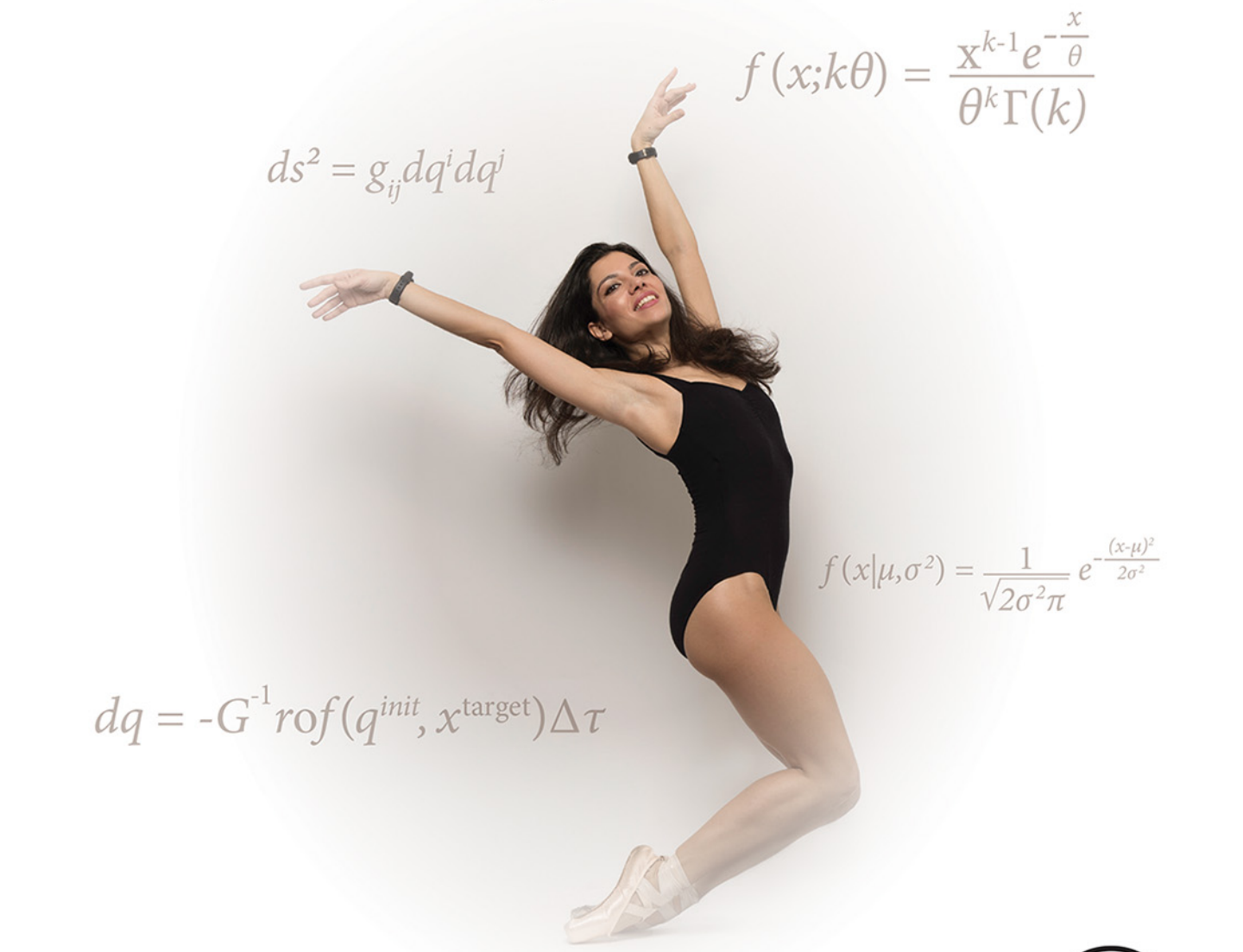
Objective Biometric Methods for the Diagnosis and Treatment of Nervous System Disorders



Elizabeth B. Torres

OBJECTIVE BIOMETRIC METHODS FOR THE DIAGNOSIS AND TREATMENT OF NERVOUS SYSTEM DISORDERS

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Elizabeth Torres

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- Sample data from selected chapters
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- Videos illustrating the experimental set up for scenarios and methods described in selected chapters

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OBJECTIVE BIOMETRIC METHODS FOR THE DIAGNOSIS AND TREATMENT OF NERVOUS SYSTEM DISORDERS

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Preface

This book is a personal journey through the science-making of my lab and the process of discovery that brought me here today. Originally, I intended to write a different book, one more formal to serve as a textbook or a recipe of sorts to perform behavioral experiments and do behavioral analyses in a new, objective and personalized manner. But as I started to write the book, the stories flowed more naturally when I narrated them as they took place over the years. Then, it became much easier and more fun to write about the process of discovery, as it happens from day to day in the collective of a laboratory. There, amidst instruments, computers, manuals, peer reviewed papers, books, and participants of all ages with different clinical conditions, is where one realizes how beautiful the scientific enquiry is and how surprising and at times serendipitous, the path to discovery can be.

Most of our studies started with a question in mind that evolved over time. The line of enquiry we followed set us on a path of detective work, deeper into hidden aspects of the problem at hand, without any preconceived agenda. We let that path of enquiry unfold and take us to unexplored places. Discovery self-emerged from these travels and in a synergistic cooperative effort, we all contributed to these discoveries. It has been so much fun to work with the people that have crossed paths with the lab on their way through life. Together, in those transient periods at my lab, we have built a harmonious environment where thoughts flow freely and creativity is nurtured. From undergraduate to doctorate students, from postdoctoral scholars to well established professors and clinicians, we have learned to respect each other's skill sets and contributed to the accumulation of new knowledge -unprecedented at times and complementary in nature. We have learned to build our own vision of the brain-body functionality and have adopted new philosophies to help unravel hidden mechanisms leading to the self-emergence of autonomy and agency, as fundamental properties of our human existence. It is my hope that you find the book interesting and useful.

There is no prescribed order to follow when reading the book. One can go in sequential order, from Chapter 1 to Chapter 8; or open the book at random in any chapter and start reading. The figures will help the reader follow the story and many of them can be reproduced using scripts in Matlab and Python, which I will place in a companion website to that end.

Although the stories are written in a somewhat informal way, the work is rigorous, and the material could be difficult at times. Because of that, I will place much of the material to reproduce figures and results in the companion site with further explanations, sample data and heavily commented sample code. This will help the reader recreate some of the key figures and use these analytics in their own work. It is my hope that the new personalized methods are adopted as a starting point for a radical departure from current subjective methods of behavioral analyses. Whether studying sports, the performing arts, or

assessing clinical cases, whether tracking a student-teacher interaction, a parent-child exchange or a clinician-patient communication, the methods in the book offer a new way to track social cohesiveness and the emergence or absence of rapport between two interlocutors, in an objective, data-driven way.

This is a starting point to create a new behavioral science. As such, the book will greatly benefit from the contributions of students and instructors who will hopefully adopt and teach the new methods. These methods are aimed at the development of a truly open objective way to do science in the brain- and health-related disciplines.

I submit to you the work of 20 years, that started when I was a graduate student. This work was done in collaboration with many colleagues, and enriched by the creative thinking and the young spirit of folks who think out of the box. Keep it moving, onwards and forward, to transform and innovate!

Elizabeth B Torres, PhD

(Dedicated to my parents)

CHAPTER

1

The Closed Feedback Loops Between the Peripheral and the Central Nervous Systems, the Principle of Reafference and Its Contribution to the Definition of the Self

Voluntary movements show themselves to be dependent on the returning stream of afference which they themselves cause. ***Erich Von Holst and Horst Mittelstaedt***

PART I: SEARCHING FOR VOLITION WHILE IN A COMMA STATE

Serendipitous Encounters

Sometime in the fall of 2016 I visited the neonatal intensive care unit (the NICU) of the Robert Wood Johnson Medical Hospital. The Director of the NICU, Dr. David Sorrentino, hosted me on occasion of setting up collaborative work between my lab and his unit. Earlier that year, I had finished the analyses of data from neonates and had discovered a way to detect stunting in the development of neuromotor control.[1] The work with the babies sparked my interest on the question concerning the emergence of volition in the nascent nervous systems of the neonate.

