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ORIGINAL ARTICLE

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# Towards assessing the sympathovagal balance

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**Abstract** Exact assessment of the autonomic nervous system's (ANS) activity by means of heart rate variability (HRV) is a long-standing challenge. Although many techniques have been proposed to take up the challenge, none ever proposed a rationale for the approach behind the technique or a satisfying discrimination of the two activities which underlie the autonomic control of HRV. We here propose a new method, providing both an understanding of the discrimination's nature and a framework which we believe leads to a thorough assessment of the sympathovagal balance, as a trajectory between points in a well-chosen space. The methodology assumes tools from scale invariance/covariance physics. The sympathovagal balance is obtained on a beat-to-beat basis with the dynamics portrayed through a trajectory. Furthermore, universal trajectories are sought which would comprehensively describe the effect of atropine and isoproterenol injections on systems underlying the heart pace variations. Non-invasive assessment of the respective activities of the sympathetic and parasympathetic subsystems of the ANS would be possible through cardiac autonomic measurements.

**Keywords** Non-invasive monitoring · Autonomic nervous system · Heart rate variability · Theoretical physics · Experimental mathematics

## 1 Introduction

Chaotic oscillations of heart pace on a beat-to-beat basis are known to be of great clinical relevance for both diagnostic and prognostic purposes. Among the different factors (e.g., neural, chemical, hormonal) which contribute [4, 16] to this heart rate variability (HRV), a major influence lies in the (ortho) sympathetic and parasympathetic (vagal) branches (respectively, SP and PSP) of the autonomic nervous system (ANS) [30]. HRV analysis is commonly accomplished, in the frequency domain, by means of spectral analysis [32] of the heart beat time series (RR intervals, RRIs) and, in the time domain, via statistical indices. While the former is controversial in its identification [10, 17, 29] of zones in the power spectrum, the latter suffers from highly correlated on-the-surface measurements [5, 30] with the sole consideration of high-frequency variations. Both lack proper accounting of the non-linear components of heart rate fluctuations, and though the former proposes the low/high frequency ratio as a measurement of the autonomic balance, the non-stationarity of HRV and the approximate nature of such a ratio preclude its wide acceptance. Analysis of HR dynamics by methods based on non-linear systems theory has opened a novel approach for studying the abnormalities in HR behavior and may provide more powerful prognostic information than the traditional HRV indices. In particular, the short-term fractal scaling exponent measured by the detrended fluctuation analysis method has predicted fatal cardiovascular events in various populations [14, 15]. Approximate entropy, a non-linear index of heart rate dynamics, that describes the complexity of RRI behavior, has provided information on the vulnerability to atrial fibrillation [28]. Many other non-linear indices, e.g., Lyapunov exponent and correlation dimensions [3, 26], also give information on the characteristics of heart rate dynamics, but their clinical utility is not well established. All these basic concepts, from chaos theory, fractal mathematics, and complexity measures of heart rate behavior in relation to cardiovascular physiology or various cardiovascular events, are still far from clinical medicine, though they are a fruitful area for future research [26, 30]. Even more elaborate attempts to use non-linear analysis such as Volterra–Wiener kernels or

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Hilbert–Huang transforms fail to responsively provide ANS measurements of a different nature than the rhythmical nature of HRV, as used respectively with principal dynamical modes [33] and empirical mode decomposition [2]. In order to separate the dynamics of the ANS' two subsystems, a new method should not only account for the non-linearity of the heart's regulation but also be void of arbitrarily applied techniques which undermine the pure nature of the sought measurement. We believe that such a method should stay in the time domain where understanding of events is kept at the dimensional level of measurements, on their very nature which is time-bound.

Before addressing the above problem of purely separating the two subsystems' activities, we shall further introduce the concept with an analogy. Taking into consideration the performances of an athlete along time, one is faced with time intervals (the performances) as a function of the performances' ranks, i.e., in function of time. As this is envisioned, the RRIs appear in a similar light, being time intervals themselves and being a function of time when considered in a time series.

The performances along time provide the athlete with yet further information than a sole time measurement; it allows the athlete to assess his preparation on which his performances depended. By way of analogy, the RRIs throughout time provide us with information beyond a time or frequency measurement; it allows us to reckon the main system behind the heart's regulation, i.e., the ANS. Just as the assessed preparation of the athlete does not relate to the only done exercise but comprises also a major component of rest, the ANS activity information relates to the activity of both subsystems, SP and PSP.

