Macro-trends in research on the central dogma of molecular biology

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ABSTRACT

The central dogma of molecular biology, formulated more than five decades ago, compartmentalized information exchange in the cell into the DNA, RNA and protein domains. This formalization has served as an implicit thematic distinguisher for cell biological research ever since. However, a clear account of the distribution of research across this formalization over time does not exist. Abstracts of >3.5 million publications focusing on the cell from 1975 to 2011 were analyzed for the frequency of 100 single-word DNA-, RNA- and protein-centric search terms and amalgamated to produce domain- and subdomain-specific trends. A preponderance of protein- over DNA- and in turn over RNA-centric terms as a percentage of the total word count is evident until the early 1990s, at which point the trends for protein and DNA begin to coalesce while RNA percentages remain relatively unchanged. This term-based census provides a yearly snapshot of the distribution of research interests across the three domains of the central dogma of molecular biology. A frequency chart of the most dominantly-studied elements of the periodic table is provided as an addendum.

MAIN TEXT

The central dogma of molecular biology, consisting of the tripartite alignment of DNA, RNA and protein, was formalized in 1970 [1] (although first put forth in 1958) and has encapsulated the main domains of focus in biological research. Although the boundaries between these domains have become ever more intangible with discoveries such as DNA-protein complexes in the form of nucleosomes [2] or RNA-protein entities such as the ribosome [3], a given research project in the molecular biology laboratory can still be categorized as mainly emphasizing or at least partially involving one of the components of the central dogma more than the remaining two constituents.

It would be informative to determine the extent to which the field of molecular biology has emphasized DNA, RNA and protein as its focus of attention and how the emphasis might have changed over time in the form of a census. Text-mining could be a suitable approach to analyze such patterns in the published literature [4,5]. To that end, 3,767,522 abstracts of all articles containing the word “cell” or “cells” in any field or as a Medical Subject Heading (MeSH) were extracted from the Medical Literature Analysis and Retrieval System Online (MEDLINE) database for a 37-year period from 1975 to 2011, inclusive. Publications indexed prior to 1975 do not necessarily reflect the expected trajectory of increasing annual publication numbers and were not included for the purpose of this study. An in-house word-frequency Java program was used to determine the annual occurrence of a total of 100 DNA-, RNA- and protein-centric terms and their plural/adjectival derivatives, in addition to the total yearly word counts (**Table S1**). Although some of the selected search terms will inevitably capture minor aspects of a domain other than the one assigned, such crossovers will be negligible in the scale and theme of the current search. Moreover, to ensure consistency across different abstracts, the search terms were single words only, and referred to biological entities (e.g., genome) rather than techniques, processes or phenomena (e.g., sequencing, transcription, etc.).

The total number of words, after adjustments for the abstract number and PubMed ID line, was 939,309,404, equalling approximately 250 words per abstract across the 37-year period (**Fig. 1**). The

slope of the total word count, however, is greater than that of the total publications per year, indicating a general trend towards longer abstracts. Whereas the average abstract length from 1975 to 1979 is 180, it increases to 271 words between 2007 and 2011.

The cumulative percentage of protein-centric terms relative to the total annual word count in abstracts from 1975 is 0.52%, whereas it is 0.32% for DNA-centric and 0.13% for RNA-centric terms (**Fig. 2A**). Protein and DNA terms show an increase until the early 1990s, followed by a decline in the late 1990s for protein and mid-2000s for DNA. The trend for RNA shows a relatively slighter variation in the 37-year period. In 2011, the relative percentages for protein, DNA and RNA had changed to 0.47%, 0.46% and 0.16%, respectively. It should be noted that although the number of publications in each domain has increased substantially every year, the percentage of search terms per total words indicates the relative focus of the field of molecular biology on each part of the central dogma. Overall, it is evident that the protein component of the central dogma of molecular biology received greater attention in research in the 1970s, followed by DNA and RNA. With a gradual decline in protein-centric percentages and relatively constant increase in DNA terms, the protein and DNA domains appear to have garnered equal focus in the 2000s. The relative attention on the RNA domain seems to have remained less fluctuating.

