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Perspective: It's all about Time

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***Abstract*—New knowledge on multi-scale temporal dynamics linking nanobio-time series, seasonal changes, immune response, and gut mictobiota can milestone (neuro)science soon.**

Time can be the subject of your poem, a variable in your equations, a fungible quantity together with space, or an expression through which geological, ecological and physiological dynamics manifest their self. Einstein's relativity enshrined in everybody's mind the importance of time and its dynamical perception throughout the brain. Since then, we have learnt how time is not all about quantity. Major funding initiatives to study the mammalian brain are currently active in the U.S. and Europe, with the main aim of deciphering the principles of brain functioning at unprecedented spatial scales. Mega-projects on such scales are also the Graphene flagship and the about-to-born "Quantum technologies project" (17). Yet it is unclear whether and how any of these mega-projects, which include scientists from many disciplines, will take time into consideration. The rationale of this perspective is that a simple, non-trivial accounting for the "time" would surely highlight new structures of different systems, new models, and radically new kind of time series that may prove useful to better understanding and approaching complex systems.

We would like to propose to study nanoparticles not only in terms of different sizes, shapes, and compositions etc., therefore assessed at time $t = 0^+$, and $\lim_{t\to\infty}$, but especially in terms of temporal dynamics as formally defined by a stochastic process. To this extent, we first introduce simple formal definitions and the mathematical framework that can be initially applied to nanobiological-time series, allowing for inferences in other fields of science.

Let us consider a certain phenomenon of interest as a sequence of random variables Y_t, whose realizations y_t are observed at a specific time t.

In a general sense, a non-trivial accounting for "time" refers to the study of models for the observed data y_t as fully characterized by a Joint Probability Density function $P[X_1 \leq x_1, ..., X_n \leq x_n]$ for all $n = 1, 2, ...$ and, consequently, its moments and cumulants. Of note, in most of the cases, knowledge on the first two moments (means and covariances) could be enough to characterize the process. It could also be possible to model additive noise, along with constrains on the stationarity and/or ergodicity.

Observations y_t along the time would also allow for possible linear or nonlinear modeling (based on classical moving average, and/or autoregressive models, Wiener-Volterra kernels, etc.), as well as multivariate and complexity analyses.

This would go beyond a traditional correlation analysis (e.g., correlation coefficient) which would be risky in detecting spurious values linking two-systems dynamics.

In this view, it seems that prospective analyses of nanobiological-time series y_t (a sequence of data hereinafter referring to nanobio-series) are nowadays limited by the "sensing" technology and related time resolution. As a matte of fact, molecular communication is currently associated with low time-resolution (it takes hours for a molecule to be transferred from source to destination) (15). Nevertheless, a future with enhanced capabilities of high-resolution in time for sensing molecular nano-machines seems possible. Ad-hoc nanorobotic sensor networks (16), being green (i.e., biocompatible and biodegradable) and touchable (i.e., externally controllable and continuously trackable), might also be a viable solution to retrieve effective nanobio-marker dynamics.

Indeed, we envision that a new scientific era will start right once nanobio-series are available to the scientific community. Nevertheless, we do not envisage a straightforward application of the biomedical signal processing current state of the art as (re-)applied to nanobio-series. Future research must be taking into account how nanoparticles exhibit unique physical and chemical properties such as particle aggregation and photoemission, electrical and heat conductivities, and catalytic activity, calling therefore for an ad-hoc nano-signal processing framework. It can be expected that, e.g., stochastic point process theory (21), which allows for mathematically estimating instantaneous dynamics for some biological discrete-event timing, may not be needed anymore. In fact, what we are currently monitoring as intrinsically discrete events (e.g., heartbeats or neural spikes), may be translated to nanobio-related dynamics defined in the continuous time. On the other hand, analytical and computational methods currently applied in biomedicine may be adapted also to treat new kind of nanobio-related physiological noise dynamics whose rejection may not be trivially achieved.

As it is not possible to get electrocardiograms using non-invasive electrode only, but there is the need of, e.g., transistors, differential/instrumental amplifiers and filters, ad-hoc nanobio-front-end would be needed for nanobio-series direct signal conditioning. To this extent, biological transistors as well as nanobio-logic doors could be employed (14).

