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Cryo-Electron Microscopy: The field of 1,000^{+} methods

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ABSTRACT

Cryo-Electron Microscopy (CryoEM) is currently a well-established method to elucidate a biological macromolecule's three-dimensional (3D) structure. Its success is due to technological and methodological advances in several fronts: sample preparation, electron optics and detection, image acquisition, image processing, and map interpretation. The first methods started in the late 1960s and, since then, new methods on all fronts have continuously been published, maturating the field as we know it now.

In terms of publications, we can distinguish several periods, witnessing a substantial acceleration of methodological publications in recent years, pointing out to an increased interest in the domain. On the other hand, this accelerated increase of methods development may confuse practitioners about which method they should be using (and how) and highlight the importance of paying attention to establishing best practices for methods reporting and usage.

In this paper, we analyze the trends identified in over 1,000 methodological papers. Our focus is primarily on computational image processing methods. However, our list also covers some aspects of sample preparation and image acquisition.

Several interesting ideas stem out from this study: (1) Single Particle Analysis (SPA) has largely accelerated in the last decade and sample preparation methods in the last five years; (2) Electron Tomography is not yet in a rapidly growing phase, but it is foreseeable that it will soon be; (3) the work horses of SPA are 3D classification, 3D reconstruction, and 3D alignment, and there have been many papers on these topics, which are not considered to be solved yet, but ever improving; and (4) since the resolution revolution, atomic modelling has also caught on as a hot topic.

1. Introduction

CryoEM is undoubtedly one of the current key techniques in Structural Biology for its ability to visualize the structure of biological macromolecules at atomic resolution and snapshots of their intermediate states, without the need for crystallization and starting from relatively small amounts of proteins. The technique owes its success to thousands of researchers who have improved its capabilities on all fronts (sample preparation, electron optics and detection, image acquisition, image processing, and map interpretation) and to other researchers who have adopted it to solve biologically challenging scientific problems. For recent reviews on the field, we refer the reader to (Bai, 2021; D'Imprima and Kühlbrandt, 2021; Bendory et al., 2020; Nakane et al., 2020; Sefernick and Lindert, 2020; Wu and Lander, 2020).

Cryo-electron microscopy has grown mainly with a broad sense of being a collaborating community. This collaboration has crystallized at multiple levels:

1. very active mailing lists as 3DEM (http://3dem.ucsd.edu/mailing-list.shtm), CCPEM (https://www.jiscmail.ac.uk/cgi-bin/webadmin?A0 = CCPEM), or 3DEM Methods (http://3demmethods.i2pc.es).
2. very active Twitter account searching for CryoEM papers (https://twitter.com/cryoEM_Papers).
3. periodic, well-subscribed conferences, such as the Gordon Research Conference on Three-dimensional Electron Microscopy (https://www.grc.org/three-dimensional-electron-microscopy-conference/) held since 1985, and the Intl. Conf. Image Analysis in Three-dimensional Cryo-EM (https://cryoem.bcm.edu/events/view_workshops) held since 2014.
4. publicly available repositories of final structures such as EMDB and PDB (https://www.emdataresource.org, https://www.ebi.ac.uk/emdb, https://pdbj.org), and repositories of acquired raw data such as EMPIAR (https://www.ebi.ac.uk/empiar).
5. open-source software packages such as Cistem (https://github.com/timothygrant80/cisTEM), Eman2 (https://github.com/cryoem/

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eman2), iMod (https://bio3d.colorado.edu/imod/openSource/), Relion (https://github.com/3dem/relion), Spider (https://github.com/spider-em/SPIDER), or Xmipp (https://github.com/I2PC/xmipp); even commercial packages like CryoSPARC (https://cryosparc.com/) have a free license for academic users.
6. And even supranational research infrastructures, such as Instruct-ERIC, (https://instruct-eric.eu) have emerged.

This collective, collaborative effort has been very fruitful, as acknowledged by the increasing trend of maps deposited at EMDB and structural models at PDB (Fig. 1).

3DEM Methods started in 2011 as an open Wiki site to gather the methodological papers related to CryoEM. At present, it holds more than 1,000 papers which are the ones that we have used to perform the present analysis (listed in the Supplementary Material). We are aware that 3DEM Methods cannot contain absolutely all methods appeared in the field, comprehensive as it is. However, it serves as an excellent basis to identify the impact of CryoEM and its current trends. This collection of papers covers sample preparation, image acquisition, image processing, and map interpretation. It does not cover electron optics and detection. The group also includes methodological reviews as they bring valuable insight into the field's current state, the methods available, and how to use them best. We have performed the bibliographic analysis in Web Of Science (https://www.webofscience.com), where more than 90% of the papers were found (to be precise, 910 out of 1,000).

2. Scientific impact

A bibliographic analysis of the set of methodological papers yields the following observations:

