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Review Article

Re-print-Understanding Spatial and Temporal Scale in Biology

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Abstract

Choice of temporal and spatial scale for querying biological systems is key to opening up nature's mysteries for investigation. For example, temporal resolution at which sampling is conducted is critical to answering granular details about a biological phenomenon, where a coarse sampling interval could not reveal fine level control on RNA transcription or protein translation. On the other hand, the spatial scale at which a biological question is posed concerns the validity of the conclusions drawn from the data obtained. Specifically, techniques and methods chosen for population level cellular assays would not be able to address questions at the single cell level, while the intricacies and caveats of single cell methodologies in understanding biological processes at the single cell level needs to be appreciated. More importantly, how single cell phenomena is aggregated to population level effects need to be factored into experiment design and data interpretation both for single cell and population level studies. Specifically, as biology transcends multiple levels of organization ranging from single cell to clusters of cells and cell population, it is critical to gain understanding of how different biological effects could manifest at different population sizes. Hence, understanding the nuances of how temporal and spatial concepts could be deployed in experiment design in biology would help yield experiments that would more likely help address specific questions posed at the interface of subpopulations and subcellular level.

Keywords: biological complexity, temporal scale, spatial scale, biological organization, RNA sequencing, single cell, population level, subpopulations, sampling points

Subject areas: biochemistry, cell biology, molecular biology, microbiology, bioengineering,

1. Introduction

Critical to designing appropriate experiments for answering specific questions in biology is a good understanding of time and spatial scale concepts [1-4]. Specifically, time course experiments are important for correlating initiator-effector relationship between biomolecules in various cellular processes, while spatial scale is increasingly critical for gaining the appropriate understanding from an experimental system where population level and single cell level studies may reveal different effects [5, 6]. But, in actual practice, time and spatial concepts often intertwin. For example, selection of a fast temporal scale may preclude analysis of biological phenomena beyond a cluster of cells, as emergent behaviour needs time for molecular level processing to yield an observable biological outcome. On the other hand, a slow timescale selected to observe single cell phenomena may result in averaging of biological effects as the sampling resolution could not keep pace with biological dynamics occurring at the single cell level. Such conundrums in experimental biology thus necessitate a good grounding of fundamental concepts in selecting appropriate time and spatial scale in experimental design by practitioners in science. These considerations, however, are less of a concern in computational biology as modern software codes typically reserves sufficient memory resources for capturing longitudinal information on molecular level dynamics at the single cell level. The dataset collected would be huge and its analysis complicated and protracted, but contemporary computational resources and algorithms do afford fine-grained analysis of many longitudinal data; thereby, making time resolution selection less of a concern compared to selection of appropriate spatial scale. In brief, sufficient memory space enables a sufficiently small-time resolution to be selected that help capture many aspects of systems dynamics in computational biology. However, the same is not true for spatial scale selection in computational biology as each order of magnitude increase in length scale may result in exponential scaling of system complexity. It is with this insight that orients the focus of this manuscript on a discussion of spatial and temporal scale effects in experimental biological science. But, nevertheless, some references to spatial and temporal scale effects in computational biology would also be mentioned.

2. Discussion

2.1 Selecting appropriate temporal scale for capturing system dynamics

Pulse chase experiments are one common tool for understanding the effect of an initiating event on a biological process. But good understanding of the resolution at which a temporal question could be answered is critical to deriving the correct interpretation from experiment data. Specifically, knowledge of the relative timescale at which molecular events could be translated into macroscopic cellular behaviour is important; for example, how transcription of a mRNA could lead to a cellular response against viral infection, that ultimately results in cell lysis. In this case, if the temporal resolution chosen is too coarse, it may not be able to capture molecular events that occur with fast kinetics. But, on the other hand, choice of fine-grained temporal resolution would also need to add in considerations about availability of appropriate imaging or analytical methods. In addition, modern imaging experiments generate large amounts of data,[7] especially with fine temporal resolution sampling; hence, availability of computational and processing capabilities for analyzing large imaging datasets is prerequisite for designing the temporal sampling resolution of a cell biological experiment. In many modern biological experiment workflows, selecting the appropriate temporal sampling regime is requisite for ensuring success of experiment inquiry. Given that size of dataset scales linearly with temporal resolution, it may be convenient to use a smaller time scale to capture unexpected dynamics in cell biological experiments if sufficient imaging, processing and analytical capability is available.

2.2 The dichotomy between single cell and cell population level assay: what about the in-between?

On the other hand, given the advent of single cell experiments and the experiment tools that supports it, [8, 9] an often-neglected area of biological inquiry that needs more careful consideration during experiment design is the level of biological organization pertinent to the question under consideration. More specifically, whether a population level or single cell approach is suitable for answering a question depends critically on the granularity and likely implications of the question. For example, RNA sequencing currently only works better and is easier to design and execute at the cell population level, where RNA transcripts from all cells in the sampled population are pooled together for observing a hypothesized biological effect. However, what can we interpret from population level data and transpose it to the single cell level? From another perspective, how do single cell events aggregate to observable biological effect at the macroscale [10], for example, cellular differentiation or cell motility events? The latter question requires a conceptual leap in understanding and the ability, of the investigator, to aggregate multiple lines of thinking to fully account for most (if not all) biological effects that manifest at the single cell level, but which can be aggregated to population level macroscopic effects. One example is the increasingly accessible single cell RNA-sequencing experiment [11]. Depending on the extent of cellular heterogeneity in the population of cells, aggregating different gene expression pattern of individual cells, or binning them into different categories of sub-populations may not help arrive at the underlying phenomenon. In this case, the size of the population of cells from which single cells are drawn from is also important. Specifically, this relates to the scale-dependent biological effects that could manifest at clusters of cells and sub-populations that may confound the interpretation of single cell data.