There is an influence of the training on each of the athlete's performances; likewise, there is an influence of the ANS on each *R* wave. The athlete does not wait for many performances in order to appreciate how effective his training/preparation was; likewise, with each new RRI value, information can be inferred on the ANS' state.

Whether relevant or not, this analogy may introduce a method where the ANS is considered with kinematical substance, as a physical system not quite like the other systems, governed by physical laws but which the authors do not pretend to unravel. This approach is thus non-model driven in the sense that no model is imposed on the autonomic regulatory process of the cardiac activity. The sole extraction of information from this latter activity is appraised here.

## 2 Methods

A first step at the exact reckoning of the separation of the two activities lies in a sound idea of how the sympathovagal balance should be represented beyond a ratio. A trajectorial representation seems fit considering the ANS as undergoing the *attraction* of two poles or *bodies* (SP and PSP). We chose here to start with a two-dimensional representation, the generalization to higher embedding dimensions being straightforward and left to the reader. Of all representations we define one which is self contained and intuitive (cf. Fig. 1), raising the evolutionary from the one-dimensional SP–PSP axis. As shown with this Fig. 1, an abstract rotation of axis suggests the existence of a (wave) function for the SP and the PSP, an evaluation of the activities beyond a sole value.

Looking for such (wave) functions is our second step whose raison d'être and congruity reside in the very rationale of signal extraction rather than analysis, an approach which privileges a non-model [31] driven measurement with profound assumptions rather than empirical techniques whose success depend on unverifiable

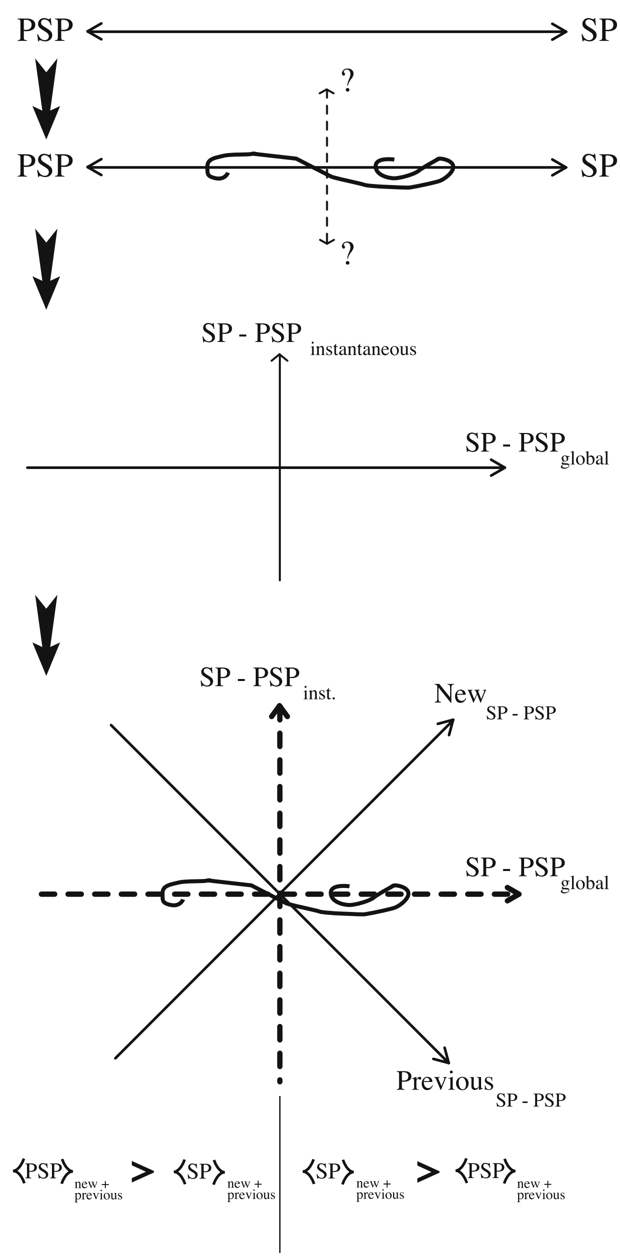


**Fig. 1** From a one-dimensional consideration of the autonomic balance to the existence of functions SP and PSP of local time