It will be useful to determine if the trend observed for each domain is mainly carried by one or more subdomains. 'Gene' and related terms are the predominant trendsetters for DNA-centric words (**Fig. 2B**). Other than 'genome' and 'epigenetics' (and related terms), which show a slow rise from early-2000s onward, all other terms have a negative or near-zero slope. The trend for RNA-centric words seems to be mainly carried in phases by three different subcategories: from 1975 to the mid-1980s by 'RNA', from the mid-1980s to the early 2000s by 'mRNA' (messenger RNA), and from then on by 'siRNA' (small interfering RNA) and 'miRNA' (microRNA) (**Fig. 2C**). The main term in the protein-centric trend is, unsurprisingly, 'protein' and related terms (**Fig. 2D**). However, the key contributors to the shape of the trend in the 1970s and 1980s are 'enzyme' and 'antibody', respectively, both of which demonstrate a steady decline in subsequent decades. The 'proteome' subdomain shows a relatively small rise in the past decade.

All 100 search terms account for an average of 1.15% of the total words in the abstracts with a standard deviation of 0.11%. If the three constituents of the central dogma encompass the principal avenues of information flow in the cell, it might then be plausible to assume that the cumulative percentage of all DNA-, RNA- and protein-related terms should be constant on a year-by-year basis, even in cases of new discoveries within the dogma which spawn new research directions and publications. Although the current census appears to corroborate this assumption to an extent, the sums of all percentages span a minimum of 0.95% in 1977 and a maximum of 1.32% in 1995 (**Fig. S1**). It is possible to speculate that publications analyzed in this study have at different times relied on biological phenomena outside of the tripartite axis (e.g., phospholipids) to complement their explanation of a given aspect of the cell's information system.

To control for the accuracy of the search algorithm, the frequency of the articles 'a', 'an' and 'the' were calculated (**Fig. S2**). The indefinite articles show a consistent percentage throughout the search period, with 'a' and 'an' representing 1.5% and 0.3% of the total words, respectively. Interestingly, the usage of the definite article 'the' shows a negative linear trend, with a decrease from 6.0% in 1975 to 3.8% in 2011.

Finally, to determine the relative focus of the field of molecular and cellular biology on the natural elements, the frequencies of occurrence of the 118 elements in the periodic table were calculated (**Fig. S3**). Calcium, oxygen, lead, iron, sodium, carbon, zinc, hydrogen, gold, copper and potassium represented the most frequently mentioned elements at present, respectively (**Fig. S3A**). Relative to other elements, calcium and sodium demonstrate a decrease in occurrence from the late 1980s to 2011 (**Fig. S3B**).

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FIGURE LEGENDS

Figure 1. Overview of analyzed abstracts. The total number of publications (bar graph, left vertical axis) shows a steady rise from tens of thousands in the late 1970s to hundreds of thousands in the late 2000s. The total number of words for each year (line graph, right vertical axis), however, increases more rapidly over the same time period and indicates a trend toward longer abstract lengths.

Figure 2. Central dogma domain trends from 1975 to 2011. Protein-centric research appears to have dominated the field of molecular biology in the late 1970s, followed by DNA-centric and RNA-centric research (**A**). With a steady rise in DNA-centric terms and decline in protein-centric terms, the DNA and protein domains converge on equal percentages relative to total words in the 2000s. The breakdown for individual trends demonstrating the contribution of each subdomain appears in **B**, **C** and **D**.

Figure S1. Annual sums of percentages. A revised **Fig. 2A** includes a cumulative line graph of the yearly DNA-, RNA- and protein-centric percentages, which range from 0.95% (1977) to 1.32% (1995).

Figure S2. Control graph of the frequency of definite/indefinite articles. The indefinite articles ‘a’ and ‘an’ demonstrate a steady frequency over the period 1975-2011, whereas the definite article ‘the’ decreases from 6.0% to 3.8% over the same period.

Figure S3. Frequency of the elements. The absolute (**A**) and relative (**B**) occurrences of elements 1-118 were calculated. Two alternative spellings were considered for four elements: aluminium/aluminum, phosphorus/phosphorous, sulfur/sulphur and caesium/cesium. The elements francium, berkelium, einsteinium, mendelevium, nobelium, lawrencium, rutherfordium, dubnium, seaborgium, bohrium, hassium, meitnerium, darmstadtium, roentgenium, copernicium, ununtrium, flerovium, ununpentium, livermorium, ununseptium and ununoctium did not occur in any abstract.

