Nicholls 6	M. Gerstein 9	A. Sharma 6	P. Deloukas 14
13	M. Crossley 3	R.A. Jensen 4	V. Gewin 5	S.G. Oliver 9	R. Gupta 5	H. Wichmann 14
14	E.V. Koonin 3	O.K. Pickeral 3	R. Gowthaman 5	J.A. Eisen 9	Y. Sun 5	A.J. Butte 14
15	J.C. Rockett 3	L. Rychlewski 3	L. Kashyap 5	B.Ø. Palsson 9	X. He 5	E.E. Schadt 13
	J.M. Bujnicki 3	G. Kelsoe 3	P.R. Painter 5	T.K. Attwood 9	S. Ranganathan 5	G.P. Raghava 13
	D.A. Liberles 3	S.L. Forsburg 3			W. Mair 5	O. Kohlbacher 13
		P. Bork 3				M. Mann 13
		H. Reichert 3				E. Barillot 13
		S.E. Celniker 3				S. Ranganathan 13
		M. Tyers 3				E. Ruppin 13
		S.W. Scherer 3				A.G. Uitterlinden 13
		J. Greene 3				
		M. Gerstein 3				
		R.A. Gibbs 3				
		R. Gonzalez-Duarte 3				
		C.A. Bonner 3				

Appendix A2. Highly cited paper.

R	2000–2003			2004–2007			2008–2011		
	Paper	Journal	No. Cited	Paper	Journal	No. Cited	Paper	Journal	No. Cited
1	Gene ontology: tool for the unification of biology. The Gene Ontology Consortium	Nat Genet	948	Bioconductor: open software development for computational biology and bioinformatics	Genome Biol	395	The Pfam protein families database	Nucleic Acids Res	112
2	Initial sequencing and analysis of the human genome	Nature	465	R: A language and environment for statistical computing	R: A language and environment for statistical computing	304	KEGG for linking genomes to life and the environment	Nucleic Acids Res	104
3	Significance analysis of microarrays applied to the ionizing radiation response	Proc Natl Acad Sci USA	349	Transcriptional regulatory code of a eukaryotic genome	Nature	234	Mapping short DNA sequencing reads and calling variants using mapping quality scores	Genome Res.	91
4	The Protein Data Bank	Nucleic Acids Res	341	Linear models and empirical bayes methods for assessing differential expression in microarray experiments	Stat Appl Genet Mol Biol	222	miRBase: tools for microRNA genomics	Nucleic Acids Res	80
5	Cytoscape: A software environment for integrated models of biomolecular interaction networks	Genome Res	325	Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles	Proc Natl Acad Sci USA	217	Mapping and quantifying mammalian transcriptomes by RNA-Seq.	Nat Methods	71
6	Initial sequencing and comparative analysis of the mouse genome	Nature	287	MUSCLE: Multiple sequence alignment with high accuracy and high throughput	Nucleic Acids Res	215	Database resources of the National Center for Biotechnology Information	Nucleic Acids Res	65
7	Exploration, normalization, and summaries of high density oligonucleotide array probe level data	Biostatistics	267	Genome sequencing in microfabricated high-density picolitre reactors	Nature	193	Ensembl 2008	Nucleic Acids Res	65
8	BLAT—the BLAST-like alignment tool	Genome Res	235	A haplotype map of the human genome	Nature	186	Accurate whole human genome sequencing using reversible terminator chemistry	Nature	64
9	A comparison of normalization methods for high density oligonucleotide array data based on variance and bias	Bioinformatics	221	WebLogo: A sequence logo generator	Genome Res	179	Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources	Nat Protoc	57
10	A comprehensive analysis of protein-protein interactions in <i>Saccharomyces cerevisiae</i>	Nature	217	A gene atlas of the mouse and human protein-encoding transcriptomes	Proc Natl Acad Sci U S A	174	Alternative isoform regulation in human tissue transcriptomes	Nature	56
11	The sequence of the human genome	Science	216	The Pfam protein families database	Nucleic Acids Res	172	The UCSC Genome Browser Database: 2008 update	Nucleic Acids Res	56
12	Transcriptional regulatory networks in <i>Saccharomyces cerevisiae</i>	Science	216	Network biology: Understanding the cell's functional organization	Nat Rev Genet	167	The complete genome of an individual by massively parallel DNA sequencing	Nature	54
13	David: Database for annotation, visualization, and integrated discovery	Genome Biol	212	MicroRNAs: Genomics, biogenesis, mechanism, and function	Cell	162	SOAP: short oligonucleotide alignment program	Bioinformatics	53
14	Functional organization of the yeast proteome by systematic analysis of protein complexes	Nature	208	Proteome survey reveals modularity of the yeast cell machinery	Nature	157	Ultrafast and memory-efficient alignment of short DNA sequences to the human genome	Genome Biol.	51
15	EMBOSS: the European Molecular Biology Open Software Suite	Trends Genet	207	Global landscape of protein complexes in the yeast <i>Saccharomyces cerevisiae</i>	Nature	153	The transcriptional landscape of the yeast genome defined by RNA sequencing	Science	48
16	Genomic expression programs in the response of yeast cells to environmental changes	Mol Biol Cell	207	The Gene Ontology (GO) database and informatics resource	Nucleic Acids Res	149	Ensembl 2009	Nucleic Acids Res	46
17	KEGG: Kyoto Encyclopedia of Genes and Genomes	Nucleic Acids Res	206	Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project	Nature	146	Widespread changes in protein synthesis induced by microRNAs	Nature	46
18	Summaries of Affymetrix GeneChip probe level data	Nucleic Acids Res	200	NCBI Reference Sequence (RefSeq): A curated non-redundant sequence database of genomes, transcripts and proteins	Nucleic Acids Res	145	The BioGRID Interaction Database: 2008 update	Nucleic Acids Res	44
19	Systematic identification of protein complexes in <i>Saccharomyces cerevisiae</i> by mass spectrometry	Nature	190	Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls	Nature	144	Velvet: algorithms for de novo short read assembly using de Bruijn graphs	Genome Res	44
20	Primer3 on the WWW for general users and for biologist programmers	Bioinformatics Methods and Protocols: Methods in Molecular Biology	187	MEGA3: Integrated software for Molecular Evolutionary Genetics Analysis and sequence alignment	Brief Bioinform	141	Highly integrated single-base resolution maps of the epigenome in <i>Arabidopsis</i> .	Cell	42

