Interrelating Different Types of Genomic Data, from Proteome to Secretome: 'Oming in on Function

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"***[It] does not consist of individuals, but expresses the sum of interrelations, the relations within which these individuals stand.***"
- adapted from Karl Marx, *Grundrisse* (1857)

Abstract

With the completion of genome sequences, the current challenge for biology is to determine the functions of all gene products and understand how they contribute in making an organism viable. For the first time, biological systems can be viewed as being finite, with a limited set of molecular parts. However, the full range of biological processes controlled by these parts is extremely complex. Thus, a key approach in genomic research is to divide the cellular contents into distinct sub-populations, which are often given an "-omic" term. For example, the proteome is the full complement of proteins encoded by the genome, and the secretome is the part of it secreted from the cell. Carrying this further, we suggest the term "translatome" to describe the members of the proteome weighted by their abundance, and the "functome" to describe all the functions carried out by these. Once the individual sub-populations are defined and analyzed, we can then try to reconstruct the full organism by interrelating them, eventually allowing for a full and dynamic view of the cell. All this, of course, is made possible due to the increasing amount of large-scale data, resulting from functional genomics experiments. However, there are still many difficulties owing to the noisiness and complexity of the information. To some degree, these can be overcome through averaging with broad proteomic categories such as those implicit in functional and structural classifications. For illustration, we discuss one example in detail, interrelating transcript and cellular protein populations (transcriptome and translatome). Further information is available at http://bioinfo.mbb.yale.edu/what-is-it

Introduction

The raw data produced by genome sequencing projects currently provides little insight into the precise workings of an organism at the molecular level (Luscombe *et al.*, In Press). Therefore, the goal of functional genomics is to complement the genomic sequence by assigning useful biological information to every gene. Through this, we aim to improve our understanding of how the different biological molecules contained within the cell – *i.e.* DNA, RNA, proteins and metabolites – combine to make the organism viable. Clearly, the main challenge is the elucidation of all molecular, cellular and physiological functions of each gene product. However, there are many subsidiary goals as part of this challenge, such as defining the three-dimensional structures of these macromolecules, their subcellular localisations, intermolecular interactions and expression levels. Although gathering and classifying the necessary information is central to this process, it is impractical to rely on individual experiments for the potentially thousands of genes in each organism. Furthermore, with large-scale proteomic experiments still yet to be used widely, computational techniques, while sometimes based on less than ideal information, provide a crucial resource for assigning biological data.

The paper by Antelmann *et al.* in this issue of *Genome Research* evaluates their earlier attempts to assign protein functions through computational means. Previously, the group used computational methods to predict all exported proteins – or members of the secretome – in *Bacillus subtilis* by searching for signal peptides and cell retention signals in the protein sequences. A better understanding of how and why a protein is secreted is valuable as the bacterium's ability to export numerous enzymes enables it to degrade extracellular substrates and survive in a continuously changing environment. Moreover, it will eventually allow these bacteria to be employed as "cellular factories" for secreting commercially valuable proteins in large quantities (Tjalsma *et al.* 2000).

Antelmann *et al*.'s present paper aims to verify their previous predictions by experimentally characterising the entire population of secreted proteins using 2D gel electrophoresis and mass spectrometry. They showed that the original predictions correctly identified about 50% of all secreted proteins. Most of the disagreements were due to the inability to predict the secretion of proteins lacking the appropriate signal, or those containing seemingly inappropriate signals (cell retention signals). In summary, Antelmann *et al.*'s work highlights both the encouraging aspects of computational assignments of biological data, and reveals some of the shortcomings in the current methods.

The path to function is filled with 'omes

To describe their studies, Antelmann *et al*. coined the term "secretome". This 'omic term is an example of the new lexicon that has recently appeared to define the varied populations and sub-populations in the cell (Figure 1). These terms are generally suffixed with "-ome", with an associated research topic of "-omics".

Broadly, the existing 'omes can be divided into those that represent a population of molecules, and those that define their actions (Figure 1). For the first, populations provide an inventory or "parts list" of molecules contained within an organism (Gerstein & Hegyi 1998; Skolnick & Fetrow 2000; Vukmirovic & Tilghman 2000; Qian *et al.* 2001). The **genome**, the entire DNA sequence of an organism, presents a basis for defining the **proteome**, a list of coding DNA regions that result in protein products. Transcription of these coding sequences produces the **transcriptome** (Velculescu *et al.* 1997), which is the cellular complement of all mRNA under a variety of cellular conditions. Note, this population is weighted by the expression level of each molecule and, ideally, should incorporate the results of alternative splicing. Following translation of the transcriptome, we suggest the term **translatome** to describe the cellular population of proteins expressed in the organism at a given time, explicitly weighted by their abundance. It is important to note that whereas the membership of the genome and proteome are virtually static, the transcriptome and translatome are dynamic and continually change in response to internal and external events. Additional 'omes describe the presence of molecules that are not encoded by the genome, but are nonetheless essential, for instance, the metabolome (Tweeddale *et al.* 1998). Owing to the newness of most 'omic terms, a few still have competing definitions. This is most evident for the proteome (see Figure 1 caption).

The second group of 'omes are fewer in number and describe the actions of the protein products. For example, the **secretome** is a subset of the proteome that is defined by its action, *i.e.* it is actively exported from the cell. The **interactome** (Sanchez *et al.* 1999)

lists all of the specific interactions that are made between macromolecules in the cell. More abstractly, the **regulome** (web references only, see Figure 1) defines the genome-wide regulatory network of the cell and most notably includes transcription regulation pathways.

The elucidation of each of these 'omes contributes to the ultimate goal of functional genomics, defining the **functome**, which describes all of the functions that are assigned to each gene in the genome (on web page associated with Rison *et al.*, 2000, biochem.ucl.ac.uk/~rison)The functions of a gene can be described at many levels, including their biochemical, cellular and physiological roles (Ashburner *et al.* 2000), and also depend on additional factors that are not immediately associated with their basic functions, such as subcellular localisation and intermolecular interactions. Therefore, aspects of the functome may be expressed in terms of other 'omes, for example those that group similar biochemical functions, *e.g.* the **immunome** (Pederson 1999), similar localisations, *e.g.* the secretome, and similar interactions, *e.g.* the interactome. For the record, we coin our own term here; at present, a large proportion of genes can only be described as members of the **unknome** – those with currently no functional information!