Figure 1

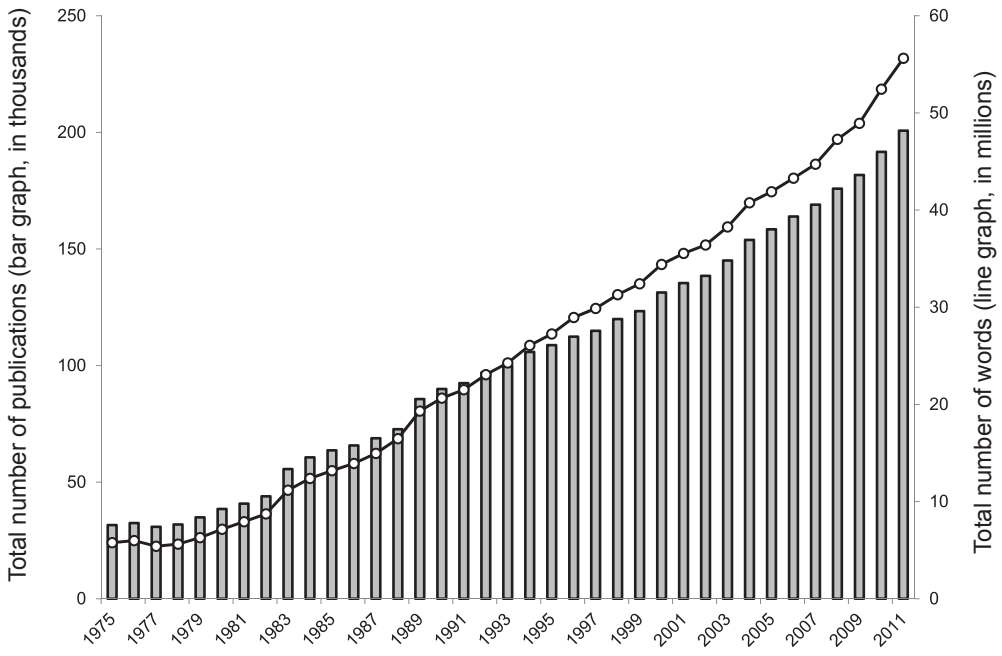
Total number of publications (bar graph, in thousands)
250
200
150
100
50
0
Total number of words (line graph, in millions)
60
50
40
30
20
10
0
1975
1977
1979
1981
1983
1985
1987
1989
1991
1993
1995
1997
1999
2001
2003
2005
2007
2009
2011

