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Understanding the Evolution of NSAID: A Knowledge Domain Visualization Approach to Evidence-Based Medicine

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Abstract

Finding the most rigorous, updated, and well received clinical evidence is a crucial and challenging task in the practice of Evidence-Based Medicine (EBM). In this article, we describe a knowledge domain visualization-based quantitative approach that is designed to support the task of searching for high-quality clinical evidence in the medical literature. We illustrate the use of this new approach with the knowledge domain of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). A sample of the literature is visualized in a base map depicting structural and temporal properties of emerging themes and references made by such themes over time. In addition, the visualization highlights the rigorousness of a published clinical trial in terms of the type of study design retrieved dynamically from PubMed. The contribution of this approach is that it offers users an integrated search environment so that the rigorousness, recentness, and consensus of clinical evidence can be assessed with the support of visual exploration facilities.

1. Introduction

In September 2004, Merck & Co. announced an immediate worldwide withdrawal of its best-selling arthritis drug Vioxx after a three-year colon cancer clinical trial revealed an increased risk of heart attacks 18 months after patients started taking the drug [1]. It was estimated that Merck's Vioxx liability could reach $38 billion.

This withdrawal has prompted researchers to re-examine the biomedical literature in order to establish whether available clinical evidence might have led to the withdrawal sooner. Many patients are now wondering what would be the best alternative for them [2]. Is there a consensus in the medical literature? What is the big picture of all the available evidence?

Evidence-Based Medicine (EBM) emphasizes the fundamental role of rigorous evidence in making clinical decisions and training [3]. The most rigorous types of evidence include randomized controlled trials (RCTs), systematic reviews (SRs), and meta-analyses because of the least amount of biases in these types of evidence. The general practice of EBM typically follows a 5-step procedure [4, 5]:

1. Identify clinical questions,
2. Search for the best external evidence,
3. Clinically appraise the validity and importance of the evidence,
4. Put it into clinical practice, and
5. Evaluate the performance.

In this article, we focus on the second step, i.e. searching for the best evidence. In addition, we also address the role of clinical evidence in understanding the evolution of a pharmacological field, which is intrinsically evidence-based medicine. The goal of the study is to identify the special needs from the perspective of evidence-based medicine and how knowledge domain visualization can facilitate some of the tasks.

Searching for the best evidence is a critical component of EBM. The complexity of the task is largely due to three factors: 1) the overwhelming size of the search space, 2) the time-critical nature of clinical evidence, and 3) the evasive context to assess the perceived value of specific evidence. The number of medical publications indexed in Medline, for example, has been growing by hundreds of thousands each year. The size of a search space of RCTs along would be still too large. We will give a concrete example of the size problem in subsequent sections of this article. The time-critical nature implies that we need to find not only the most rigorous evidence, but also the most recent and the most valuable ones as perceived by others in the field.

We propose an approach that could potentially compliment conventional search methods with a reduced complexity and reduced costs. In addition to using the type of study design as a search criterion for high-quality evidence, we propose that the citations of a clinical trial article can be used as an additional

indicator of quality. Furthermore, we believe that the position of such articles in networks of other evidence and other articles is also a potentially valuable clue of quality.

The rest of the article is organized as follows. We explain the motivations of our work and introduce the basic concepts and techniques. We describe the implementation of the new method and discussed the findings of preliminary results with reference to existing approaches. The scope of underlying assumptions and their limitations are discussed. Finally, we identify challenging issues to be addressed.

2. Background

2.1. The Strength of Clinical Evidence

In EBM, the quality of clinical evidence is measured by its strength, primarily in terms of its methodological rigorous. A number of widely known classification schemes are outlined below.

Oxford Centre for EBM recommends five levels of evidence, from level 1 (the strongest) to level 5 (the weakest). SRs with homogeneity of RCTs are classified at level 1a. RCTs with a narrow confidence interval are the second best (level 1b).

