To what degree has the vast space of higher-order knowledge combinations been explored and how has it evolved over time? To address these questions, we first develop a systematic approach to measuring combinatorial innovation in the biomedical sciences based upon the comprehensive ontology of Medical Subject Headings (MeSH) developed and maintained by the US National Library of Medicine. As such, this approach leverages an expert-defined knowledge ontology that features both breadth (27,875 MeSH analyzed across 25 million articles indexed by PubMed that were published from 1902 onwards) and depth (we differentiate between Major and Minor MeSH terms to identify differences in the knowledge network representation constructed from primary research topics only). With this level of uniform resolution we differentiate between three different modes of innovation contributing to the combinatorial knowledge network: (i) conceptual innovation associated with the emergence of new concepts and entities (measured as the entry of new MeSH); and (ii) recombinant innovation, associated with the emergence of new combinations, which itself consists of two types: peripheral (i.e., combinations involving new knowledge) and core (combinations comprised of pre-existing knowledge only). Another relevant question we seek to address is whether examining triplet and quartet combinations, in addition to the more traditional dyadic or pairwise combinations, provide evidence of any new phenomena associated with higher-order combinations. Analyzing the size, growth, and coverage of combinatorial innovation yield results that are largely independent of the combination order, thereby suggesting that the common dyadic approach is sufficient to capture essential phenomena. Our main results are twofold: (a) despite the persistent addition of new MeSH terms, the network is densifying over time meaning that scholars are increasingly exploring and realizing the vast space of all knowledge combinations; and (b) conceptual innovation is increasingly concentrated within single research articles, a harbinger of the recent paradigm shift towards convergence science.

Scholars of the living world have long been faced with the monumental task of systematically cataloging the vast space of biological entities and subtypes. The emergence of computational and informatic capabilities has since accelerated our ability to measure interactions within and between biological entities [1], such that the task has since shifted towards modeling multi-scale spatio-temporal complexity [2–4]. This new representation is manifestly a problem of combinatorics. Yet surveying the entire frontier of that which is presently known—what scholars have termed the ‘adjacent possible’ [5, 6]—is a compounding task. For this reason, many computational approaches seek to leverage vast ontologies of codified knowledge and their relationships in order to automate the survey of higher-order multi-component interactions. Examples of this systematic approach to accelerating search and discovery include combinatorial exploration of chemical compound ontologies to identify new drugs [7] and novel thermoelectric materials [8].

For the same reasons, combinatorial approaches to search and discovery may prove valuable in exploring the vast solution space associated with many complex multi-dimensional challenges faced by society [4, 9–11]. Against this backdrop, here we develop and apply a systematic ontology-based approach for measuring the size, growth and structure of combinatorial innovation in the biomedical sciences. This work contributes to prior innovation research utilizing article-level keywords that have either been manually assigned [1, 12–15] or inferred by way of natural language processing of full or partial article text [8, 16–18]; other notable approaches to the same end involve identifying atypical citation combinations occurring within the reference lists of individual article [19].

In order to avoid redundant and misspecified keywords, we leverage an existing and exogenously-defined ontology of article-level keywords known as Medical Subject Headings (MeSH) [20]. As such, this work contributes to a growing literature operationalizing measures of innovation and knowledge networks [1, 13, 14, 21–23] that take advantage of the clean structure and impressive historical coverage of research annotated by MeSH. This multi-level biomedical ontology was developed and continually maintained by the US National Library of Medicine [20, 21], and is comprised of more than 30,000 Medical Subject Headings (MeSH) used as article-level keywords to classify ∼30 million articles indexed within PubMed. MeSH are organized in a quasi-hierarchical ontology organized around 16 branch categories extending up to 13 levels deep, thereby defining different knowledge domains at various levels of specificity, while further facilitating the definition of a metric distance between individual keywords [1, 9, 11].

As in related work [14, 24, 25], our main objective is to measure the size and marginal growth of recombinant innovation associated with the entry of new knowledge, operationalized here by tracking the first appearance of new MeSH terms and also...
higher-order MeSH combinations. To this end, Mishra and Torvik [14] recently analyzed the age of MeSH terms and MeSH-MeSH pairs occurring in research articles in order to develop quantitative measures of conceptual novelty. Continuing in this spirit, we track all MeSH combinations up to 4th order (i.e., tabulating unique quartets comprised of 4 MeSH combinations) according to the following four objectives:

1. develop a measurement framework for combinatorial knowledge production that supports analyzing higher-order MeSH-MeSH (knowledge-knowledge) combinations;

2. quantify the evolution of biomedical innovation by systematically recording all unique MeSH combinations over time, in particular the first appearance of each. At the aggregate level, this integrative tabulation facilitates defining the size, growth, and coverage of all possible combinations within the knowledge network;

3. analyze the relative rates of two principal modes of innovation – conceptual and recombinant – by tracking the entry of new MeSH, in particular the degree to which new MeSH combinations correspond to two submodes of recombinant innovation – core and peripheral. To be specific, here peripheral recombinant innovation refers to non-incremental innovation in which a new MeSH combination also includes a new MeSH term, a mechanism capturing combinatorial innovation at the knowledge frontier. The complementary scenario, core recombinant innovation, refers to new combinations constructed from pre-existing entities only, and is a proxy for more integrative refinements to the knowledge network.