As I toured the unit and saw six premature babies fighting for their lives, I marveled at the miracle of life winning small battles day by day. Amidst tubes and probes recording the vital signs of the baby, autonomy was gradually emerging and gaining stability. First, the heartbeat stabilizes, and then the respiration gains autonomy. Finally, the digestion

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and gut providing nourishment and cleansing the body through autonomic processes supported by the neuroimmune systems[2] begins the path of shifting from peripheral to central control. The central nervous systems (CNS) will stabilize and find its way to the volitional control of the body in motion. The evolution and critical milestones of this precognitive state of being, even prior to the development of cortical and subcortical bodily maps of actions and their consequences, can be captured by statistically tracking the adaptive capacity of biophysical rhythms and their stochastic signatures.

The work on neonates involved collaborating with an infant-development lab from the University of Southern California (USC) directed by Dr. Beth Smith. Beth and I had met at an Autism conference hosted by the Profectum Foundation. This conference took place on March 21, 2014, in Pasadena, CA (https://profectum.org/awakening-potential-through-brain-science-conference-agenda/). I was invited by Dr. Serena Wieder and Dr. Ricki Robinson to deliver a keynote lecture. At the end of the lecture, Beth came to the podium and showed me a wearable sensor developed by a company in Portland Oregon, APDM (Fig. 1.1); with a number of features amenable to expand the type of research I was doing using high-grade tethered sensors. The size, weight, battery functioning, and memory storage capacity of the sensor made it ideal for the type of "on the go" research concept I was starting to develop in the lab. Indeed, we had created a new statistical platform for individualized behavioral analyses (we called it SPIBA). I was using SPIBA to develop new data types and methods for Precision Medicine[3] and mobile Health (m-Health). These new research programs in the lab required the type of portability such sensors offered. During that time and as a result of funding granted by the National Science Foundation (NSF), my PhD student Jillian Nguyen and I had taken the path of Innovation Corps (I-Corps) aimed at translating scientific discoveries into societal innovations. Our patent pending technology (https://www.google.com/patents/US20140336539) was disruptive as it called for a radical change in the ways we conduct scientific work and measure the outcome of interventions in clinical practices.[4] As part of the NSF program, we needed to find the market fit for our technology. To that end, we interviewed over 100 stakeholders in the autism ecosystem. This interview process revealed a critical need for objective outcome

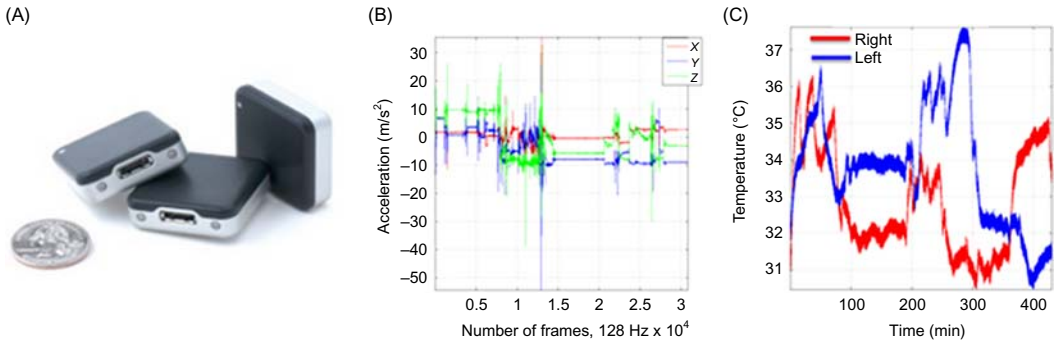

FIGURE 1.1 **Sample wearables and output traces.** (A) Wearable sensors from the APDM company shown at scale next to a dime. APDM sensors 128 Hz, (Portland, OR) at the time of our study in 2014 could register data from triaxial accelerometers shown in (B), gyroscopes, temperature shown in (C) and a magnetometer. They could store 8 Gb of data and had a battery that lasted at least 12 h of continuous recordings.

measures of the types we had developed using high-grade sensors in the lab. As it turned out, a huge problem in autism is the lack of insurance coverage to enable the diversification of therapeutic interventions leading to improvements on *sensory-motor patterns* and better motor control. Most such interventions involve occupational therapists (OTs) in the pediatrics field. Our SPIBA was something OTs really needed and desperately wanted.

To provide a complete platform for m-Health (also known as smart and connected health), we needed to add the portability of wearables with the ability to harness biophysical rhythms from the nervous systems. Such biorhythms could be collected as the person *naturally* interacted with the environment, performed activities of daily living, and rested during sleep. The market was beginning to be flooded with such sensors, ranging from Fitbits to smart watches from major companies like Google, Samsung, and Apple. However, using off-the-shelf sensors we could only access already-filtered data and outcome measures that lacked the reliability we needed for our research program. Our clinical research in particular required access to the actual raw data because the filtered data that off-the-shelf sensors offered may miss or mask frequencies with physiological relevance, particularly in nascent nervous systems or in nervous systems with pathology of unknown origins.

The activity trackers or the wellness and fitness bracelets in the market did not offer the features we needed for our clinical research. The APDM wearables that Beth showed me at the conference did offer the possibility of accessing raw signals of broader bandwidth than other commercial sensors (Fig. 1.1).

Beth and I kept in touch after the meeting and developed a collaborative link that led us to the discovery of patterns of stunting in the neonate[1] that I will describe in the second part of the chapter. Her lab coordinated the study—a major feat—and collected the data to track the development of walking patterns in preterm versus full-term babies.[5] My lab designed biometrics to track the longitudinal evolution of such patterns across many hours per day, during multiple visits. I used this Big Data set to design indexes of stunting in the neurodevelopment of their nascent nervous systems.

The data type and analytics that I originally developed to study the emergence of neuromotor control in the neonates did not come from newborn babies though. They came from work I did concerning the biophysical rhythms that the wearables harnessed from the nervous systems of a pregnant lady who had slipped into a coma because of a debilitating seizure linked to a large brain tumor in her frontal lobe.[6]

The work with the coma patient gave me the ability to study a nervous system where most likely the bridge between the CNS and the peripheral nervous systems (PNS) had been disrupted. The work with the neonates provided me with access to a nascent nervous system where that bridge was developing. Both data sets could give me a window into the inner workings of the PNSσCNS closed-loop connection as the nervous systems gained deliberate autonomous control, control at will of the brain over the body in motion. This form of control is called *volition* in our movement neuroscience field.

From Spontaneous Random Noise to Well-Structured Signals

Looking back at that Profectum Conference, a series of serendipitous events took place the day of my lecture that led me to the development of the methods I describe in this

chapter. But before I delve into the methods, let me first take a detour into how I came to derive the analyses of the data from Melissa Carleton, the pregnant patient undergoing a coma state at the time (https://www.facebook.com/supportmelissacarleton/).

The day of the Profectum Conference where I met Beth, as I was approaching the podium to deliver the keynote address, I received a phone call from Brian Lande. At the time, Brian was a consultant for one of the Defense Advanced Projects Agency (DARPA) programs on strategic social interactions. I had met him while attending a DARPA meeting in Washington, DC, on December 2013. At that meeting I delivered a lecture that Brian recalled during the phone call that day in Pasadena, a few months later, on March 2014.

I barely knew Brian and had no name on the caller ID, but answered the call anyways because I recognized the area code was from the Bay Area, where I have family. To my surprise, Brian re-introduced himself and explained what had happened to his pregnant wife Melissa. At the DARPA meeting, he had talked about their recent wedding. I remembered the picture from her as she looked strikingly beautiful (Fig. 1.2). I was frankly a bit shaken by the news that she had slipped into a coma. Brian sounded quite desperate. He mentioned my research on intentional motions and asked me if there was anything that I could think of, to help him proof that his wife was still there (i.e., that she had will.) He was worried that with a few months left of her pregnancy and the sudden coma diagnosis it was hard to know the full prognosis of her case and the possibilities for the birth of their baby. Clearly, between the shocking news and the talk I had to immediately give, I was a bit perturbed. I asked Brian to give me a moment to think about it and told him that I would call him back soon. I somehow put that question on hold in the back of my head for the next hour or so. At the end of my talk, when Beth brought me the APDM sensor, and I saw the portability of it, I got my answer.