National Cancer Institute [6] regards randomized, double-blinded controlled clinical trials as the gold standard, i.e. the best evidence. However, it does not give meta-analysis a higher status than randomized studies because of various known weaknesses of meta-analysis [7, 8].

A highly regarded source of evidence is the systematic reviews prepared and maintained by the Cochrane Collaboration [9, 10]. Cochrane reviews' reputation is partly drawn from their regular updates and revisions. Medline, through its web-based interface PubMed, is probably the most widely used source of evidence. A Medline record contains a publication type field to index the type of study design, including *randomized controlled clinical trial*, *clinical trial*, and *meta-analysis*. The provision of the publication type [pt] makes it possible to search for RCTs related to a given topic.

In a recent study of general thoracic surgery, the publication type in Medline records was used to identify meta-analysis and RCTs [5]. They followed the strategy described in [11] by searching for meta-analysis in the publication type field. Similarly, the publication type was also used for searching for RCTs.

Selection criteria based on study types are widely used. However, the task could be further simplified by taking into additional criteria.

2.2. Additional Criteria of Quality

A potentially effective criterion for high-quality evidence is how frequently a clinical trial article or a meta-analysis article has been referenced by subsequent studies of others. The assumption is that clinical evidence reported in a highly cited article tends to be more important than one in a less frequently cited article. We acknowledge that articles can be cited for many reasons, including both positive and negative citations. The rational of our assumption is, regardless of varying citation motivations, if an article has drawn sufficient attention, then it in effect has a place in the knowledge structure.

The citation-based quality indicator is derived from citation analysis of scientific literature. The widely known source of scientific citations is the Science Citation Index (SCI) maintained by the Institute for Scientific Information (ISI).

Citation counts of articles can be seen as the first-order measurements of the perceived values of these articles. One could compile a list of evidence along with citation counts to corresponding articles. However, such lists do not reveal salient relationships between clinical trials. From such lists, we would only know that two clinical trials are highly cited, but we have no way to tell whether the two have ever been considered together and, if so, how frequently.

Co-citations are higher-order relationships that can reveal more insights into a broader context of an article's role in a knowledge domain. Co-citations are instances in which two articles are referenced together in subsequently published articles [12, 13].

2.3. Visualizing Emerging Trends

CiteSpace is a series of design, implementation, and refinement efforts [14-17]. Its primary goal is to enable users visually identify emerging trends and transient patterns in scientific literature. CiteSpace visualizes the evolution of citation and co-citation patterns associated with a knowledge domain over time.

CiteSpace is built on two basic concepts: research fronts and intellectual bases [17]. A research front is defined as a cluster of topical terms that have a sharp increase in their usage. A detected sharp increase is called a burst. Therefore, these terms are called burst terms. A research fronts corresponds to an intellectual base.

We used CiteSpace in a number of domain visualization studies of paradigm shift and abrupt changes, including the superstring revolutions in physics, the mass extinction debates, and emerging trends in research of terrorist events. However, we have not applied the approach to a domain like EBM,

where it is essential to understand the consensus concerning available evidence and how the consensus changes in light of new evidence. To our knowledge, we are not aware of visual exploration tools designed for searching specific types of evidence in the context of their home domain. We propose a conceptual framework to extend the knowledge domain visualization techniques to support evidence search tasks in EBM.

3. Conceptual Framework

The conceptual framework aims to facilitate the search for the best evidence in the medical literature by simplifying the assessment process concerning the rigorous, recentness, and consensus of evidence in a visual exploration environment. In this article, we focus on integrating various cues that can be retrieved from PubMed and the Web of Science. The framework can be extended to incorporate additional sources.

A practical issue is that although PubMed is openly accessible, the Web of Science is subscription-based and it does not permit programmatic access. As the first step towards supporting EBM, we design and implement the following method to easy this problem. Suppose our aim is to locate the best evidence regarding lung cancer treatments. The procedure is as follows:

1. Search for articles in the Web of Science on lung cancer (the search is intentionally broad).
2. Visualize the search results in CiteSpace, including emerging trends and temporal patterns.
3. Automatically annotated articles with specified publication types, namely meta-analysis, randomized controlled clinical trial, and clinical trial.
4. Explore the visualization map and select articles for critical appraisals.
5. (Repeat the procedure periodically or as needed).

