# Using non-stationary extreme value analysis to characterize blood glucose curves

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***Abstract*—Introduction: The application of extreme value statistics provides a novel way to characterize the risk of high blood glucose levels. Its statistical methodology works well for dependent data, but the impact of non-stationarity is unclear.**

**Material and Methods: 14.7 million blood glucose measurements from 225 patients were analyzed with stationary and non-stationary extreme value models. In case of the latter, the location parameter was allowed to vary with time using spline expansion to allow for a flexible, data-driven functional form.**

**Results: Estimated scale and shape parameters were almost identical (correlation $> 0.99$) and estimated location was also similar (correlation $= 0.9$). One-year return level and estimated time spent in a year above the clinically relevant threshold of 600 mg/dl was also very similar, and estimated time spent above 400 mg/dl was similar with the exception of a single patient, who had much higher value with the stationary model.**

**Discussion and Conclusion: Non-stationary extreme values models can be applied to analyze blood glucose measurements with the aim of measuring the risk of hyperglycaemia. Obtained results are similar to those with stationary models, but whether it is possible (and if so, to what extent) that the estimated long-term trend in location picks up some effect of true extremity requires further investigation.**

***Index Terms*—extreme value, non-stationary, spline, blood glucose.**

## I. Introduction

Extreme value statistic (EVS) investigates the properties of the extremities (minima or maxima) of a set of random variables, thus finds important applications in engineering, finance and climatology, among others [1]–[3]. Applications in biomedicine are however much less numerous, despite the fact the such extremities play an important role in physiological and pathophysiological process, the reason being primarily the unavailability of sufficient quantity of measurement (i.e., the lack of long-term and/or high frequency measurements).

One exception is diabetology, where the introduction of continuous glucose monitoring (CGM) made the collection of adequate time series data possible: CGM sensors can record blood glucose (BG) levels with adequate precision for a long period, typically with 5 minute sampling time [4]. Szigeti et al investigated how EVS can be applied to such data, and how results compare to those obtained with traditional methods that describe glycaemic variability [5].

Classic results from EVS employed in the Szigeti et al paper, including the central result of this field, the Fisher-Tippet-Gnedenko theorem [6] assume independent and identically distributed (iid) random variables, whose maximum (or minimum) are considered. Real-life time series data, including relevant biomedical data are often not iid however.

Two aspects have to be considered. The first is stationarity: a time series is stationary in the strong sense of the word if every finite dimension marginal distribution is shift invariant, i.e., for any $n > 0$ and for any $i_1, i_2, \ldots, i_n$, the joint distribution of $X_{i_1}, X_{i_2}, \ldots, X_{i_n}$ is the same as the joint distribution of $X_{i_1+h}, X_{i_2+h}, \ldots, X_{i_n+h}$ (assuming that the indices are all valid) [7]. Stationarity is important, because – along with ergodicity – it allows the estimation of parameters from time series data, in spite of having a single realization. Strong stationarity however is rarely used is practice: typically a weak form is employed, where $n = 2$ and instead of the complete equality of the distributions only the equality of the first two moments is required. It is easy to check that it boils down to three conditions: time-invariant mean, time-invariant variance and autocorrelation function only depending on the lag [7]. The second aspect is that even if the data are stationary, there might be temporal dependence, i.e., non-zero autocorrelation, which is entirely possible for a stationary time series, see the definition above, but also violates the iid assumption. How and to what extent these two violations violate the Fisher-Tippet-Gnedenko theorem and the EVS approach based on it is a complex question [1].

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The paper of Szigeti et al discussed this latter aspect, i.e, how to handle time series that are dependent. In brief, the block maxima (BM) method that is applied in that paper is largely resistant to dependence: local dependence is not a concern – in contrast to the peak-over-threshold approach – and global dependence is also subject to only weak restrictions (to so-called Leadbetter $D(u_n)$ condition [8]) so that original results can be still applied. This is due to the fact that if this condition is satisfied, the distribution of the extremum will still follow the same family of distribution as in the Fisher-Tippet-Gnedenko theorem. The parameters will be different compared to what could be obtained if the series were iid, but as the parameters are estimated from the sample anyway, it poses no problem [1].