- These papers have involved almost 2,300 researchers from all over the world.
- The most prominent countries are USA (37.5% of the papers), Germany (11.3%), England (10.4%), Spain (9.5%), France (5.0%), China (4.1%), Switzerland (3.3%), Canada (3.1%), Netherlands (2.9%), Japan (2.5%), Sweden (1.8%), Australia (1.6%), Israel (1.4%). 13 countries account for almost 95% of the methods. Instruct-ERIC countries account for 31.2% of them.
- Considered as a whole, methodological papers would have an H-index (Hirsch, 2005) of 133. According to Scimago Journal Ranking (https://www.scimagojr.com/journalrank.php), this H-index is better than 96.2% of all journals in all scientific disciplines.
- Methodological papers tend to be published in J. of Structural Biology (JSB), that holds 31.2% of them. We need the following 11 journals to equal this share of papers, namely by decreasing order: Ultramicroscopy, 9.8%; Nature methods, 3.6%, Structure, 3.5%; Acta Crystallographica Section D Structural Biology, 3.1%; J. of Chemical Information and Modeling, 2.4%; Bioinformatics, 2.1%; Elife, 1.9%; IUCRJ, 1.4%; J. of Molecular Biology, 1.2%; Nature communications, 1.2%; BMC Bioinformatics, 1.1%. The whole set was published in 181 different journals. Note, however, that some journals, like IUCrJ, have only started in recent years.
- The top 10 most cited papers of JSB and the top 3 of Ultramicroscopy are about image processing methods (in both cases, with more than 1,000 citations).
- Each methodological paper receives an average of 92 citations. We may compare this number to the average number of citations of a JSB paper, 39, and the 73 citations in average of a paper of Nature Structural and Molecular Biology (considered to be the best journal in the Structural Biology field according to Scimago).
- The set of methodological papers accumulated 83,849 citations from 33,364 papers (see Fig. 2).
- We may identify five periods: $\leqslant$1995, 1996–2002, 2003–2012, 2013–2014, $\geqslant$2015 (see Fig. 2). In this plot, it is clear that the technological change implied by the introduction of direct electron detectors not only resulted in a resolution revolution around 2014 (Bai et al., 2014; Kühlbrandt, 2014) but also in a methodological revolution, as shown by Period 5 in the figure. The Chemistry Nobel prize was awarded in 2017, that is, when the technology was already mature enough.
- Since 2015, there has been an average of 74 new method papers every year, six every month (on average, two of them in JSB, and the other four scattered in 180 journals).
- 172 articles had more than 100 citations. We show the word cloud of their titles in Fig. 3. It gives a good summary of what the methods have been dealing with. Fig. 4 shows a word cloud of the associated authors. We have calculated word clouds with 250 word and a weight given by the square root of the number of appearances.

More important than the bibliographic numbers, it is to measure the contribution of these methodological papers to other scientific domains. This is summarized in Web Of Science through Research Areas (Fig. 5), MeSH headings (Fig. 6), and MeSH qualifiers (Fig. 7). The categorization of the papers into fields is internally done by Web Of Science and the specific techniques are unknown to us. We can see that CryoEM has contributed to the scientific understanding of most biological processes at the molecular and cellular level, understanding the action of drugs, and undoubtedly fostered new ideas in image processing that can be exported to other imaging domains (an example of this would be

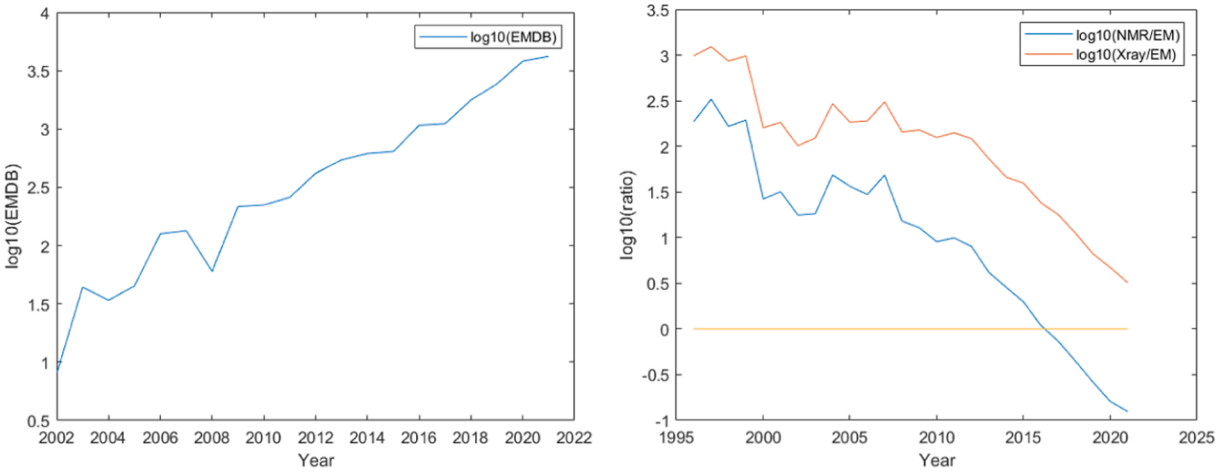

Fig. 1. Evolution of the total number of released (cryoEM) maps in EMDB (left) and of the ratio of atomic models in PDB coming from NMR and Xrays with respect to EM (right). Note the logarithmic scale in ordinates in both graphs, and that this data refers to yearly releases, not a cumulative account.

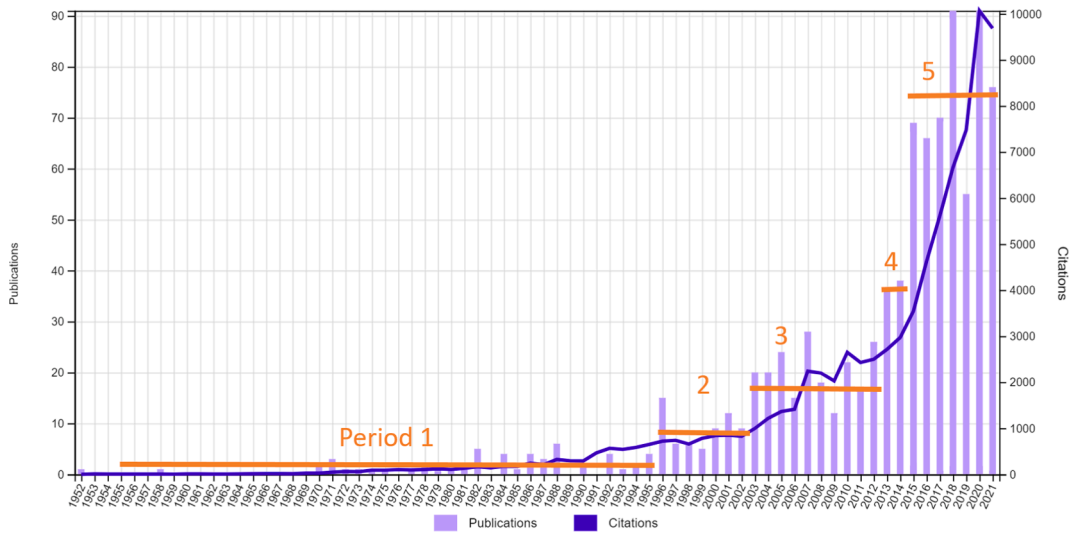

Fig. 2. Evolution of the number of publications and citations over time according to Web Of Science.

