

# Complex Temporal Biology: towards a unified multi-scale approach to predict the flow of information

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## Abstract

Two hallmarks of biological processes are complexity and time. While complexity can have many meanings, in this paper we propose an explicit link to the flow of time and how it is experienced by the organism. The flow of time is rooted in constraints of fundamental physics. Understanding the experience of time, particularly in terms of flow and tempo, is more elusive. Fortunately, the convergence of new computational and methodological perspectives will provide a means to transform complicated, nonlinear paths between related phenomena at different time scales into dynamic four-dimensional perspectives. To enable this vision, we argue that the flow of information between time scales of multiple lengths is a critical component of life's complexity. We can address interactions between sizes of different magnitude and otherwise loosely-related mechanisms more effectively by focusing on time scales as the glue that binds biocomplexity. The interactions between time scales can yield surprising outcomes, from complex behaviors to the persistence of lineages. Building a foundation of rules based on common interactions between orders of time and common experiential contexts would help to reintegrate biology. Emerging methodologies such as state-of-the-art imaging, visualization techniques, and computational data analysis can help us uncover these interactions. In conclusion, we propose educational and community-level changes that would better enable our vision.

## Introduction

A major component of biological phenomena is the unfolding of interrelated processes over time. The *arrow of time* is a basic concept in physics which denotes the unidirectional flow of unfolding events and energetic processes (Heinrich et.al, 2014). The arrow of time is also applicable to biology, and when applied to processes such as circadian rhythms can result in a continuous statistical signature that is visually explorable (Bailly et.al, 2011). Yet our approach is much more inclusive than simply an observation of physical biology. Our interest is in the multiple timescales that define life, whether they be short (protein folding, occurring on the order of  $10^{-14}$  years) or long (macroevolution, occurring at a range of  $10^6$  to  $10^9$  years).

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Since these multiple timescales can interact to affect the existence of a single organismal lineage, we are interested in how the interrelations between time scales influences an individual at the organismal level. This can best be measured by the flow of *information* between multiple timescales: a process that occurs at a very short time scale (protein folding at  $10^{-14}$  years) can create cumulative informational conditions that influence another process occurring at longer time scales (cognition at  $10^{-11}$  to  $10^{-8}$  years). This necessitates a systems-view of multiple timescales, as there is a role for regulatory mechanisms that transcends different tempos of activity (Gould and Eldredge, 1977; Hughes et.al, 2013). One example of this is the aggregation of mutations and their overall contribution to evolutionary change. We understand the mechanisms of mutation and selection, but not as much with respect to how these individual processes sample the physical world and interact to create temporal order.

Even more intriguing is the temporal experience of an organism relative to multiple processes all occurring at different time scales. In an example from the area of brain and behavior, the phenomenon of nested behaviors (Tinbergen, 1951) can be produced by neural processes occurring at different timescales (Kaplan et.al, 2019). More generally, however, the relationships between time scales occurring at vastly different orders of magnitude pose a problem of causality and transferability. We resolve this by referring to all interactions between time scales as *flow*, and is rooted in the currency of information. In this case, flow refers not only to the progression of time and the regulatory consequences of this progression, but also the sampling rate of information. Sampling rate is an explicitly temporal phenomenon (Rosenbluth et.al, 1943), and the consequences of this (particularly across time scales) are not well understood. The cascading regulation of processes is only one consequence of this view. A more integrative view of this process is that organisms are embedded in a world shaped by this information. This world is not a simulation as some have argued (Tegmark, 2007; Hoffman, 2016), but rather a world shaped by the unique history of each organism, its interactions with the environment, and the physical constraints of time.