4. account for variation in the significance of article descriptors by distinguishing between primary and secondary keywords.

As in related work [1], this last objective manifests as parallel analyses, one based upon “All” MeSH, and the second focusing only on “Major” MeSH which capture just the primary research topics, which thereby facilitates insightful juxtaposition.

**Background**

This work contributes to the literature on combinatorial innovation, which has been developed in several research streams: from theoretical approaches in economics to specify the knowledge production function as it relates to economic growth [26]; to non-equilibrium statistical physics models of evolutionary processes based upon combinatorial interactions [6]; and empirical research on the evolution of industrial innovation based upon analysis of the frequency of International Patents Classification (IPC) categories [24, 27, 28].

Approaches to quantifying the growth of knowledge production use various methods to define the space of entities and their combinations, which together serve as a proxy for recombinant innovation. For example, scholars have sought to measure the number of inventive classes and their distinct inventive combinations, showing that the number of distinct combinations increases proportion to the number of new patents, meaning that the amount of new combinations per new patent is roughly constant [24]. Supporting evidence in the academic domain, based upon research spanning all fields of science, finds that the number of unique phrases in research article titles (a proxy for knowledge production based upon the total size of the topic space) also follows a linear growth pattern, despite the volume of scientific research production (measured as the total number of research articles published per year) following exponential growth pattern [25] a. From this perspective, the dichotomy of exponential growth of production and linear growth of innovation [24, 25] suggests that the knowledge network – comprised of entities and their relationships that are codified and accepted by communities of scholars – evolves by way of densification, as opposed to expansion at its surface deriving from the addition of new concepts – which is a research question that the present work seeks to address.

Another consideration are the drivers of change. The exponential growth of the researcher population combined with invaluable productivity innovations (e.g. computer-aided word processing and the digitization of journals) together largely explain the exponential trends in scientific production [29]. Drivers of innovation are less well-understood, as they more acutely depend on institutional and behavioral factors. The propensity for researchers to integrate existing knowledge, as opposed to exploring new knowledge and knowledge-knowledge combinations, is largely affected by the risks associated with exploration [19, 27]. One should also consider the practical limits that define the situational objectives and outcomes of knowledge producing activities. A research project is typically focused around a few specific research questions grounded in prior research, which may explain why contributions to innovation by individual articles appears to be incremental (linear) [24, 25]. Another consideration is the compounding effort associated with combinatorial integration of new knowledge. That is, for each incremental advancement

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[a] The details of how knowledge and its proxies are defined are likely to affect the assessment of innovation and its dynamics. For example, measuring the space of entities by tokenizing natural language [25] adopts an endogenous definition of the concept space, since authors independently construct titles from select words that largely reflect disciplinary and other contextual factors. Instead, exogenous constructions of the concept space are likely to be more uniform, and thereby avoid the challenges of accounting for stylistic and semantic aspects of language evolution. However, the tradeoff to an exogenous classification is the effort required to systematically tag all research articles, either manually or automatically. In the present case, individual MeSH terms are manually assigned to research articles by expert annotators at the US National Library of Medicine.
This strategy is not just practical, but also reasonable, considering that the average PubMed article is tagged by numerous MeSH keywords. While we only present results for 1975 and onwards, it’s important to note that we started tabulating the first occurrence of each realized simplex from 1902 and onwards to avoid left-censoring bias of cumulative tallies.

### Methodology

#### Motivation

We build on recent work analyzing higher-order multi-entity relationships, extending beyond the dyadic network framework whereby at most two fundamental entities or nodes are connected by a link, to a higher-order representation based on a simplicial set, whereby connectivity among multiple nodes is represented by a hyperedge. Such a generalization is in principle a powerful elaboration; however, depending on the underlying processes giving rise to multi-entity combinations, such higher-order representation may not necessarily yield new insights beyond the information contained in the traditional pairwise-interaction network representation.

Indeed, it could be that new phenomena identified by higher-order representations are redundant, or otherwise inconsequential, given that they may be increasingly rare, with implications at the margins of what is measurable or inferable. By way of analogy, consider the diagramatic framework for tabulating all contributions to particle-particle scattering amplitudes championed by physics Nobelist Richard Feynman, which brilliantly reduces to a multiplicity of fine-structure constants $\alpha = 1/137$, such that each Feynman diagram vertex contributes a relative likelihood factor of $\sqrt{\alpha}$.