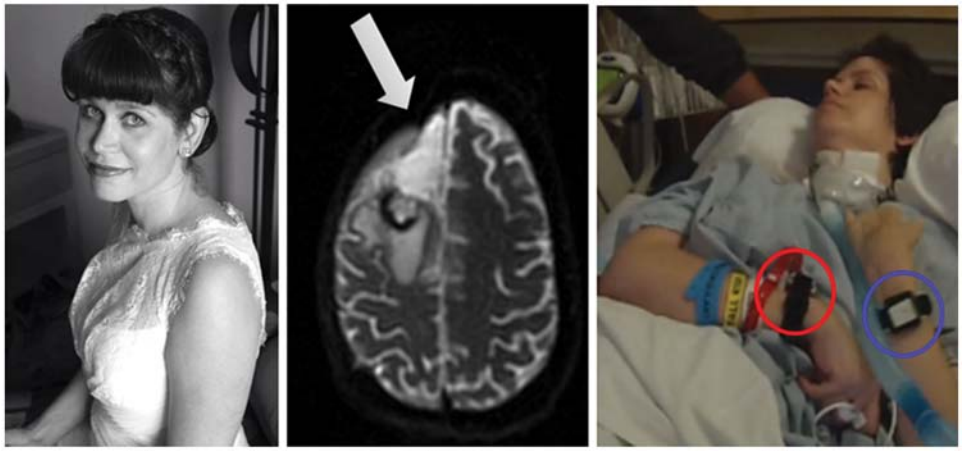

FIGURE 1.2 **The comma patient.** (A) Melissa Carleton photographed at her wedding day. (B) Brain scan showing the frontal lobe after the removal of a tumor that induced a debilitating seizure preceding her coma state. (C) The use of wearables at the hospital.

All I needed to do was to monitor her motions continuously and detect volition. But volitional control was precisely what I had been working on since 1998, the year when I finished the first draft of a computational model of volition in systems with redundant degrees of freedom (such as the arms and their end effectors). The preliminary work toward my PhD Thesis at the University of California, San Diego, performed under the supervision of Prof. David Zipser,[7] was a model that embodied the guiding principles of the research program I later developed in my lab, a program that I used to help detect volition in Melissa's motion. I will discuss that model in great detail in Chapter 4.

At the heart of this problem are spontaneous fluctuations inherently present in the biorhythms that we can harness from the nervous systems. At a first glance, these moment-by-moment fluctuations are random and have high noise-to-signal ratio (NSR). They are subtle in nature and tend to go unnoticed by the naked eye of an observer. One may generally need proper instrumentation to capture their evolving signatures. Nevertheless, the ever-changing peaks and troughs of the nervous systems biorhythms contain information of relevance to our quest on volition. But to extract such information, one needs to employ techniques that *empirically* characterize the inherent variability of such data, i.e., without enforcing theoretical assumptions that do not fit the data well.

Up until that point, the bulk of the research from my field (motor neuroscience) had a main focus on the neuromotor control of overt goal-directed movements.[8] However, research on the types of spontaneous motions that I was interested in was nonexistent. I had to create a new notion of different and interlayered classes of movements[9] with taxonomy of controllability and phylogenetic order of emergence and maturation.

This architecture of the neuromotor control problem afforded the measurement of biorhythms harnessed from the nervous systems output to profile their stochastic signatures and find their typical ranges (e.g., those in Fig. 1.3). In this way we could begin the path of identifying deviations from typical neuromotor control trajectories. Yet, to study such biophysical signals, we required a new statistical platform and new data types to accomplish two tasks: (1) integrate data from different interconnected layers of the nervous systems (e.g., the systems for autonomic and voluntary control) and (2) map the different levels of variability inherently present in these different systems onto different levels of neuromotor control (Fig. 1.3).

The first step toward gaining a better understanding of the various nervous systems pathologies was to begin an exhaustive statistical characterization of the nervous systems biorhythms as they naturally evolved and matured across the human life span. In this sense, we had to break away from the current "*one-size-fits-all*" statistical model of the brain and health sciences. Such a model did not leave room for the emerging concept of personalized medicine[3] that my lab was already pursuing. The current statistical approach (Fig. 1.4) simply assumes "ideal" populations' mean and averages out as noise the very signals we needed to understand: the subtle moment-by-moment fluctuations in the amplitude and timing of these biorhythms peaks and valleys. To accomplish these two tasks we created *the micro-movements* and paired them with the SPIBA framework (Fig. 1.5).

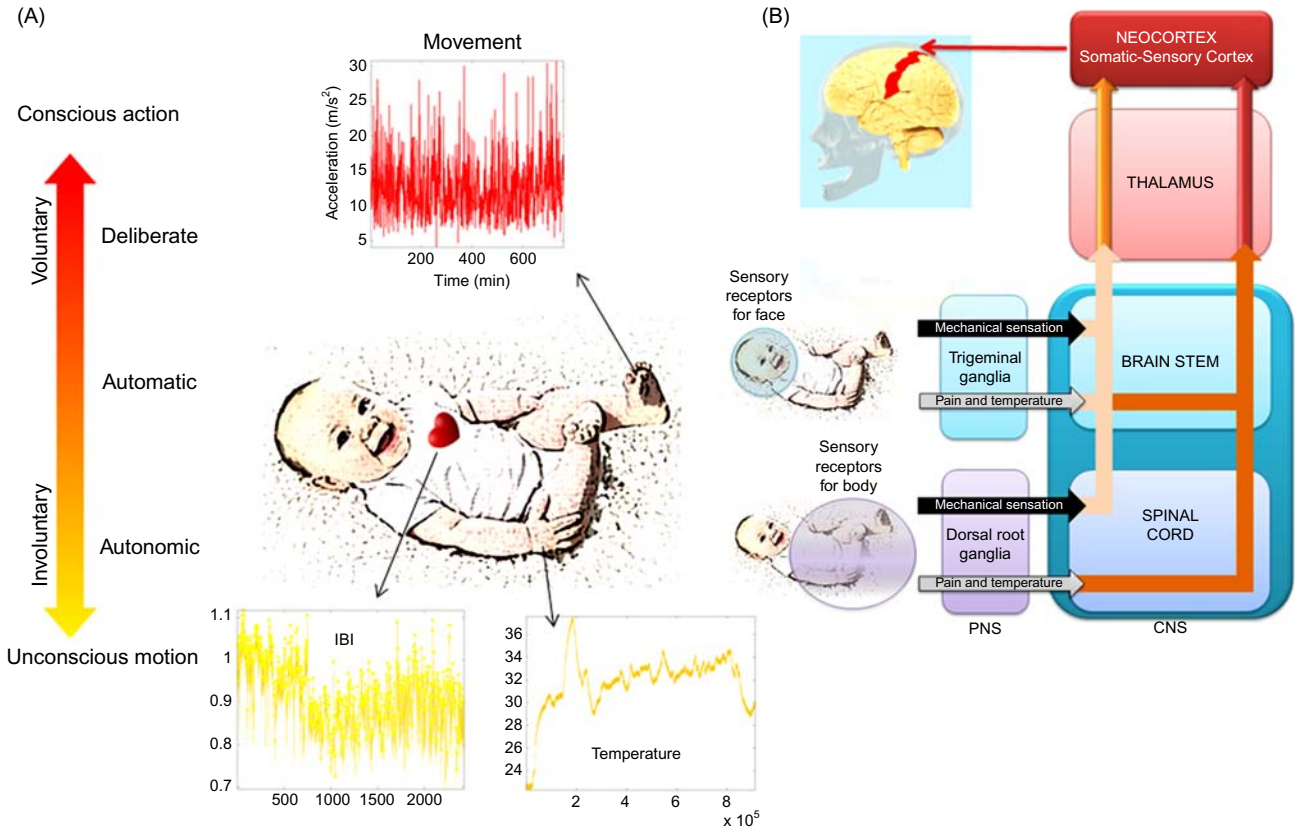

FIGURE 1.3 **Taxonomy of neuromotor control and ways to measure variability in the nervous systems biorhythms from interlayered levels spanning from autonomic to voluntary control** . (A) Phylogenetically orderly appearance and maturation of control levels in the PNS and CNS and their composition of involuntary motions contributing to or interfering with volition (voluntary control at will). Examples of involuntary motions with "good" variability facilitating the emergence of voluntary control manifest in the evolving reflexes of the neonate, leading to the awakening of the body and the mapping of peripheral motions, their sensations and consequences onto the CNS. Examples of involuntary motions with "bad" variability interfering with volition are the various types of resting and intentional tremors in Parkinson's disease. All these biorhythms can be harnessed with wearables today. They can also be integrated in combined signals from multiple layers and their combined contribution to neuromotor control statistically characterized as such. (B) Different maps in the PNS contribute to different maps in the CNS. They involve the probabilistic sampling of self-generated and self-sensed biorhythms' fluctuations and their statistics. Source*: Adapted from Purves Neuroscience 2008.*