However, Szigeti et al does not discuss the second concern: the possible non-stationarity of the time series. This is due to the fact that the appropriate analysis in this case is much less straightforward, there is no clear theorem as for the dependent – but still stationary – case, and the whole approach is much more heuristic [1], [9], [10]. Yet, in the last decades, several application focused specifically on non-stationary extreme value (NEVA) analysis [11]–[13]. The traditional solution is to make the – shape ($\xi$), scale ($\sigma$) and location ($\mu$) – parameters of the resulting extreme value distribution to be functions of certain covariates (instead of being constants) [14], [15]. The inclusion of appropriately chosen covariates, so that the result is stationary *after* covariates are accounted for is the usual approach to handle non-stationarity. (This bears resemblance to the detrending of time series: instead of fitting a trend and subtracting it from a time series, one could simply add the trend to the list of covariates that are later used for modeling to achieve the same goal [16].)

Here, covariate is time, and "appropriately chosen" means the proper specification of the functional form for time. For instance, many applications [17], [18] prefer the simple linear dependence in location $\mu = \mu_0 + \mu_1 t$, with the scale and shape being time-invariant. One could also imagine more complex functional form, such as higher-order polynomial [13], change-point model, or even a sinusoidal (harmonic) one [19]. While even more complicated structures could be considered [20], a statistically tempting – rather flexible, data-driven, without the assumption of any parametric functional form, yet using few degrees of freedom – solution is the application of splines, i.e, the expansion of the time with splines [21].

To re-analyze the data of Szigeti et al, only such approach makes sense, as it is obviously not meaningful to assume linear relationship. Splines have already been used for this aim [22], [23].

One elegant way to incorporate the spline expansion as the functional form for the time-varying parameter is to integrate this into the framework of the vector generalized additive models (VGAM), as described by Yee and Stephenson [24].

The present paper investigates the possibilities of applying such approach to a large BG measurement database used by Szigeti et al to better understand extremes of BG levels that is a fundamental aim in the study of diabetes.

## II. Material and Methods

### A. Patient data

Data from the REPLACE-BG study were used [25] as provided by the T1D Exchange [26] network was used in the present investigation. This database consists of 14.7 million CGMS measurements of 225 patients (with a median duration of 33 weeks) with Type I diabetes and using insulin pump. The sampling frequency was 5 minutes using Dexcom G4 Platinum CGM device (Dexcom, San Diego, CA).

### B. Checking dependence and stationarity

Stationarity was checked with augmented Dickey-Fuller (ADF) test [27], Kwiatkowski–Phillips–Schmidt–Shin (KPSS) test [28] and Phillips–Perron (PP) test [29]. Note that these are all unit root tests, hence they test stationarity only if explosivity is ruled out.

### C. Non-stationary extreme value analysis with splines

Data were modelled with a VGAM model using either no covariate (i.e, intercept-only model, corresponding to stationary analysis) or the spline-expanded time. In the latter case, only location was allowed to be varying, scale and shape was fixed in both cases. The link function was the identity for the location, logarithm for the scale and offset logarithm with an offset of $0.5$ for the shape.

Intercept-only and spline models were statistically compared with deviance test.

The values of $\mu$, $\sigma$, and $\xi$ were extracted from both models. In case of the spline model, the intercept was extracted, which – as splines are zero-centered – can be considered to be an "average" location parameter.

Clinically relevant metrics for the risk of hyperglycaemia, as suggested by Szigeti et al, namely one-year return level (BG level that is likely exceeded once in a year), and estimated hours spent in a year above the clinically important thresholds of 400 and 600 mg/dl were also calculated.

### D. Programs used

Calculation were carried out under the R statistical environment version 4.1.2 [30] using package VGAM version 1.1-5 [31].

## III. Results

The final (hourly maxima) dataset consisted of 225 patients, with a total of 1,256,235 observations.

The distribution of test statistics over these patients using all three types of stationarity tests are shown on Figure 1.

Every ADF and every PP test was significant, and 64% of the KPSS tests were significant at 0.05 significance level.

Comparison of the results with the stationary and the non-stationary models obtained for the three parameters and the three clinically relevant hyperglycaemia risk indicators is shown on Figure 2.

The correlation between the results from the two models is $> 0.90$ (linear correlation) and $> 0.89$ (Spearman-$\rho$).