Hence, increasingly elaborate Feynman diagrams involving higher-order particle interactions are also significantly less likely to occur, and hence contributes just marginally to the overall likelihood of particle-particle interaction. Such could also be the case for the information captured in higher-order knowledge combinations, and is one of the motivations for the systematic approach developed in this study.

More specifically, in order to explore whether any “new physics” emerges when accounting for higher orders of combinatorial innovation, we systematically tabulated all combinations of article-level keywords through the fourth order – i.e., tracing all distinct $k$-simplices of order $k = 1$ (i.e., MeSH pairs), $k = 2$ (MeSH triads) and $k = 3$ (MeSH quartets) – over time as they emerge in the biomedical literature. In this way, we are primarily using the simplex framework to facilitate exact counting of unique keyword combinations, and as such in this work we do not analyze the aggregate simplicial complex comprised of the union of all simplices into a higher-order network.

Systematic assessment of the number of distinct knowledge combinations takes explicit advantage of the ontological features of the MeSH system, which catalogs unique concepts and entities by way of its thesaurus-like design. In this way, the MeSH ontology overcomes the limitations of entity representations that suffer from redundancy (two different terms that represent the same concept) and simplicity (terms that are too shallow in their definition, such as in the case of broad category systems). These problems tend to emerge when the system of entities are not homogenized, reflecting variation in authors, disciplines or other linguistic features of their description that manifests as a big challenge when defining topic categories from raw text. In this way, the MeSH ontology reduces the degrees of freedom in the representation of biomedical knowledge, while at the same time accounting for the vast variability in research topic breadth and depth. For example, “Telomere Homeostasis” [MeSH Unique ID D059505] which is synonymous with other entry terms “Telomere Length Maintenance” and “Telomere Lengthening”, yet is distinct from “Telomere Shortening” [MeSH Unique ID D059506], which is a distinct concept relating to the process of Telomere growth as opposed to the “Telomere” entity itself, which is an altogether distinct MeSH term [D016615].

In summary, the hierarchical structure of the MeSH knowledge tree provides adequate breadth, specificity, and uniformity to systematically perform historical analysis of combinatorial innovation at high conceptual resolution. In particular, since the ontology is controlled and maintained by a select unit at the National Library of Medicine, which has back-catalogued articles to the early 20th century (the first article with MeSH is from 1902), then the first appearance of a given MeSH or MeSH simplex can be accurately recorded and tabulated. In what follows, we focus on comparing trends observed in the modern era of biomedical research (1975-present) since the coverage of PubMed vastly expanded in the post-war era, and also because the number of MeSH per article approached present levels since around 1975 [13, 14].

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[b]This strategy is not just practical, but also reasonable, considering that the average PubMed article is tagged by numerous MeSH keywords – see Fig. 1B. At this resolution level, the set of $n_p$, MeSH, on average ranging between 8 to 10 per article, are sufficient to capture both core and peripheral concepts defining the research. And so the value of one additional MeSH term is marginal at this level of detail. Yet, if we were to consider two articles, one with $n_p$ MeSH and another with $n_p + 1$ MeSH, where all MeSH in the first article belong to the second article, then the articles differ in just the one additional MeSH term. It seems unreasonable to consider these articles as completely distinct, which would be the case if for each article we only tabulated the single ($n_p$-1)-simplicial complex formed by all the MeSH. Instead, we systematically decompose an article into all $k$-simplex combinations sampled from the set of $n_p$, MeSH, which is also robust to the time-dependent variation in the average number of MeSH per article over time.

[c]While we only present results for 1975 and onwards, it’s important to note that we started tabulating the first occurrence of each realized simplex from 1902 and onwards to avoid left-censoring bias of cumulative tallies.
FIG. 1: Framework for quantifying the growth of combinatorial knowledge associated with conceptual and recombinant innovation.

We used the vast ontology of Medical Subject Headings (MeSH) developed and systematically implemented by the U. S. National Library of Medicine within the PubMed research article index. Owing to our focus on measuring recombinant innovation, we only analyzed articles featuring at least two MeSH belonging to at least one of the following biomedical-oriented MeSH branches: A, B, C, D, E, F, G, J, L, N.