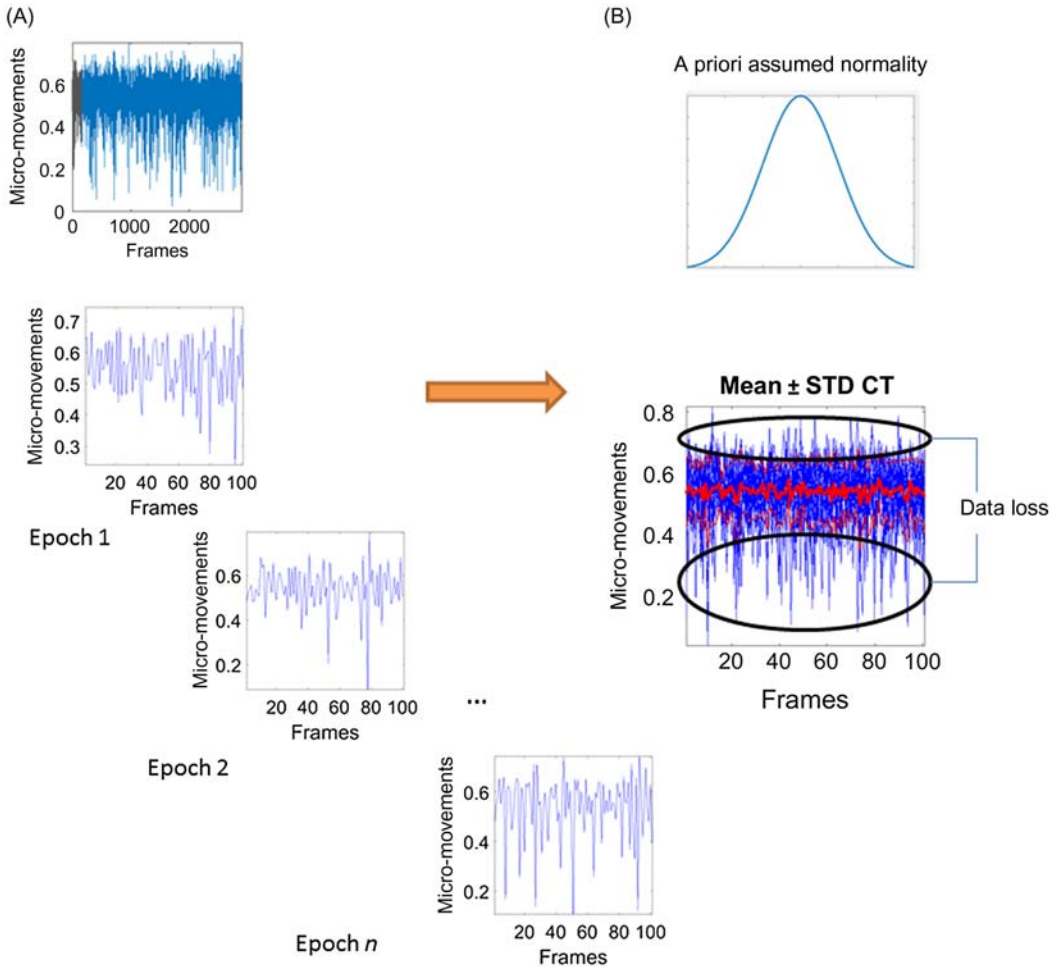

FIGURE 1.4 **Data waste with current statistical assumptions.** (A) The standardized micro-movements extracted from some nervous system signal are scaled between 0 and 1. These spike trains represent a continuous random process modeled here as a Gamma process. The NSR of these spike events are of interest in the statistical analyses of the SPIBA framework. Traditional models assume a Gaussian random process with additive statistics. As such, the assumed theoretical (population) Gaussian moments (the mean and the variance) are used to process the data using the average of the waveform's peaks across a preset number of frames. (B) Typically, preselected epochs of the data are averaged under this Gaussian population mean assumption. This grand averaging method smooths out the fluctuations in the signal, thus incurring in gross data loss. This example shows the mean $+/-$ the standard deviations comprising the data that gets analyzed. The circled 'excess' is thrown away as noise, but it actually contains the very information we need. This is the traditional "*one-size-fits-all*" approach to data analyses in the health and brain sciences today.

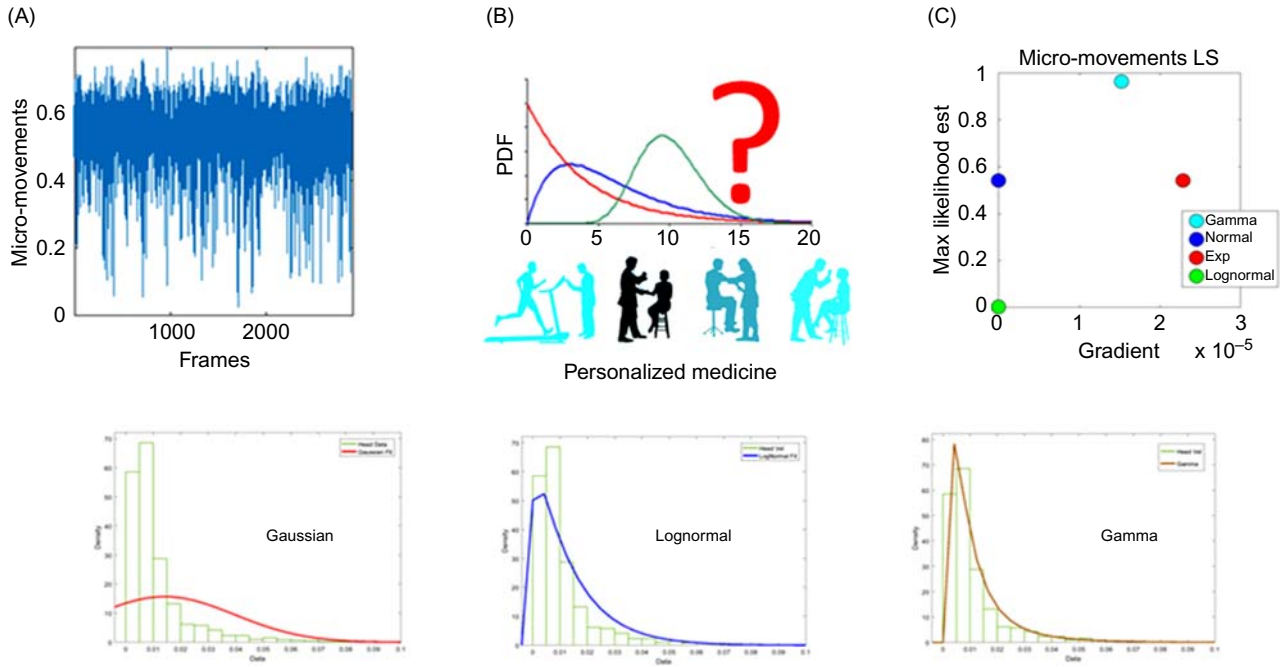

FIGURE 1.5 **SPIBA as a new step toward personalized approaches and the analyses of natural human behaviors over time.** (A) The micro-movements waveform of fluctuations in amplitude of a nervous system biorhythm in Fig. 1.4A is analyzed using SPIBA. This step provides a data transform that scales the original waveform and standardizes it to avoid allometric effects that arise from disparities in anatomical lengths across the population. (B) SPIBA does not assume a priori any theoretical distribution. Instead, it accumulates events till the estimation process yields tight confidence intervals for the fitting of various families of PDFs. (C) In this case, maximum likelihood estimation (MLE) is used to evaluate the goodness of the fitting of various sample probability families shown at the bottom panels: the Gaussian distribution, the lognormal distribution, and the Gamma distribution. Panel C shows the results of running MLE. The horizontal axis shows the values of the gradient output from the optimization function (they should be very small) and the vertical axis shows the likelihood value, which is clearly highest for the Gamma family. One should test different families of probability distributions before settling on one to characterize the random processes our data represent. In this way we do not waste as much data as it is currently done and have a chance to use better statistical inference and interpretation of our data's inherent variability.