In our current implementation, the automated annotation is made possible by retrieving the publication type information from PubMed simultaneously as the system layouts the network. The major advantage of this method is its non-intrusive nature. The only way the user can tell the behind-the-scene search is when an increasing number of articles are annotated with publication types retrieved from PubMed. Because the additional search is so cost-effective and efficient, the user does not even have to save the information locally.

Given the assumption that highly cited clinical evidence tends to be the strongest evidence, we focus on several types of relationships between high-quality evidence and its first- and second-order properties in bibliographic networks. By visualizing various structural and temporal properties of such relationships, we expect that our method can provide a useful tool for EBM practitioners to find the best evidence with improved efficiency.

We expect that the best evidence should demonstrate unique features in the visualizations of associative networks of articles and topic terms. For example, evidence reported in highly cited publications tends to be more valuable than evidence in less frequently cited publications. Evidence appears as hubs of co-citation clusters of articles should be more significant than peripheral ones. We expect to find Meta-analysis as a hub more often than other types of studies.

In the new visualization, the publication type of three types of EBM evidence are marked as '**r**' for randomized controlled clinical trial, '**c**' for clinical trial, and '**m**' for meta-analysis. PubMed allows both '**r**' and '**c**' to be assigned to the same article, hence we may see articles marked with **rc**'s in the map. According to the general consensus in EBM, articles marked with **r**'s or **m**'s are top-level evidence. In addition, **rc**'s and **m**'s with unique topological properties in co-citation networks visualized by CiteSpace should be particularly important, including positions such as hubs and bridges as well as visual attributes such as the size of citation tree rings.

4. Case Study

We illustrate the approach with an analysis of clinical evidence in the literature of Non-steroidal Anti-inflammatory Drug, or NSAID (1990-2004). NSAID has a complex history and it is also involved in recent headline news. More importantly, it is a topic that will continue to evolve. Note that the following background information regarding NSAID was based on a study of the resultant visualizations and a limited number of follow-up searches guided by these visualizations, but we present them earlier so that it gives the reader a meaningful context.

4.1. NSAID

The goal of research in NSAIDs is twofold: improving the effectiveness of anti-inflammatory drugs and reducing adverse side-effects [18]. Vioxx is a member of a family of drugs called Cox-2 selective inhibitors [19]. Cox-2 selective inhibitors were originally introduced as a replacement of an earlier generation of drugs known as non-selective inhibitors, which indiscriminately suppress cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). However, one of the major adverse effects of inhibiting COX-1 is the lower stomach prostaglandin levels, which in turn may cause stomach ulcers and internal bleeding. Compared with non-selective inhibitors, selective

inhibitors of COX-2 do not upset the stomach as much as their earlier counterparts.

Both proton pump inhibitors and histamine H2-receptor blockers can be used to suppress gastric acid. Proton pump inhibitors were found to be more effective. More importantly, proton pump inhibitors have minimal side effects and few significant drug interactions, and they are generally considered safe for long-term treatment. Therefore, proton pump inhibitors are often given as co-prescriptions of non-selective inhibitors. We will return to this topic when we discuss the visualizations.

NSAIDs are widely used not only for their anti-inflammatory, but also analgesic, antipyretic, and (as in case of aspirin) anti-coagulating activity. Studies suggest that NSAIDs prevent colorectal cancer and may protect against the development of Alzheimer's disease. As it was later reported in the mass media on December 22, 2004, the same colon cancer clinical trial that led to the Vioxx withdraw found that Vioxx prevented precancerous colon polyps in some patents.