Figure 2

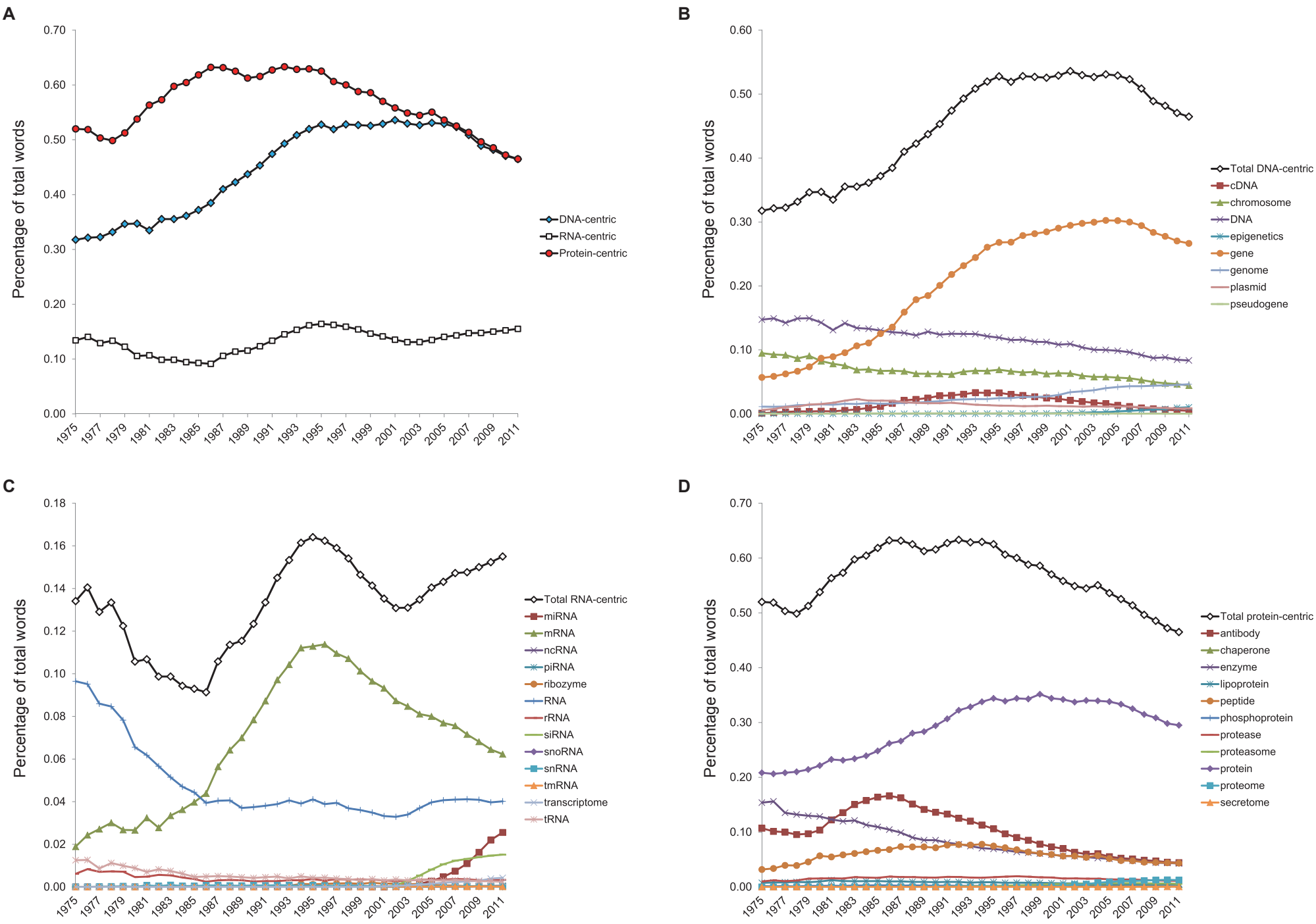
A
Percentage of total words
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
1975 1977 1979 1981 1983 1985 1987 1989 1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011
DNA-centric
RNA-centric
Protein-centric
B
Percentage of total words
0.60
0.50
0.40
0.30
0.20
0.10
0.00
1975 1977 1979 1981 1983 1985 1987 1989 1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011
Total DNA-centric
cDNA
chromosome
DNA
epigenetics
gene
genome
plasmid
pseudogene
C
Percentage of total words
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
1975 1977 1979 1981 1983 1985 1987 1989 1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011
Total RNA-centric
miRNA
mRNA
ncRNA
piRNA
ribozyme
RNA
rRNA
siRNA
snoRNA
snRNA
tmRNA
transcriptome
tRNA
D
Percentage of total words
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
1975 1977 1979 1981 1983 1985 1987 1989 1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011
Total protein-centric
antibody
chaperone
enzyme
lipoprotein
peptide
phosphoprotein
protease
proteasome
protein
proteome
secretome

Table S1. Annual publications, total word counts and DNA-, RNA- and protein-centric word counts