Computational methods for defining 'omes

There are a variety of computational approaches for defining 'omes (Gerstein & Honig 2001):
(i) Algorithmic methods for predicting genes, protein structure, interactions, or localization based on patterns in individual sequences or structures – e.g. defining the proteome or orfeome using a gene-finding algorithm on the genome (Claverie 1997; Guigo *et al.* 2000; Harrison *et al.* 2001; Yeh *et al.* 2001), determining the foldome from structure prediction of the proteome (Simons *et al.* 2001), determining the interactome from the foldome, using known binding sites (Teichmann *et al.* 2001), and determining the secretome from identifying signal sequences in the proteome (Tjalsma *et al.* 2000).
(ii) Annotation transfer through homology, *i.e.* inferring structure or function based on sequence and structural information of homologous proteins (Brenner 1999; Hegyi & Gerstein 1999; Wilson *et al.* 2000; Thornton 2001; Hegyi and Gerstein (In Press) Gerstein 1997; Gerstein 1998;)
(iii) Using a "guilt-by-association" method based on clustering where functions or interactions are inferred from clusters of functional genomic data, such as expression information. For example similar functions can sometimes be inferred through interactions with other proteins or similar expression profiles (Eisen *et al.* 1998; Marcotte *et al.* 1999; Gerstein & Jansen 2000; Ito *et al.* 2001).

Experimental methods for defining 'omes

Although still in their infancy, several large-scale experimental techniques are designed to assess the nature of different 'omes. Gene expression studies are now well established and microarray or GeneChip technologies can be used to measure mRNA abundance in the cell and hence define the transcriptome (Epstein & Butow 2000). Detection of protein concentration and definition of the translatome is more difficult, however, as evidenced by the dearth of such data. At present, the most prominent method employs two-dimensional electrophoresis to isolate proteins followed by mass spectrometry for their identification (Futcher *et al.* 1999; Gygi *et al.* 1999; Naaby-Hansen *et al.* 2001) followed

by quantification (Appel *et al.* 1997; Aebersold *et al.* 2000; Gygi *et al.* 2000). The two-hybrid system enables detection of specific protein-protein associations to build the interactome (Walhout & Vidal 2001; Uetz, 2000 *et al*; Ito *et al* 2001). Antelmann *et al.* in this issue used two-dimensional electrophoresis to determine the membership of the secretome.

Given the goal of determining the functome, perhaps the most exciting technology is the protein chip system, which is capable of high-throughput screening of protein biochemical activity. (Zhu *et al.* 2000; Zhu In Press). Other methods for obtaining large-scale protein functional characterization include a transposon insertion methodology (Ross-Macdonald *et al.* 1999).

Although we discuss the computational and experimental methods separately, there is, in fact, an inseparable relationship between the two. On the one hand, data resulting from high-throughput experimentation require intensive computational interpretation and evaluation (Carson *et al.* 2001). On the other, computational methods use empirical data to build a knowledge base for predictions. Furthermore, they sometimes produce questionable predictions that should be reviewed and confirmed through experiments, as Antelmann *et al*. point out. In addition to these high-throughput techniques, another interesting tactic is to aggregate the results of individual experiments through comprehensive literature searches. Although there clearly are difficulties with differing experimental conditions and varying interpretations, preliminary results have shown this to be an effective method (Jenssen *et al.* 2001; Marcotte *et al.* 2001; Ono *et al.* 2001).

Interrelating different 'omes

Having categorized the organism into different sub-populations, a fundamental approach in genomics is to establish relationships between the different 'omes. In other words, by piecing the individual 'omes together, we hope to build a full and dynamic view of the complex processes that support the organism. For example, how do the proteome and regulome combine to produce the translatome?

As with defining the 'omes, these relationships can be explored in different ways:
(i) Defining or assigning one 'ome based on another, as described above.
(ii) Comparing one 'ome with another to better understand the processes that shift one population into its successor. For instance, this could be done by correlating expression measurements for the transcriptome and translatome (see below).
(iii) Calculating "missing" (experimentally unattainable) information in one 'ome based on information in another one – *e.g.* using the known relationships between gene expression level and subcellular location to help predict the destination of proteins of unknown localization (Drawid & Gerstein 2000; Drawid *et al.* 2000).
(iv) Describing the intersection between multiple populations. For example, combining data from the transcriptome and the functome could describe the array of biochemical, and potentially, physiological functions that are available to the cell at any given time (Hegyi & Gerstein 1999).

The use of broad categories to interpret noisy data

Functional genomics experiments generally give rise to very complicated data that are inherently hard to interpret. Furthermore, these data are often plagued with noise (Kerr *et al.* 2000). Both factors can lead to inaccuracies and conflicting interpretations.

A good example is gene expression measurements, which are known to fluctuate between experiments even if the conditions are apparently identical (Baldi & Long 2001). These fluctuations are often due to measurement errors, but there are also inherent biological variations of expression levels, relating to the stochastic nature of gene expression (Szallasi 1999). One cause is the very low cellular concentrations of many transcription factors, meaning, that they bind promoters very rarely. Such events approximate to a Poisson process, and in fact, macroscopic chemical kinetics would fail to describe the resulting expression level of the gene (McAdams & Arkin 1999; Thattai & van Oudenaarden 2001). In another example, the interactome, when determined using the yeast two-hybrid technique is notorious for false positives and negatives (Ito *et al.* 2000; Serebriiskii *et al.* 2000; Ito *et al.* 2001; Legrain *et al.* 2001).

A useful way to tackle noise and complexity of functional genomics information is to average the data from many different genes into broad 'omic categories (Jansen & Gerstein 2000). For instance, instead of looking at how the level of expression of an individual gene changes over a time-course, we can average all the genes in a functional category (*e.g.* glycolysis) together. This gives a more robust answer about the degree to which a functional system changes over the time-course. Likewise, if one wants to investigate the relationship between a gene's essentiality (whether or not it is essential(Winzeler *et al.* 1999) and its subcellular localization, it might be useful to combine the results for all proteins in the same compartment. This would give the average degree of essentiality of all nuclear proteins, cytoplasmic proteins, and so forth. In an actual study for predicting protein subcellular localization, we obtained more accurate predictions for the overall populations (96% accuracy) of a given subcellular compartment than for individual genes (75%) (Drawid *et al.* 2000).