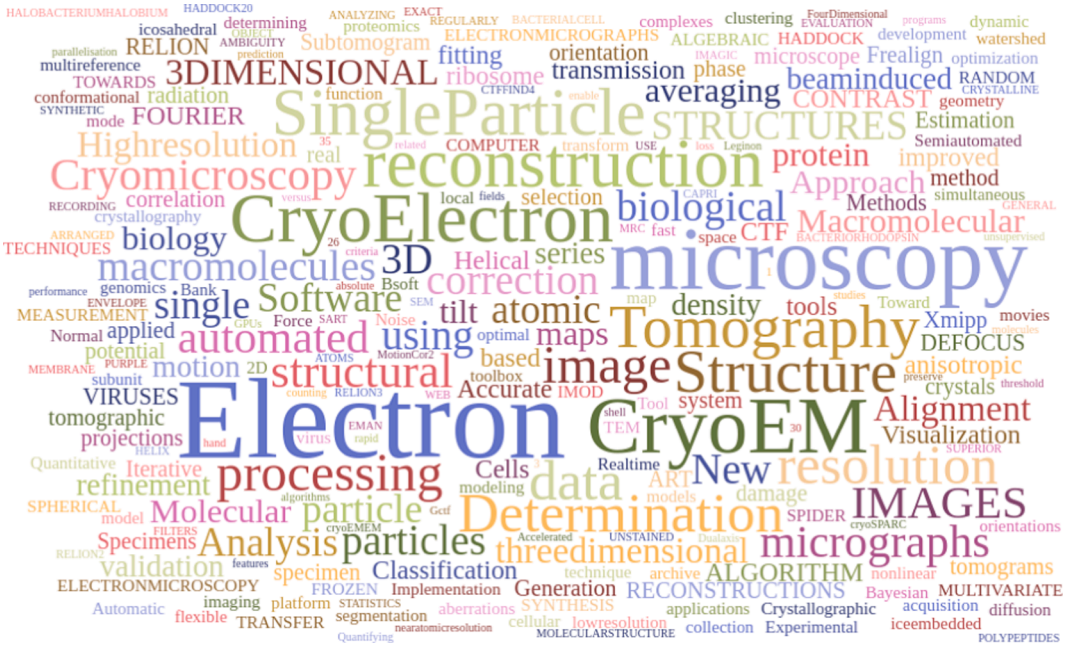

Fig. 3. Word cloud of the titles of the articles with more than 100 citations according to Web of Science.

fluorescence microscopy (Broeken et al., 2015; Salas et al., 2017; Strack, 2017; Fortun et al., 2018; Shi et al., 2019; Phillips et al., 2020; Huijben et al., 2021)). Just to give an idea of the versatility of the tool, CryoEM has been used to solve the structure of SARS-CoV2 proteins (Wrapp et al., 2020), their interaction with drugs (Yin et al., 2020) or neutralizing antibodies (Barnes et al., 2020), the structure of individual virions (Ke et al., 2020), the infection process in many systems (Klein et al., 2020), specific protein structures obtained from patient tissues (Falcon et al., 2018), or the nano-scale structure of tissues (Reznikov et al., 2018).

3. Scientific trends

There are $2^{1000} \approx 10^{301}$ ways of classifying 1,000 articles into different groups (this number is given by the power set of a set of 1,000 elements). We have chosen a variant of the classification followed in the 3DEM Methods wiki, which has arisen from the community of editors of the wiki itself (actually, any researcher can be an editor). Although imperfect, and certainly showing some areas of overlap, this classification largely reflects the main topics without being too specific or too general. In this way, we can identify topical trends over time.

In our first analysis, we focus on a high level. We distinguish between the following categories: 1) sample preparation, 2) image formation, 3) image acquisition, 4) single particle analysis, 5) electron tomography, 6) 2D crystallography, 7) helical particles, 8) icosahedral particles, 9) microED, 10) relationship to other structural biophysical techniques, and 11) databases. We show the results in Fig. 8. We have separated these categories into three classes: topics with five or fewer publications per year (Fig. 8 top), topics with 5 to 15 publications per year in the last five years (Fig. 8 middle), and topics with more than 15 yearly publications in at least one of the last five years (Fig. 8 bottom). For comparison purposes in the last plot, we added the combined sample preparation + image acquisition (1 + 3) and all other categories (2 + 6+7 + 8+9 + 10 + 11).

Fig. 4. Word cloud of the authors of the articles with more than 100 citations according to Web of Science.