Appendix A3. Highly cited first and second authors.

R	2000–2003				2004–2007				2008–2011			
	First author	No. Cited	Second author	No. Cited	First author	No. Cited	Second author	No. Cited	First author	No. Cited	Second author	No. Cited
1	M. Gerstein	168	D. Botstein	2752	M. Gerstein	161	E. Lander	1391	M. Gerstein	54	R. Durbin	421
2	J. Storey	160	P. Bork	1933	J. Yates	114	P. Bork	1317	M. Mann	35	E. Birney	295
3	T. Speed	157	E. Lander	1835	D. Smith	109	R. Apweiler	1250	A. Wagner	34	M. Snyder	211
4	E. Koonin	151	P. Brown	1812	M. Mann	94	E. Birney	1091	B. Palsson	33	E. Eichler	206
5	R. Tibshirani	125	G. Rubin	1735	A. Wagner	87	R. Irizarry	1085	M. Kuhn	32	R. Finn	198
6	B. Palsson	103	G. Sherlock	1651	B. Palsson	87	W. Kent	1036	R. Stevens	29	T. Hubbard	195
7	D. Swofford	100	E. Koonin	1558	L. Serrano	82	M. Gerstein	1032	M. Vingron	27	P. Flicek	189
8	J. Yates	100	S. Lewis	1510	B. Smith	81	D. Haussler	1025	D. Smith	26	E. Mardis	185
9	A. Brazma	94	W. Kent	1489	L. Shi	77	R. Durbin	925	Y. Guo	26	J. Ruan	177
10	M. Vingron	94	E. Birney	1464	J. Storey	76	D. Wheeler	907	M. Ritchie	24	D. Wheeler	176
11	S. Henikoff	86	M. Ashburner	1459	H. Hermjakob	72	G. Smith	904	E. Ruppin	24	A. Bateman	176
12	R. Russell	80	R. Tibshirani	1436	P. Bourne	70	B. Palsson	897	H. Hermjakob	23	S. Jones	171
13	G. Churchill	80	D. Haussler	1426	S. Mukherjee	70	R. Gibbs	880	J. Yates	23	J. Vogel	170
14	A. Wagner	72	J. Cherry	1403	R. Russell	69	M. Vidal	857	R. Breaker	23	R. Gibbs	169
15	M. Mann	69	T. Speed	1386	S. Oliver	67	M. Daly	841	E. Koonin	23	J. Smith	167
16	D. Smith	68	C. Ball	1361	J. Reed	67	T. Consortium	826	S. Jones	22	B. Ballester	163
17	I. Kohane	66	J. Matese	1308	S. Roy	66	S. Griffiths-Jones	819	A. Millar	22	E. Kulesha	162
18	E. Lander	65	S. Eddy	1225	A. Brazma	66	D. Bartel	811	A. Johnson	21	P. Bork	159
19	D. Jones	64	H. Butler	1211	J. Johnson	65	R. Gentleman	788	O. Keskin	21	E. Sonnhammer	159
20	J. Johnson	64	M. Harris	1209	R. Stevens	64	R. Edgar	777	N. Barkai	21	S. Haider	155
					W. Noble	64			J. Johnson	21		
					D. Rhodes	64						

Appendix A4. Emerging stars.

R	2004–2007 New Stars		2008–2011 New Stars	
	Name	Citation Count	Name	Citation Count
1	L. Shi	77	D. Goldstein	18
2	H. Hermjakob	72	S. Guo	18
3	S. Roy	66	W. Baumgartner	18
4	F. Spencer	55	P. Kharchenko	17
5	G. Smyth	53	R. Nussinov	17
6	X. Guo	51	T. Manolio	17
7	B. Shapiro	50	F. Leitner	16
8	K. Strimmer	49	M. Pop	16
9	D. Robertson	48	S. Cheung	16
10	E. Ruppin	47	T. Gibson	16
11	M. Bauer	47	M. Brylinski	15
12	S. Wilhite	46	A. Dunker	14
13	Y. Guo	46	B. Ge	14
14	M. Cortese	44	C. Croce	14
15	C. Myers	40	H. Saini	14
16	G. Ast	39	J. Shendure	14
17	L. Hunter	39	M. Tasan	14
18	L. Pachter	39	P. Froguel	14
19	D. Kell	38	R. Nilsson	14
20	P. Tompa	38	S. Horvath	14
			Y. Nikolsky	14