Scale-space analysis of time series in circulatory research

Kim Erlend Mortensen,1 Fred Godtliebsen,2 and Arthur Revhaug3

1Surgical Research Laboratory, Medical Faculty, and 2Department of Mathematics
and Statistics, Faculty of Science, University of Tromsø, Tromsø, Norway; and
3Department of Digestive Surgery, University Hospital of Northern Norway, Tromsø, Norway

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Mortensen, Kim Erlend, Fred Godtliebsen, and Arthur Revhaug. Scale-space analysis of time series in circulatory research. Am J Physiol Heart Circ Physiol 291: H3012–H3022, 2006. First published July 28, 2006; doi:10.1152/ajpheart.00168.2006.—Statistical analysis of time series is still inadequate within circulation research. With the advent of increasing computational power and real-time recordings from hemodynamic studies, one is increasingly dealing with vast amounts of data in time series. This paper aims to illustrate how statistical analysis using the significant nonstationarities (SiNoS) method may complement traditional repeated-measures ANOVA and linear mixed models. We applied these methods on a dataset of local hepatic and systemic circulatory changes induced by aortoportal shunting and graded liver resection. We found SiNoS analysis more comprehensive when compared with traditional statistical analysis in the following four ways: 1) the method allows better signal-to-noise detection; 2) including all data points from real time recordings in a statistical analysis permits better detection of significant features in the data; 3) analysis with multiple scales of resolution facilitates a more differentiated observation of the material; and 4) the method affords excellent visual presentation by combining group differences, time trends, and multiscale statistical analysis allowing the observer to quickly view and evaluate the material. It is our opinion that SiNoS analysis of time series is a very powerful statistical tool that may be used to complement conventional statistical methods.

The analysis, interpretation, and description of various phenomena within science is dependent and limited by the method employed by the observer. Whether the phenomenon in question is a static event like a radiological image or a dynamic event like hemodynamic changes in a subject over time, the scale of resolution with which the event is analyzed and the method with which true signals are selected from noise will influence what we see and, accordingly, which conclusions we can infer.

The scale-space theory (10) is a statistical method of image analysis at multiple scales, employed in interpretation of magnetic resonance images (MRI; see Refs. 3 and 14), positron emission tomography, functional MRI (13), and other digital images (4). The significant zero crossings for derivatives (SiZer) method, derived from the scale-space theory by Chauduri and Marron (2) allows multiscale testing of signals, facilitating the detection of significant features on different scales within a dataset over time. The varying level of resolution afforded by this method yields different pictures of the observed phenomena, showing statistically significant features at each scale of resolution. Godtliebsen et al. (5) applied a Bayesian S$\acute{\text{a}}$Zer method on ice core data to analyze past climatic conditions and predict future trends. SiZer regards all data points as independent events, which influences the significance level of the testing. Godtliebsen et al. (6) have addressed this problem by recently developing the method significant nonstationarities (SiNoS) and applied it to several simulated and real data sets. The method proves a valuable tool in identifying the different time scales at which statistically significant changes appear while adjusting for multiple testing.

Statistical analysis of serial measurements is still inadequate in many peer-reviewed papers within circulation research (8, 9, 12). With the advent of growing computational power and real-time recordings from hemodynamic studies, we are increasingly dealing with vast amounts of data in time series. For example, one experiment with real-time recording of blood pressure every 4th s over 10 h would result in 9,000 data points. These recordings are often distorted by signaling noise resulting from surgical manipulation and technical disturbance. In seeking a statistical solution to this novel situation, we believe to have found a reliable method in the SiNoS analysis and have applied it to a dataset of local hepatic and systemic circulatory changes induced by aortoportal shunting and graded liver resection.

Accordingly, the primary aim of this article is to illustrate how analysis of real-time data derived from hemodynamic research using the SiNoS statistical method may complement traditional statistical methods, since the method enables the observer to utilize all data points and explore the data at multiple time scales.

MATERIALS AND METHODS

Experimental Layout

Twelve pigs were divided into four groups of three animals (Fig. 1). Three were randomized to receive an aortoportal shunt (shunt group) and three randomized as controls (sham group). A further three pigs underwent a 60% liver resection (low-portal-pressure resection, LPR), and the last three underwent a 72% resection (high-portal-pressure resection, HPR). Surgery lasted for ~3 h and observation for 6 h.