4.2. Data Collection

Bibliographic records were retrieved from the Web of Science using a search query of (NSAID or (Non-steroidal Anti-inflammatory Drug)). We use the systematic review and meta-analysis [20] as our gold standard. The NSAID dataset consists of 4,921 records. Among them, 3,514 records have cited references. These records are known as citing records. Visualizations represent references cited by these records. Citing records are included if themselves are cited by others.

CiteSpace imports datasets directly and selects the terms of up to four consecutive words from titles, abstracts, and descriptors of citing records. The subsequent analysis includes burst terms only, which are terms with sharply increased frequencies over time. CiteSpace divides the entire time interval into a number of sub-intervals, or time slices. A snapshot network is derived for each time slice. The resultant time series of networks are subsequently merged into a global network. Technical details of the algorithms are described in [14, 17]

CiteSpace supports two visualization views: cluster views and timezone views. Cluster views show networks as the commonly seen types of node-and-link diagrams, whereas timezone views arrange articles and terms in correspondence to the time of their publication or their peak time.

5. Results

5.1. The Profile of the NSAID Literature

Figure 1 depicts the volume of annual publications in NSAID. Articles at Level 0 were cited once or more within the sample of 3,512 articles retrieved from the Web of Science. Articles at Level 3 were cited three times or more. Articles at Level 5 were cited five times or more. It is clear that Level 5 articles are exceptionally rare in comparison to the vast volume of less frequently cited articles. Visualizations generated by CiteSpace typically feature the thin layers only – the cream of the crop – rather than the entire sample.

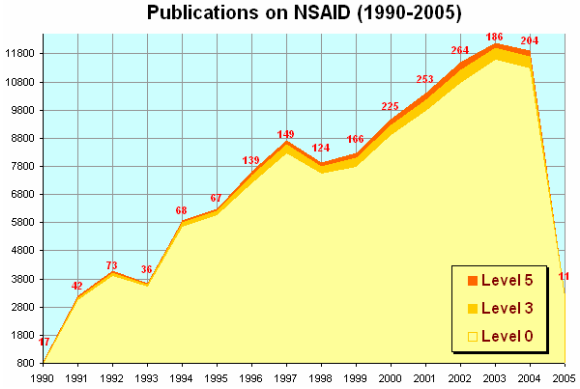

Figure 1. The cream of the crop by citations.

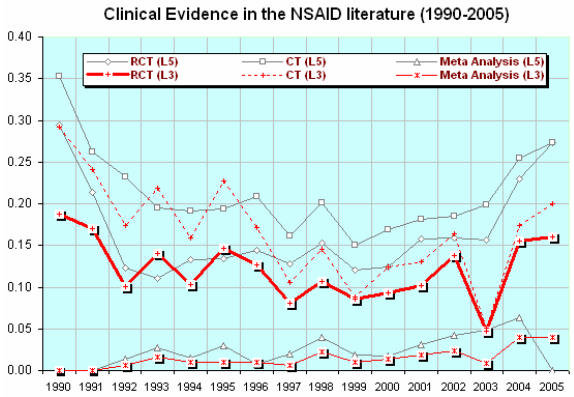

Figure 2. The proportions of various types of Level 3 and Level 5 clinical trial articles in the NSAID literature.

Figure 2 shows the proportions of various types of evidence in the NSAID literature. The average percentage of RCTs among Level 5 and Level 3 articles is 16.6% and 12.2%, respectively. The average percentage of Meta-analysis among Level 5 and Level 3 articles is 2.3% and 1.5%. These figures suggest that evidence papers tend to be cited more often than other types of papers.

5.2. Cluster Views and Time-zone Views

CiteSpace supports two types of visualizations: cluster views and time-zone views. Cluster views visualize a network as a patchwork of a series of snapshot networks taken in consecutive time intervals known as time slices. Common nodes between networks in adjacent time slices are shared in the merged network.