conditions. For a few decades now, *experimental* Mathematics [20] (as some call them) has led the way beyond [20] *applied* Mathematics and today yielding subjects such as scale (invariance [19] and) covariance physics (SCP) directly stem from these mathematical observations. SCP theories have not yet found application or extension in the biomedical field. With the present method we extend and unify tools, tools which one of the authors had participated to develop. Starting with visionary considerations of Mandelbrot [18], discoveries of Feigenbaum [11] and the Universality Theory [21], and continuing with parallel developments of Nottale [22, 23], Dubrulle [6], Dubrulle and Graner [7, 8] and Dubrulle et al. [9], we propose a new type of renormalization-group-like [19] treatment of the RR time series.

This renormalization is composed of two parts: (1) a recovery of a fractal continuity, with a loss of differential time reflection invariance (implicit symmetry of Physics which *R*. Feynman depicts as "all fundamental processes are reversible"); (2) a recovery of this time *reversibility*, with a final loss of continuity. These parts parallel, in their usage, two observations on the RRIs, namely: (1) a graphical continuity and (2) a graphical self-similarity throughout time.

Let us detail these parts. The first step assumes, as scale relativity does, that space–time is fractal and non-differentiable, i.e., that such is Nature [18]. This giving-up of the hypothesis of differentiability of space–time coordinates entails at least three effects. (a) Geodesics exist, their number becoming infinite. This will have a consequence on the geometry of the autonomic balance. (b) Each geodesic is of dimension 2, in agreement with what Feynman had demonstrated [1, 24] on the typical quantum paths [13]. This will also have a consequence on the long-term geometry of the autonomic balance but will exhibit a rectifiable (outwardly regular) nature for the short-term trajectories. (c) The symmetry $\mathrm{d}t/-\mathrm{d}t$ which was a hidden symmetry of the standard theory is broken by non-differentiability. This leads to a two-valuedness of the average velocity vector, which is, in the framework of scale relativity [25], the origin of the complex nature of the probability amplitude (for quantum mechanics). This will have a direct consequence for part (1) of our renormalization.

The first part (continuity recovery) makes great usage of this fractal space–time assumption. It is a fractal continuity which is recovered from the graphical continuity of the otherwise discrete (by nature) RRI, whose domain of application lies for $t$ between $C{\cdot}l_{\mathrm{Planck}}$ and $t_{\mathrm{rega}}/5$, where $l_{\mathrm{Planck}}$ and $t_{\mathrm{rega}}$ are defined in Table 1. The upper bound is a threshold between the fractal and observed continuity of the signal. Now as point (c) stated, the average velocity (or time derivative of a coordinate) is now made of two values, two instantaneous *velocities* from the fractal continuous-recovered RRI. RRI are time measurements and as such their *velocities* (their rates of change) do not possess the physical properties of a proper velocity. Employing ancient considerations of Luzzatto [27] on the nature of time, we introduce a 'covariant' velocity $\boldsymbol{V}'$ vector (locally similar to that used in the scale relativistic framework) by the use of an operator on the two-valued velocity. Hence with part (1), we gain knowledge of the proper velocity of the ANS as a physical system in an abstract space–time.

The second part of our renormalization-group treatment recovers the local time symmetry which was freshly broken in the first part. A slight digression is here needed on the nature of the ANS' regulation of the heart fluctuations. This regulation is iterative by nature, in the sense that the heart's pace is influenced by the ANS and the state of the ANS depends in part on the heart's behavior. This fundamental observation is at the core of our renormalization-group effort and helps to explain this $\mathrm{d}t/-\mathrm{d}t$ symmetry: forward time and backward time correspond, respectively, to the action of the ANS on the heart pace and the reaction of the heart on the ANS' state. The ANS would be of a semi-classical nature, where quantum effects take place. Now that this is said, we may proceed unto the details of this part (2). Recovery of this symmetry is organic to a change of scale from the known RRI before a certain present time to the very time scale which consists of the period between the last two *R* waves. This part (2) was paralleled to the observation of a time self-similarity in the RRI, for this observation enables the change of scale. As Table 1 explicates, an upper hull calculation is combined with this time reversal in order to obtain the change of scale. The result of this change is locally a vector with forward and backward time components. Just like any RRI, it is a time interval, here called $\boldsymbol{\Delta t}$.