Likewise less than 20 years ago, when application of nonlinear signal processing methods to human physiology and medicine were to be published in high-impact journals (18,19), and nowadays they all go to (just) conference proceedings and focus journals, accounting for the time in a very formal sense, together with very small (nano) spatial scale, will impact many different research fields to the extent of biology, ethology and

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climate changes.

Time matters when the brain concurrently accumulate and integrate information over multiple timescales (e.g., order of milliseconds for neural activity, order of seconds for astrocyte calcium dynamics), leveraging also on time-locked firing patterns strongly influenced by probabilistic axonal conduction delays and spike-timing-dependent plasticity (1). In plants, the vasculature clock for photoperiodic control, and the epidermis clock for temperature-dependent elongation are know to control developmental outputs in response to environmental changes (1). Seasonal timing shifts phenological changes (e.g., reproduction and migration) in some species (2), and triggers cellular immune response (4). Humans born in winter months have been associated with higher incidence of developing Kawasaki disease (a rare childhood disease in which blood vessels throughout the body become inflamed) whereas peak rates of ADHD were found in November babies in New York, or American people born in March facing the highest risk for heart failure (5,6). Knowledge on temporal dynamics of human immune cell response would also revolutionize our current understanding of the autonomic and central nervous systems (7,8), with major achievements in the study of stress and depression (9). It might be discovered that a very fractal relationship between nanobio-series, physiological series, and temperature/meteorological series exist, whose theoretical quantifiers (e.g., correlation dimension, multifractal spectra, etc.) may be used for diagnosis, prognosis, and prediction of adverse brain-related pathologies.

Novel avenues would also be directed to gut microbiota, whose temporal dynamics (measured with low resolution) has already been linked to a variety of diseases, among irritable bowel syndrome, obesity, cardiovascular disease, colon cancer, major depression, Parkinsons disease and autism spectrum disorder (10). We cannot avoid to mention circadian rhythms, whose primary function refer to anticipate and adapt physiological dynamics to the constraints of the earth's 24-hour light cycle (11). Perturbations in the circadian timing, at scales of organismal, cellular, and system level have been linked to numerous molecular and behavioral dysfunctions (e.g., inconsistent sleep-wake schedules) and may result in severe pathologies including cancer (12,13). Likely, within the next 20 years, new nanobio-pseudo-circardian rhythms will be discovered.

We envision major significant advances in the recent scientific field of nano-medicine for immuno-oncology. Nanoparticle dynamics, in fact, has been exploited to change the pharmacokinetic profiles of conventional chemotherapeutic agents and of selectively delivering high concentrations of cytotoxic compounds into tumour cells, or to activate in-body anti-tumour immune cells to exert their therapeutic effects (20).

From a research and development perspective, the design of nanoparticles allowing to retrieve nanobio-series will require a new mindset that indeed departs from that for traditional approaches. Instead of focusing on designing nanoparticles of different kinds, there should be some (may be attached) components allowing the tracking in time.

Importantly, genomics studies may also benefit for having multiple observation in time constituting nanobio-series. As a matter of fact, nanoparticles can provide an effective delivery platform to induce precise gene editing (20).

There might also be the need of redefining psychiatric guidelines since specific, objective temporal dynamics of some nanobio-markers of autonomic and brain-gut dynamics might be associated with a specific psychological dimension. These new technological avenues could also be applied for good to animals for ethological studies and biological dynamics thereof, at unprecedented time resolution. It would also be possible to study human-animal interactions through multivariate nanobio-series quantifying, may be chaotic, probably nonlinear coupling mechanisms between humans' and animals' nanobio-markers. In this context, consequent, altogether expected, implications for a new type of economic business (e.g., the market of nanobioparticles able to be monitored in space and time with a resolution as high as possible) are expected.

It is also worthwhile noting that time is only one (albeit very important) parameter in the emerging field of cognitive analytics connecting metadata of seemingly uncorrelated scientific fields. In this view, current high-impact advances on deep-learning strategies and other computational methods for heterogeneous big data analytics could be of great help to gain major insights for specific (may be medical) applications.

And it will go without saying that astronomers and meteorologists, as well as physiologists and physicians, ethologists, bioengineers and nanobio-scientists should all research together to the same aim: have "time" highlighting structures of different systems and models which, in turn, may prove useful in better understanding and approaching a large variety of complex systems.

Future scientists will yet look at their own variable of interest, keeping in mind that indeed it's all about time.

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