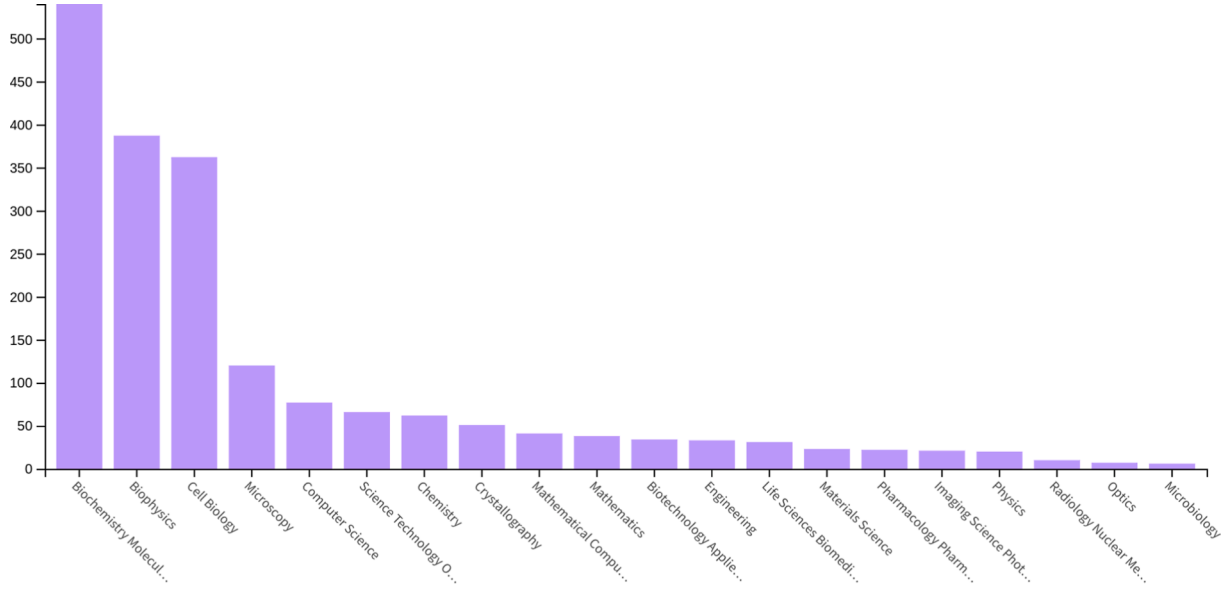

Fig. 5. Top 20 Research areas citing CryoEM methodological papers according to Web Of Science.

From this analysis, it is clear that the most active field in the last years is Single Particle Analysis, followed by Sample Preparation and Image acquisition, and then Electron Tomography. All other topics have been much quieter in the most recent years. Due to this increased interest in sample preparation and image acquisition, especially in connection to Single Particle Analysis, it is clear that the means are being set for a very substantial widening on the type of specimens being analyzed and on the quality of the results. The most active areas are about having more reproducible freezing, with thinner ice, obtaining more stable samples under the microscopes, less sample denaturation, time-resolved or 4D CryoEM, automating the acquisition and implementing a closed feedback loop to the microscope, etc. One of the most interesting results of this analysis is that image formation is being revisited. Having access nowadays to higher resolution allows reevaluating concepts of radiation damage, the behavior of the sample under the electron beam, the measurement of the high-order aberrations, nonlinear effects of the image formation model, etc. On the other hand, Electron Tomography is clearly “the next frontier”, not yet with the methodological development push of Single Particle Analysis, perhaps because some fundamental issues may still act as bottlenecks for broader growth in terms of methods development, but with a clear shift of interest to this domain. In particular, particle selection in tomograms, subtomogram classification and averaging are clearly three of the most limiting factors at the moment due to their high computational time and their limited success in many cases due to the low SNR, the presence of the missing wedge or nearby ”interfering” structures as is the case of the membrane in membrane proteins.

By far, the most active methodological area is Single Particle Analysis. We have decomposed this large topic into smaller subtopics: (1) CTF, (2) 2D Preprocessing, (3) Particle picking, (4) 2D Classification, (5) 3D Alignment, (6) 3D Classification, (7) 3D Reconstruction, (8) Map postprocessing, (9) Resolution measurements, (10) Map validation, (11) Modelling, (12) Reviews, (13) Software tools. The number of methods per year for each of these subtopics can be seen in Fig. 9. The three most

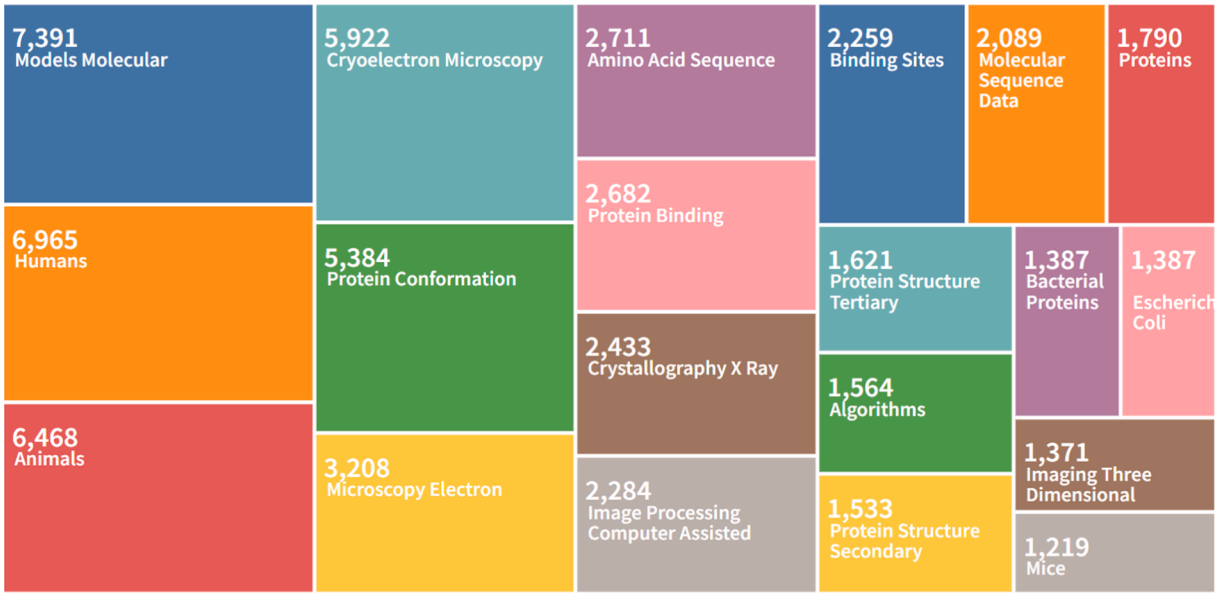

Fig. 6. Top 20 MeSH headings citing CryoEM methodological papers according to Web Of Science.