The six branches excluded from our analysis (H, I, K, M, V, Z) tend to focus around non-biomedical concepts and entities such as geographic locations and disciplinary contexts; see [1] for more details regarding the MeSH knowledge network ontology as well as our select biomedical branch criteria. (A) Number of research articles from PubMed index analyzed by year; we only analyzed article types classified in PubMed as “Journal Article” or “Review” and excluded other content types such as commentaries, editorials and the like. (B) The average number of MeSH terms per article counted in two ways: (i) counting “All” MeSH terms (dashed line); (ii) counting only “Major” MeSH terms indicated by an (*) in PubMed records (solid line). (C) An illustrative article published in year $Y_p$ that features eight total MeSH ($m_p=8$), with four of those being Major category descriptors ($M_p=4$), which represent the article’s principal research topics. (D) From the resulting set of MeSH (either All or just Major) we then calculate all combinations of $k+1$ MeSH represents a unique k-Simplex. (E-F) Distinguishing between two modes of innovation. (E) Conceptual innovation: the entry of new MeSH terms representing new concepts, entities and existing entity sub-types is one source for new k-Simplices. (F) Recombinant innovation: The reconfiguration of pre-existing MeSH into novel combinations is a second source for new k-Simplices. (G) Conceptual (recombinant) innovation tends to occur at the periphery (core) of the knowledge network.
Data
We represent the combinatorial knowledge network as it manifests at the article-level in the form of MeSH keywords, which belong to controlled vocabulary of scientific concepts and entities organized in a quasi-hierarchical relational tree. The official MeSH tree is maintained by the U. S. National Library of Medicine and is comprised of 16 top-level category branches: A, B, C, D, E, F, G, H, I, J, K, L, M, N, V, Z (see https://meshb.nlm.nih.gov/treeView). Following previous work focusing on the biomedical and health science branches [1], here we also focus on 10 branches: Anatomy [A], Organisms [B], Diseases [C], Chemicals and Drugs [D], Analytical, Diagnostic and Therapeutic Techniques, and Equipment [E], Psychiatry and Psychology [F], Phenomena and Processes [G], Technology, Industry, and Agriculture [J], Information Science [L], Health Care [N]. These branches are comprised of 27,875 individual MeSH terms, providing a comprehensive and detailed representation of biomedical knowledge. At the same time we ignore non-technical MeSH that are tangential to biomedical innovation – specifically, 1763 MeSH terms belonging to the following 6 branches: Disciplines and Occupations [H], Anthropology, Education, Sociology, and Social Phenomena [I], Humanities [K], Named Groups [M], Publication Characteristics [V] and Geograficals [Z].

We downloaded all articles indexed by PubMed in 2020. In what follows we present results based upon the subset of research-oriented content indexed by PubMed defined by the following criteria: (a) publications classified as “Journal Article” or “Review”; (b) annotated by 2 or more MeSH terms, resulting in a sample of ~25 million articles. Figure 1(A) shows the total number of articles by year, distinguishing between articles with 2, 3 and 4+ MeSH terms. To account for variability in the weight associated with an article keyword, we leveraged additional annotation information that identify the “Major MeSH” terms, a subset of the entire set of keywords that represent the primary research topics. This two-level annotation system is implemented in PubMed by way of an asterisk (*) next to those MeSH that are distinguished as Major. Hence, in what follows we perform and compare calculations based upon the entire set of MeSH annotations (denoted by “All”) versus just the Major MeSH subset (denoted by “Major”).

Figure 1(B) shows that the average number of Major MeSH belonging to the focal 10 branches has increased from around 2.5 to 4 over the period 1975-2018; whereas, the average total number of MeSH has increased from 8 to roughly 10 over the same period. Hence, this refinement significantly reduces the number of MeSH per article considered in the Major representation. By way of example, not all articles will have sufficient numbers of Major MeSH to contribute to our analysis of quartets, which requires there to be at least 4 Major MeSH; hence, we cannot include those research articles with just 1, 2 or 3 Major MeSH in our analysis of quartets. Consequently, we must also account for the variable sample sizes by year, depending on whether a sample includes articles with 2+ or 3+ or 4+ keywords. As such, we denote the set of articles having k or more MeSH terms by $P_k$.

Measures and Notation
Figure 1(C) illustrates the process for counting simplices of order k based upon the set of MeSH annotating a given publication $p$ published in year $Y_p$. The set of $M_p$ Major MeSH terms is a subset of the full set of $m_p$ MeSH terms. From these two MeSH sets we systematically tabulate all $\binom{M_p}{k}$ (respectively, $\binom{m_p}{k}$) combinations for a given simplex order k. For example, Fig. 1(D) shows the number $\binom{M_p}{k}$ of unique k-simplices derived from a set of four Major MeSH terms for $k = 1, 2, 3, 4$. For a given set of articles we repeat this tabulation procedure, which yields a set $S_k$ of unique k-simplices, e.g. tabulated either within a specific year t or aggregating all articles thru that year t. In the latter scenario, we denote the cumulative number of distinct simplices of order k thru year t as $C_t(S_k)$. Consequently, the number of new simplices emerging in t is given by $\Delta C_t(S_k) = C_t(S_k) - C_{t-1}(S_k)$. Similarly, the number of unique MeSH tabulated across a particular set of articles is $N_m$; we represent the cumulative number of distinct MeSH thru year t as $C_t(N_m) \equiv C_t(S_0)$, where the last equality follows since individual MeSH terms are also 0th order simplices; the number of new MeSH appearing in year t is $\Delta C_t(N_m) = C_t(N_m) - C_{t-1}(N_m)$. Given a set of $C_t(N_m)$ unique MeSH realized thru year t, the total number of possible k-simplices is given by $\binom{C_t(N_m)}{k}$. Hence, we can measure the exact fraction of all possible k-simplices appearing thru year t as $F_t(S_k) = C_t(S_k) / \binom{C_t(N_m)}{k}$. One limitation to our counting method is that we neglect simplex frequencies. Consequently, the tally $C_t(S_k)$ may include many spurious k-simplices that occurred just once. A potential future avenue of research would develop a measure that incorporates a counting weight that is proportional to the k-simplex frequency, or that implements a counting threshold to eliminate spurious k-simplices that only occurred once.