As a third part of our method, beyond obtention through renormalization of the velocity vector $\boldsymbol{V}'$ and the time interval vector (past and future) $\boldsymbol{\Delta t}$ around the present *R* wave, the local displacement of the ANS' state is calculated as the dot product of both vectors. This combination of the two data (velocities, time-scaled time intervals) provides displacements of the ANS' state: $\delta' \boldsymbol{s} = \boldsymbol{V}' \cdot \boldsymbol{\Delta t} = \mathrm{SP\ displacement}\ + \boldsymbol{i}\cdot\ \mathrm{PSP\ displacement}$ (here on local level). (The real and imaginary parts of this complex number are the infinitesimal displacements of the state, respectively, for the SP and PSP subsystems.)

To conclude the unclosed second part, the $\delta' \boldsymbol{s}_i$ are taken, sweeping all positions of the new time scale in a considered window; this 'sweeping' is done discretely, thus losing [19] the continuity obtained with part (1). Hence, we are left with a complex vector $\boldsymbol{\Delta s}$ whose real and imaginary components form the aforementioned functions for, respectively, the SP and PSP. These functions can be considered as discrete wave functions, or even as cumulative frequencies; they are the state of the ANS' subsystems between the most recent *R* waves up to the time corresponding to the last *R* wave. One should stress that such functions are in no way averages and that for each new heart beat, two such functions can be extracted.

As envisioned these functions help define the sympathovagal balance as a trajectory: the discrete points,

**Table 1** Succinct formulations behind the methodology

| | |
|---|---|
| $(V_{+dt}, V_{-dt})$ From two valued *velocity* $\Rightarrow$ to a complex velocity vector $$v` = \begin{pmatrix} V_{+dt} + i\cdot(V_{+dt} - V_{-dt}) \\ V_{-dt} + i\cdot(V_{-dt} - V_{+dt}) \end{pmatrix}$$ (simplified case) | This is similar to the Scale Relativity $$v^j = \frac{d'}{dt}x^j = \frac{v_+^{\ j} + v_-^{\ j}}{2} - i\cdot\frac{v_+^{\ j} - v_-^{\ j}}{2}$$ |
| Upper Hull is decomposed in forward and backward time components $$2\cdot\overline{H}_a^{\ b} = \overline{H^{+dt}}_a^{\ b} + \left(\overline{H^{-dt}}_b^{\ a}\right)^R \qquad \text{then, } \Delta t_j = \left(\frac{\overline{H^{+dt}}}{\overline{H^{-dt}}}\right)_{j-w_{self-similarity}}^{j}$$ The hull is considered on a window of self-similarity | |
| The local infinitesimal displacement of state is expressed as $\partial' s_j = v'_j \cdot \Delta t_j$ where, $\Delta s_k = (\partial' s_{k-f(w_{self-similarity})}, \ldots, \partial' s_k)$ corresponds to the 'sweeping' of all time locations, the window of locations being function of the above self-similarity window. This is our complex discrete function whose real and imaginary parts are respectively the SP and PSP considered functions | |
| $$t_{rega} = \frac{Hour}{58888}, \qquad l_{Planck} = \sqrt{\frac{\hbar\cdot G}{c^3}}$$ | |

with coordinates obtained from a representation of the point-by-point subtraction of the discrete functions of SP and PSP, form as joined a rectifiable trajectory with illusion of the non-fractal continuity. Only on the long term and with unique consideration of the discrete points is the fractal nature of space revealed through what we term a static autonomic balance.