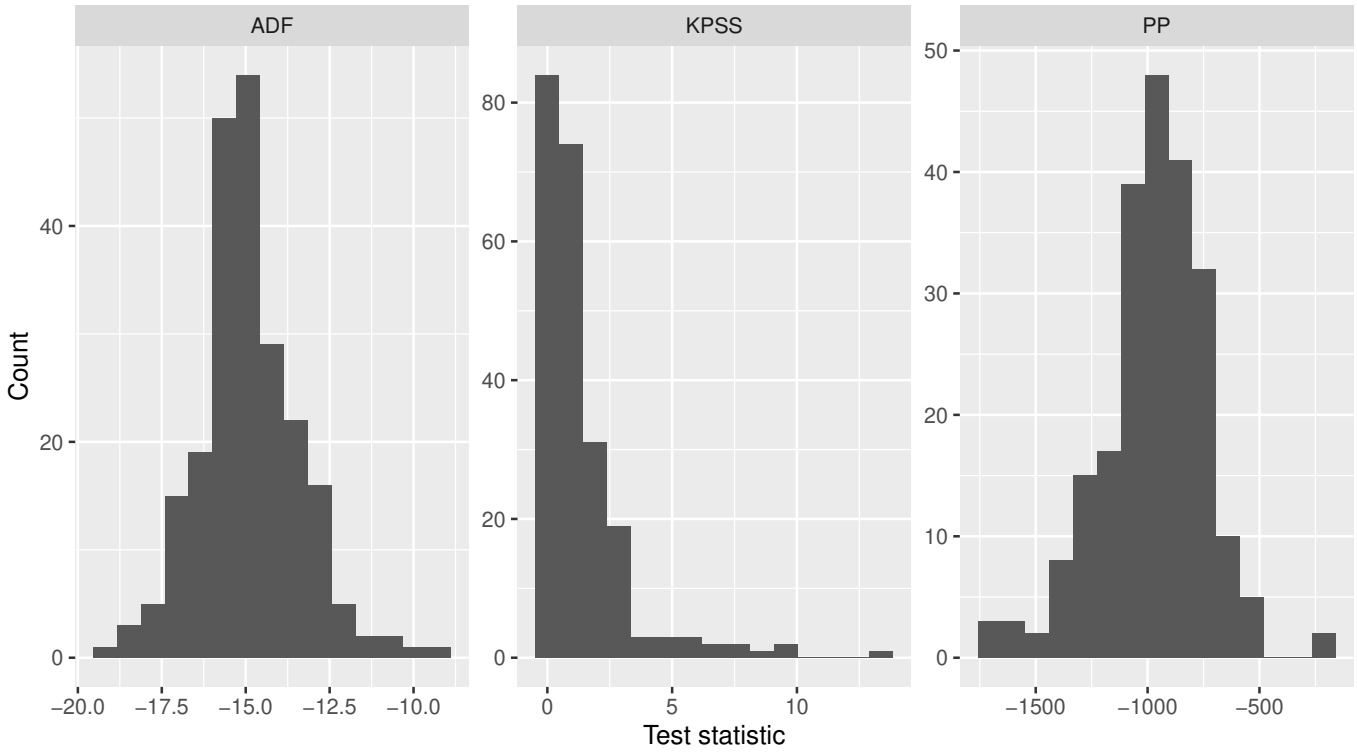


Fig. 1. Distribution of the test statistics of augmented Dickey-Fuller (ADF) test, Kwiatkowski–Phillips–Schmidt–Shin (KPSS) test and Phillips–Perron (PP) test.