Time-zone views are generated based on a modified force-directed placement algorithm such that nodes are placed in a series of parallel strips known as time zones. CiteSpace also supports visualizations in grayscale as well as visualizations in full color to depict temporal patterns. The tree-ring like circle surrounding a node represents the citation history of the underlying article. The history progresses from the center outwardly.

The type of clinical evidence is marked as **rc**, **c**, or **m**. The position of an evidence node and the size of its citation tree ring can be used as additional search criteria by an EBM practitioner.

Figure 3 shows an example of the visualization of clinical evidence in the literature of NSAID (1995-2005), including four RCTs in unique positions in terms of the network topology and one meta-analysis in a similar position. In essence, papers in such positions have high betweenness centrality, which measures how often an arbitrarily chosen shortest path in the network goes through such nodes.

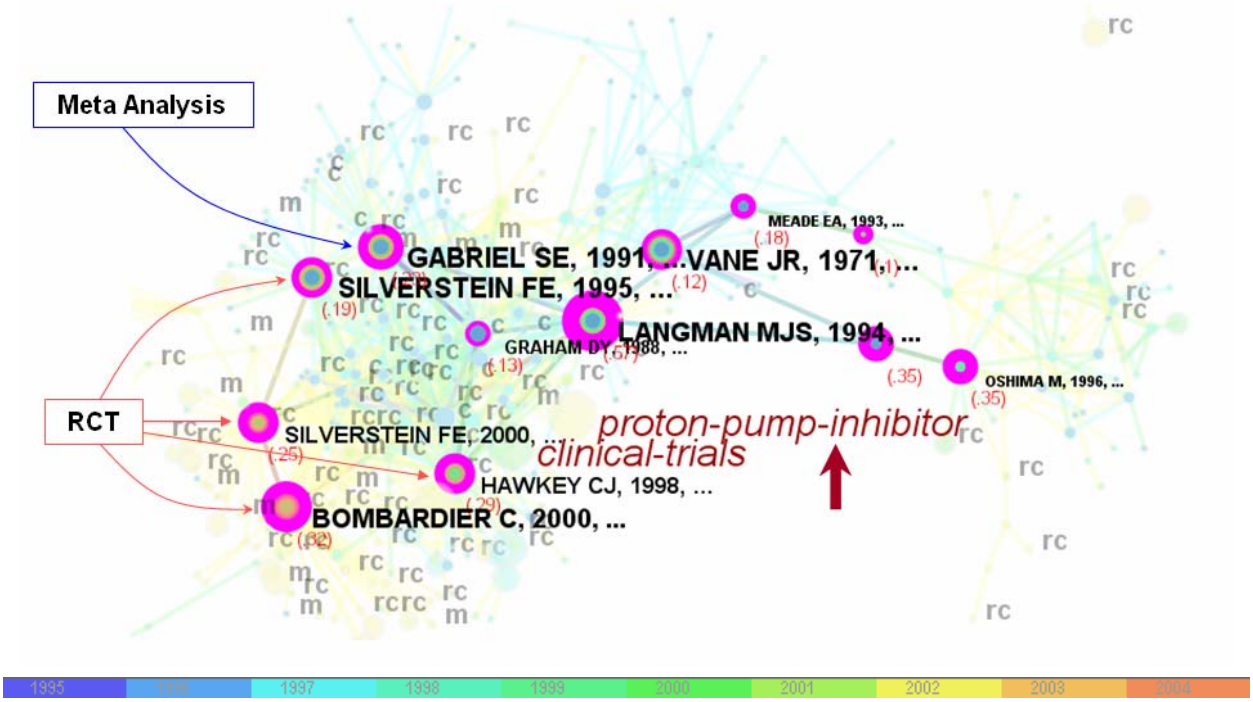

Figure 3. RCTs (rc) and meta-analysis (m) available in a synthesized network visualization of the NSAID literature (1995-2005) (Nodes=399, Links=734). Articles in this visualization must have at least 6 citations. Clinical evidence at strategic positions (in terms of high centrality) is marked by arrowed lines. The sharply increased use of the term proton pump inhibitor is identified.