Thus, the strength of genomic studies lies in the global comparisons between biological systems rather than detailed examination of single genes or proteins. Genomic information is often misused when applied exclusively to individual genes. If one is interested only in one particular gene, there are many more conclusive experiments that should be consulted before using the results from genomics datasets. Therefore, genomic data should not be used in lieu of traditional biochemistry, but as an initial guideline to identify areas for deeper investigation and to see how those results fit in with the rest of the genome.

Moreover, most genomics datasets give relative rather than absolute information, which means that information about a single gene has little meaning in isolation. For example, they are best used to identify "outlier" genes that are particularly highly expressed or have especially many interactions rather than to focus on the individual measurements for a particular gene. A gene that makes a particularly large number of interactions may indicate that it is a key component of the cell. One numerical technique that is particularly useful with regard to dealing with this information is expressing results through ranks – *i.e.* not giving the number of interactions of a particular gene product, but how it ranks when compared with others. Furthermore, it provides a powerful way to combine many different heterogeneous sources of information into a common and

statistically robust numerical framework (Gerstein & Levitt 1997; Gerstein & Hegyi 1998; Qian *et al.* 2001).

These observations should be kept in mind when interacting with genomics tools and databases. Many websites focus on providing a lot of information for a single gene sequence or protein, in a "non-genomic" fashion. Rather, such sites should be designed to simultaneously display and manipulate large populations of genes. In the absence of such an 'omic interface, it is important that information resources at least accommodate bulk downloading of standardized data.

A case study: Inter-relating the transcriptome and the translatome

A specific example of comparing the transcriptome and translatome will illustrate the points we made about interrelating 'omes and using categories to interpret noisy data. Here the question is to what degree do highly expressed genes (transcriptome) correspond to highly expressed proteins (translatome)? We can get very different answers depending on the perspective we take:

(i) Theoretical view
Turning to the entire mRNA and protein populations, the change in protein concentration over time is equal to the rate of translation minus the rate of degradation. Borrowing from chemical kinetics, this is approximately expressed by the equation $dP(i,t)/dt = SE(i,t) - DP(i,t)$, where P is the abundance of protein i at time t, E is the corresponding expression level of this protein, S is a general rate of protein synthesis per mRNA, and D is a general rate of protein degradation per protein. Obviously, this is highly simplified and in a more general context one would expect the rates of synthesis and degradation to be different for each gene and dependent on the regulatory effects of other genes over time. In addition, the equation does not take into account the stochastic nature of gene expression (see above) (Chen *et al.* 1999).

(ii) Direct comparison of individual mRNA and protein data
At the moment, we do not have good enough data to apply models like the equation above. However, there is an intuitive sense that highly expressed genes correspond to highly abundant proteins. (One can see this by imagining the situation at steady-state, when the left-hand side of the equation is zero and a positive correlation between E and P results.) Figure 2A shows the direct comparison between raw measurements of mRNA expression and protein abundance data for 181 genes in yeast drawn from two recent studies (Futcher *et al.* 1999; Gygi *et al.* 1999). The two variables show a high degree of variation for individual data pairs and investigators have come to different conclusions about the general correlation between the them. This is, to some degree, dependent on the subjective way of analyzing the data.

(iii) Analysis of the data in terms of categories
Although, the relationship between mRNA and protein levels is vague for individual genes, some of the statistics for broad categories of protein properties are much more robust. Figure 2B shows the protein secondary structure and functional composition in the genome, the transcriptome (*i.e.* weighted by mRNA abundance), and in the translatome (*i.e*. weighted by protein abundance). In contrast to the differences between mRNA and protein data for individual genes, the broad categories show that the

transcriptome and translatome populations are remarkably similar; both contain roughly the same proportions of secondary structure and functional categories. Moreover, this contrasts the difference with the genome, which appears to have a distinctly different composition of functional categories. This illustrates that we get a more consistent picture when we average across the population, *i.e.* there is broad similarity between the characteristics of highly expressed mRNA and highly abundant proteins.

Conclusion

The ultimate goal of genomics is the elucidation of the functome, but there are many intermediate steps. Through viewing the cell in terms of a list of distinct parts, we can define, part by part, each 'ome in an effort to determine and categorize functional information for each gene. High-throughput experimentation and computational techniques are valuable and complementary, *i.e.* conclusive results often cannot be made based on a single methodology. It must be noted that this data is only valuable with regard to large populations, and as such, should only be used as a secondary source for single gene queries. Moreover, genomic approaches result in inaccurate and noisy data. This noise, while deafening on the single gene level, can be tolerated through the use of broad categories to analyse the data.

Figure Legends

Figure 1. An overview of the current 'omic terminology.

(A) A schematic of the main 'omes in the process of gene expression. **(B)** A table of 'omes, together with the occurrence in the literature and on the web. Updated versions of the is table will be available through our website http://bioinfo.mbb.yale.edu/what-is-it . Note that we define five new 'omes: the translatome, the foldome, the functome, the pseudome and the unknome Our definition of the translatome is partially motivated by the ambiguities in term proteome, which has two competing definitions. First, broadly favoured by computational biologists, is a list of all the proteins encoded in the genome (Gaasterland 1999; Doolittle 2000). In this context, it is equivalent to what some refer to as the orfeome, *i.e.* the set of genes excluding non-coding regions. Experimentalists, especially those involved in large-scale experiments such as expression analysis and 2D electrophoresis, favour a second definition. Here, it is used to describe the actual cellular contents of proteins, taking into account the different levels of protein concentrations (Yates 2000). We prefer the former definition for proteome, and use the term translatome for the latter. See www.genomicglossaries.com/content/omes.asp for listing of other 'omes and their definitions. **(C)** The literature citations of four of the most widely used 'omes over time.
* this term is used by other fields as well
** First Citation according to the Oxford English Dictionary

