ISSN: 2687-8100

Archives in Biomedical Engineering & Biotechnology

DOI: 10.33552/ABEB.2026.06.000693

Iris Publishers

Opinion Article

Towards Single Cell and Single Molecular Sociology

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Received Date: June 22, 2026

Published Date: July 13, 2026

Introduction

The advancement of post-genomic technologies is fundamentally underpinned by the electronics industry, particularly the computational throughput of microprocessors. In the context of mass spectrometry as the primary methodology for proteomic analysis, the resolution, and consequently the sensitivity of the method, are inextricably linked to the signal response acquisition rate registered by the detector. Nucleotide sequencing technologies are evolving along a parallel trajectory, governed by similar computational constraints.

Nevertheless, it must be recognized that the electronics driven enhancement of analytical instrumentation for investigating living systems has yet to yield qualitative breakthroughs in the diagnosis, let alone the treatment, of diseases of major public health significance. Although personalized CAR T cell therapy, based on sequencing followed by the synthesis of tumor neoantigens [1], has undoubtedly emerged, the current duration of patient follow up remains insufficient to definitively exclude long term adverse effects. In the field of proteomics, clinical translation remains limited to adjunctive applications, such as the OVA1 assay for determining the extent of tumor resection in ovarian cancer [2]. Moreover, with regard to high density transcriptomic microarrays such as Oncotype DX [3], their practical utility is largely confined to high profile prophylactic cases, as exemplified by the widely publicized clinical intervention involving Angelina Jolie.

While unfavorable findings are rarely welcome, the titles of several publications in this field speak for themselves. Recalling a remark delivered at a Human Proteome conference: "Proteomics, as a discipline, has contributed virtually nothing to clinical medicine, and its impact on fundamental science remains highly questionable." To elaborate on this premise, several articles merit the attention of the interested reader: "Deja Vu in Proteomics" [4], "Where Are All the Biomarkers?" [5], "Lost in Translation" [6], and studies highlighting the lack of correlation between the transcriptome and the proteome [7]. Remarkably, as early as 1958, Academician Vasily Orekhovich-notably, the scientist who, alongside his colleagues, first discovered angiotensin-converting enzyme (ACE)-articulated this exact limitation in a public lecture, stating unequivocally: "Even if we detect over 100 proteins in the blood, we will never be able to correlate these proteins with the molecular pathogenesis of the early stages of the disease".

The advancement of bioengineering technologies over the past decade has delineated potential avenues for overcoming the objectively entrenched post-genomic impasse. Methodological breakthroughs have enabled the precise manipulation and analysis of individual cells and single molecules. It is particularly noteworthy that progress in DNA sequencing is intrinsically linked to a paradigm shift in technological platforms. While earlier optically based systems, such as those developed by Roche and Illumina, relied on signal acquisition from individual incorporated nucleotides, contemporary electronic microchip technologies, exemplified by PacBio and Oxford Nanopore, employ GPU-driven registration and recognition of signals derived from nucleotide clusters [8,9].

Two primary barriers must be overcome in the field of biomedical engineering in the coming years. The first is molecular heterogeneity, which arises predictably from genetically programmed ab-

errations and genetic mosaicism during cellular pool turnover, but predominantly from permanent or transient modifications [10,11]. These modifications encompass messenger RNA modification, alternative splicing during processing, interactions with silencing and interfering molecules of both nucleotide and peptide nature, chaperone-assisted protein folding, and post-translational modifications, alongside numerous other processes that are currently suspected to contribute but remain incompletely characterized. The second barrier is a direct consequence of the first. Cells that are morphologically and microscopically identical are by no means homogeneous at the molecular level, a critical point highlighted in a recent publication in Nature Protocols [12]. Given that the metabolic profiles of phenotypically identical cells exhibit significant divergence, we take the liberty of introducing the controversial concept of molecular-cellular sociology to contextualize these observations within this brief overview.

Consider the social stratum of "scientists" as a proximate analogy. At any scientific conference, it suffices to look around to observe the following: one participant appears in torn jeans and with long hair, another in a suit from leading fashion houses and with a hairstyle from an elite barbershop. By grouping them under the generalizing cluster concept of "scientists," we erase their individuality. By the same token, with regard to molecules and cells, we must concede that these inanimate objects also possess individuality. Are these individuals truly homogeneous? For instance, atomic force microscopy (AFM) studies by Pleshakova T, et al. [13] have demonstrated functional heterogeneity within enzyme populations. Approximately 20% of the enzymes exhibit high catalytic activity, whereas the remaining 80% appear catalytically inactive. This inactivity was confirmed by substrate addition and the monitoring of conformational "breathing", the structural fluctuations of the enzyme during catalysis, on the substrate surface [13,14]. This distribution closely mirrors the Pareto principle observed in human organizational dynamics, where approximately 20% of the workforce drives the majority of operational output, while the remaining 80% exhibit comparatively lower engagement. Remarkably, within the framework of molecular-cellular sociology, if these 80% of "inactive" molecules were to be eliminated or functionally blocked, the biological system would rapidly degrade and ultimately collapse [15].

As a culminating consideration, it is imperative to account for molecular entanglement, conceptualized as the "entanglome", a portmanteau of "entanglement" and "metabolome" [16]. The classical paradigm of "one enzyme, one substrate, and/or one inhibitor" is fundamentally incompatible with the vast corpus of accumulated data available in contemporary repositories such as HMDB [17], REACTOME [18], and the Prot-Met dataset [16,19,20]. Substrates are now known to interact with multiple enzymes, while structurally distinct metabolites can function as co-ligands (COLIGs). Specifically, two structurally distinct metabolites (co-ligands) can bind simultaneously to a single protein, thereby simulating each other's chemical transformations.

The period following the decoding of the human genome and the subsequent transition into the post-genomic era has unequivocally demonstrated that the inherent complexity of living systems requires profound conceptual re-evaluation. The initial, highly optimistic expectations of the Human Genome Project, specifically, the promise of definitive cures for cancer, diabetes, age-related frailty, schizophrenia, autism etc.? failed or just have been only partially realized. However, the advanced instrumental toolkit necessary to generate novel insights beyond the initial genomic framework is already at our disposal. The key literature cited herein is highly recommended for meticulous review and critical analysis by the reader.

I extend my sincere gratitude to "Archives in Biomedical Engineering & Biotechnology" for providing a vital platform for the advancement of future biomedical sciences. Furthermore, I wish our scientific community sufficient computational power and energy resources to sustain the massive data storage and processing demands of emerging paradigms, a critical necessity underscored by the enduring trajectory of Moore's Law.

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