	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Publications ("cell")	31607	32446	30834	31857	34881	38488	40798	43919	55610	60644	63637	65755	68811	72707	85631	89973	92468	96988	99833	105841	108746	112407	114908	119936	123355	131329	135394	138484	145045	153876	158447	163913	168999	175871	181714	191652	200718
Total words	5774934	5990895	5404861	5629292	6288805	7159837	7930864	8735668	11170969	12383537	13184025	13926819	14958598	16478895	19317118	20651136	21514072	23060053	24273183	26075605	27251612	28953715	29882048	31299937	32420790	34412018	35545593	36414253	38268984	40754339	41893009	43283478	44726598	47285437	48931004	52446905	55630518
cDNA	53	117	157	209	231	284	301	446	711	1055	1433	2094	2868	3355	4237	5115	5449	6167	6938	7402	7785	7562	7467	7276	6889	7044	6549	6165	5769	5770	5037	4473	3755	3182	2835	2616	2423
cDNAs	11	3	7	10	7	21	14	31	63	86	116	188	287	386	549	737	765	920	1131	1126	1165	1182	1148	1102	1170	1062	913	844	815	750	602	513	422	428	287	274	270
chromatin	1293	1535	1138	1176	1277	1373	1409	1386	1670	1806	1597	1489	1412	1337	1526	1419	1383	1458	1447	1609	1865	1941	2237	2531	2451	2896	3180	3475	3704	4457	4798	5333	5703	5758	6435	6846	7295
chromatins	26	46	21	18	22	19	9	13	23	14	11	11	8	13	4	5	4	11	11	12	9	2	3	3	7	1	3	1	2	7	7	14	4	6	7	3	7
chromosomal	635	688	616	590	757	830	787	1058	1142	1204	1468	1504	1686	1736	2098	2324	2286	2567	2772	2708	3032	3147	3178	3550	3339	3708	3811	3753	3870	3948	4010	4053	4007	3835	3636	3849	3762
chromosome	2149	1988	2025	2001	2361	2403	2681	2730	3387	4008	4046	4579	4990	5369	6407	6827	7222	8530	9357	10072	10847	10846	10735	10958	10924	11423	11514	10751	10676	11033	11037	10929	10322	10322	9641	10158	9847
chromosomes	1377	1298	1172	1096	1289	1285	1320	1403	1454	1581	1716	1815	1867	1906	2073	2349	2384	2646	2785	3111	3066	3327	3193	3505	3522	3845	3968	3687	3883	4132	3873	3761	3660	3604	3680	3544	3766
DNA	8418	8827	7609	8263	9245	10027	10175	12114	14697	16217	16873	17459	18611	19866	24443	25189	26528	28368	29920	31209	32088	33030	34318	34905	36155	36985	38609	37546	38118	40454	41088	41493	40863	41101	43007	44187	46251
DNAs	93	116	81	133	160	192	214	272	294	275	303	334	325	370	367	398	418	456	377	448	388	397	363	350	293	289	239	311	271	283	239	238	238	184	234	224	206
epigenetic	8	5	15	12	13	17	15	20	23	48	27	49	31	36	46	76	62	73	86	104	111	154	168	221	225	359	440	608	843	1015	1462	1841	2276	2688	3210	4164	4692
epigenetics	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	2	2	3	1	1	3	2	13	19	38	46	61	110	138	202	281	285	465	615
epigenome	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	3	9	9	27	34	56	66	84	156	180
epigenomes	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	3	1	2	10	14	21	23
epigenomic	1	0	0	0	0	0	0	0	0	0	1	0	2	0	0	0	0	0	1	0	0	0	0	0	1	1	0	4	13	6	4	13	19	33	55	96	118
epigenomics	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	9	2	4	9	9	22	25	58	87	104
exome	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	51	204
exomes	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	14
exomic	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3
exomics	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
gene	1331	1422	1351	1599	2187	3004	3564	4390	6764	8188	10209	11854	14942	18072	22209	25992	29671	34121	38042	44437	47496	50484	53787	55622	57963	60935	62270	63347	65451	69127	69163	69959	69654	70312	70197	72499	74736
genes	707	864	861	957	1118	1655	1917	2246	3058	3474	4169	4759	5845	7094	8316	9798	11035	12269	13195	14914	16109	17185	18644	20194	20988	23739	26274	28614	31613	35184	37014	38968	40165	40784	41359	43616	45367
genetic	1103	1082	1031	1076	1174	1407	1434	1586	1877	1896	2004	2068	2246	2560	3239	3497	3819	4357	5186	5603	6187	6645	7211	8185	8871	10071	10794	11154	11915	12899	14062	14434	15283	16015	17220	18472	20384
genetics	152	149	137	120	146	162	169	134	185	169	161	219	759	1709	1969	2200	2393	2708	2923	2993	3271	3423	3700	4193	4471	5193	5450	5364	5725	6107	6363	6469	6600	7062	7078	7250	7846
genome	547	544	532	615	680	797	816	898	1119	1280	1139	1194	1369	1440	1656	1744	1999	2180	2288	2390	2741	3022	3406	3516	3825	4615	5542	6126	6893	8036	8608	9252	9615	10284	11139	12285	13622
genomes	87	89	59	103	124	163	163	207	236	287	293	232	256	224	313	381	433	404	430	441	505	504	619	618	712	755	1017	1054	1282	1430	1690	1674	1804	1878	1959	2016	2168
genomic	19	28	29	50	77	105	151	276	370	516	644	810	934	1143	1468	1734	1956	2198	2502	2745	2988	3146	3391	3691	3765	4172	4652	4643	4872	5360	5594	5897	5820	6413	6458	6854	7141
genomics	0	0	0	0	0	0	0	0	0	0	0	0	41	85	193	231	343	430	396	468	459	460	455	445	481	606	835	1029	1101	1536	1665	1854	2016	2149	2185	2374	2385
metagenome	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	6	7	14	18	13	30	15	41
metagenomes	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	2	5	6	7	18
metagenomic	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	3	0	17	19	41	28	42	77	120
metagenomics	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	8	3	13	25	26	22	31
plasmid	264	331	362	479	658	744	991	1257	1737	1792	1870	2023	2052	1994	2349	2583	2735	2703	2606	2603	2638	2787	2711	2931	3197	3163	3282	3170	3448	3554	3888	3859	3684	3519	3427	3388	3680
plasmids	73	126	222	165	259	359	385	552	849	768	862	829	714	831	864	853	988	953	860	934	874	887	894	918	938	975	930	913	1071	1023	1016	1039	1070	1021	1037	1023	1125
pseudogene	0	0	5	2	0	5	21	15	21	53	38	38	61	65	79	70	110	115	110	129	135	110	129	129	135	121	121	118	68	75	116	75	70	84	55	58	58
pseudogenes	0	0	0	0	0	5	26	7	16	34	53	32	26	52	63	62	56	66	73	47	70	87	54	80	89	81	128	148	93	112	124	115	100	123	54	89	78
Total DNA-centric	18347	19258	17430	18674	21785	24857	26562	31041	39696	44751	49033	53580	61332	69643	84469	93585	102039	113700	123438	135507	143832	150329	157812	164926	170413	182056	190544	192877	201559	216380	221643	226476	227506	231238	235742	246791	258580
microRNA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	36	101	181	274	507	928	1374	2169	2644
microRNAs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	18	51	116	231	356	613	1060	1463	2083	2480
miRNA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	20	70	171	346	639	1019	1500	2369	3316	4265
miRNAs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	41	100	197	384	778	1192	1691	2744	3963	4838
mRNA	922	1214	1201	1326	1301	1460	1894	1682	2527	2956	3400	4077	5604	7281	9536	11442	13375	16054	17962	20957	22524	24222	24168	24923	24357	24892	24975	23816	24277	24813	25106	25031	25163	25041	24700	24948	25303
mRNAs	78	148	133	163	180	218	351	397	603	745	806	871	1153	1223	1453	1752	2003	2287	2576	2915	2703	2926	2637	2597	2610	2696	2647	2417	2482	2367	2485	2259	2327	2583	2505	2400	2584
ncRNA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	6	1	0	7	0	16	38	49	54	82	86	107
ncRNAs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	4	8	2	33	63	66	69	142	165	173
piRNA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	4	30	48	90	85	156
piRNAs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	20	62	76	100	90	124
ribozyme	0	0	0	0	0	0	0	0	1	0	1	2	1	1	19	7	27	97	90	253	206	267	294	370	283	457	357	380	328	395	301	222	193	123	149	110	98
ribozymes	0	0	0	0	0	0	0	0	0	0	0	1	1	0	10	10	14	41	41	125	128	158	187	176	192	219	181	254	168	201	156	90	92	42	60	56	62
RNA	5399	5480	4436	4509	4576	4370	4464	4553	5214	5257	5299	4958	5414	6048	6589	7102	7486	8254	9040	9376	10260	10449	10833	10713	10919	11124	10963	11055	11840	13765	15068	15796	16473	17390	17672	18385	19666
RNAs	172	220	210	256	346	325	438	396	534	566	551	531	636	644	571	634	704	707	812	823	927	802	954	835	775	879	859	919	1148	1313	1550	1811	1861	2065	2329	2418	2686
rRNA	340	462	352	381	419	300	335	453	585	526	471	315	438	499	567	509	555	590	719	766	949	821	1029	1036	1084	1127	1015	976	1073	1335	1380	1419	1626	1639	1472	1602	1727
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snoRNAs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	4	13	10	47	34	52	80	69	52	50	68	27	20	22	34	41	41	71	64	61
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tmRNA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	7	11	33	62	53	49	54	70	69	94	45	105	89	79
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Figure S1