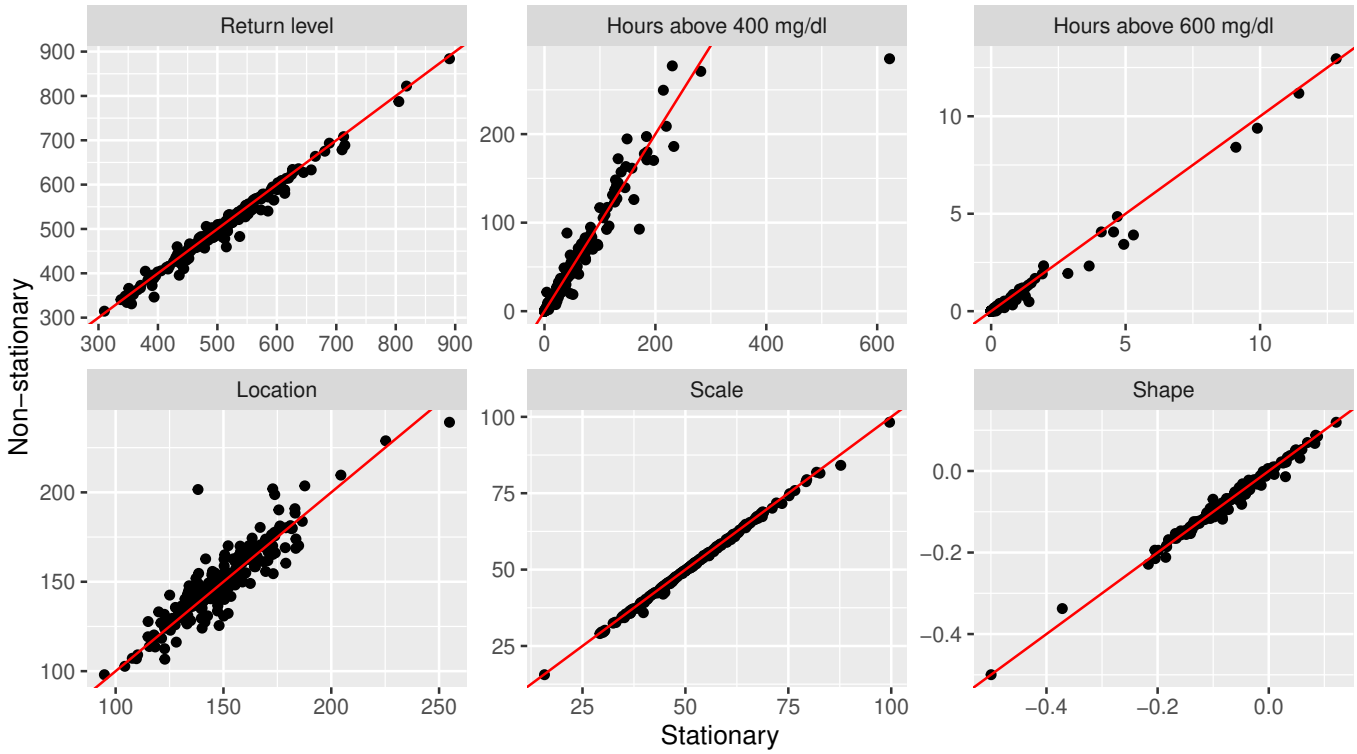


Fig. 2. Scatterplot of the parameters and clinically relevant hyperglycaemia risk indicators between the intercept-only model (horizontal axis) and the non-stationary model using varying location with spline expansion of time (vertical axis).

The single patient were there is a visually obvious discrepancy (in estimated time spent above 400 mg/dl) is patient #186. The estimated scale parameters are very close (99.59 for the intercept-only model and 98.23 for the spline-model) and the shape parameters are virtually identical (-0.4995 and -0.4997). The difference lies in the location parameter which was estimated to be 254.82 in the intercept-only model and 239.21 in the spline-expanded non-stationary model.

Deviance test found significant difference at 0.05 significance level for all, but one case.

## IV. Discussion and Conclusion

The present investigation proves that the reliable estimation of non-stationary models for BG measurements, as an extension to the framework provided by Szigeti et al [5] is possible.

It also suggests however, that the differences are likely small between the two approaches. In particular, differences in return level were between -55.5 and +27.6 mg/dl (relative differences: -12.0% to +6.8%), they were between -337.1 (but only -78.5 with a single outlier removed) and +47.6 hours for the estimated time spent above 400 mg/dl and between -1.5 and +0.38 hours for the estimated time spent above 600 mg/dl.

The estimated scale and shape parameters were almost identical (correlation $\geq 0.99$). These were, however stationary in both models. The handling of the location parameter was different, but estimated parameters (a sort of time-average for the non-stationary model) was nevertheless similar (a correlation of 0.9).

It should be noted that statistical testing of stationarity is close to meaningless at this sample sizes: tests are so powerful that almost always leads to the rejection of the null hypothesis. (Most clear from the completely opposite answers given by the ADF and the PP test.) This also pertains to the interpretation of the results of the deviance test.

It is also important to note that one can not choose between stationary and non-stationary models based on a test performed on the same sample. This would give rise to the same problems as with pre-testing (akin to deciding whether to use test assuming normality based on a normality test).

The present study employed the elegant, unified framework of VGAMs. It should be noted however, that are approaches are also possible, such as the Bayesian estimation of such models [32].

We note that there are other possible approaches to the whole problem of managing non-stationarity, including "manual detrending" (as with fitting and subtracting the trend in our time series detrending analogy) [33]–[35].

The most important limitation of the present approach, that is worthy of further investigation is whether it is possible (and if so, to what extent) that the long-term trend in location picks up some effect of true extremity. Based on how wiggly the estimated trend is, the two might be confounded. (As an extreme example, consider a "smoother" which exactly follows the data – removing this would entirely remove the information on extremities too.) This likely depends on how well the applied smoothing is able to pick up the true underlying trend (and therefore non-stationarity) from the data.

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