This counting framework facilitates systematically measuring two modes of innovation – conceptual and recombinant. The rate of conceptual innovation is measured by $\Delta C_t(N_m)$. Similarly, the rate of recombinant innovation is measured by $\Delta C_t(S_k)$. Moreover, we can also specify what fraction of $\Delta C_t(S_k)$ involve new MeSH appearing for the first time in the same year, corresponding to peripheral recombinant innovation, and its complement core recombinant innovation referring to new $S_k$ that are only comprised of pre-existing MeSH.
The set of MeSH combinations realized in published biomedical literature reveals the explored portion of the knowledge network. We operationalize measuring this revealed knowledge network by tabulating the cumulative number of distinct simplices of order $k$, measuring the size of the knowledge network as it grows in relation to (A) the total volume of research published, and (B) the total number of MeSH entities (corresponding to vertices, or simplices of order $k=0$). By way of example, $C_t(S_k)$ counts the total number of realized MeSH-MeSH dyads (links) comprising the first-order knowledge network analyzed in ref. [1].

(A) Common trends observed for the cumulative number of distinct $k$-Simplices $C_t(S_k)$ as a function of total volume of articles published, $C_t(P_k)$ — with a decreasing slope appearing in the early 2000s, corresponding to a decreasing rate of new simplices per publication relative to the earlier period. (B) Persistent exponential growth of $C_t(S_k)$ with total size of the MeSH ontology. Each solid gray line represents the best exponential model fit.

**Results**

**Growth of the biomedical knowledge network**

**Combinatorial innovation and scientific production**

Figure 2(A) shows the total number of MeSH simplices of order $k$, denoted by $C_t(S_k)$, as function of the cumulative number of research articles indexed by PubMed, denoted by $C_t(P_k)$. There are six curves, because for each simplex order $k = 1, 2, 3$ we calculated $C_t(S_k)$ and $C_t(P_k)$ for each of the two MeSH refinements (All, Major). Since there needs to be at least $k$ MeSH for an article to contribute to tallies for that simplex order, the total number of research articles $P_k$ is conditioned by the simplex order $k$ under consideration. For this reason, curves for larger $k$ are shifted towards smaller research article count values, since the total number of MeSH per article is variable and generally increasing over the sample period, see Fig. 2(B).

Aside from this variation, the growth curves are largely consistent, each exhibiting an early period of relatively fast growth that declines in the early 2000s. Growth before and after this kink are best-fit by a linear model, indicating that there is an overall constant rate at which new simplices emerge that is in proportion to the rate of knowledge production, consistent with the results for patent IPC classes [24] and scientific article title-word combinations [25]. Fitting the curves with a linear model ($Y = A + \beta X$) over the more recent period 2005 to 2018, we obtain the slope $\beta$ corresponding to the average number of new simplices per article: $\beta_{k=1, \text{Major}} = 0.7$ and $\beta_{k=1, \text{All}} = 1.4$ pairs per article; $\beta_{k=2, \text{Major}} = 4.7$ and $\beta_{k=2, \text{All}} = 52$ triads per article; $\beta_{k=3, \text{Major}} = 8$ and $\beta_{k=3, \text{All}} = 418$ quartets per article. While this latter number may seem unreasonably high, consider that there are $\binom{12}{4} = 495$ different combinations of 4 items selected from 12 items, and so any article with more than 12 MeSH might easily contribute 100s of new combinations to $C_t(S_d)$.

All curves vary according to a systematic offset in both directions; the difference in $C_t(S_k)$ values is smaller for $k = 3$ relative to $k = 2$ than for $k = 2$ relative to $k = 1$, meaning that there is diminishing marginal increase in $C_t(S_k)$ with increasing $k$. In other words, despite there being more possible combinations to tally for increasing $k$, fewer and fewer of these combinations appear to be realized. We return to the measurement of the coverage of the combinatorial space in Section .