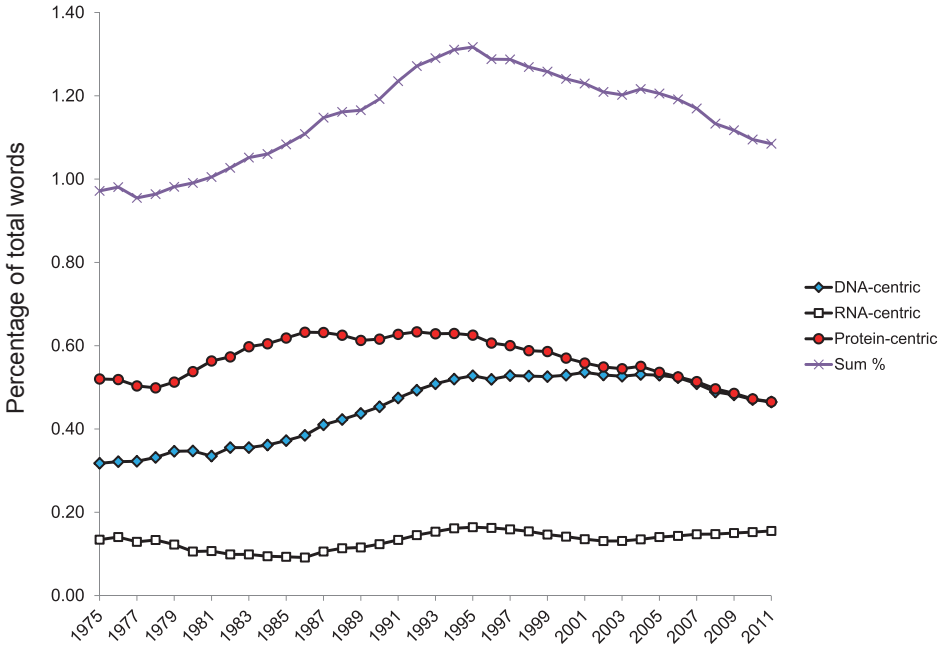
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Figure S2