Figure 2. Interrelating the transcriptome and the translatome

(A) A direct comparison of protein abundance and mRNA expression. The abundance data is from two recent studies (datasets 1 and 2) of a global comparison of protein and mRNA expression levels in yeast (Futcher *et al.* 1999; Gygi *et al.* 1999). The combined protein abundance dataset is an average of the data points from the two studies if the given gene product appears in both studies. The mRNA expression data is mainly derived from Holstege *et al*. (Holstege FC 1998). Although there is a general trend for protein concentration to rise with mRNA levels, the actual correlation is weak and protein concentrations can sometimes vary by more than two orders of magnitude for a given mRNA level. Similar observations were reported by a study in human liver cells (Anderson & Seilhamer 1997). The mRNA expression data was scaled and the process is described on our website (http://bioinfo.mbb.yale.edu/expression). **(B)** The composition of the genome (proteome), transcriptome and translatome in terms of broad categories: protein secondary structures and functions. This is based on the analysis in Jansen and Gerstein (2000) with updates to include protein abundance data. The bottom pie charts give the composition in the genome, the middle charts in the transcriptome and the top charts in the translatome. The compositions for the transcriptome and the translatome are calculated by weighting each mRNA/protein with its respective expression level. The secondary structure composition does not vary significantly between the different 'omes, mainly because transcription and translation are independent of secondary structure. The right five pies analyse the functional composition. We highlight the Energy and Cellular Organisation categories determined from MIPS (Mewes *et al.* 2000). A problem in comparing the different 'omes is that each represents a different set of genes. For instance, protein levels have been measured only for a fraction of genes whereas mRNA

levels are known for almost all genes. The pie charts show the compositions for the whole genome in the right column and a representative subset of genes with known protein levels in the left column. Comparing the left to the right immediately shows the experimental bias of two-dimensional electrophoresis (the method for measuring protein abundance) with respect to certain functional categories. There is good agreement between the composition in the translatome and the transcriptome, despite the low correlation of protein and mRNA levels for individual genes. In comparison, the compositions in the genome are much lower.

References

Aebersold, R., Rist, B. and Gygi, S. P. 2000. *Ann N Y Acad Sci* **919**: 33-47.

Anderson, L. and Seilhamer, J. 1997. *Electrophoresis* **18**: 533-7.

Appel, R. D., Vargas, J. R., Palagi, P. M., Walther, D. and Hochstrasser, D. F. 1997. *Electrophoresis* **18**: 2735-48.

Ashburner, M., Ball, C. A., Blake, J. A., Botstein, D., Butler, H., Cherry, J. M., Davis, A. P., Dolinski, K., Dwight, S. S., Eppig, J. T., Harris, M. A., Hill, D. P., Issel-Tarver, L., Kasarskis, A., Lewis, S., Matese, J. C., Richardson, J. E., Ringwald, M., Rubin, G. M. and Sherlock, G. 2000. *Nat Genet* **25**: 25-9.

Baldi, P. and Long, A. D. 2001. *Bioinformatics* **17**: 509-19.

Brenner, S. E. 1999. *Trends Genet* **15**: 132-3.

Carson, J. H., Cowan, A. and Loew, L. M. 2001. *Trends Cell Biol* **11**: 236-8.

Chen, T., He, H. L. and Church, G. M. 1999. *Pac Symp Biocomput*29-40.

Claverie, J. M. 1997. *Hum Mol Genet* **6**: 1735-44.

Doolittle, W. F. 2000. *Curr Opin Struct Biol* **10**: 355-8.

Drawid, A. and Gerstein, M. 2000. *J Mol Biol* **301**: 1059-75.

Drawid, A., Jansen, R. and Gerstein, M. 2000. *Trends Genet* **16**: 426-30.

Eisen, M. B., Spellman, P. T., Brown, P. O. and Botstein, D. 1998. *Proc Natl Acad Sci USA* **95**: 14863-8.

Epstein, C. and Butow, R. 2000. *Current Opinions Biotechnology* **11**: 36-41.

Futcher, B., Latter, G. I., Monardo, P., McLaughlin, C. S. and Garrels, J. I. 1999. *Mol Cell Biol* **19**: 7357-68.

Gaasterland, T. 1999. *Curr Opin Microbiol* **2**: 542-7.

Gerstein, M. and Levitt, M. 1997. *Proc Natl Acad Sci U S A* **94**: 11911-6.

Gerstein, M. and Hegyi, H. 1998. *FEMS Microbiol Rev* **22**: 277-304.

Gerstein, M. and Jansen, R. 2000. *Curr Opin Struct Biol* **10**: 574-84.

Gerstein, M. and Honig, B. 2001. *Curr Opin Struct Biol* **11**: 327-9.

Gerstein, M. 1997. J. Mol. Biol. **274:** 562-576

Gerstein, M. 1998. Proteins **33:** 518-534

Guigo, R., Agarwal, P., Abril, J. F., Burset, M. and Fickett, J. W. 2000. *Genome Res* **10**: 1631-42.

Gygi, S. P., Rochon, Y., Franza, B. R. and Aebersold, R. 1999. *Mol Cell Biol* **19**: 1720-30.

Gygi, S. P., Rist, B. and Aebersold, R. 2000. *Curr Opin Biotechnol* **11**: 396-401.

Harrison, P. M., Echols, N. and Gerstein, M. B. 2001. *Nucleic Acids Res* **29**: 818-30.

Hegyi, H. and Gerstein, M. 1999. *J Mol Biol* **288**: 147-64.

Hegyi, H. Gerstein, M. *Genome Research*. In Press.

Holstege, F. C., Jennings, E. G. Wyrick, J. J. Lee, T. I. Hengartner, C. J. Green, M. R. Golub, T. R. Lander, E. S. Young, R.A. 1998. *Cell* **95**: 717-728.

Ito, T., Tashiro, K., Muta, S., Ozawa, R., Chiba, T., Nishizawa, M., Yamamoto, K., Kuhara, S. and Sakaki, Y. 2000. *Proc Natl Acad Sci U S A* **97**: 1143-7.