**Combinatorial innovation and new knowledge**

Figure 2(B) shows the total number of MeSH simplices of order $k$, denoted by $C_t(S_k)$, as a function of the total number of MeSH ever used thru the same year. Knowledge network growth parameterized according to vocabulary size are consistent with the results of the previous section, in that the vertical separation also decreases with increasing $k$. In contradistinction to Figure 2(A), there is no prominent kink in the empirical curves. As such, an exponential growth model ($Y = A \exp(\gamma X)$) provides a consistent fit over the entire range. We plot the best exponential fit for each empirical curve, with $100\gamma$ corresponding to the percent increase in $C_t(S_k)$ per new MeSH term (i.e., those MeSH appearing for the first time that year): $100\gamma_{k=1, \text{Major}} = 1.6 \times 10^{-2}$ and $100\gamma_{k=1, \text{All}} = 1.9 \times 10^{-2}$ percent increase in total pairs per new MeSH; $100\gamma_{k=2, \text{Major}} = 1.5 \times 10^{-2}$ and $100\gamma_{k=2, \text{All}} = 1.8 \times 10^{-2}$ percent increase in total triads per new MeSH; and $100\gamma_{k=3, \text{Major}} = 1.3 \times 10^{-2}$ and $100\gamma_{k=3, \text{All}} = 1.5 \times 10^{-2}$ percent increase in total quartets per new MeSH.
with relatively high rates of recombinant innovation per new MeSH term. Major MeSH shifts from densification to diffusication as (B,D,F) with densification generally increasing from 1994 onward. k network constructed from All MeSH exhibits uniform densification for all of F increase in total quartets per new MeSH. These values are less than unity, indicating a decreasing marginal increase in C increase the combinatorial knowledge network constructed from All MeSH exhibits uniform densification for all k. Notably, Fk(Sk) doubles over the sample period in each case, with densification generally increasing from 1994 onward. (B,D,F) As k increases the combinatorial knowledge network constructed from Major MeSH shifts from densification to diffusification as Ck(Nm) increases. The k = 2 scenario represents the margin for this behavior, as the amplitude of Fk(Sk) varies relatively little in this case; lacking an overall trend, this scenario highlights 1994-2001 and 2007-2013 as periods with relatively high rates of recombinant innovation per new MeSH term.

2.5 × 10−2 percent increase in total triads per new MeSH; 100γk=3,Major = 8.6 × 10−3 and 100γk=3,All = 2.7 × 10−2 percent increase in total quartets per new MeSH. These values are less than unity, indicating a decreasing marginal increase in Ck(Sk) with each new MeSH, in analogy to the decreasing need for new words observed in a historical analysis of written language [34].

It is also worth noting that there is typically just an order of magnitude or less difference between the curves for Major and All for a given k. This means that the bulk of Ck(Sk) are explained by combinations among research articles’ primary concepts. Yet the gap between Ck,All(Sk) and Ck,Major(Sk) does appear to be widening over time for each k, and so the role of peripheral-mediated recombinant innovation does appear to become increasingly relevant.
Dynamics of combinatorial coverage – Densification or Diffusification?

Regarding the total realm of possibilities – how much has been explored by researchers over time? While the quantity \( C_t(N_m) \) measures the growth of the revealed space of MeSH combinations in an absolute sense, it does not account for all the combinations that have not been realized. The total number of k-simplex combinations possible can be calculated exactly using the binomial coefficient \( \binom{C_t(N_m)}{k} \), which grows as \( n^k/k! \sim n^k \) with \( n = C_t(N_m) \). By way of example, since the total number of MeSH realized through 2018 is \( C_{2018}(N_m) = 27,875 \), then the total number of possible k-simplices are: \( \binom{27,875}{2} = 388,493,875 \sim 10^{10} \) pairs; \( \binom{27,875}{3} = 3,609,496,592,625 \sim 10^{12} \) triads; and \( \binom{27,875}{4} = 25,150,972,257,411,000 \sim 10^{16} \) quartets. Of course, not all of these combinations have been realized, nor do they merit exploring, and so the real question is what proportion of the combinatorial space has been sampled over time. To this end, Fig. 3 shows the fraction \( F_t(S_k) = C_t(S_k) / (C_t(N_m)) \) of the total space of combinations realized in research as a function of the growing MeSH vocabulary size.

Focusing first on the calculating of coverage based upon the representation of the combinatorial knowledge network calculated using All MeSH, the main pattern is the strong and persistent growth in \( F_t(S_k) \) across each \( k \), which more than doubles in each case. Hence, research is increasingly covering all knowledge combinations and so the knowledge network is densifying, even after accounting for the increasing volume of knowledge. The rate of densification appears to have increased since the mid 1990s.

An alternative perspective is offered by focusing on just Major MeSH, highlighted by two prominent differences across the curves for varying \( k \). First, the baseline levels of \( F_t(S_k) \) decrease rapidly with increasing \( k \), meaning that less and less of the combinatorial space has been covered when considering higher-dimensional representations of knowledge recombination (this is also the case for All MeSH). To be specific, roughly 4% of all Major MeSH pairs have been combined thru 2018, whereas only 6 per billion possible quartets have been revealed thru the same year. Second, there is a systematic shift from a \( F_t(S_1) \) that increases with time, to \( F_t(S_2) \) that decreases with time. The \( F_t(S_2) \) curve increases marginally over the sample period, and so the sudden bursts during 1994-2001 and 2007-2013 are more visible (although trend deviations are also visible in the \( k = 1 \) and \( k = 3 \) curves as well), and reflect the high rates of recombinant innovation per new MeSH term during these periods.