Animal Preparation

All experiments were conducted in compliance with the institutional animal care guidelines and the National Institute of Health’s (NIH) Guide for the Care and Use of Laboratory Animals [Dept of Health and Human Services Publication no. (NIH) 85–23, Revised 1985]. Anesthesia was induced and maintained as described in previously from our laboratory (7).

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Catheters. A 16-gauge central venous catheter (CVK; Secalon T) was placed in the left femoral artery for continuous arterial blood pressure recording (MAP). A 7-Fr 110-cm angiographic catheter (Cordis; Johnson & Johnson) was placed in the hepatic vein draining segments V and VIII via the right internal jugular vein for right hepatic venous pressure monitoring. A pediatric CVK (Arrow; International) was placed in the portal vein with the tip ~5 cm from the liver hilus for portal pressure monitoring.

Measurements. Calibrated transducers (Transpac 3; Abbott Critical Care Systems, Chicago, IL) were used for real-time pressure registration. The transducers were connected to an amplifier (2800S; Gould). Pulsatile signals were displayed on a monitor, digitized, and stored electronically (Advantech; Industrial Computer). All recordings were logged every 4th s. Perivascular ultrasonic flow probes (CardioMed Systems; Medistim, Oslo, Norway) were placed around the portal vein (12-mm probe). Signals were displayed on a monitor and stored electronically (Advantech; Industrial Computer).

Surgery
Operative procedure in the shunt and sham group. In the shunt group, a 5-mm Propaten Gore-Tex graft was anastomosed end-to-side from the aorta to the left portal vein (P1) supplying segments II, III, and IV. In the sham group, P1 and the aorta were excluded for an equal amount of time without attachment of a graft. The left portal vein, now anastomosed to the graft, was ligated proximal to the graft, and time 0 was noted upon shunt opening. Operative procedures in the resection series were as follows: after a midline laparotomy and placement of all catheters as described above, segments II, III, IV, V, and VIII were removed (low pressure resection). In the high-pressure resection series, the resection was continued, removing segments VI and VII as well.

Statistical Methods
All hemodynamic parameters were recorded in real time, with a measurement documented every 4th s. The following five sets of hemodynamic data were analyzed: MAP, heart rate, right hepatic venous Pressure, portal venous pressure, and portal venous flow. Each set was analyzed with the following three different statistical methods:

1) repeated-measures ANOVA, 2) linear mixed models, and 3) time series analysis with the SiNoS method. For analysis with the two first methods, data were extracted from the real-time data material with exact 10-min intervals and analyzed using SPSS 13 for Windows statistical package. For analysis with the two first methods, data were extracted from the real-time data material with exact 10-min intervals and analyzed using SPSS 13 for Windows statistical package. *P* values ≤0.05 were considered statistically significant.

When analyzing with repeated-measures ANOVA, we studied within-group trends with within-subjects effects for time and group × time. Overall group difference was analyzed with between-subjects effects.

When analyzing with linear mixed models, we performed multiple local ANOVAs for consecutive 1-h time periods starting at *t* = 0 min (0–1 h, 1–2 h, etc.) and *t* = 30 min (30–90 min, 90–150 min, etc.) and for 2-h time periods starting at *t* = 0 min (0–2 h, 2–4 h etc.). We defined time as a fixed factor and subject as a random effect. As recommended by Marija and Norusis (11), an autoregressive AR1 covariance matrix was used. Time, group, and group × time interaction were tested.

To analyze all data points from the real-time data, we used time series analysis with the SiNoS method. Briefly, in SiNoS, the data are analyzed simultaneously for several time horizons by basing the inference on repeated tests along the time series, comparing the estimated parameters on consecutive segments of the series. The lengths of the segments represent the time scales for the analysis, and different lengths are used to detect changes on different time scales, making it possible to judge which scales seem to have the most meaningful interpretation. For a chosen test point, *t*₁, we perform two-sample hypothesis tests for the mean (μ), the variance (σ²), and the first lag autocorrelation coefficient (ρ), comparing estimated values in the two windows W₁ and W₂ on each side of *t*₁. The total length of the two windows W₁ and W₂ represents the scale for the analyses. For each scale, the hypothesis testing is repeated along the time series by sliding the two consecutive windows to the next chosen test point *t*₂. By applying different window lengths, potential changes are explored on different time scales. To avoid a large number of false detections, we adjust for multiple testing with the method of false discovery rate introduced by Benjamini and Hochberg (1). The pro-

![Fig. 1. Experimental layout.](http://ajpheart.physiology.org/)

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gramming software needed to run SiNoS may be freely attained by contacting Godtliebsen. See APPENDIX for a more detailed description.