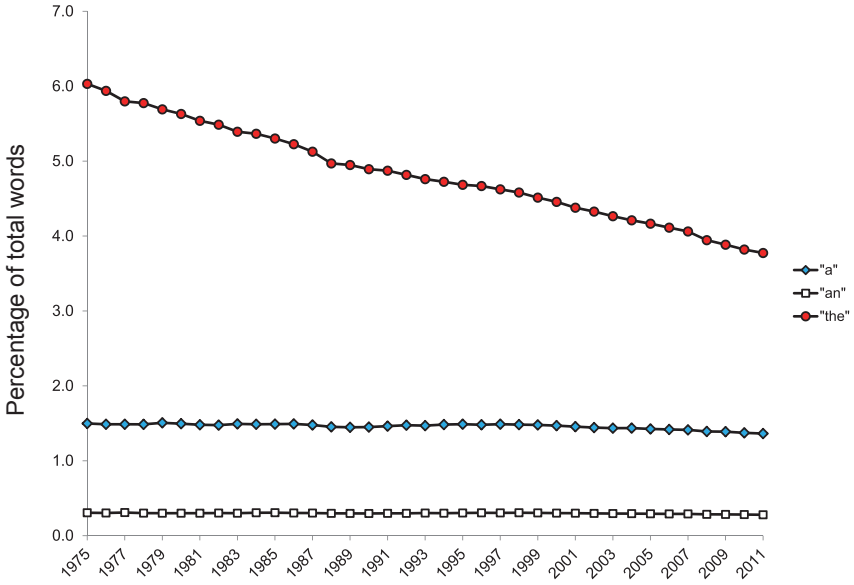
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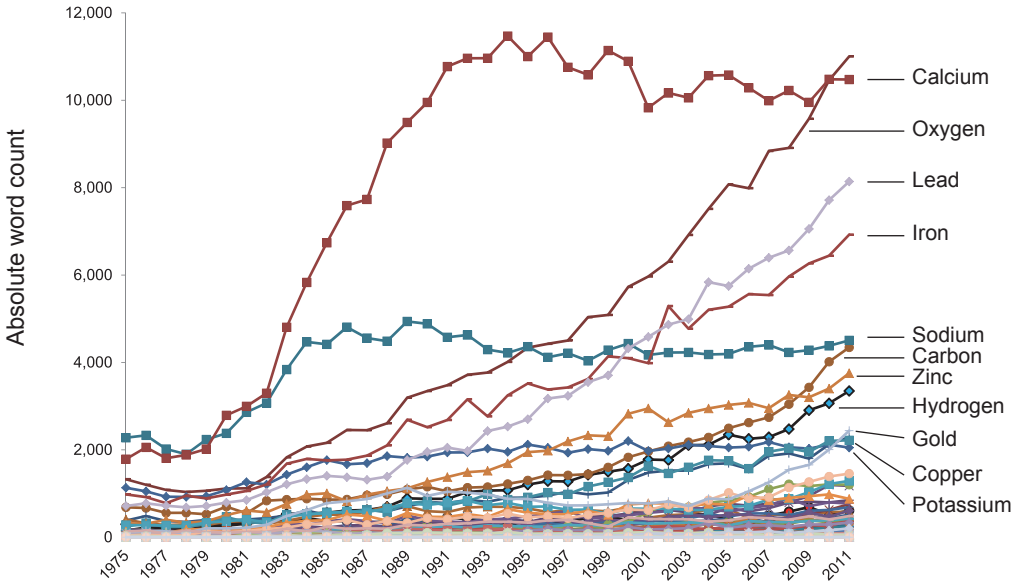
Figure S3