Ito, T., Chiba, T., Ozawa, R., Yoshida, M., Hattori, M. and Sakaki, Y. 2001. *Proc Natl Acad Sci U S A* **98**: 4569-74.

Jansen, R. and Gerstein, M. 2000. *Nucleic Acids Res* **28**: 1481-8.

Jenssen, T. K., Laegreid, A., Komorowski, J. and Hovig, E. 2001. *Nat Genet* **28**: 21-8.

Kerr, M. K., Martin, M. and Churchill, G. A. 2000. *J Comput Biol* **7**: 819-37.

Legrain, P., Wojcik, J. and Gauthier, J. 2001. *Trends Genet* **17**: 346-52.

Luscombe, N. Greebaum, D. and Gerstein, M. *Methods of Information in Medicine*. In Press.
Marcotte, E. M., Pellegrini, M., Ng, H. L., Rice, D. W., Yeates, T. O. and Eisenberg, D. 1999. *Science* **285**: 751-3.
Marcotte, E. M., Xenarios, I. and Eisenberg, D. 2001. *Bioinformatics* **17**: 359-63.
McAdams, H. H. and Arkin, A. 1999. *Trends Genet* **15**: 65-9.
Mewes, H. W., Frishman, D., Gruber, C., Geier, B., Haase, D., Kaps, A., Lemcke, K., Mannhaupt, G., Pfeiffer, F., Schuller, C., Stocker, S. and Weil, B. 2000. *Nucleic Acids Res* **28**: 37-40.
Naaby-Hansen, S., Waterfield, M. D. and Cramer, R. 2001. *Trends Pharmacol Sci* **22**: 376-84.
Ono, T., Hishigaki, H., Tanigami, A. and Takagi, T. 2001. *Bioinformatics* **17**: 155-61.
Pederson, T. 1999. *Mol Immunol* **36**: 1127-8.
Qian, J., Stenger, B., Wilson, C. A., Lin, J., Jansen, R., Teichmann, S. A., Park, J., Krebs, W. G., Yu, H., Alexandrov, V., Echols, N. and Gerstein, M. 2001. *Nucleic Acids Res* **29**: 1750-64.
Rison, S. C. G, Hodgman, T. C. and Thornton, J.M. 2000. *Funct Integr Genomics* **1**: 56-59.
Ross-Macdonald, P., Coelho, P. S., Roemer, T., Agarwal, S., Kumar, A., Jansen, R., Cheung, K. H., Sheehan, A., Symoniatis, D., Umansky, L., Heidtman, M., Nelson, F. K., Iwasaki, H., Hager, K., Gerstein, M., Miller, P., Roeder, G. S. and Snyder, M. 1999. *Nature* **402**: 413-8.
Sanchez, C., Lachaize, C., Janody, F., Bellon, B., Roder, L., Euzenat, J., Rechenmann, F. and Jacq, B. 1999. *Nucleic Acids Res* **27**: 89-94.
Serebriiskii, I., Estojak, J., Berman, M. and Golemis, E. A. 2000. *Biotechniques* **28**: 328-30, 332-6.
Simons, K. T., Strauss, C. and Baker, D. 2001. *J Mol Biol* **306**: 1191-9.
Skolnick, J. and Fetrow, J. S. 2000. *Trends Biotechnol* **18**: 34-9.
Szallasi, Z. 1999. *Pac Symp Biocomput*5-16.
Teichmann, S. A., Murzin, A. G. and Chothia, C. 2001. *Curr Opin Struct Biol* **11**: 354-63.
Thattai, M. and van Oudenaarden, A. 2001. *Proc Natl Acad Sci U S A* **98**: 8614-9.
Thornton, J. M. 2001. *Science* **292**: 2095-7.
Tjalsma, H., Bolhuis, A., Jongbloed, J. D., Bron, S. and van Dijl, J. M. 2000. *Microbiol Mol Biol Rev* **64**: 515-47.
Tweeddale, H., Notley-McRobb, L. and Ferenci, T. 1998. *J Bacteriol* **180**: 5109-16.
Ito, T., Chiba, T., Ozawa, R., Yoshida, M., Hattori, M. and Sakaki, Y. 2001. *Proc Natl Acad Sci U S A* **98**: 4569-74.
Uetz, P., Giot, L., Cagney, G., Mansfield, T. A., Judson, R. S., Knight, J. R., Lockshon, D., Narayan, V., Srinivasan, M., Pochart, P., Qureshi-Emili, A., Li, Y., Godwin, B., Conover, D., Kalbfleisch, T., Vijayadamodar, G., Yang, M., Johnston, M., Fields, S. and Rothberg, J. M. 2000. *Nature* **403**: 623-7.
Velculescu, V. E., Zhang, L., Zhou, W., Vogelstein, J., Basrai, M. A., Bassett, D. E., Jr., Hieter, P., Vogelstein, B. and Kinzler, K. W. 1997. *Cell* **88**: 243-51.
Vukmirovic, O. G. and Tilghman, S. M. 2000. *Nature* **405**: 820-2.
Walhout, A. J. and Vidal, M. 2001. *Methods* **24**: 297-306.
Wilson, C. A., Kreychman, J. and Gerstein, M. 2000. *J Mol Biol* **297**: 233-49.
Winzeler, E. A., Shoemaker, D. D., Astromoff, A., Liang, H., Anderson, K., Andre, B., Bangham, R., Benito, R., Boeke, J. D., Bussey, H., Chu, A. M., Connelly, C., Davis, K.,

Dietrich, F., Dow, S. W., El Bakkoury, M., Foury, F., Friend, S. H., Gentalen, E., Giaever, G., Hegemann, J. H., Jones, T., Laub, M., Liao, H., Davis, R. W. and et al. 1999. *Science* **285**: 901-6.
Yates, J. R., 3rd 2000. *Trends Genet* **16**: 5-8.
Yeh, R. F., Lim, L. P. and Burge, C. B. 2001. *Genome Res* **11**: 803-16.
Zhu, H., Klemic, J. F., Chang, S., Bertone, P., Casamayor, A., Klemic, K. G., Smith, D., Gerstein, M., Reed, M. A. and Snyder, M. 2000. *Nat Genet* **26**: 283-9.
Zhu, H. B., M Bangham, R Hall, D Casamayor, A Bertone, P Lan, N Jansen, R Bidlingmaier, S Houfek , T Mitchell, T Miller , P Dean, R Gerstein , M Snyder, M. *Science*. In Press.