RESULTS

We found repeated-measures ANOVA not well suited to analyze the datasets in the present paper. However, since it is a common method of statistical analysis, we will present the results of its analysis on one dataset (MAP).

Figure 2A shows curves representing a measurement of MAP every 4th s over a period of 9 h. The curves in both sham and aortoportal shunt groups are almost superimposed until shunt opening at 180 min (corresponding to measurement number (nr.) 2,800) where we observe an immediate and sustained fall in MAP in the shunt group. For the sake of illustration and comparison, a vertical line representing the time of aortoportal shunt opening is drawn through Figs. 1–7.

Figure 2B shows the plot of smooths derived from the Gaussian Kernel smoothing with different bandwidths, and the mean SiNoS plot (Fig. 2C) displays the corresponding significance in the MAP. Significant changes in the difference in MAP between the shunt and sham group are shown for the whole period of observation. The y-axis in Fig. 2C represents the window width of analysis and the x-axis the time points throughout the experiment. White areas depict time windows in which there is a statistically significant decrease in the MAP difference between the shunt and sham groups and black areas time windows in which there is a statistically significant increase in the MAP difference. Dark gray areas represent time frames of no statistical significant change and light gray areas time frames with too few data points for statistical inference to be made at the respective scale of analysis.

At window width 800 (on the y-axis of Fig. 2C) in the time period of measurement nr. 1,000–1,500, the MAP in the shunt group rises transiently above the MAP in the sham group (which is seen on closer inspection of Fig. 2A, in the time period of ~58–90 min). This pressure increase is flagged as significant, since there is a white area in the mean SiNoS map corresponding to this time period (Fig. 2C). Despite the statistical significance, the change probably only represents random pressure fluctuation. However, further on, in the time period measurement nr. 2,500 to nr. 3,200, the MAP difference changes again significantly in the opposite direction. By referring to Fig. 2A, we see that this corresponds to the fall in MAP in the shunt group when the shunt is opened. SiNoS analysis detects instantly the fall in MAP upon shunt opening. When the time frame is increased, the change in difference is also significant over a longer time period. For example, taking the window width 2,520 we see a significant change in MAP difference from shunt opening to measurement nr. 5,000, that is, if we take any time point from measurement nr. 2,500 to nr. 5,000 and compare the MAP of the preceding 168 min with the following 168 min, there will be a significant change in MAP difference from the first time period to the next. It follows from this that the steeper the changes in MAP difference, the smaller time frame needed to detect it.

Sampling MAP with 10-min intervals yields a somewhat similar picture graphically (Fig. 2D). In contrast to the ~8,000 data points used in Fig. 2, A–C, we are now dealing with 54 data points. As in the real-time raw data, several noise spikes appear, although fewer, and a fall in MAP in the shunt group at time point 180 min is seen corresponding to shunt opening.

Analysis of this dataset with repeated-measures ANOVA (Fig. 3) indicates significant within-subject effects of time ($P = 0.000$) and time × group interaction ($P = 0.008$). However, it is not until 260 min after shunt opening (at time point 440 min) that a significant difference in MAP trends in the two groups is detected (within-subject contrasts, $P = 0.042$). This is followed by a period of significant and nonsignificant within-subject contrasts until experiment termination, with significance values varying from $P = 0.029$ to $P = 0.044$. Analyzing between-group effects reveals no group difference. In other words, contrary to SiNoS analysis, repeated-measures ANOVA does not detect the fall in MAP upon shunt opening until 4 h has passed and only at a few and sporadic time points does ANOVA find significant group differences.

Performing local ANOVAs with a linear mixed model along the MAP dataset reveals significant group differences in the mean MAP in several time periods after shunt opening (marked with “G” for the respective time periods in Fig. 2D). Only from 40 to 100 min do we find a significant group × time interaction (marked with “GT” in Fig. 2D). This corresponds to the time period where SiNoS also detected a group difference (marked by a white area in Fig. 2C). Interestingly, mixed-models ANOVA performed over a 1- and 2-h time period immediately after shunt opening does not find a significant group × time interaction upon shunt opening, although the two curves split and stay so at this point (Fig. 2, A and D). We observe, however, that mixed-model ANOVA does find significant group differences over almost the entire period after shunt opening (Fig. 2D). We do, of course, believe that the group difference occurring after shunt opening found by SiNoS, mixed-models ANOVA, and partly repeated-measures ANOVA is biologically significant, since the MAP would be expected to fall upon opening a large central arteriovenous shunt.