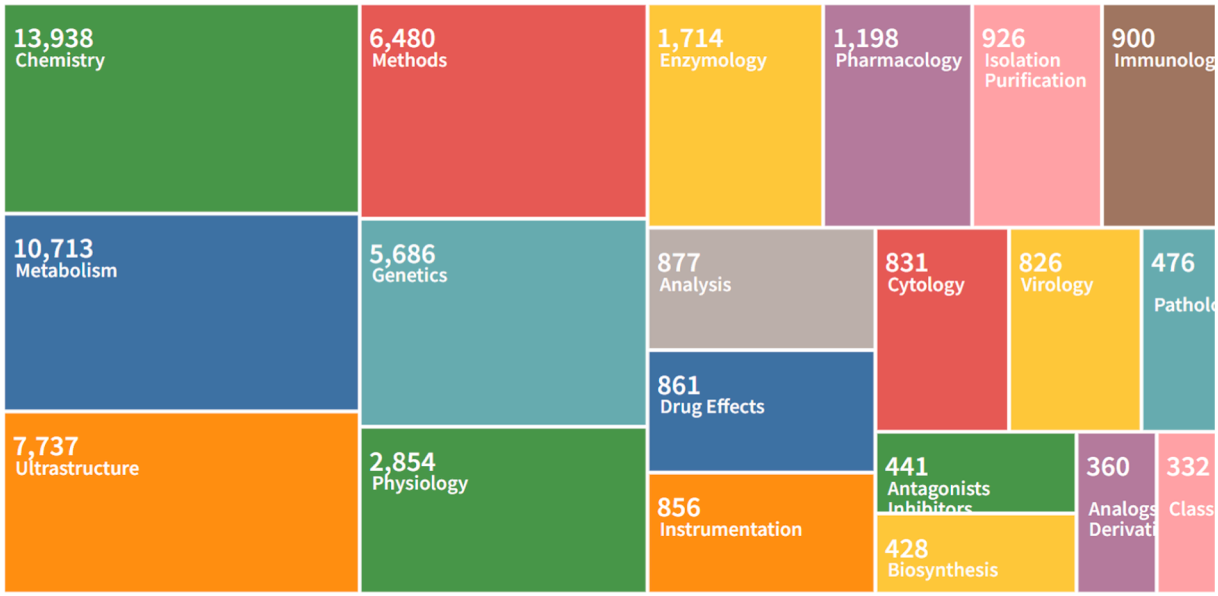

Fig. 7. Top 20 MeSH qualifiers citing CryoEM methodological papers according to Web Of Science.

active areas are the atomic modeling of the map, 3D classification, and 3D reconstruction. The first topic is logical, given the higher resolution of the maps. The second one stems from the fact that 3D classification is one of the most challenging tasks, especially considering the dynamics and continuous flexibility of the macromolecule being studied, with several papers published just in 2021 addressing this latter issue. Indeed, solving the continuous flexibility problem would imply an important step forward in the Structural Biology and Biophysics areas. Given its importance, we have further divided the 3D classification methods section into subsections depending on whether they are based on cross-correlation and variants of the multireference projection matching approach (correlation), analysis of the map variance or its covariance matrix (Multivariate Statistical Analysis, MSA), Maximum Likelihood (ML), local analysis (Local), continuous flexibility (Continuous), or others. Fig. 10 shows the evolution of these methods over time. In the last years, continuous flexibility is clearly the hottest topic. Despite the relative lack of new methods in ML or correlation, they are currently some of the most used algorithms (e.g., they are at the core of Relion, CryoSparc, and Cistem discrete 3D classification). The 3D reconstruction field is exploring how to incorporate signal or biological priors into the process, how to be more robust to the presence of artifacts, uneven resolution or angular distributions, different regularization schemes, etc.

4. Conclusions

From this bibliographic analysis, we can draw a few essential ideas:

- The field is very active in methodological exploration. The whole process aims to have better and more reproducible results from all aspects of the problem: sample preparation, image acquisition, image processing, and map interpretation.
- The trend towards automation at all levels is essential, so that there are fewer subjective decisions, mainly in the image processing part

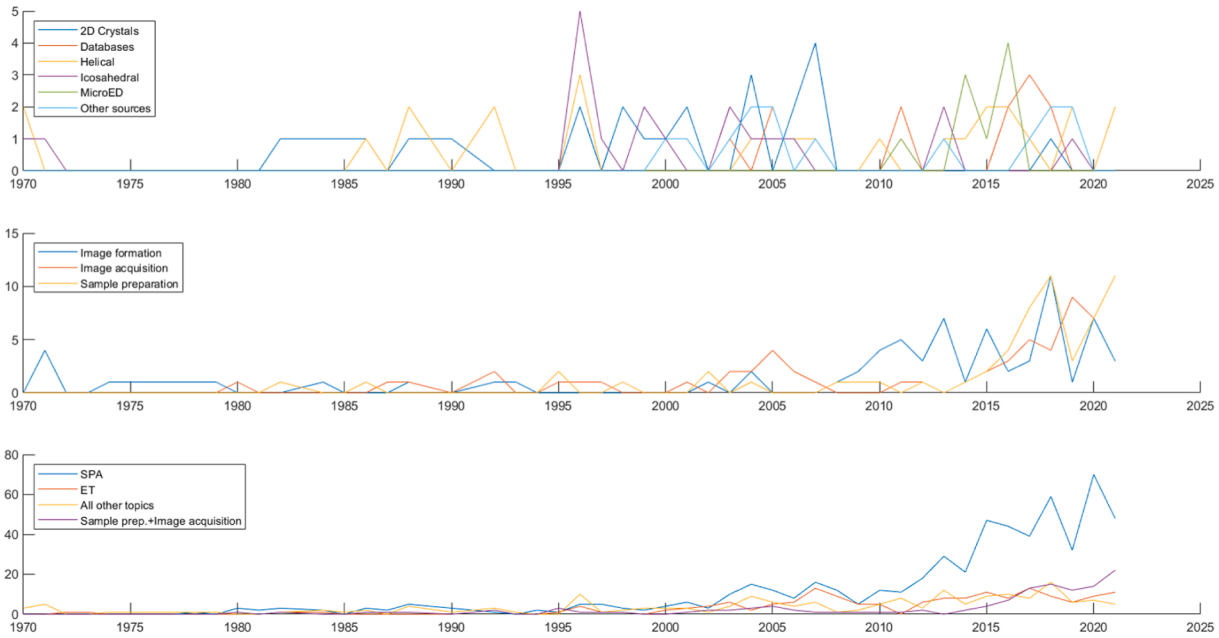

Fig. 8. Trends of the number of CryoEM methodological papers over time.