In order to illustrate this extraction process, we here provide the reader with means to compare on one example (patient at rest before injections) the outcome of this new method with what is obtained through a Poincaré plot. Both our method and the scatter plot of the first return maps for RRI stay dimensionally in the time domain. From 60 RRIs, 40 points are obtained for the sympathovagal balance trajectory and 60 points for the scatter plot; both are represented, respectively, in Figs. 3 and 2. The points are numbered in both graphs so as to enable a straightforward comparison between the 40 most recent points in both representations. It appears that a meaningful and continuous chronological order is retrieved from the RRI in the sympathovagal balance trajectory points. In fact, this novel approach can be abridged to a choice at every heart beat between e.g., SP activation and PSP inhibition (and other possibilities) as being the cause of e.g., a decrease between two RRIs (increase of instantaneous heart rate). The choice is weighted by the preservation of the graphical continuity of the RRI into the continuity over time of both the SP and PSP changes of state. This continuity-oriented decisional process allows for the identification of the cause of a local increase/decrease in heart rate. Figures 2 and 3 serve to illustrate that an increase in

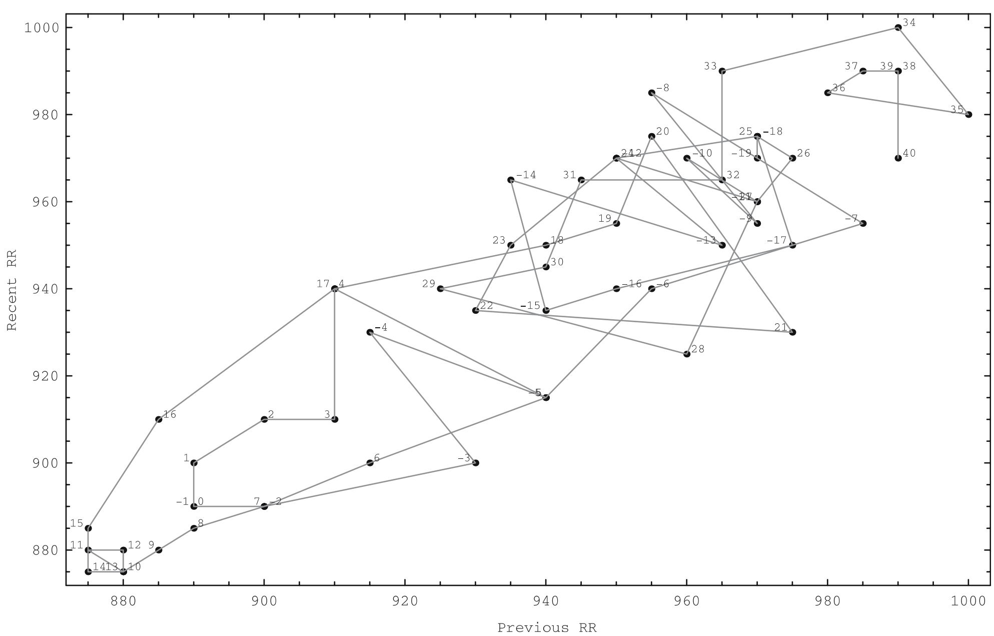


**Fig. 2** A Poincaré plot is represented as a scatter plot of the first return maps for RRIs (patient at rest before injections)