Figure 4 shows the compensatory increase in heart rate (in the shunt group) upon shunt opening. SiNoS analysis reveals two statistically significant increases in heart rate (Fig. 4C), a primary response occurring immediately upon shunt opening at approximate measurement nr. 2,000 and a secondary increase in the period from measurement nr. 3,200 to 4,400. Significant changes in heart rate are detected here with time windows of 800 points, corresponding to 53 min before and 53 min after each time point. A decrease in pulse rate is seen toward the end of the experiment, denoted by the white areas in the mean SiNoS plot. The statistically significant increase in pulse rate is certainly biologically significant, since the fall in MAP triggers a vasoreactive increase in heart rate to increase cardiac output to restore the MAP. When extracting data at 10-min intervals and showing this data in a more “traditional” way, we observe the same main trends graphically (Fig. 4D). With mixed-model analysis, we find a group difference only in the period 200–260 min. Interestingly, in the time period from 300–360 min, this analysis finds a significant time trend, indicating that the heart rate decreases for both groups, whereas SiNoS analysis finds a decreased heart rate difference in the same period.

The pressure in the right hepatic vein remains relatively stable in both groups throughout the experiment (Fig. 5). An abrupt fall in pressure in the shunt group around the time of shunt opening is marked by a black area in Fig. 5C (from measurement nr. 800 to 1,100). We regard this as a biologically nonsignificant pressure fluctuation. However, later, it may be
observed that the pressure curve in the sham group gradually crosses the curve for the shunt group. Biologically, this makes sense, since the free (nonwedged) hepatic venous pressure will not be expected to fall in the part of the liver being shunted directly from the aorta because of the distending effect of the high flow rate. Testing with SiNoS reveals that the change is in fact significant over a wide time frame (window width 2,100–800; Fig. 5C). Mixed-models ANOVA of 10-min interval

Fig. 2. Mean arterial pressure (MAP) in shunt vs. sham series. A: MAP curves for the shunt (black) and sham (gray) groups based on real-time recordings over 9 h. B: plot of smooths. C: mean significant nonstationarities (SiNoS) plot for the difference in MAP between shunt and sham groups. D: MAP curves based on sampling every 10 min. Multiple, consecutive local mixed-model ANOVAs were performed on the 10-min sampled data. Significant group (G), time (T), and group × time effects (GT) are marked for the respective time periods where a significant ($P < 0.05$) effect was found. Red lines, 1-h periods starting at time ($t$) = 0 min; blue lines, 1-h periods starting at $t = 30$ min; green lines, 2-h periods starting at $t = 0$ min.
When analyzing the dataset sampled at 10-min intervals over a wide window width ranging from 2,400 to 240 (Fig. 5C). No group \times time interaction is found when testing in the period \( \sim 200 \text{–} 300 \) min, where the pressure curve for the sham group falls relative to the shunt curve (Fig. 5A; this corresponds to the period where SiNoS finds a significant pressure decrease in the sham group; white area in Fig. 5C).

Figure 6A shows averaged raw data of the portal pressure in the two groups. By inspection, we see that the portal pressure decreases gradually in the sham group relative to the shunt group. This is seen as it crosses the sham curve. (The fall in portal pressure is a reflection of the general decrease in MAP, cardiac output, and splanchinic flow observed in all animals because of prolonged anesthesia. However, the fall is not manifest in the shunt group since the left portal vein branch is ligated proximal to the aortoportal shunt in these animals, consequently increasing the portal pressure.) SiNoS analysis detects a significant change in the portal pressure difference over a wide window width ranging from 2,400 to 240 (Fig. 6C). When analyzing the dataset sampled at 10-min intervals with mixed-models ANOVA, we only find a significant time trend from 30 to 90 min since the pressure falls in both groups (Fig. 6D). The method does not detect the abrupt pressure fall at time point 300 min, where one would expect a significant group \times time interaction.