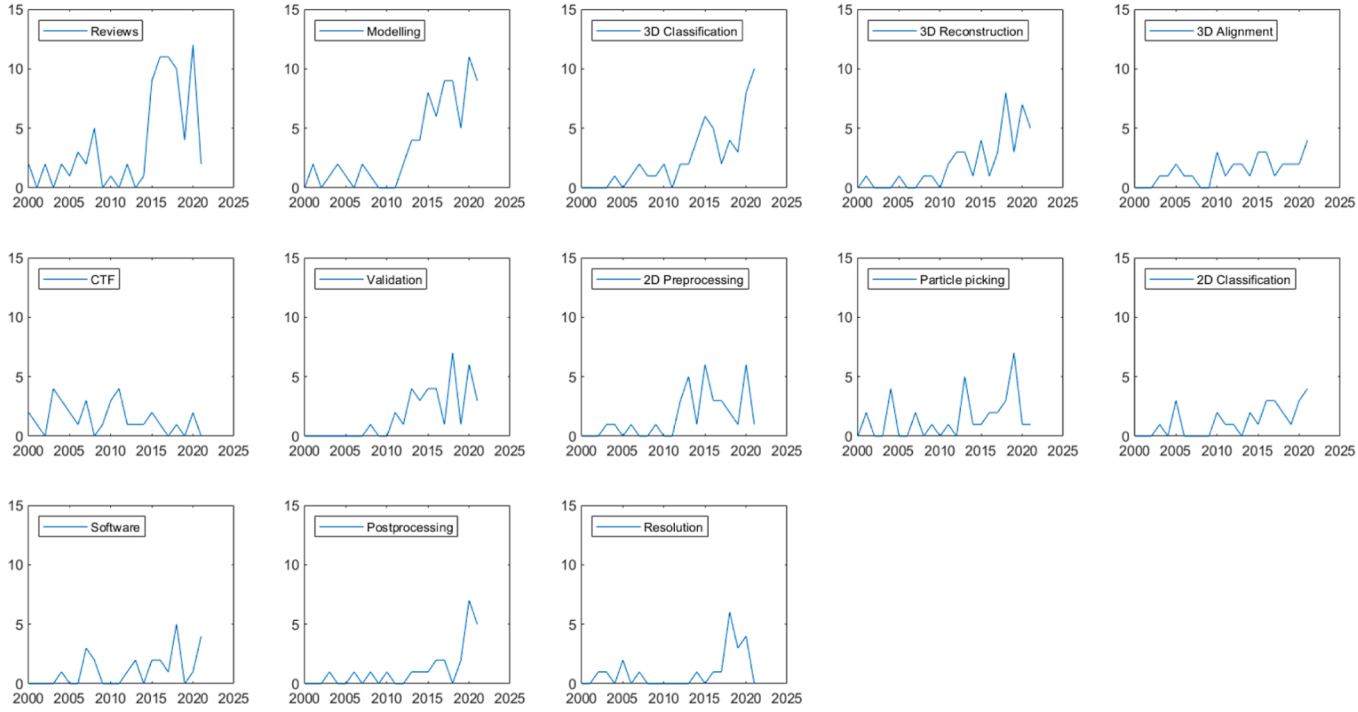

Fig. 9. Trends of the number of Single Particle Analysis methodological papers over time.

(while automation and increased reproducibility in sample preparation is the next challenge).

- Single-particle analysis is not perceived as an exhausted domain. On the contrary, it is a domain in which many additional topics are yet to be explored, as is shown by its current high publication rate.
- Electron Tomography has not yet reached the explosive methodological development trend of single-particle analysis. It is undoubtedly related to the maturation of the field and the existence of still substantial issues to address.
- Methodological papers are scattered in many different journals, although JSB is one of the most natural journals for them.
- CryoEM as a whole has had a considerable impact in many levels of Structural, Molecular, and Cell Biology as well as in the Pharmaceutical industry.

Among so many computational methods, an interesting question would be about which of the different methods we should use. A sensible answer is that several of them. There are a few reasons for this: (1) having multiple methods gives resilience to the practitioners' community as there is not any method that always works the best for all datasets; (2) all methods have to estimate parameters, and this estimation may go wrong for a fraction of the input dataset, the only way to identify