The Micro-Movements Perspective

How could we study Melissa's subtle movements, i.e., those movements seemingly spontaneously generated by her nervous systems? Were they volitional in nature? Averaging those fluctuations, as it was commonly done, would smooth out the very signal I was interested in. It would throw away as noise the information that I needed to determine if these motions had in any way a nonrandom signature. In other words, was there anything anticipatory or predictable about these seemingly spontaneous random motions? The micro-movements that we had invented to study volition in autism[10] could hold the answer to our questions here.

But, what are the micro-movements that the SPIBA framework uses? The raw biophysical data continuously registered from physiological sensors (i.e., sensors registering *physiological rhythms* such as electroencephalography, electrocardiogram, respiration patterns linked to muscles electromyographic activity, kinematics from bodily, head and eye movements, tremor data, etc.) give rise to continuously changing peaks and valleys of various amplitudes occurring at variable times within a time series. These peaks understood as spikes of variable fluctuations in amplitude and timing can be construed as a continuous point process, i.e., following a continuous random process. In this process, events in the past may (or may not) accumulate evidence toward prediction of future events. The spike trains derived from such peaks and valleys in the continuous analogue data from high sampling resolution sensors could serve as input to different classes of (stochastic) random processes. These "*micro-movements*" data type that I invented are described at length in the Supplementary Materials of various papers from my lab, e.g., 1,11,12. To create them, I was first inspired by electrophysiology research on neocortical neurons,[13] but then realized their utility in the context of other bodily biorhythms from the periphery.[9]

The micro-movement waveforms derived from the time series of multiple parameters harnessed from the nervous systems biorhythms (e.g., kinematics signals in Fig. 1.3) are used to represent a continuous random process under the general rubric of Poison random process. To be more precise, we treat the spikes in the first rate of change in various signals' motions as spikes of random amplitudes and random times. To model them, we build on our original work[10] whereby the amplitudes and inter-spike interval times are modeled as independent and identically distributed (iid) random variables following a Gamma process where the continuous Gamma family of distributions is used to model the process. This iid assumption is one that we relax later in Chapter 8, to be in tune with the time dependencies of nervous systems processes and their accumulation over time. In this chapter, however, I will focus primarily on iid assumptions because even with the limitations they may impose on data harnessed from a self-supervising and self-correcting biological system—such as the nervous system—these new methods pose nontrivial improvements over old ones in the field. As such, this is a first step of many iterations until we get closer to the true nature of an intelligent system that learns to heal itself. Sample pipeline of data processing are shown in (Fig. 1.6)

Under iid assumption and upon empirical estimation of the Gamma parameters, we track their values on the Gamma parameter plane, compute the empirical probability distribution functions (PDFs), obtain the empirical summary statistics (the moments), and integrate various such signals from multiple layers of the nervous systems (Fig. 1.7).

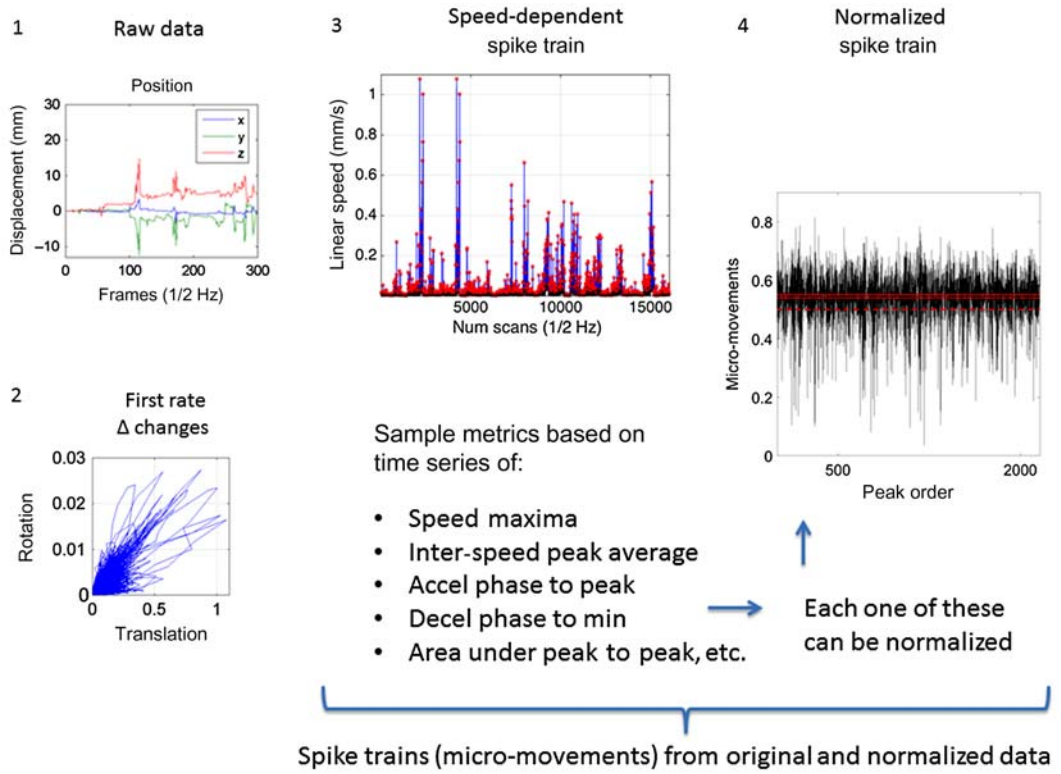

FIGURE 1.6 **Example of micro-movements extraction from kinematics data** (Step 1) Obtain raw positional data (these can be from linear displacements or angular rotations). (Step 2) Examine excursions of various types, e.g., first rate of change in displacements and rotations (plotted here), cumulative excursions, etc. (Step 3) Obtain the scalar (speed) magnitude of the first-order rate of change time series (i.e., commonly termed velocity-dependent data). In this case the velocity obtained from positional data is computed and the scalar value (speed) obtained. The peaks are used to study their fluctuations in amplitude and timing (spike trains). Sample kinematic metrics derived from the velocity-dependent data are (among others) spike trains of speed maxima, of inter-speed peak average, inter-minima speed average, acceleration (rising phase) to the peak, deceleration (decay phase) to the minima, area under peak to peak, area under minima to minima, etc. (Step 4) Normalize the micro-movements to create unit-less quantities that provide a standard scale and account for allometric effects due to disparity in anatomical features in cross sections of the population, age disparity, among others.

Amidst this process of gathering data in tandem from multiple layers of the nervous systems and performing stochastic analyzes to empirically characterize their inherent variability, we profiled the micro-movements from multiple layers of the nervous systems across the human population.[11] Part of the goals of our research program was to provide a standardized measure of all these levels of control and their neurodevelopment, independent of anatomical differences and chronological age. Another long-term goal was to provide a scale-invariant metric amenable to integrate *discrete* (ordinal) clinical scores, currently used