As outlined under MATERIALS AND METHODS, we also conducted two series of liver resections. As progressively more liver is removed during resection, the resistance to portal vein blood flow per gram of remaining liver tissue increases and, accordingly, the total flow decreases (Fig. 7). Resection is completed at time point 125 min, marked with a vertical line. The portal flow in the HPR group falls to a lower level under the surgical procedure. This is caused by the surgical manipulation and compression of vena cava inferior when resecting liver segments VI and VII necessary to accomplish the 72% resection in the HPR series. This has the effect of compromising the venous return to the heart, the cardiac output and splanchinic flow, and finally the portal flow. When the pressure on vena cava is relieved upon completion of resection, we observe a rebound effect in the portal flow in the high-pressure group as it increases and later levels out with the flow level in the low-pressure group. The hemodynamic effect of this manipulation is detected in the SiNoS analysis down to a window width of 240 (=16 min, marked by the open arrow in Fig. 7C). Mixed-model analysis does detect a trend for both groups the 1st h and a group \times time interaction at the time when the two curves cross at \( -40 \) min (Fig. 7D). This corresponds to the increasing pressure difference found by SiNoS and denoted by the black area between measurement nr. 300–800 in Fig. 7C. Mixed-model analysis does not, however, mark the rebound effect described above as significant. This shows that even transient hemodynamic changes can be detected with the SiNoS method.

**DISCUSSION**

This paper shows that SiNoS analysis of data in time series is potentially a very useful adjunct to repeated-measures ANOVA and linear mixed-models ANOVA because SiNoS analysis filters signals from noise, makes use of all data points, and permits analysis on multiple time scales. The method also offers an excellent visual presentation with the plot of smooths and the mean SiNoS plot. To our knowledge, this paper is the first to report on scale-space analysis of time series in circulatory research.

The above propositions are based on four observations in the present material: 1) the method’s plot of smooths gives good resolution of signal from noise, a great advantage when interpreting hemodynamic data from experimental surgery; 2) the method allows for analysis of all data points from real-time recordings, which seems to increase the ability to detect significant features in the material; 3) analysis with multiple scales of resolution facilitates a more differentiated observation of the material; and 4) the graphical display afforded by this method enables the researcher to appreciate the data in a more varied manner than is likely with more traditional graphics.

We can illustrate our first point on signals and noise by referring to the pressure curves from the right hepatic vein (Fig. 5). The real-time data show a gradual fall in the sham group, detected by SiNoS analysis as significant over a wide range of time windows (window width from 800 to 2,100; Fig. 5C). When sampling this dataset with exact 10-min intervals (Fig. 5D), several spikes appear in the dataset, giving the visual impression of abrupt and large pressure variations. This noise leads to large within-group variance, in turn influencing the statistical analysis; mixed-models ANOVA does not detect any group \times time interaction in the period from 200 to 260 min, where the pressure falls steadily in the sham group relative to the shunt group. The same may also be seen in Fig. 2D in the period from 320 to 360 min where no group difference is found.
because of the pressure spike in the shunt group. Mean SiNoS, under the null hypothesis, assumes that the observed data are multinormal. This is assumed to be reasonably satisfied in our situation, since mean SiNoS is applied to periodically averaged (binned) data. In our binning procedure, we have used 20 observations in each bin. Because the data contain spikes due to instrumental recording errors/noise, we have also run mean SiNoS on the same data where the spikes have been removed. The output from the mean SiNoS is approximately the same for the scales we are considering.