In CiteSpace visualizations, a line between a term and an article denotes that the article is cited by the hosting article of the term. The colors of lines are time-stamped with earlier connections in blue and the latest in red. The nature of each cluster can be identified by the most prominent term associated with it.

In CiteSpace, one can use a function called marquee selection to select and analyze a cluster of nodes by dragging a rectangle area around nodes of interest. Figure 4 shows five clusters selected in such way. For example, the left-most cluster of 19 nodes is about Alzheimer's disease in relation to NSAID. The upper right cluster of 65 nodes is about selective cox-2 inhibitor.

The overall colors of a cluster indicate its age, either as an emerging one or a long established one. The Alzheimer's disease cluster in Figure 4 has many light-colored lines, suggesting its relatively young age. Similarly, the selective cox2 inhibitor cluster is also relatively young. There are three clusters in the center of the cluster view. We refer them as the upper center, the lower center, and the cluster on the right. The upper center cluster contains 160 nodes, including both articles and terms. It is a long established cluster,

containing terms such as H2-receptor. The lower center cluster is much recent, containing terms such as proton pump inhibitor and non-selective NSAIDs.

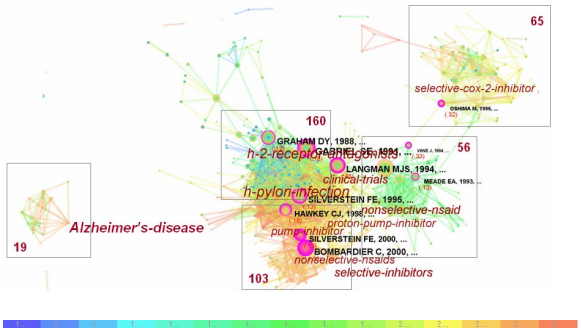

Figure 4 Five clusters selected in a network visualization of the NSAID literature (1990-2004) (Nodes = 499, Links =2,018). The number at the corner of each selected area is the number of nodes included.

Table 1 lists the most frequently found Medical Subject Heading (MeSH) terms in the five clusters. Based on the MeSH terms, the five clusters are identified as the Alzheimer's diseases cluster, the Cyclooxygenase cluster, the colon cancer cluster, the adverse effects of selective inhibitors cluster, and the adverse effects of non-selective inhibitors cluster. The visualization provides an alternative way to locate high-quality evidence. For example, amount the 19 nodes in the Alzheimer's disease cluster, there is a highly cited meta analysis [21], which was cited 43 times in the dataset.

Table 1. Top-5 MeSH terms assigned to the five selected clusters shown in Figure 4.

19	**CLUSTER: Alzheimer Disease**
14	Anti-Inflammatory Agents, Non-Steroidal/*therapeutic use
10	Alzheimer Disease/*epidemiology
8	Alzheimer Disease/*prevention & control
8	Alzheimer Disease/*drug therapy
6	Alzheimer Disease/*pathology
56	**CLUSTER: Cyclooxygenase**
28	Anti-Inflammatory Agents, Non-Steroidal/*pharmacology
26	Cyclooxygenase Inhibitors/*pharmacology
12	Prostaglandin-Endoperoxide Synthase/*genetics
12	Prostaglandin-Endoperoxide Synthase/*metabolism
8	Aspirin/*pharmacology
8	Prostaglandins/*biosynthesis
8	Thiazines/*pharmacology
8	Thiazoles/*pharmacology
65	**CLUSTER: Colonic Neoplasms**
22	Anti-Inflammatory Agents, Non-Steroidal/*pharmacology
20	Colonic Neoplasms/*prevention & control
18	Apoptosis/*drug effects
16	Aspirin/*therapeutic use
14	Anti-Inflammatory Agents, Non-Steroidal/*therapeutic use
103	**CLUSTER: Adverse Effects of Selective Inhibitors**
46	Anti-Inflammatory Agents, Non-Steroidal/*adverse effects
34	Cyclooxygenase Inhibitors/*therapeutic use
34	Anti-Inflammatory Agents, Non-Steroidal/*therapeutic use
24	Cyclooxygenase Inhibitors/*pharmacology
22	Isoenzymes/*antagonists & inhibitors
160	**CLUSTER: Adverse Effects of Traditional, Non-selective Inhibitors**
160	Anti-Inflammatory Agents, Non-Steroidal/*adverse effects
42	Gastrointestinal Hemorrhage/*chemically induced
36	Aspirin/*adverse effects
28	Gastrointestinal Diseases/*chemically induced
26	Peptic Ulcer/*chemically induced
24	Helicobacter pylori