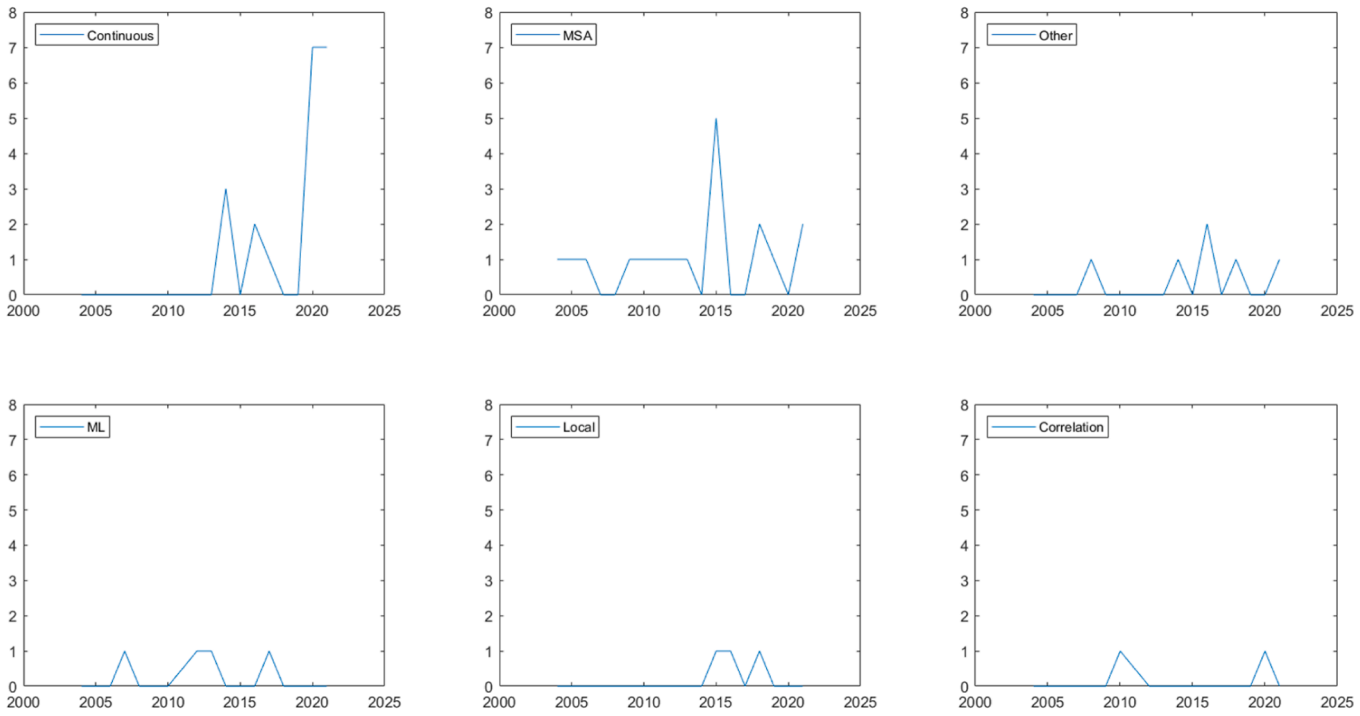

Fig. 10. Trends of the number of 3D classification methods over time.

the poorly estimated parameters is by comparing them with the estimations of the same parameters by a different algorithm (assuming that these parameters are comparable, for instance, the angular assignment of an experimental image or its discrete classification) (Sorzano et al., 2022); 3) the continuous exploration of new methods will result in a better set of good practices at all levels, from algorithms reporting to their use by practitioners.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jsb.2022.107861.

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Supplementary material

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December 2021

Categories and papers in each category as in the 3DEM Methods (http://3demmethods.i2pc.es)

- **Image formation**: [239, 298, 339, 845, 835, 865, 918, 147, 145, 917, 351, 161, 274, 856, 916, 857, 1017, 359, 201, 224, 780, 862, 243, 58, 679, 40, 48, 125, 305, 988, 50, 302, 556, 685, 1000, 49, 102, 747, 222, 34, 494, 756, 494, 914, 913, 915, 177, 146, 350, 452, 466, 502, 545, 300, 449, 241, 450, 560, 26, 204, 182, 245, 347, 374, 451, 451, 593, 689, 687, 688, 624, 96, 320, 585, 1001, 850, 899, 973, 1002, 223, 229, 301, 939]
- **Collection geometry**: [386, 658, 653, 627, 536, 508, 473, 981, 488, 552, 465, 387, 775, 327, 831, 203, 607, 139, 950]
- **Sample preparation**: [209, 486, 487, 208, 207, 876, 6, 95, 201, 389, 10, 819, 638, 996, 995, 690, 100, 127, 619, 625, 667, 828, 844, 28, 212, 248, 352, 710, 712, 730, 23, 29, 30, 175, 291, 492, 593, 612, 674, 735, 935, 198, 684, 772, 157, 220, 246, 446, 576, 832, 974, 76, 98, 120, 279, 237, 400, 408, 413, 435, 911, 1004, 587]
- **Automated data collection**: [94, 195, 455, 281, 997, 1024, 646, 1010, 484, 824, 976, 991, 454, 495, 294, 499, 881, 15, 80, 326, 782, 153, 235, 226, 329, 520, 736, 837, 843, 57, 323, 496, 694, 713, 809, 937, 247, 89, 152, 214, 432, 673, 967, 936, 955, 967, 975]
- **Single particle analysis**:
  - Automatic particle picking: [869, 589, 1022, 761, 904, 946, 1021, 129, 947, 794, 27, 5, 348, 384, 751, 879, 472, 720, 895, 924, 675, 1023, 396, 356, 700, 13, 12, 67, 115, 493, 919, 931, 992, 701, 600]
  - 2D Preprocessing: [116, 681, 780, 793, 794, 93, 102, 1008, 598, 34, 494, 756, 879, 719, 4, 312, 312, 683, 807, 1006, 38, 404, 72, 68, 543, 1011, 606, 951, 1026, 66, 155, 156, 393, 611, 817, 242]
  - 2D Alignment: [277, 706, 760, 163, 162, 729, 8, 777, 25, 657, 480, 534, 138, 154, 358]
  - 2D Classification and clustering: [872, 870, 273, 108, 521, 522, 523, 532, 547, 548, 614, 615, 616, 617, 725, 727, 777, 767, 968, 798, 1009, 392, 441, 669, 73, 952, 87, 758, 558, 664]