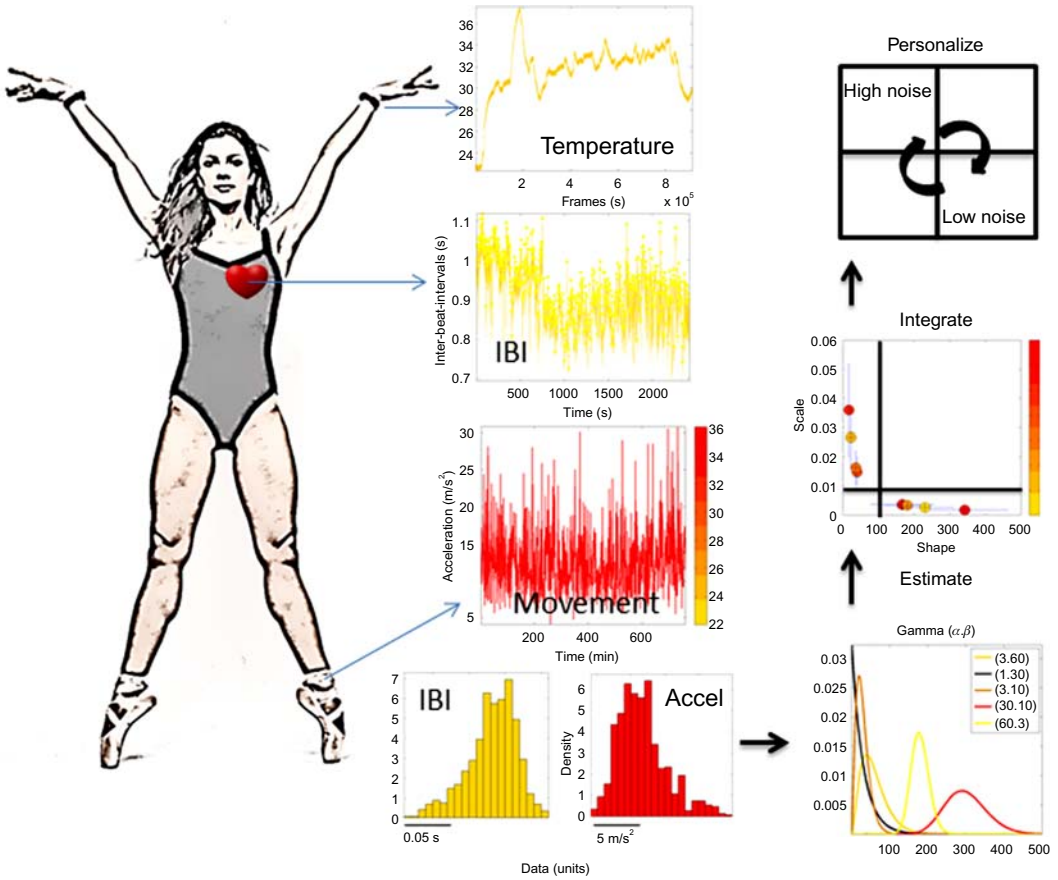

FIGURE 1.7 **Integrated micro-movements from different nervous systems' biorhythms to provide an empirical characterization of volitional control or lack thereof.** Wearables provide different signals. The micro-movements waveforms are extracted and their statistical signatures estimated from the Gamma process to derive the shape and dispersion (signal-to-noise ratio) of the micro-movements. They determine transitions from spontaneous random noise to well-structured signal with systematically predictive power indicative of adaptive control and the emergence of volition.

to classify pathologies of the nervous systems, with *continuous* physiological signals obtained noninvasively from the naturally functioning nervous systems.

In this sense, our research program aimed at creating new ways to track and visualize performance outcome in near real time, involving various levels of enquiry. These levels of enquiry range from a macro-level of observational description of behavior to a functional micro-level, considering as well within these disparate scales, different states of controllability (from spontaneous to intentional). Ultimately, our goal has been to produce objective outcome measures that enable evaluation of the person's quality of life, through the assessment of his/her volitional control and self-agency over the body in action. Arguably, without such autonomy it becomes difficult to have high quality of life.

The medical field is filled with observational inventories and self-reports. This is their data. As such, somehow basic science registering continuous physiological data is constantly forced to correlate "apples and oranges." The medical literature has abundant cases where the continuous biophysical data has been (inappropriately) correlated with discrete ordinal data without any justification about their underlying statistical assumptions. For example, observational scores that a neurologist or trained clinician may take from a patient with Parkinson's disease using the Universal Parkinson's Disease Rating Scale are often correlated with kinematics data (speed, acceleration, end-point kinematic errors in a target-pointing task, etc.) However, while the clinical scores assume normality to build their scales, such data from kinematics parameters are not normally distributed. Furthermore, the kinematics of human movements arise from highly nonlinear interactions across systems in motion. Such motions are generated with a high number of degrees of freedom causing highly nonlinear interactions. Yet, the basic research literature tends to apply multivariate linear regression analyses and other parametric tests based on assumed statistical features that such data violate.

The same type of problem exists in the literature of basic research on developmental disorders like autism spectrum disorders (ASD). There, the Autism Diagnosis Observational Schedule,[14,15] built under assumptions of normality and linearity, generates discrete scores with no proper metric. Further, there is no neurotypical data to build a relative scale of departure from normality. Researchers are forced to correlate these ordinal discrete scores with continuous physiological data in the real or complex domain. It is all very puzzling to me. The kinematics of bodily biorhythms also arises from highly nonlinear processes. The developmental data obtainable from trajectories describing voluntary movements show evolving families of distributions unique to each child (Fig. 1.8). These distributions are empirically well characterized by the continuous Gamma family spanning skewed distributions, inclusive of the (memoryless) exponential. As such, the Gaussian assumption of a population ideal mean tends to mask the maturation process that typically takes place in a growing child with a developing nervous system.[11] The methods currently in use by most of the developmental research of the brain and health sciences mask the very information we need to detect the risk of developing a problem during neurodevelopment. This methodological flaw of the static statistics enforced on the dynamically changing data also prevents us from intervening early, before the neurodevelopmental problem becomes obvious to the naked eye. In Part II, we will revisit these issues in the context of neonates and detection of risk for neurodevelopmental stunting. This will soon be important to help us develop a proper understanding on the differences between staged actions and spontaneous motions.

Distinguishing Deliberateness From Spontaneity in Kinematics Signals

The spontaneous covert motion segments I discovered in an earlier work involving athletes[9] were far more sensitive to the external environmental and the internal bodily-driven influences than the overt deliberate motion segments coexisting in complex boxing routines. In that sense, the mental intent to move in a certain way could be captured in the physical realization of the actions carrying high certainty in the prediction of their possible consequences. Indeed, using our SPIBA I could extract and differentiate the

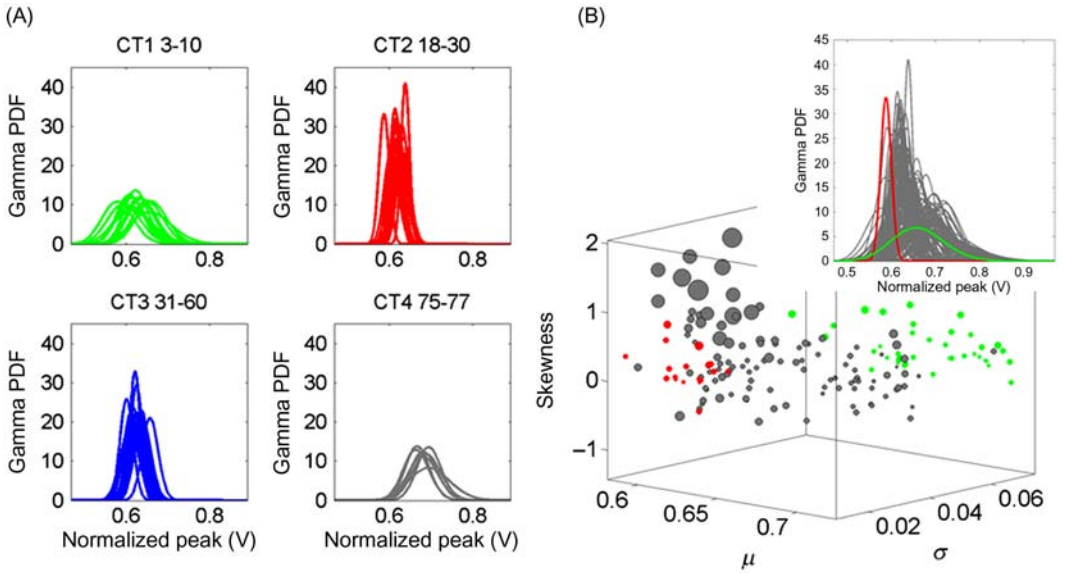

FIGURE 1.8 **Developmental evolution throughout the human life span of PDFs characterizing the peak speed in our voluntary motions.** (A) From 3 years of age to 77 years of age, the stochastic signatures of the hand trajectory speed in route to a spatial target change dramatically. This simple pointing experiment was performed in 178 participants of multiple ages and conditions. This figure focuses on a subset of neurotypical individuals (with no diagnosis of a nervous systems disorder). Each curve represents one participant who performed over 100 of the pointing task in different intervals (to avoid fatigue). Then the micro-movements were extracted from the speed profiles of the goal-directed hand motions to the target and a Gamma process used to empirically estimate the signatures of the PDF best fitting the data in an maximum likelihood estimation sense (as in Fig. 1.5). From 3 to 10 years old the distributions are skewed and have large dispersion, then they turn more symmetric and with less dispersion (low NSR). By middle age they start to regress toward more dispersion and skewness and by the 70s they begin to look a lot like those of a 3-year-old child. (B) The estimation of the Gamma moments in the population at large are represented in a four-dimensional plot. The *x*-axis is the mean, the *y*-axis is the variance, the *z*-axis is the skewness, and the size of the circle is the kurtosis. The plot includes patient data as well, from participants with Schizophrenia (bigger circles with large kurtosis); Parkinson's disease of various levels of severity (middle of the plot) and the college (red) students contrasting with the 3-year-old (green) participants. Even without knowing the age labels, we can blindly identify two clusters far apart in this Gamma moments' space. The health and brain sciences assume Gaussian distributions regardless of age.