### **What's the big question?**

As discussed in the introduction, biological systems evolve with time and phenomenologically unfold at vastly different time scales. Although biology shares some common traits with chemistry and physics in terms of length-scale, it is unique in being a *dynamic* science as organisms and their lineages change significantly with time. Specifically, DNA transcription/replication can occur in minutes-hours ( $10^{-6}$  to  $10^{-4}$  years), cell division occurs in days ( $10^{-3}$  years), and differentiation can take anywhere from minutes to months ( $10^{-6}$  to  $10^{-2}$  years), all depending on the complexity of the organism in question. Across the diversity of animals, we observe differences in biological rhythms and life span that range from a single day ( $10^{-1}$  years) to hundreds ( $10^3$ ) of years. Outside the scope of a single organism but nevertheless

affecting its lineage, evolutionary change can take hundreds to thousands ( $10^3$  to  $10^5$ ) of years, resulting in vast changes of phenotype and behavior.

Although it seems to be common knowledge that biological events that occur at short time scales, the effect of repeated function over this short time scale can be cumulative. This ultimately contributes to events occurring at longer time scales. Alternatively, processes occurring at short time scales can become cyclical, as time scales are replicated in the course of evolution and ultimately function as a loop with respect to longer time scales (Winfrey, 1980). Given all of this complexity, simple answers to the question of whether information acquired at short time scale will be sufficient to predict long-term behavior remain elusive. If we can indeed predict longer time scale events from shorter time scale function, how can such functional information be used to predict long-term behavior? We propose that the answer be heterogeneous, and apply to both simplistic additive relations as well as interactions arising from complex networks. However, if our short- to long-time scale prediction is insufficient, then we need to reconsider exactly what is required to introduce systemic feedback sufficient for more precise prediction of dynamic behaviors. Given this example, the gap in existing knowledge is clear: *we lack theoretical concepts and experimental tools to bridge between different time-scales creating a barrier for understanding dynamic biological processes*. Such biological processes are quite diverse, and include processes such as evolution, development, learning, and aging. Furthermore, these barriers hinder our ability to predict phenotypic change and evolutionary trajectories under ever-changing environmental conditions.

### **Potential Research Questions**

In this paper, we advocate for a unified multi-scale approach to capture the vastly different time-scales at which changes occur. Specifically, we want to emphasize the notion of an *interface* between interacting time scales of different length. Biological information needs to be transferred across different organizational scales (molecular, physiology, and ecosystem), and thus warrants the development of a theoretical framework to integrate such information. Principles governing how information is sampled and integrated across time scales is essential for reconstructing a dynamic picture of biological systems across time-scales. Further, we want to have enabling strategies for predicting biological system behavior using information that transcends multiple orders of temporal magnitude. For example, the mapping of genotype to phenotype (Orgogozo et.al, 2015; Nichol et.al, 2019) involves several layers of interactions *in time*. Implementing our vision will enable us to establish what we need to know in addition to what we know and do not know. Recognizing the intrinsic complexity and heterogeneity of a biological system, interfaces captured by a hierarchical-structured network-based approach might enable us to reconstruct the informational relationship between time scales of different magnitudes.

There are also a number of unanswered questions that stem from our vision that could be answered through implementation of the proposed approach. For example, is the flow of information from shorter time scale to longer time scale always unidirectional? We assume from the arrow of time conception that information flows are constrained by the flow of time. Yet there may be feedback mechanisms in which the activity of longer time scales affect the sampling rate and information produced at shorter time scales. One example of this (Dudek and Fields, 1999; Chen et.al, 2017) is the interactions between long-term potentiation ( $10^{-6}$  to  $10^{-2}$  years) on gene expression ( $10^{-6}$  to  $10^{-5}$  years).

Another area of potential inquiry involves the existence of bi-directional flows and the relative order of magnitude between relevant time-scales. In the case of long-term potentiation, there is overlap between the two sets of processes. In cases such as macroevolution, time scales may be many orders of magnitude apart, requiring different mechanisms for information sampling, transfer, and integration. There is also a stochastic element to complex temporal biology, and it related to how stochastic and deterministic events are differentiated and integrated across varying time-scales. While these examples add layers of complexity to our vision, we also view them as an essential problems to be solved.