But biology seems to verge towards newer trends in research as epitomized by the recent upsurge in research interest in single cell experiments such as single cell RNA sequencing [12, 13]. There exists, however, an alternative perspective to the single cell vis-à-vis population level assay dichotomy: specifically, what lies in-between at the cell cluster level. This level of biological organization is seldom of interest in many modern biological inquiries, but which represents a grey area ripe for analysis and work-up to yield new and interesting biological insights at organizational scale in-between single cell and population level. Clusters of cells is currently ill-defined, which meant that it is an interesting subject of inquiry. Imagine differing experimental readouts and emergent behaviour from tens, hundreds to thousands of cells that hold serious implications for our current understanding of spatial organization and multicellularity in biology. The latter is of profound importance given our as-yet relatively poor understanding of the evolutionary and fundamental underpinnings of multicellular behaviour and its evolution [14-16]. Overall, choice of spatial scale sets the constraints for the biological phenomenon that could be interrogated. While the current trend is towards inquiring the single cell level, building biological understanding from the cell cluster to population level may be the way forward to lend clarity to the impact of spatial scale on biological effects across the whole gamut of organizational scales.

2.3 Cell as fundamental unit of life bestows uniqueness to the single cell perspective

However, special considerations need to be given to single cell biology as the cell is the fundamental unit of life, whereupon biological complexity and emergent properties are progressively built-up [17, 18]. Take, for example, the desire to understand, at the single cell level, the relative contribution of cytosolic and mitochondrial proteins in assembling the oxidative phosphorylation pathway in single mitochondrion. Could single cell RNA sequencing of the RNA transcript provide a distinction between cytosolic RNA and mitochondrial RNA? The answer is yes, if it has the requisite spatial sensitivity. Hence, whether a research question could be successfully addressed critically depends on the close intertwin of spatial resolution for compartmentalization, and whether contemporary techniques and assays could probe and differentiate different compartments in the defined spatial space. Given the relative lack of spatial sensitivity of the emerging technique of single cell RNA sequencing, it is currently difficult to apportion sampled RNA transcripts to specific subcellular fractions at the organelle level. Thus, understanding the spatiotemporal limits of techniques and instrument is important to appropriate choice of analytical tools from the biologist's toolbox during experiment design.

While attempts have been made at modelling the metabolism and workings of single cells [19-21], only coarse representations have been created for the structural and system level aspect of single cell *in silico* [22-25]. Computer simulation is one viable approach for biologists to model and understand phenomenon at the single cell level [26, 27], particularly for assays which as-yet could not be effectively scaled down to this level such as single cell Western Blot [28-30]. However, many aspects of cell biology remain inadequately understood which hampers the use of physics, chemistry and mathematics to arrive at a quantitative description of a single cell. This relates to recent efforts to highlight the quantitative facet of single cell biology, but, at present, modelling of the functioning of single cell such as at the cell movement dynamics level remain inadequate to afford predictive capabilities. Without such predictive capabilities and attendant inability to correlate with experimental data, we remain at the initial stages of using *in silico* methods to understand single cell biology.

2.4 Integrating spatial and temporal considerations in biological inquiry

Hence, knowledge of the importance of time and spatial constraints to biological phenomenon is crucial for understanding experiment data derived, and more importantly, to the design of suitable experiments for understanding macroscopic phenomenon at a level of detail useful for yielding mechanistic knowledge detectable with contemporary

techniques. Specifically, temporal scale is necessary for inserting time points into biological phenomenon under observation for demarcating initiation and lapse. Thus, using experiment tools and sampling points appropriately would help provide crucial verification of phenomenon hypothesized but non-observable at a poorer resolution of temporal sampling; for example, understanding how fast cells react to the infusion of nutrients from a growth medium. Spatial considerations on the other hand, is predicated by the level of detail required to answer a question. But, more importantly, it is heavily tied in to a perspective of viewing biological complexity such as from the top-down (population level) or bottom up (single cell). What is of emerging interest is the length scale in-between single cell and cell population. Known as the cell-cluster level, it represents a poorly studied and characterized biological space rich with understanding ready to be uncovered by biologists.

3. Conclusion

Biological complexity at the spatial level remains the most neglected aspect of experiment design as graduate students are typically used to thinking at the population level in both designing and understanding experiments. More importantly, ability to transcend different organizational scales such as the multitude of organizations between single cell and a population of cells remains a skill less practiced by students. Either population level or single cell, what about the in-between? Biological complexity spans many levels ranging from the single cell to an entire population in a shake flask, hence, where do we start in asking a question is as important as the question itself. A single cell, a hundred cells or a ten thousand cells subpopulation, each with its own biology for investigation. Thus, ability to think in spatial scales at different levels, and more importantly, to relate between them is a crucial skill for the modeller and experimentalist.

But an equally important aspect of experimental and theoretical biology is the concept of time scales. Similar to length scales, biological processes transverse multiple temporal scales ranging from the extremely fast events of enzyme catalysis to the slow turnover of cell surface receptors. Choice of time scale dictates whether a particular research question could be answered. However, limitations in bioassays and analytical instrumentation may constrain the questions that could be asked, and time scale chosen. To this end, biologists increasingly turn to simulations and theoretical reasoning to arrive at coarse estimates of a solution. Correct interpretations of such simulations of biological phenomena are paramount, and critically tests the fundamental knowledge of the graduate student and principal investigator.

Conflict of Interest

The author declares no conflicts of interest.

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