signatures of intentionally performed motions from motions spontaneously performed and largely beneath awareness. The key feature of the kinematics was that the variability patterns of the deliberate segments of the continuous trajectories from the body in motion were far more robust to changes in the body dynamics (e.g., changes in speed) than those which were spontaneously co-occurring. I will show these features in detail in Chapter 4, but for the purposes of this chapter, the important piece of information is that the stochastic signatures of the Gamma process used to describe the transitions from high to low noise, or those from random to predictable micro-movements, were well defined and consistently different for each type of motion. Volition had distinct signatures captured in the rates of change and transitions across the left upper (LUQ) and the

right lower quadrants (RLQ) of the Gamma plane (denoted by LUQ and the RLQ in Fig. 1.9).

In the case of Melissa, her coma state was preventing her from performing overt movements and timely controlling her limbs in tandem with her mental commands. However, the micro-fluctuations of her seemingly spontaneous and small motions could also carry the stochastic signature of deliberate actions signaling the degree of intent her brain had to control her body. Our methods are scalable. They harness the micro-movements from both large overt movements and invisible minute motions. The stochastic nature of the fluctuations in amplitude and timing that these continuous biorhythms have could be tracked from day to day, over 12 hours of continuous recordings each day. These stochastic

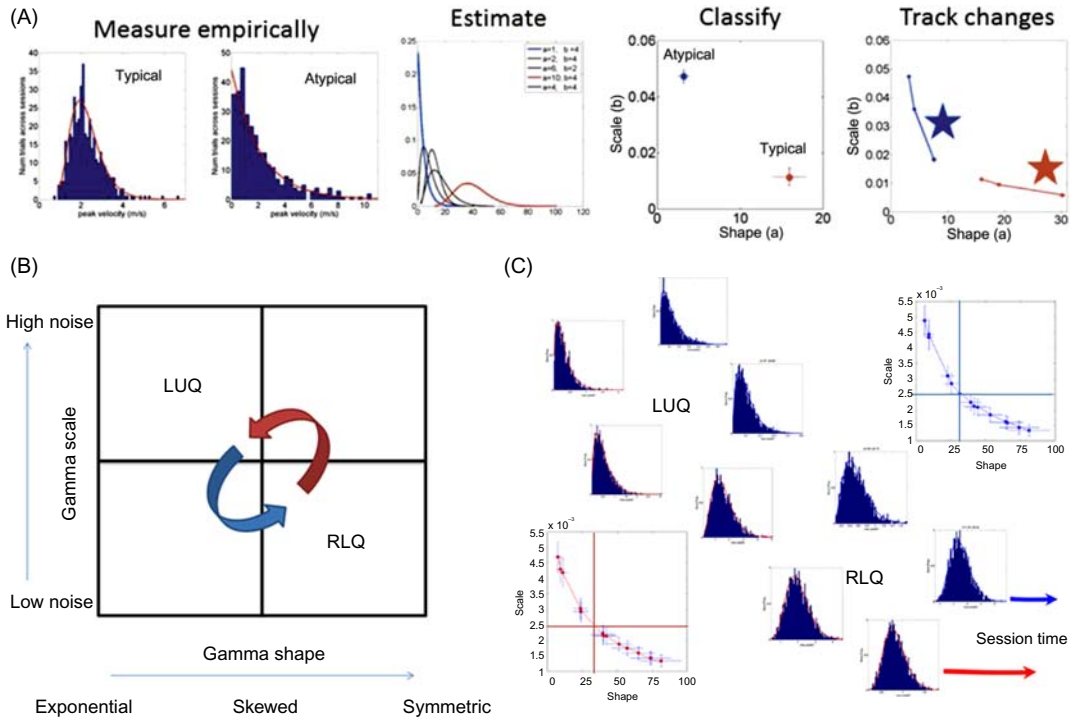

FIGURE 1.9 **SPIBA for independent identically distributed (IDD) events assumed in the spike trains (micro-movements) derived from biophysical rhythms harnessed from the nervous systems using non-intrusive wearable sensors.** (A) Gather the micro-movement signals into a frequency histogram. Estimate the probability density function, e.g., using the maximum likelihood estimation (MLE) methods. In this case the continuous Gamma family of probability distributions is a good fit. As such the Gamma process is used to estimate for each minute-long block of data the shape and scale parameters, plotted here on the Gamma parameter plane with 95% confidence intervals for two representative cases (TD vs ASD). The coordinates of the Gamma estimates on the Gamma parameter plane are tracked over time, as they shift along a stochastic trajectory across the 13 h of recordings. (B) The shifts jump from the LUQ of the Gamma plane (higher NSR and more skewed distribution shapes) to the RLQ with higher signal content (lower NSR) and more symmetric shapes. The amplitude and frequency of the shifts can be measured and tallied to quantify stationary from nonstationary transitions (see Fig. 1.16). (C) Representative evolution of probability distributions and their empirically estimated PDFs representing the correspondence to the LUQ and RLQ scenarios.

rhythms could then be construed as an amalgamate of random events coming from different levels of the nervous systems, ranging from autonomic to automatic to voluntary (as in the taxonomy of Fig. 1.3) and nonetheless tell us about the level of mental intent the brain was exerting over the physical body.

From Volition to the Path of Rehabilitation

Immediately after my talk ended at the conference, I called Brian and texted him a picture of the APDM sensor that Beth had introduced me to. Through the magic of the internet I sent the picture along with the company information. Brain called APDM and miraculously fast, he secured two sensors that he placed on his wife's wrists (Fig. 1.2). We set up a data-transfer system whereby he could send me the wearable sensors' data regularly (via the cloud) for 4 consecutive months. From April to July 2014 I regularly checked for patterns of wrist acceleration, rotation, and temperature in search of a sign of self-organizing patterns and changes in somatic-motor physiology suggestive of deliberate control. I reasoned that through the continuous tracking of the PNS activity—as we were routinely doing in the lab while using overt movements, I could gain a window into the amount of control Melissa's brain was likely exerting over her bodily motions. Indeed, the peripheral activity at the end effectors (the wrists in this case), as subtle as they may be, could serve as a proxy of her internal self-control and agency; perhaps she was trying to show others around her that she was still there, despite her clinically declared comma state.

Minute by minute, the methods integrated the micro-movements from the wrist acceleration and those harnessed from sensor's temperature combining the readings from her skin temperature, the battery's energy consumption and the ambient temperature (Fig. 1.10). The more actively she moved, the higher the fluctuations in temperature were on average. But it was the NSR derived from the Gamma process that told us something about her volition. The rates of change in this quantity served to distinguish, over the course of four months, those motions that were spontaneous and random in nature from those which were systematically predictive and high in signal content (Fig. 1.10C).

On the week of May 19–25 I detected a flurry of self-organized activity and a spike of change in the temperature output by the sensors. Tracking the patterns on the Gamma plane quadrants alerted me of a dramatic change in the levels of re-organization and predictability in her self-generated motions (Fig. 1.11A and B). Such systematic patterns flagged a level of volition that emerged during those days, i.e., the type of body control that we know from the literature on intentional actions that the brain exerts at will, with a form of consistent deliberateness that contrasts with spontaneous random fluctuations in motion patterns.[9,16]

The emergence of increasingly organized signals showed a clear transition from spontaneous random noise on the Gamma plane LUQ to well-structured signal on the Gamma plane RLQ. The statistical meaning of the Gamma plane that we had empirically mapped across a large cross section of the general population (represented schematically in Fig. 1.9B) paired with our empirical evaluation of Melissa's nervous system—as it longitudinally evolved, helped me statistically infer the potential significance of these stochastic shifts in the biorhythms these sensors were continuously outputting at the periphery. Indeed the precise prediction of the week when her baby was born (shown months later with his mom Melissa in Fig. 1.11C) was very encouraging for us.