### **Why now?**

Emerging technologies enable high-throughput measurements of processes at multiple time-scales with unprecedented details. In addition, digital imaging and visualization tools enable us to create easily interpretable flows of various types (from visual maps to mathematical models). At the same time, the integration of data in multiple systems requires the need for a higher degree of understanding. This vision provides a unified conceptual and technical framework for creating a “science of biological time”, or the multiple interrelated temporal phenomena experienced by a system.

### **What’s the potential impact?**

This approach will enable us to understand and define the rules of life at different temporal scales. These necessarily point to rules that predominate at single scales, and those which transcend multiple scales. These rules collectively will enable us to predict the flow of information, how living species adapt to environment challenges, how genotype predicts phenotypes and ultimately evolutionary outcomes of individual species and ecosystems. Prediction is useful in terms of defining transfer of information between time scales of various tempos as well as the inference of function from incomplete empirical data. Our approach might also enable us to examine phenomena such as human aging (Partridge, 2010; DiLoreto and Murphy, 2015), where model systems are severely limited in their resolution and translational impact. By studying the time course of aging’s candidate mechanisms at multiple scales, we can use the proposed time flow approach to acquire new insights into the whole phenomenon.

## **Disciplinary engagement**

This paper is intended for students and researchers interested in any of the following areas: Biological Science, Biomedical Science, Data Science/Informatics, Physics, and Bioengineering. However, we also welcome and encourage transdisciplinary engagement. Students and researchers who have interests bridging biology and engineering will find our approach particularly fruitful, as will molecular biologists who are also interested in Evolution and Ecology.

As for future development of the Complex Temporal Biology vision, we encourage participation from people with interests in one or more of the following areas: Organismal Biology, Open Science, Integrative Data Science, Bioinformatics, Philosophy of Science, Ecology and Evolution, Molecular Biology, Cell Biology, Systems Biology, and Biological/Biomedical Engineering. There are also emerging topical areas such as the study of paleo-proteomics (Cappellini et.al, 2012; Welker et.al, 2015) that could be revolutionized by this approach.

## **Required Methodological Advances**

Traditionally, the study of biological systems is based on snapshot (discrete) views of a system as well as studies that provide a correlational/association view of biological relationships. Advances in computation and instrumentation have provided unprecedented opportunities for biological scientists to turn our static (3D) viewpoints into dynamic (4D) perspectives. To turn our vision into reality, we anticipate the use of state-of-the-art biochemical/biophysical/bioengineering tools, coupled with data and computational science to advance our understanding of complex temporal biology.

One example of this is coupling single-molecule and single-cell tracking tools with advanced fluorescence (e.g., ultrafast and nano-scale microscopy) and electron microscopy. These approaches will provide us with a unique opportunity to track biological events at nanoscale spatial resolution and sub-microsecond ( $<10^{-11}$  years) temporal resolution. Combined with conventional tracking tools, we can theoretically record all major biological events occurring at varying time-scales. Advances in omics tools, such as genomics, epigenomics, metabolomics, proteomics, interactomics, and physiomics, enable us to get a deep and thorough view of a biological system. Sampling system using these tools in various functional and temporal contexts will allow us to generate massive datasets that characterize this complexity.

Another example of this are remote sensing and video monitoring tools, which will enable the high-resolution study of animal and plant behavior in the context of ecosystem evolution. While our vision offers an unprecedented view of such systems, significant challenges stand in terms of planning for experiments and data integration. Various data-integration and multi-scale modeling tools are thus in need for reconciling dataset collected at different time scales.

To facilitate data interpretation and dissemination, visualization tools that include but are not limited to virtual reality, movies and dynamic simulations are also expected to play a significant role. Dynamical models and machine/statistical learning might also be used to facilitate the design of optimal time-sampling strategies. Collectively, we envision that integrated and trans-disciplinary efforts are needed to move the field forward so that we can ultimately understand the temporal milieu of biological systems. Yet we should also keep an eye on the broader context that exists across organisms, which will truly allow us to establish the governing rules and laws of temporal biology.