A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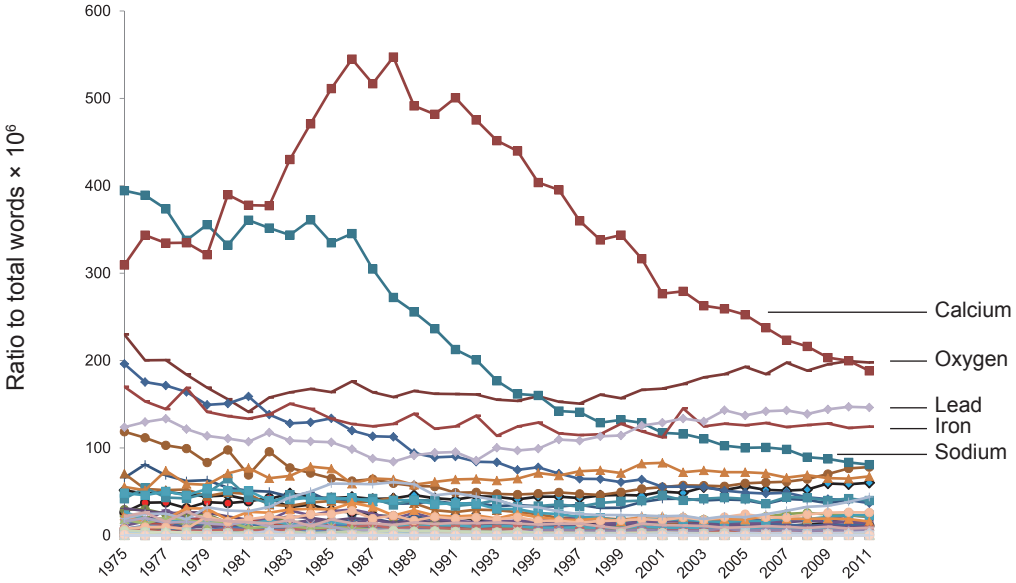
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