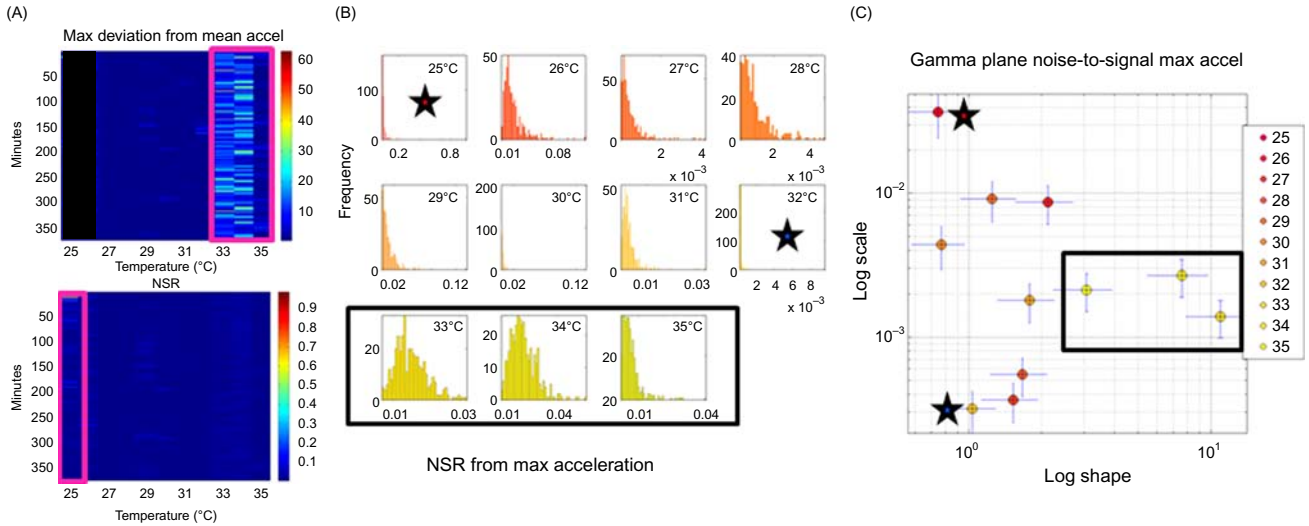

FIGURE 1.10 **Integrated micro-movements waveform from kinematics and temperature.** (A) The Gamma scale parameter is the NSR of the micro-movements. Here we can integrate acceleration and temperature by selecting for each temperature degree those acceleration peaks above the mean overall acceleration. This data type is provided on the top panel, where the highest range of acceleration peaks (minute by minute) is highlighted by a square and the color bar provides the actual range of motion (m/s^2). The micro-movements from this integrated waveform (temperature-dependent motion) are then obtained and input to a Gamma process. The resulting color map matrix reveals the temperature range with the highest and the lowest NSR. The color bar shows the overall range of the data from 360 min. During those 6 h of continuous data registration we can track the evolution of the stochastic signatures in (B). Here we highlight the temperature-dependent motions with the least skewed shapes corresponding in (C) to the points on the Gamma plane enclosed in a rectangle. These are the data for 1 day across 6 h. By itself such data provides limited information, but the evolution of these stochastic signatures over 4 months revealed very important trends regarding volition.

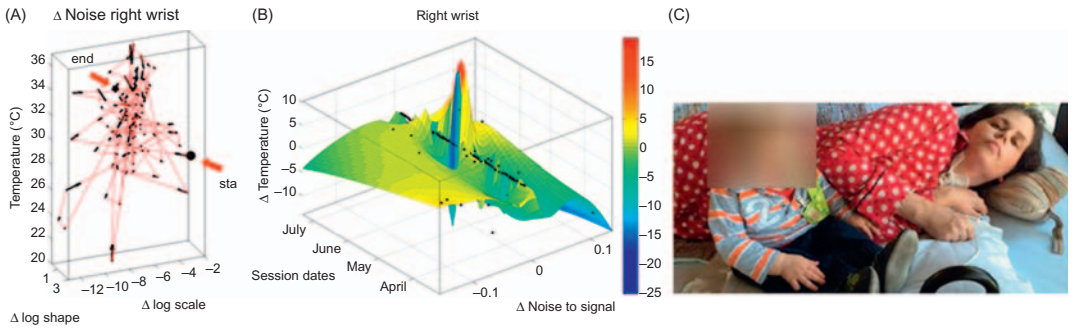

FIGURE 1.11 **Detection of adaptive change and the re-emergence of volitional control over time.** (A) As the micro-movements transition from spontaneous random noise to well-structured signal over 4 months of continuous recordings from Melissa's nervous systems, the fluctuations in temperature-dependent motion turn high in signal content and (B) pinpoint the birth date of her baby. (C) Melissa and her baby some months later.

FIGURE 1.12 **Volition.** Melissa reached for a bottle and moved the hand away from it using a controlled retraction motion.

At their end, Melissa and her family had initiated the path toward rehabilitation with the ups and downs the recovery period from such a traumatic brain injury entails. At some point, I was able to see Melissa reaching for a bottle in a short video that I decomposed frame by frame in Fig. 1.12. Executing such a motion is the hallmark of volitional control. She was without a doubt trying to do so very hard. Her resilience and strong will are extraordinary. Her family knows that, but as a researcher who has spent over 20 years studying volition and modeling the mathematics of reaching actions I know what performing that motion entails. This figure told me much more than meets the eyes. What an incredible journey this has been for her!

Revisiting the Principle of Reafference

From moment to moment and from day to day, the data that I analyzed predicted with ever-growing certainty the extent to which future events could be statistically linked to past events. In a way, I was stochastically characterizing von Holtz and Mittlestaedt principle of reafference[17–19] stating that "*Voluntary movements show themselves to be dependent on*

the returning stream of afference which they themselves cause." The powerful notion of this principle lies in the system's self-recognition of cause and effect, assumed to be directly derived from the expected consequences of its self-generated motions. What the research work with Melissa suggested was that spontaneous fluctuations (up to now neglected in the literature of motor control) provide a window into the *unexpected consequences* of self-generated motions, i.e., the sort of stuff that made visible to the nervous system these otherwise invisible motions.

In this sense, contrary to common belief, the type of variability the field rendered useless and averaged out as noise or a nuisance contained the signal I was looking for to detect volitional control in Melissa's case. Once discoverable, e.g., by "the surprise factor" with an outcome that was unexpected to her awakening nervous system, the spontaneous micro-movements could turn controllable and then transition from "invisible" to "visible" and meaningful. Through their evolution from totally spontaneous to discoverable fluctuations, the CNS could deploy trial and error states, whereby initially nonobvious goals would become interesting to the system. Something emerging as a detectable feature in the environment could serve as an anchor for trial and error (e.g., to the sense of touch, something as simple as a skin ripple could be detectable by the touch sensors on the hand surface). In this sense, trial and error could evolve from seemingly random to systematic. The signatures of fluctuations in the amplitude and timing of wrist acceleration could provide such information. We will see later that in the neonate system such evolution also manifests as the newborn infant transitions from flailing of the arms to goal-directed pointing. The theoretical model I had derived earlier on in my scientific career[7,20] to study sensory-motor integration, action ownership (agency), and volition within redundant, highly nonlinear systems once again provided me with a road map to pose my questions and formalize the problems I needed to solve.

Our work with Melissa suggested that our SPIBA framework and micro-movements data type integrating these multiple biorhythms across the developing layers of controllable signals were appropriate to capture change in their statistical patterns. Armed with these tools we proceeded to examine the longitudinal changes that neonates undergo as their bodies move and their brains begin building maps to help form a bridge between the PNS and the CNS.

PART II: PHYSICAL GROWTH AND NEURODEVELOPMENT IN NEONATES

Some Detective Work

How does volition emerge in neurodevelopment? How is neurodevelopment linked to physical growth? And how does physical growth is measured? These were some of the questions my lab started to ask after we completed the research work with the comma patient.

Then, I learned that according to the Food and Agriculture Organization (FAO) of the United Nations, as of 2013, there are 161 million children under 5 years of age estimated to be *stunted* on their growth, with half of all stunted children located in Asia and over a third in Africa. Wasting from starvation and malnutrition are considered among the causes of stunting with a global prevalence of stunting at almost 8% of the reported total