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Table 1

Term	Description	Google	PubMed	Year of first PubMed citation
Genome	The full complement of genetic information both coding and non coding in the organism	~1880000	66171	1932 **
Proteome	The protein-coding regions of the genome	~63,000	703	1995
Transcriptome	The population of mRNA transcripts in the cell, weighted by their expression levels	3520	72	1997
Physiome	Quantitative description of the physiological dynamics or functions of the whole organism	2980	15	1997
Metabolome	The quantitative complement of all the small molecules present in a cell in a specific physiological state	349	12	1998
Phenome	Qualitative identification of the form and function derived from genes, but lacking a quantitative, integrative definition	4980	6	1995
Morphome	The quantitative description of anatomical structure, biochemical and chemical composition of an intact organism, including its genome, proteome, cell, tissue and organ structures	238	2	1996
Interactome	List of interactions between all macromolecules in a cell	56	2	1999
Glycome	The population of carbohydrate molecules in the cell	46	1	2000
Secretome	The population of gene products that are secreted from the cell	21	1	2000
Ribonome	The population of RNA-coding regions of the genome	1	1	2000
Orfeome	The sum total of open reading frames in the genome, without regard to whether or not they code; a subset of this is the proteome	42	-	-
Regulome	Genome-wide regulatory network of the cell	18	-	-
Cellome	The entire complement of molecules and their interactions within a cell	17	-	-
Operome	The characterization of proteins with unkown biological function	8	-	-
Transportome	The population of the gene products that are transported; this includes the secretome	1	-	-
Functome	The population of gene products classified by their functions	1	-	-
Translatome	The population of proteins in the cell, weighted by their expression levels	-	-	-
Pseudome	The complement of pseudogenes in the proteome	-	-	-
Foldome	The population of gene products classified though their tertiary structure	-	-	-
Unknome*	Genes of unknown function	-	-	-

Figure 1a

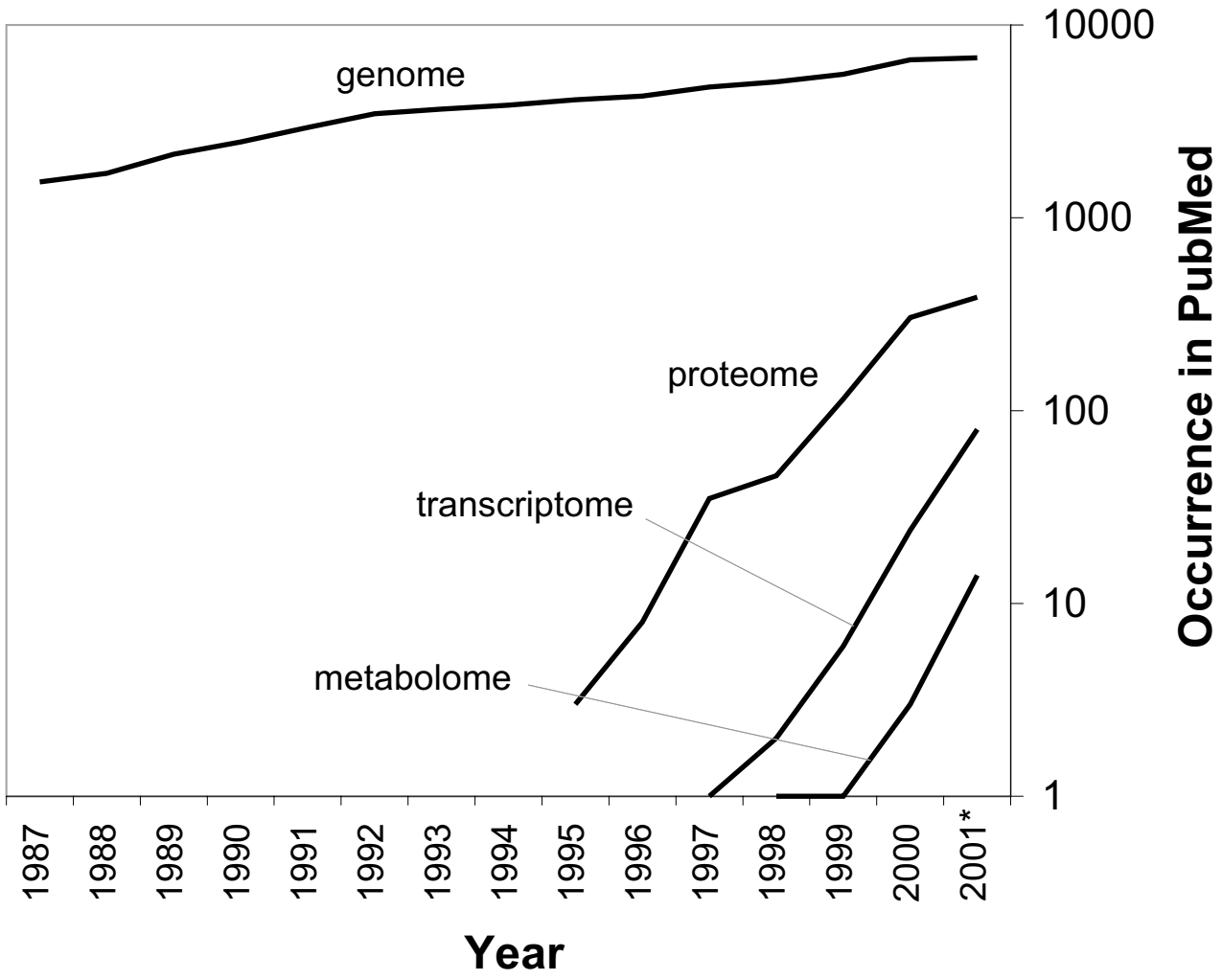

genome
proteome
transcriptome
metabolome
10000
1000
100
10
1
Occurrence in PubMed
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001*
Year