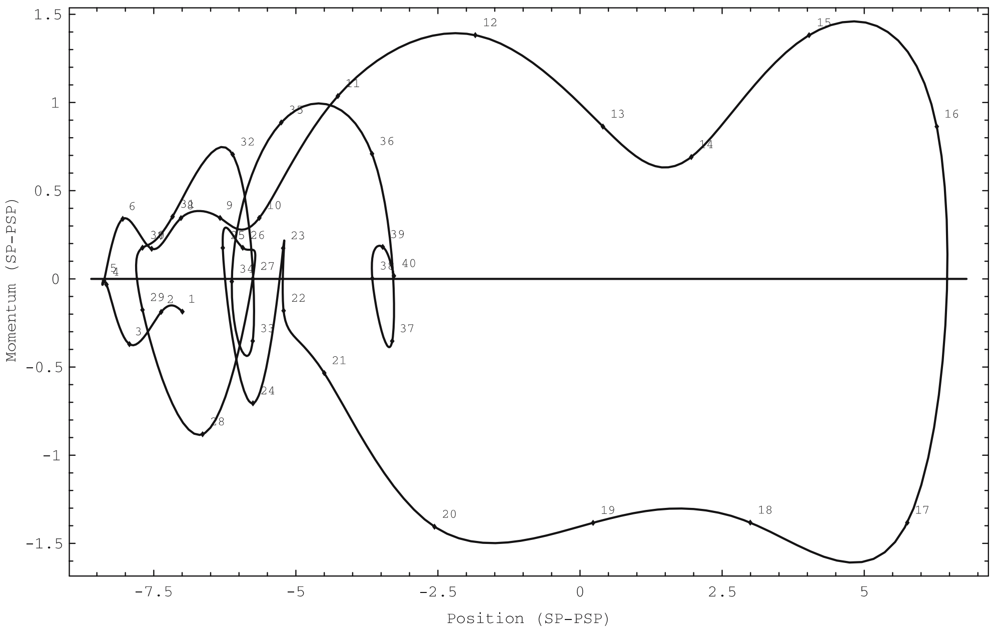


**Fig. 3** The smooth sympathovagal balance is given as a trajectory between 40 reference points devised from the 60 RRIs used in Fig. 2. Although here there are 20 points less than in the Poincaré plot, these 40 essential points of autonomic information coincide in time with the 40 last points of Fig. 2

heart rate (i.e., a movement towards the lower left in Fig. 2) does not necessarily mean a movement towards more SP activity (i.e., towards the right in Fig. 3) but highly depends on the history of both systems' activities.

## 3 Results

The sympathovagal balance trajectories present various characteristics among which the existence of modes (or periods) in addition to the d$t$/−d$t$ near-to-repetition (cf. Fig. 4), thinner loops towards the PSP and positive area

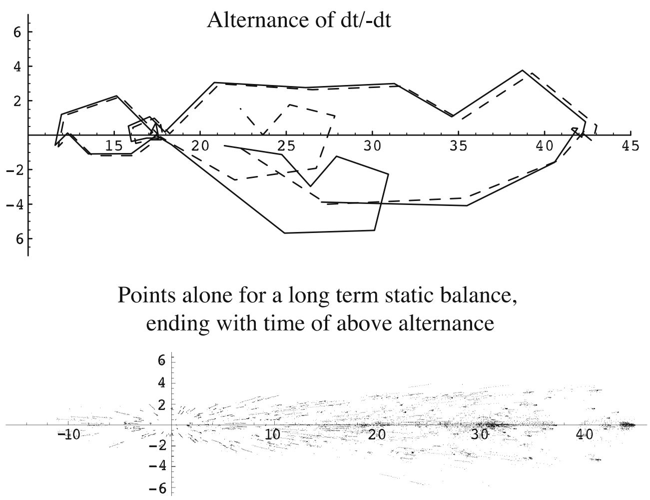


**Fig. 4** The trajectory illustrating the alternance +d$t$/−d$t$ corresponds to the input of exactly two consecutive $R$ waves. The rectifiable trajectory of this illustration is contrasted to the fat fractal (*positive area set below*) nature of the points unconnected for a longer time observation yet leading to the very moment seized by the above trajectory

self-complimentary sets for a static balance over a variable time scale... The trajectories evolve here in a two-dimensional phase space (also called phase diagram). Both the momentum and position axes (cf. Fig. 3) follow the order from PSP to SP predominances, from negative to positive values. Hence, a trajectory above the position axis may only move towards more SP activity (i.e., to the right), whereas a trajectory below the position axis may only move towards more PSP activity (i.e., to the left). The momentum of the ANS may be understood here as indicating impulse or more simply a direction of activity change.

A first study on 15 patients has moreover illustrated the adequacy of conclusions reached here in describing the method with the measures obtained. Using data from this study [15 patients (13 male, 2 female); mean age: 60 (± 18) years; no structural heart disease; no antiarrhythmic drug treatment], we hereby hint to the exactitude of the measure by obtaining 'theoretical' balances for injections of atropine and isoproterenol (respectively, 1.0 mg intravenously and by infusion using individual dosage in order to increase the basic sinus rate to 110–120 bpm). What is here meant by a 'theoretical' sympathovagal balance is a trajectory whose structure would be common to all instances sharing a same condition (i.e., atropine injection). Table 2 contains descriptive statistics of these instances,