Distinguishing two modes of innovation: Conceptual and Recombinant

Conceptual innovation and growth of the network

Figure 4(A) shows the bursty relationship between number of new k-Simplices appearing in a given year, denoted by \( \Delta C_t(S_k) \), coinciding with the number of new MeSH occurring in the same year. While it would be easy to naively assume that a large number of new MeSH in a given year would result in a burst of new combinations, as a counterexample there are several notable periods with relatively few new MeSH entering the vocabulary, and relatively large increases in \( \Delta C_t(S_k) \). The entry of new MeSH is a proxy for conceptual innovation, and the lack of a strong relationship likely reflects the relatively slow rate of diffusion through the combinatorial knowledge network. Hence, a future avenue of research could incorporate a larger time-window for \( \Delta C_t(S_k) \) to the time-scale of this combinatorial diffusion.

The burstiness of the relationship is common in magnitude and overall timing across the \( k = 1,2,3 \) curves. Of particular note are the \( k = 2 \) and \( k = 3 \) curves which are quite similar in shape, which indicates that the \( k = 4 \) representation provides no significant new insights (a conclusion that can also be drawn from Fig. 2). Hence, the additional information contained in higher-order representations appears to be marginal, providing additional support for measurement frameworks based upon pairwise combinations [32]. As such, the \( k = 2 \) and \( k = 3 \) representations of the knowledge network appear sufficient to capture the essential dynamics of combinatorial innovation as measured here.

Increasing concentration of conceptual innovation within single research articles

As illustrated in Fig. 2(E,F), conceptual innovation deriving from the birth of new knowledge gives rise to many new possible configurations. Yet there are so many missing configurations among already existing entities, that this alternative channel serves as a very deep well providing many new recombinant options. So which innovation mode dominates? To address this question, we separate the new combinations in a each year, into two subsets: those that feature a new MeSH term (corresponding to peripheral recombinant innovation), and those that feature pre-existing MeSH (corresponding to core recombinant innovation). We calculate the rate of peripheral recombinant innovation \( r_p(t) = \Delta C_t,\text{In}cluding\text{newMeSH}(S_k)/\Delta C_t(S_k) \); the rate of core recombinant innovation is the complement, \( r_c(t) = 1 - r_p(t) \). Naturally, the baseline for comparison is the entry rate of new MeSH, measured in relative terms is given by \( r_m(t) = \Delta C_t(N_m)/C_t(N_m) \).

Figure 4(B) compares \( r_m(t) \) and \( r_p(t) \) for \( k = 1,2,3 \), calculated for Major MeSH. Clearly, and not surprisingly, the dominant proportion of recombinant innovation is among existing primary knowledge, \( r_c(t) \gg r_p(t) \). More interesting is the increasing gap between \( r_m(t) \) and \( r_p(t) \), meaning that peripheral recombinant innovation is increasingly concentrated in relatively fewer k-simplices. By way of counterexample, if new knowledge did not tend to cluster in new k-simplices, then the rates \( r_m(t) \) and \( r_p(t) \) would be nearly identical, notwithstanding random fluctuations. Because each k-simplex is a higher-order representation of the conceptual dimension of a single research article, this pattern means that conceptual innovation is increasingly concentrating in single research articles.
The dominant mode of recombinant innovation is novel reconfigurations of pre-existing core knowledge. (A) Weak relation between the emergence of new knowledge (proxied by rate of new MeSH) and the emergence of new recombinant knowledge associated with all new k-simplex configurations tallied in a given year. The burstiness of the relationship between new concepts and recombinations may indicate a significant lag between new knowledge and downstream integration into knowledge recombination. (B-D) Measurement of combinatorial knowledge production associated with two innovation modes illustrated in Fig. 1(E-G): (a) new k-simplices arising from the introduction of new MeSH (peripheral recombinant innovation), or (b) new k-simplices comprised of pre-existing MeSH only (core recombinant innovation). Plotted in panels B, C, D is the peripheral innovation rate \( r_p(t) = \Delta C_t(\text{IncludingNewMeSH}(S_k))/\Delta C_t(S_k) \) (dashed curves) corresponding to mode (a) (i.e., the frequency of new k-simplices incorporating new MeSH, as a proportion of all new k-simplices identified in a given year; note that a complementary frequency \( r_p(t) \) corresponding to mode (b) is very close to unity). For visual comparison, solid curves represent the rate of conceptual innovation, \( r_m(t) = \Delta C_t(N_m)/C_t(N_m) \), measured as the percent increase in the total number of MeSH. In most years, the rate of peripheral recombinant innovation (a) is highly correlated with, and typically less than, the rate of conceptual innovation. Moreover, the difference between the peripheral and conceptual rate of innovation is increasing. The common patterns independent of \( k \) suggest that higher order representations of combinatorial knowledge do not capture new phenomena, indicating that the traditional conceptualization as a knowledge network comprised of 1-simplices (links) is sufficient for understanding biomedical innovation dynamics. Data shown are calculated using only the Major MeSH terms.
Discussion