Fig. 4. Heart rate (HR) in shunt vs. sham series. A: HR curves based on real-time recordings over 8.5 h. B: plot of smooths. C: mean SiNoS plot for the difference in HR between shunt and sham groups. D: HR curves based on sampling every 10 min. Multiple, consecutive local mixed-model ANOVAs were performed on the 10-min sampled data. Significant group, time, and group × time effects are marked for the respective time periods where a significant ($P < 0.05$) effect was found. Red lines, 1-h periods starting at $t = 0$ min; blue lines, 1-h periods starting at $t = 30$ min; green lines, 2-h periods starting at $t = 0$ min.
Fig. 5. Right hepatic venous pressure (RHVP) in shunt vs. sham series. A: RHVP curves for the shunt (black) and sham (gray) groups based on real-time recordings over 7 h. B: plot of smooths. C: mean SiNoS plot for the difference in RHVP between shunt and sham groups. D: RHVP. Multiple, consecutive local mixed-model ANOVAs were performed on the 10-min sampled data. Significant group, time, and group × time effects are marked for the respective time periods where a significant ($P < 0.05$) effect was found. Red lines, 1-h periods starting at $t = 0$ min; blue lines 1-h periods starting at $t = 30$ min; green lines, 2-h periods starting at $t = 0$ min.
Fig. 6. Portal pressure (Pp) in shunt vs. sham series. A: Pp curves for the shunt (black) and sham (gray) groups based on real-time recordings over 8 h. B: plot of smooths. C: mean SiNoS plot for the difference in Pp between shunt and sham groups. Open arrow marks time point illustrating the sensitivity of short window width analysis. D: Pp curves based on sampling every 10 min. Multiple, consecutive local mixed-model ANOVAs were performed on the 10-min sampled data. Significant group, time, and group × time effects are marked for the respective time periods where a significant ($P < 0.05$) effect was found. Red lines, 1-h periods starting at $t = 0$ min; blue lines 1-h periods starting at $t = 30$ min; green lines, 2-h periods starting at $t = 0$ min.
Fig. 7. Portal vein flow (Pf) in liver resection series. A: Pf curves for the low-pressure resection (LPR) and high-pressure resection (HPR) groups based on real-time recordings over 8 h. B: plot of smooths. C: mean SiNoS plot for the difference in Pf between the LPR and HPR groups. D: multiple, consecutive local mixed-model ANOVAs were performed on the 10-min sampled data. Significant group, time, and group × time effects are marked for the respective time periods where a significant ($P < 0.05$) effect was found. Red lines, 1-h periods starting at $t = 0$ min; blue lines 1-h periods starting at $t = 30$ min; green lines, 2-h periods starting at $t = 0$ min.
The benefit of including all data points from the real-time recordings is exemplified in the analysis of MAP in the shunt vs. sham groups. The immediate fall in MAP seen upon shunt opening (Fig. 2A) is detected immediately with the SiNoS analysis (Fig. 2C) because this method employs sampled recordings of every 4th s. However, it is not until 10 min after shunt opening that a group difference is identified with mixed-models ANOVA. The effect of sampling frequency is also shown in the portal venous pressure data. The abrupt pressure change at $\sim$300 min (Fig. 6, A and D, marked by open arrows) is detected down to a window width of 240 measurements ($=16$ min) by SiNoS, but no group $\times$ time interaction is found with a local ANOVA in the same time window, based on a 10-min sampling frequency.

The benefit of analyzing the data at different levels of resolution is exemplified in the analysis of the pressure in the right hepatic vein and the portal vein (Figs. 5 and 6, respectively). Here we observe statistically significant differences in pressure trends in the sham groups as the pressure in the right hepatic and the portal veins gradually falls in these animals. The window width of significant change varies from 2,100 to 800 (Fig. 5) and 2,400 to 240 (Fig. 6). This means that the general trend of gradual decrease in both sham curves is detected on both long and short time scales. Notice how even the sudden fall in portal pressure at $\sim$300 min (marked with open arrow in Fig. 6A) is detected in the SiNoS analysis with a window width of 240 (at measurement nr. 4,990, marked with open arrow in Fig. 6C).

Finally, it is our opinion that the graphics afforded by this method (plot of smooths and mean SiNoS plot) are superior to traditional illustrations. The traditional line graph show trends and perhaps SE bars but do not include the multiscale analysis of significance included in the present method. The combination of group difference, time trends, and multiscale statistical analysis lets the observer quickly view and evaluate the material.

One could argue that evaluating the SiNoS method by comparing it with repeated-measures ANOVA is not a valid tool of assessment. As noted by Kristensen and Hansen (8) repeated-measures ANOVA may be suitable if the number of repeated measurements is small, and there are certainly many other statistical methods of analyzing repeated measures as, for example, area under the curve, linear and nonlinear mixed-effects model, and random intercept polynomial regressions. We have included repeated-measures ANOVA for comparison in this paper because this is, in our opinion, a widely used statistical method. However, as stated in the results, we chose to present only one dataset analysis with this method, since repeated-measures ANOVA is not suited to analysis of the type of datasets in the present study. We did however perform numerous local ANOVAS with a mixed-effects model, adjusting for the covariance structure and random effects. This method, although relatively time consuming compared with SiNoS analysis in our opinion, offers the investigator an excellent examination of within- and between-group trends with time, group, and group $\times$ time effects. However, neither mixed-models ANOVA nor the other methods described by Kristensen and Hansen allow for simultaneous analysis of time series on multiple scales like SiNoS does.