**Table 2** Heart rate response to injections, compared with the center of gravity of the sympathovagal balance (mean average ± standard deviation)

| | Heart rate (bpm) | Center of gravity |
|---|---|---|
| Basal | 76 ± 17 | −1 ± 15 |
| Atropine | 95 ± 18 | 36 ± 9 |
| Isoproterenol | 121 ± 33 | 25 ± 13 |

corroborating for both injections the overall position of the sympathovagal balance with the heart response, from basal to after injections. One example of the positional evolution of the sympathovagal balance is given in Fig. 5 for one patient undergoing both injections. The center of gravity index allows quantification of the sympathovagal balance, where negative indices indicate overall PSP predominance and positive indices SP predominance. In Fig. 6, the theoretical sympathovagal balances are drawn for the two types of injection. These 'theoretical' balances are brought by identifying and removing the periods and $dt/-dt$ loops, normalizing the coordinates according to a common time referential between the different patients, and taking a spline interpolation of the point-wise average of the then normalized individual balances. Although measurement conditions were non-ideal (following cardiac catheter ablation), for both the atropine and isoproterenol injections, the average obtained was highly stable under change of time referential and random elimination of 12% of data set. These 'theoretical' sympathovagal balance trajectories are properly universal, in the sense that they universally portray the change in the ANS of patients undergoing such injections. The selective humoral stimulation/inhibition of the ANS by isoproterenol/atropine suggests that the trajectories obtained by the present mathematical method evolve under the attraction of the PSP pole and its SP opposite. Inhibition (e.g., PSP inhibition achieved through atropine injection) is manifested in longer horizontal trajectories leading to the system gaining predominance, whereas activation presents more loops indicating a global displacement of the sympathovagal trajectory towards the activated system. Although more work is needed before reaching definite conclusions, we can speak of a common topology of injection between all cases of a same pharmacological maneuver while identifying different individual geometries proper to the patients.

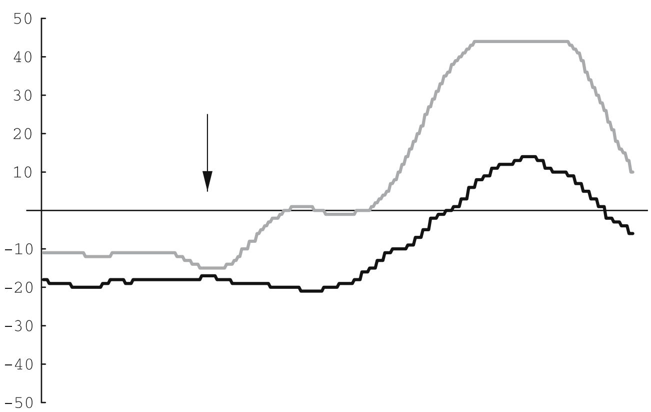


**Fig. 5** The distance (given a sign, respectively, positive and negative for overall SP and PSP predominances) of the center of gravity of the sympathovagal balance trajectory to the origin (pure neutral state) is graphed in *gray* and *black*, respectively, for the injections of atropine and isoproterenol. The *arrow* indicates the time of injections