### **What are the broader impacts?**

There are a number of broader impacts our vision can have on the broader scientific community. Complex temporal biology provides a framework for understanding the temporal context of life with varying complexity, from the molecular scale to the evolutionary scale. As such, we offer a way to better understanding of how information is transferred across timescales and organismal subsystems. Our vision will also allow for the creation of new investigative fields and analytical techniques. more sophisticated models of regulatory processes, including temporal processes that unfold over multiple orders of magnitude. Yet these broader impacts are not limited to research innovation: our vision also provides opportunity to establish training opportunities for students and life-long learners alike to acquire skills in different subdisciplines of biology and data science.

### **How does it reintegrate biology?**

This vision serves to reintegrate biology in a number of ways. The first is to establish the means to acquire fundamental rules that apply to different time scales, and provide greater inferential and predictive power to the study of complex biological systems. These fundamental rules will be used to guide the development of research questions and empirical inquiry relevant to a variety of time scales. Complex temporal biology also provides a deep understanding of how biological information flow between time-scales and a means to bring different modes of biological inquiry together. from molecule to cell, and from organism to ecological context. Last but certainly not least, our vision advocates for the foundation of new, interdisciplinary subfields of training and concerted research efforts related to time and information.

### **Barriers, Limitations, Challenges**

There are a number of barriers, limitations, and challenges to our vision. For one, current approaches to looking at different time scales are usually done using different experimental paradigms. There thus exists a challenge to merge the data together calling for standardized time-stamping and collection protocols. For example, how can we convince molecular biologist to conduct experiments relevant to a cell biologist who documents the entire lifespan of a cell using imaging techniques. Is it more important to measure fast kinetics while ignoring long-term response or the other way round. Another challenge related to data collection and incorporating

measurement techniques and data from multiple fields is that the resulting feature space, which will consist of measurements and events of interest in attending the needs of various biological disciplines, is potentially very large. This is not only an informatics challenge, but potentially requires a methodological sea change.

This vision is also critically dependent upon how time is viewed and operationalized by the scientists themselves. One key question involves how the concept of biological time is defined by passive observers of a given biological process. In the case of plant growth, the quality and number of days in the growing season are more informative than clock-based measurements occurring in continuous measurements of minutes and seconds. In the case of animal perception, the most relevant period of time is the millisecond to second regime. Linkages to other time scales must be consistent with this construct of temporal measurement. As for the complex temporal biology vision itself, our conception of time is different than what has traditionally been used in biology. Our conception is one of continuous flows of information, whereas traditional approaches result from discrete snapshots of time. As in the previously-mentioned case of plant growth, this will require dealing with missing values and interpolating processes to a common frame of reference.

Our last challenge is that of tool and personnel integration, which will be key in realizing this vision. As opposed to proposing a host of new tools, we proposed that the focus be on two . The first involves the learning and dissemination of new techniques to the broad biology community. Secondly, we propose the development of community standards governing the use of tools, measurement techniques, and associated data management. This would narrow gaps between subfields and differences between current paradigms. We also recognize that people have to be willing to step outside of their comfort zone. This presents a barrier to entry problem related to how much are people willing to invest to do the work. Another barrier to entry involves conceptual barriers. In particular, can we accomplish potential solutions to conceptual roadblocks such as developing a common language and creating a shared concept of time scale that is transferable between sub-disciplines such as molecular and organismal biology.

### **Required Institutional Changes**

We also propose a number of institutional changes that, if implemented, would help facilitate this vision. The first of these changes involves hosting interdisciplinary workshops on Biological Time. This would allow us to foster collaboration and collectively work on problems. We also recommend that we (through our institutions) offer training on topics such as data science competence/computational thinking, biological measurement, and conceptual integration.

The final recommendation is the creation of a center focused on the *Integrative Visualization of Biological Time*. This would combine various forms of imaging data (data

integration core), modes of visualization (Virtual Reality, HPC Simulation), science outreach (alternative modes of representation for education), and production of visualizations (systems modeling, computer graphics, interactive simulations).

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