Figure 5 shows a time-zone view of the evolution of NSAID. The visualization contains two types of entities: cited articles, and citing terms. The distributions of various types of clinical evidence are marked in terms of their study design types. For example, the 1991 article by Gabriel near to the upper left corner of the map is marked with a letter **m** on the right shoulder of the node, which means that the article is a meta-analysis. Similarly, we know that the 1998 article by Hawkey at the top of the 1998 time zone is a randomized clinical trial because it is marked as **rc**.

The visualization reveals several important clues of the evolution of NSAID. The earliest prominent term is prostaglandin-synthesis in the 1991 time zone, which is the foundation and the early focus of NSAID. The next term peaked is h-2 receptor antagonists in 1994. In the 1999 time zone, terms such as proton pump inhibitors and anti-inflammatory drug gastropathy are attached to the main stream, highlighting the adverse effects of non-selective inhibitors. The term selective-cox-2-inhibitor is prominent in the 2000 time zone. The term cost-effectiveness also appeared in the same time, underlying the fact that selective inhibitors are more

expensive than traditional ones. The 2001 time zone contains terms colon-cancer-cells and h-pylori-infection. More terms related to cox-2-sepcific-inhibitors and gastrointestinal-safety in 2002. In 2003, Alzheimer's disease emerged strongly (shown in the map as s-disease near the top). In 2004, the most prominent research front terms are proton pump inhibitor and pump inhibitor. Note that this is the second peak of proton pump inhibitor; its first peak was in 1999.