Finally, type I error is an important issue. We try to do a “global inference” in the sense that our aim is to get results where “the probability of rejecting null hypothesis ($H_0$) when $H_0$ is correct” is approximately equal to the significance level $\alpha$. As previously mentioned under statistical methods, when adjusting for multiple testing, SiNoS does not employ the often-used Bonferonni correction but the method of false discovery rate introduced by Benjamini and Hochberg (1). Simulation results from several stochastic processes indicate that the observed level for mean SiNoS is good as long as a reasonable (nonparametric) estimate of the autocovariance can be obtained. For the data in this study, we believe that the autocovariance is well estimated since 1) a positive correlation of autoregressive type seems to be present, 2) SiNoS performs well for autoregressive correlation structures, and 3) the findings in the SiNoS plots are very much in agreement with the behavior in the family plots. Furthermore, when examining the data after statistical analysis, one must bear in mind the various biological and technical explanations for the trends detected. When this is done, many trends falsely labeled statistically significant by SiNoS may be explained by viewing them in light of the experimental or technical intervention. This is exemplified in the discussion on the increase in portal vein flow upon completion of the HPR.

In conclusion, this study has shown that SiNoS analysis of time series is a very powerful statistical tool and may be used as a complement to conventional methods in evaluating datasets from circulatory research.

**APPENDIX**

The idea in SiNoS is to use sliding windows to search for changes in the mean, variance, or first lag autocorrelation of the time series. During this search, the data in the windows are assumed to follow a stationary Gaussian process. In the present paper, we only search for changes in the mean, i.e., we utilize the “mean part” of SiNoS. Because of this, our procedure is entitled mean SiNoS.

Let the time series under study be represented by $\{z_i, i = 1, \ldots, T\}$, where $z_i$ denotes the observed value at time point $ti$ and $T$ denotes the total number of observations in the time series. We assume that $\theta_1$ and $\theta_2$ denote the true values of the means in the two windows on each side of a test point. The following hypothesis

$$H_0: \theta_1 = \theta_2, \quad H_1: \theta_1 \neq \theta_2$$

test the mean at each test point. Let

$$x = (x_1, x_2) = (x_1, x_2, \ldots, x_{1,n}, x_{2,1}, x_{2,2}, \ldots, x_{2,n})$$

represent the true vector of observations in the two windows, where $n$ denotes the sample size in each window. When the null hypothesis is correct, the vector $x$ is assumed to be multinormal. We apply the following test statistics

$$T_\mu(x_1, x_2) = \frac{\bar{x}_1 - \bar{x}_2}{s'}$$

where

$$\bar{x}_i = \frac{1}{n} \sum_{j=1}^{n} x_{ij}$$

and

$$s'^2 = \frac{1}{n-1} \sum_{j=1}^{n} (x_{ij} - \bar{x}_i)^2$$

denote the ordinary sample estimators for the means and variances in the two windows to be compared, $i = 1, 2$. $T_\mu$ = Test statistic for a
given testpoint \( x = (x_1, x_2) \), \( s_p^2 \) = Variance of the pooled sample, and \( x_{ij} = The j\text{th} \) observation in the i\text{th} time window. Given the null hypothesis, a common variance for the two windows is assumed and estimated by the pooled estimator

\[
s_p^2 = \frac{s_1^2 + s_2^2}{2}
\]

Accurate approximations for tail probabilities of the test statistics can now be found by a saddlepoint method when the vector \( x \) is multi-normal. Note that this means that the data, under the null hypothesis, follow a stationary Gaussian process.

For each scale, we do numerous tests along time in mean SiNoS. To avoid a large number of false detections, we therefore adjust for multiple testing. In SiZer, various suggestions are given to get an overall significance level of 0.05, whereas in SiNoS, the method of false discovery rate introduced by Benjamini and Hochberg (1) controls the number of false rejections of the null hypothesis. The performance of SiNoS is good (in terms of type I error) for a broad range of stochastic processes as long as a reasonable estimate of the covariance structure in the data set can be obtained.

Finally, the SiNoS method may be employed in both balanced and unbalanced designs, since it is the mean value within each group at each time point that is used in calculations. However, the present version cannot handle missing data.

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