In this work we present a framework for systematically representing higher-order combinations of research article topics as a tool for measuring and better understanding the role of combinatorial innovation in science. We leverage the Medical Subject Heading (MeSH) ontology of keywords that are uniformly implemented within PubMed, are constantly being updated, and consisting in the present study of 27,875 individual keywords spanning a wide range of biological, medical, chemical, ecological concepts as well as equipment and other techno-informatic entities and methods [1]. The excellent coverage and consistency of this ontology implemented within PubMed facilitates historical analysis to the extent that we can measure with certainty the year in which a new concept and new combination of concepts first appeared in the literature.

In an effort to systematize our approach, we adopted a framework for counting all $k$-simplex variants of order $k = 1$ (corresponding to MeSH pairs), 2 (triads) and 3 (quartets) in order to explore whether unexpected patterns of combinatorial innovation emerged at higher-order representations (see Fig. 1). For the most part, we did not uncover information at $k = 3$ that was not revealed at $k = 1$. Nevertheless, three orders of $k$ were needed in order to differentiate spurious differences from trends. Consistent with prior research, we conclude that new combinations emerge roughly at a constant rate [24, 25] (see Fig. 2).

In addition to varying $k$, we also explored differences based upon the two-level MeSH assignment, where Major MeSH represent primary research topics and entities, and the remaining MeSH represent more peripheral elements that were nevertheless integral to the research. Results using Major and All MeSH to measure the growth of the combinatorial knowledge network were overall consistent (see Fig. 2). The exception being the analysis of the fraction of MeSH combinations that have been realized, which did yield fundamental differences between the representations based upon just Major versus All MeSH (see Fig. 3). In particular, for All MeSH we observe a consistent densification for all $k$, whereas for Major MeSH we observed densification for $k = 1$, marginal densification for $k = 2$, and diffusification for $k = 3$. Since the knowledge network constructed from Major MeSH represents the backbone of scientific concepts, this result indicates that most combinations are sampled from a primary set of conventional topics, consistent with prior research analyzing the co-occurrence of articles cited in reference lists [19].

Another phenomena highlighted in Fig. 3(D) is the identification of 1994-2001 and 2007-2013 as periods with relatively high rates of recombinant innovation per new MeSH term. The burst during 1994-2001 coincides with the genomics revolution and the culminating success of the Human Genome Project [35], a period featuring deep convergence of technological applications and informatic methods from computer science to transform and accelerate the capabilities, scale and scope of biological sciences [1]. In a similar fashion, the second innovation burst coincides with the continuation of transdisciplinary convergence efforts worldwide, many driven by national funding initiatives aiming to harness convergence, as exemplified by the emergence of Human Brain projects in the US, Europe and Asia aiming to transform our understanding of the structure-function problem as it relates to understanding complexity, addressing the global burden of mental health problems, and the understanding and development of artificial intelligence [9, 36].

Another objective in this work was to compare the rates of conceptual (i.e., the entry rate of new concepts) and recombinant innovation (i.e, the entry rate of new combinations) (see Fig. 4), which confirms that the rate of recombinant innovation is overwhelmingly dominant. Because this disparity was largely anticipated, reflecting the sheer size of the MeSH knowledge corpus and the vast number of possible combinations, we instead focused on two types of recombinant innovation – those new combinations that combine only pre-existing concepts (core) and those that incorporate new concepts (peripheral). Results show that 99% of new combinations did not incorporate new concepts, with the dynamics of peripheral recombinant innovation closely matching (albeit typically lower) than the rate of conceptual innovation. Yet comparing the difference between these two fundamental innovation rates for increasing $k$ revealed a widening gap, meaning that with each new piece of knowledge, there is a decreasing relative impact on the connectivity of the combinatorial knowledge network. Another interpretation of this trend considers the rapid integration of computational methods within the domain of biomedical science [1], such that innovative research increasingly incorporates multiple innovations simultaneously, e.g. a new algorithm or instrument facilitating a new insight about a new biological process, such that neither would have happened without the demand for the other. Such “combination reactions” are the analog of chemical reactions requiring multiple reactants, and provide support for a triple-helix model of biomedical innovation in which technology plays an increasingly important role as catalystizer [13, 35]. Indeed, the accelerating innovation by tapping higher-order interactions is a principle value propositions of convergence science, which ascribes to the coming together of originally distinct fields and sectors [9, 11, 35, 37, 38], and thus represents a more macro-level representation of combinatorial innovation.

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