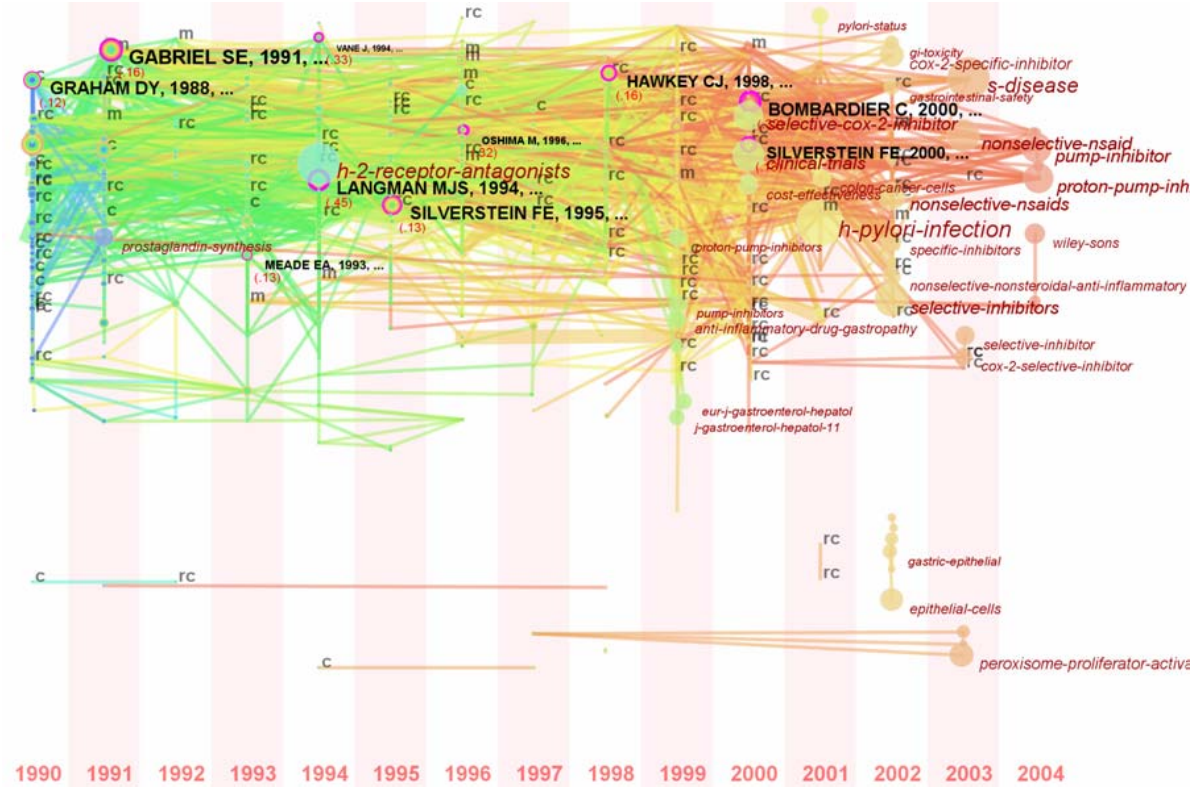

Figure 5 The time-zone view of the evolution of the NSAID literature. The network contains 499 nodes and 2,018 lines. Clinical evidence is marked according to its publication type.

6. Discussions and Conclusions

From these prominent thematic terms we can form a number of hypotheses of what happed in the literature as the field of NSAID evolved over the past decade. As the first step, we want to establish that there are evidently a few lines of research running in parallel in NSAID. The next step is to verify the role of specific clinical evidence in the process of change.

The most interesting and potentially intriguing hypothesis is that the revival of proton pump inhibitor in 2004 was connected to the increased heart-attack risk found in selective inhibitors such as Vioxx. If there is indeed a tendency to fall back to the earlier non-selective anti-inflammatory agents, then the regained attention of proton pump inhibitors will make sense because they were co-prescribed in the past with non-selective inhibitor drugs.

We found that clinical evidence as a group tends to be cited higher than other types of articles in the NSAID example. The visualizations have enabled us to identify RCTs and meta-analysis in unique positions within the network of research front terms and intellectual base articles. Meta-analysis in such positions would be the best candidate for examining the consensus based on existing evidence. RCTs in similar positions would be the strongest evidence that must be taken into account when making clinical decisions.

The purpose of the visualization is not to provide direct answers to the questions raised. Instead, we intend to provide the practitioners of EBM with an alternative tool that allows them to identify high-quality clinical evidence in the changing literature of medicine more effectively, especially in light of the rigorous, recentness, and consensus of available clinical evidence. In terms of training and education, it is particularly encouraging that the visualization appears to portrait a convincing timeline of the evolution of NSAID. This approach can be valuable for researchers who are preparing systematic reviews of clinical evidence by simplifying the search and selection of critical evidence to review. Furthermore, the contextual view of how

existing evidence is cited in the literature provides valuable alternative viewpoints for systematic reviews.

The preliminary results are encouraging because the automatic annotation technique provides a harmonic way to combine two different sources of evidence, namely the citation patterns and the study design types of clinical evidence. There is a substantial amount of work to be done before it can be used by healthcare educators and practitioners. For example, it requires systematic validations of detailed findings against existing gold standards. This case study also has practical and theoretical implications to knowledge domain visualization. Since events such as the Merck's withdraw of Vioxx might fall outside the range of a traditional domain analysis, it remains to be done to integrate various interrelated components into a fully responsive system so that trends detected in the literature of medicine and life sciences can be directly connected to decision making and other healthcare activities in more timely manner.

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Note

CiteSpace is available at
http://cluster.cis.drexel.edu/~cchen/citespace

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