Figure 1c

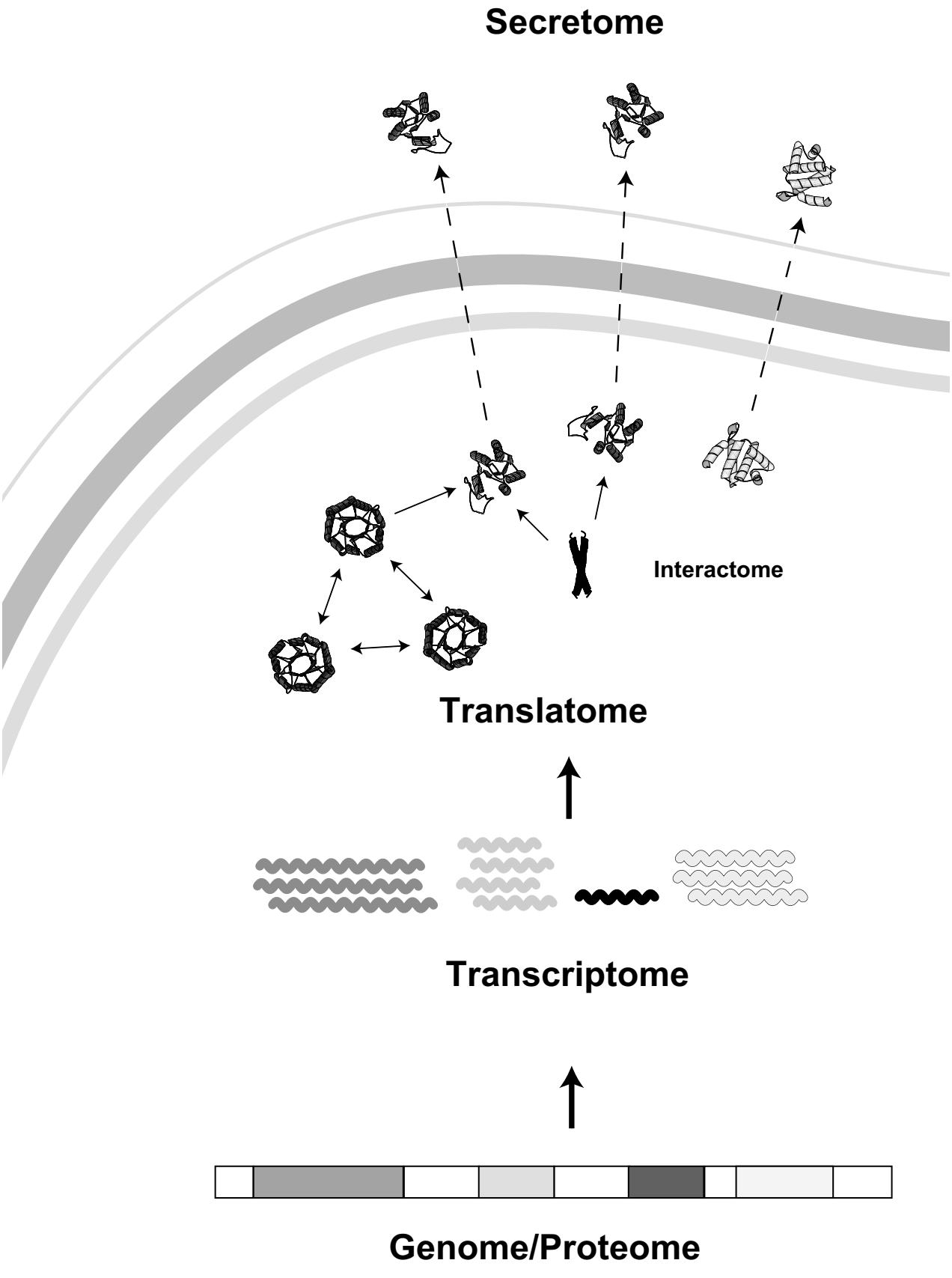

Secretome
Interactome
Translatome
Transcriptome
Genome/Proteome

Figure 2a

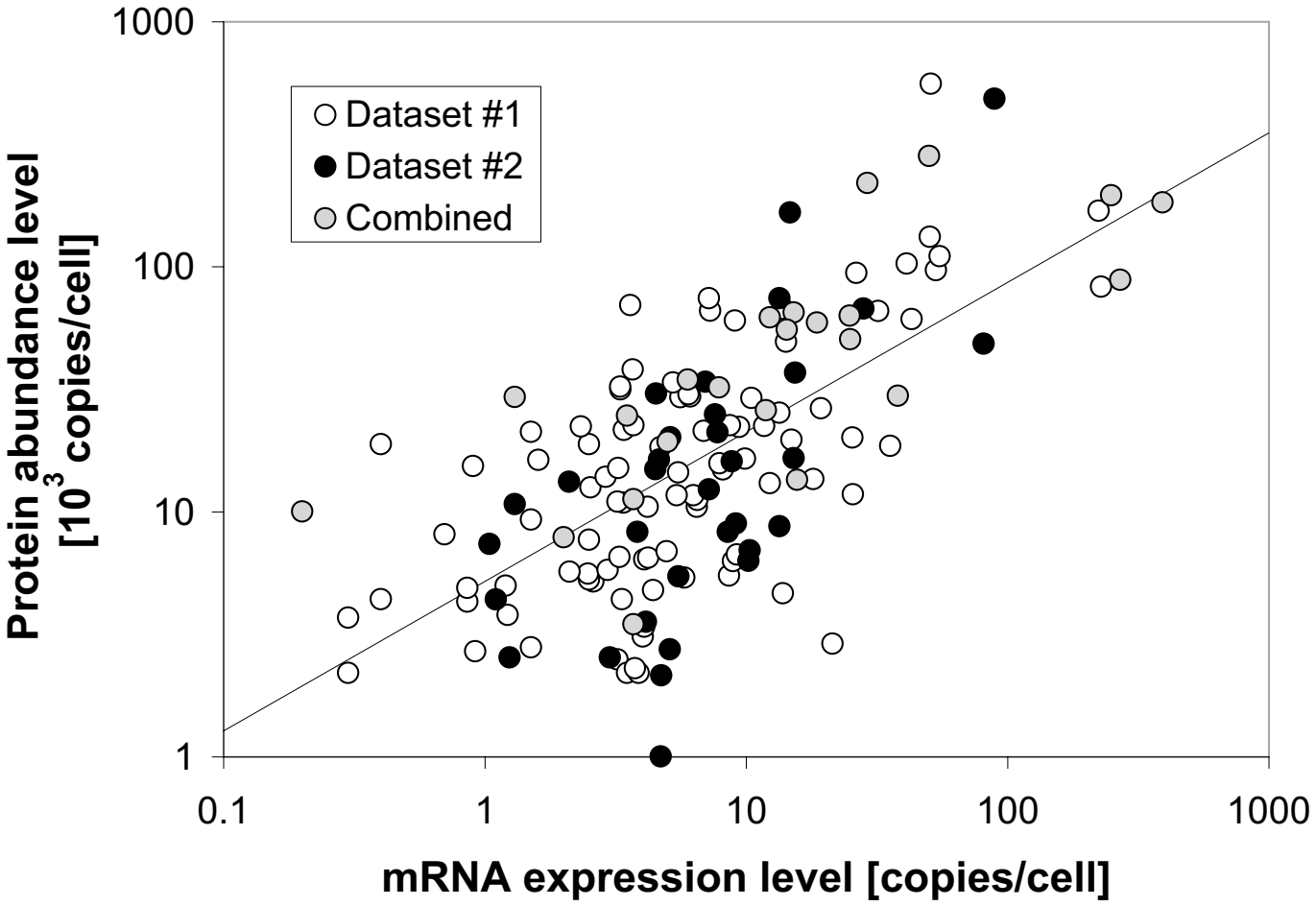
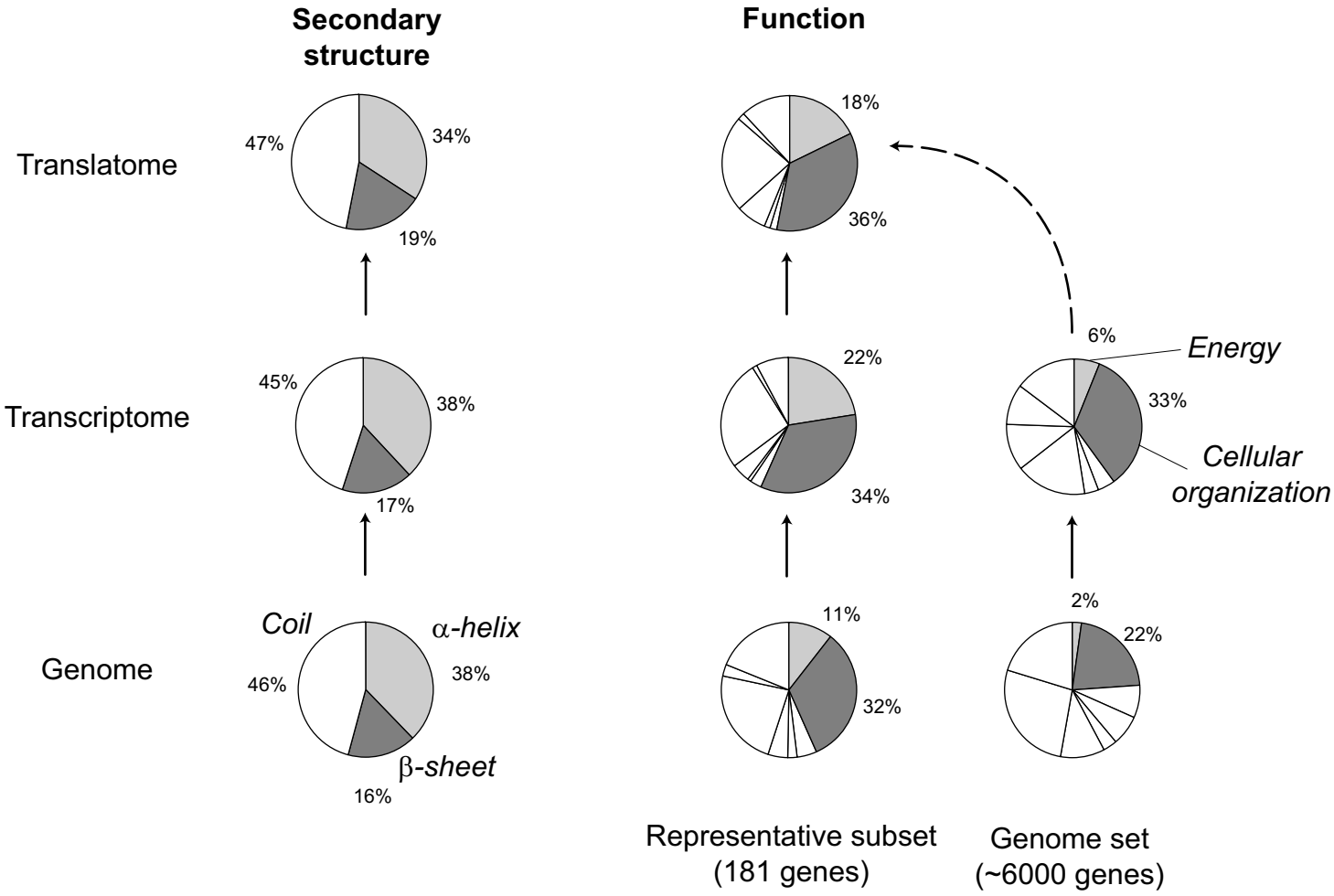

1000
100
10
1
0.1
1
10
100
1000
Dataset #1
Dataset #2
Combined
Protein abundance level
[10^3 copies/cell]
mRNA expression level [copies/cell]

Figure 2b


Secondary structure
Function
Translatome
Transcriptome
Genome
47%
34%
19%
45%
38%
17%
Coil
α-helix
46%
38%
β-sheet
16%
18%
36%
22%
34%
11%
32%
6%
Energy
33%
Cellular organization
2%
22%
Representative subset (181 genes)
Genome set (~6000 genes)