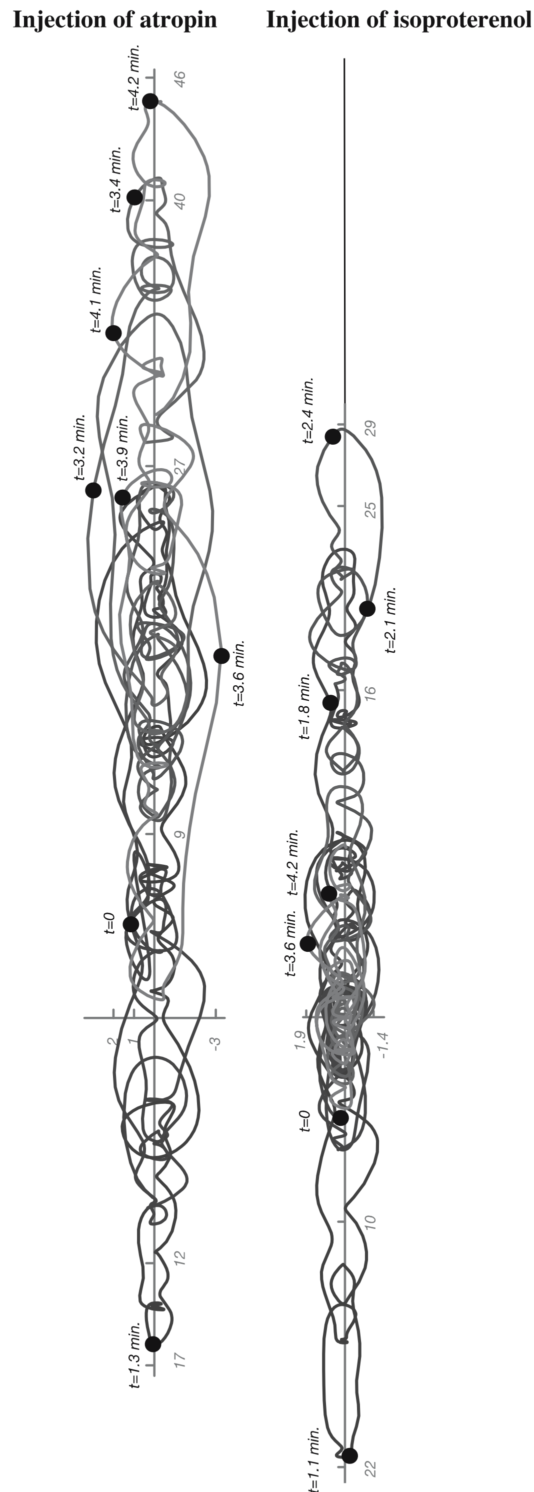


**Fig. 6** Trajectorial representation of the dynamical changes of the sympathovagal balance during autonomic maneuvers. These are the theoretical balances of universal nature. Time given is only indicative and should be taken relative to the total time (4.3 min) and considered as the maximum time among all cases of study; these are not universal if considered absolute. Normalization was performed between injections of the same drugs and not between theoretical balances of the two drugs. Hence $t = 0$ does not correspond to a same starting point; however, the values along the SP–PSP axis being meaningful, it is better kept as it is

## 4 Discussion

The ANS by being autonomous provides a rare case of study for theoretical physics considerations in the exploration of biomedical phenomena. This autonomy is furthermore manifested in the always-present-time situation which sees constant alternance of positive and negative time activities. The sympathovagal balance trajectory, which is obtained by pure discrimination of the SP and PSP subsystems' activities in the ANS, is a semi-quantum path. Just as Feynman could synthesize [12] the interactions in quantum electrodynamics through schematic descriptions, such diagrams for SP and PSP interactions [20], while various conditions, could be devised from the 'theoretical' trajectories obtained with our method. Though it proved handy to describe the space of trajectories using momentum and position, it may be convenient to consider instead acceleration (''gravitational'' force for the attraction of poles) and velocity, or even time and position. More than a new theory of the ANS, a first step towards a systematic portrayal of biological behavior could be investigated.

However, before any of this, there is further need for robust clinical studies to verify our strong assertion that we indeed discriminate purely the SP from the PSP in the activity of the ANS as it is passed onto the RRI. It follows from A. Einstein's principle of relativity that ''no phenomena possess properties corresponding to the concept of absolute rest''. Thus we expect here that in verifying assertions of system blockade, we may find inhibition without absolute rest of the very system inhibited. Indeed, this is what was found with the case of cardiac PSP inhibition by atropine.

Just as the antagonist nature of the SP and PSP is not absolute, the rigid dichotomy between activation and inhibition may broaden out to include de-activation among the possible behaviors of each system. This undoing alternative may be responsible for the loops-without-displacement in the sympathovagal balance trajectory; the baroreflex loop may be one example.

Perspectives like the precise measurement of autonomic function imbalance (i.e., autonomic dysfunction) are now at reach. Assessment of this dysfunction should amount to the evaluation of the time proportion taken by this dysfunction. Representative indices of the SP and PSP activities should be found beat-to-beat for enabling such precise (or other) measurements of coupling. This could be achieved by a combination of quartiles in the SP and PSP functions seen as cumulative frequencies.

Constrained to variable time periods, the static balance points visit and form self similar sets which have non-empty interiors (i.e., with positive area) and are not simply connected (i.e., with holes), sets that possess deterministic mathematical descriptions. Such descriptions could be thought of as signatures of the ANS.

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