- 3D Alignment: [428, 306, 871, 648, 653, 902, 289, 307, 342, 631, 656, 633, 681, 786, 780, 419, 966, 599, 315, 401, 705, 764, 765, 292, 757, 234, 927, 880, 425, 71, 799, 554, 647, 168, 314, 802, 796, 985, 985, 749, 957, 411, 453, 583, 1014]
- 3D Reconstruction: [295, 371, 428, 22, 343, 983, 104, 654, 984, 287, 1020, 84, 525, 110, 788, 972, 789, 803, 250, 804, 77, 491, 907, 309, 462, 723, 763, 234, 513, 926, 467, 2, 211, 568, 797, 959, 971, 650, 650, 801, 52, 390, 490, 555, 670, 802, 796, 1019, 304, 349, 940, 11, 613, 651, 663, 957, 890, 1016, 3, 324, 511, 442, 795]
- 3D Heterogeneity: [105, 938, 630, 632, 481, 489, 714, 724, 368, 370, 728, 806, 231, 752, 717, 1013, 929, 513, 135, 180, 739, 412, 20, 36, 429, 444, 497, 826, 308, 665, 746, 776, 792, 961, 650, 731, 21, 344, 578, 744, 771, 783, 990, 179, 325, 341, 518, 570, 743, 1015, 892, 133, 297, 330, 372, 434, 539, 580, 649, 778, 1014, 213]
- Validation: [810, 365, 668, 366, 166, 134, 196, 361, 510, 574, 690, 811, 934, 375, 603, 682, 949, 189, 680, 883, 439, 563, 586, 882, 7, 377, 381, 421, 526, 610, 640, 373, 130, 165, 605, 708, 816, 852, 659, 546, 641, 602]
- Resolution: [343, 864, 183, 626, 681, 863, 875, 805, 463, 639, 800, 31, 119, 440, 686, 894, 970, 32, 378, 660, 45, 62, 628, 898]
- Sharpening of high resolution information: [848, 692, 681, 257, 263, 443, 808, 416, 420, 402, 662, 572, 661, 842, 898, 61, 430, 261, 699]
- CTF estimation and restoration: [732, 856, 275, 770, 1018, 259, 634, 812, 1020, 186, 403, 692, 394, 557, 704, 887, 1028, 790, 922, 210, 519, 945, 417, 637, 787, 794, 405, 433, 485, 302, 533, 762, 909, 908, 884, 629, 524, 678, 754, 993, 820, 357, 1027]
- Segmentation: [41, 642, 695, 592, 60, 62, 244, 839, 353]
- Fitting and docking: [905, 39, 406, 414, 458, 829, 829, 888, 889, 188, 501, 447, 886, 691, 855, 42, 79, 885, 126, 240, 503, 597, 14, 644, 672, 900, 51, 70, 117, 338, 504, 737, 830, 799, 424, 424, 575, 742, 768, 930, 137, 423, 388, 538, 553, 561, 859, 925, 944, 121, 131, 431, 459, 588, 840, 932, 956, 977, 85, 436, 445, 823, 1003, 169, 202, 383, 385, 422, 437, 483, 535, 604, 877, 151, 170, 337, 476, 498, 566, 636, 698, 841, 851, 912]
- Books and reviews: [367, 426, 148, 815, 833, 873, 270, 733, 360, 822, 150, 813, 149, 260, 271, 793, 489, 785, 243, 250, 418, 571, 836, 191, 781, 193, 35, 109, 144, 141, 232, 362, 596, 737, 867, 954, 118, 219, 227, 262, 300, 416, 559, 416, 544, 595, 821, 901, 143, 176, 233, 272, 272, 415, 549, 666, 800, 800, 97, 142, 167, 317, 573, 652, 709, 897, 906, 228, 65, 178, 512, 783, 1, 9, 64, 206, 471, 391, 540, 740, 579, 766, 898, 953, 994, 33, 199]
- Software: [269, 874, 528, 507, 509, 780, 47, 376, 315, 726, 745, 718, 948, 184, 159, 140, 185, 721, 316, 569, 63, 158, 313, 542, 1025, 101, 46, 517, 750, 784, 818]

- **Electron tomography**:
  - Image preprocessing: [964, 951]
  - Image alignment: [322, 474, 627, 608, 318, 90, 90, 941, 123, 122, 794, 103, 854, 336, 334, 537, 255, 335, 254, 332, 779, 331]
  - CTF estimation and restoration: [942, 260, 982, 958, 225, 74, 861, 468]
  - 3D reconstruction: [295, 371, 22, 654, 529, 249, 655, 250, 962, 369, 995, 311, 91, 550, 609, 891, 190, 321, 860, 965, 701, 774, 261, 290]
  - Noise reduction: [267, 253, 407, 258, 868, 256, 251, 78, 460, 516, 858, 564, 951]
  - Segmentation: [268, 903, 37, 174, 478, 702, 703, 288, 479, 16, 959, 834, 17, 132, 960, 986, 696]
  - Resolution: [113, 635, 194, 896]
  - Subtomogram analysis: [83, 266, 618, 591, 69, 282, 265, 54, 734, 716, 722, 18, 978, 136, 470, 751, 979, 135, 980, 910, 74, 469, 75, 773, 124, 278, 382, 1007, 264, 332, 55, 205, 340, 505, 711, 769, 838, 987]
  - Single-particle tomography: [53, 1005, 283, 285, 284]
  - Missing-wedge correction: [457, 562, 989]
  - Molecular 3D dynamics: [999]
  - Books and reviews: [56, 456, 697, 360, 506, 260, 271, 541, 785, 243, 250, 418, 464, 92, 238, 59, 286, 643, 738]
  - Software: [461, 128, 276, 791, 590, 551, 379, 995, 200, 594, 866, 499, 333, 921, 99]
- **2D Crystals**
  - 2D Preprocessing: [19, 706, 707, 364, 107, 355, 293]
  - Classification: [274, 252, 753]
  - 3D Reconstruction: [923, 106, 363, 530, 81]
  - Books and reviews: [920, 299, 230, 360, 260, 785]
  - Software: [791, 296, 173, 376, 637]
- **3D Crystals - MicroED**
  - Sample Preparation: [755]
  - Data Collection: [582]
  - Data Processing: [943, 345, 346]
  - Software: [397]
  - Books and Reviews: [581, 500, 676]
- **Helical particles**

  - Filament picking: [849]
  - Filament corrections: [215, 82, 933, 969, 601]
  - Reconstruction: [160, 448, 187, 814, 565, 928, 216, 217, 192, 677, 998, 354, 645]
  - Validation: [218]
  - Books and reviews: [187, 565, 360, 693, 221]
  - Software: [114, 173, 608]

- **Icosahedral particles**
  - Reconstruction: [172, 171, 280, 846, 847, 1012, 303]
  - Alignment: [753]
  - Classification: [715]
  - Books and reviews: [43, 164, 847, 482, 584, 319]
  - Software: [44, 173, 269, 874, 791, 184, 567]

- **Liquid-cell TEM/in-situ TEM**: [671]

- **Databases**: [531, 181, 111, 112, 427, 827, 410, 88, 380, 514, 438, 475, 621, 398, 399, 527, 622, 825, 310, 620, 748, 853, 741, 623, 515, 878]

- **Relationship to other structural information sources**: [236, 197, 577, 477, 86, 893, 328, 963, 439, 24, 759, 395, 409]

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