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A New Paradigm For Predicting Past And Future Out of Control Events In Internal Quality Control: Gaussian Process For Machine Learning

İç Kalite Kontrol Süreçlerinde Geçmiş ve Gelecekteki Kontrol Dışı Olayları Tahmin Etmede Yeni Bir Paradigma: Makine Öğrenimi için Gaussian Modeli

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Abbreviations:

IQC: Internal quality control

TAE: Total analytical error

TEa: Total allowable error

GPR: Gaussian process regression

GPML: Gaussian process for machine learning

PQCA: Predictive quality control algorithm

CI: Confidence interval

OOCE: Out-of-control event

FSH: Follicle stimulating hormone

SD: Standard deviation

TAEp: Predicted total analytical error

RBF: Radial basis function, a.k.a squared exponential covariance function

TAEp: Total analytical error-predicted

ABSTRACT

Internal Quality Control (IQC) is the process of evaluating and controlling the reliability of a laboratory test before running patient samples. Currently used IQC process focus on the management of Total Analytical Error (TAE) using rule-based approaches. The process cannot predict timings of Total Allowable Error (TEa) violations, precisely. In the study, we proposed a predictive computational approach for IQC, Predictive Quality Control Algorithm (PQCA), to solve with this problem using Gaussian Process for Machine Learning (GPML) method. The software implementation carried out in Python and Scikit-learn library running

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on a standard Windows-based PC. A digital control chart based on PQCA was introduced. It is demonstrated that observations fall within the 95% confidence intervals of their corresponding predictions generated by PQCA. It also presented that TAE calculated using classical formula is unable to capture all violations of TEa. PQCA is a simple procedure that can directly relate raw control data to quality targets and enabled a predictive approach with a high degree of accuracy. The classical TAE calculation model is based on a univariate Gaussian model. GPML, which PQCA is based on, is generalized by a multivariate Gaussian. Therefore, PQCA can be viewed as a generalization of the classical IQC model. Using PQCA, laboratories can take a proactive approach to the control of analytical quality, meet regulatory institutions' requirements, and hence provide better patient outcomes. PQCA based IQC can achieve controlling of analytical variability using a single algorithm overcoming the shortcomings of conventional methods. In the future, newly available computational models make possible more sophisticated, predictive mathematical frameworks for IQC.

ÖZET

İç Kalite Kontrol (İKK), hasta numunelerini çalıştırmadan önce bir laboratuvar testinin güvenilirliğini değerlendirme ve kontrol etme sürecidir. Mevcut İKK süreci, kural tabanlı yaklaşımlar kullanarak Toplam Analitik Hatanın (TAE) yönetimine odaklanmaktadır. Toplam İzin Verilebilir Hata (TEa) ihlallerinin zamanlamasını tam olarak tahmin edemez. Çalışmada, Tahmine Dayalı Kalite Kontrol Algoritması (PQCA) için Gaussian Process for Machine Learning (GPML) yöntemini kullanarak İKK sürecini değerlendirmede tahmine dayalı bir hesaplama yaklaşımı önerildi. Python ve Scikit-learn kütüphanesinde yürütülen yazılım uygulaması, Windows tabanlı standart bir PC üzerinde çalıştırıldı. PQCA'ya dayalı bir dijital kontrol tablosu oluşturuldu. Gözlemlerin, PQCA tarafından üretilen karşılık gelen tahminlerinin %95 güven aralığı içinde kaldığı gösterildi. Ayrıca, klasik formül kullanılarak hesaplanan TAE'nin tüm TEa ihlallerini yakalayamadığı da ortaya konuldu. PQCA, ham kontrol verilerini doğrudan kalite hedefleriyle ilişkilendirebilen basit bir prosedür olup, yüksek derecede doğrulukla tahmine dayalı bir yaklaşım sağlamıştır. Klasik TAE hesaplama modeli, tek değişkenli bir Gauss modeline dayanır. PQCA'nın temel aldığı GPML, çok değişkenli bir Gaussian modeldir. Bu nedenle PQCA, klasik IQC modelinin bir genellemesi olarak görülebilir. Laboratuvarlar, PQCA'yı kullanarak analitik kalitenin kontrolüne proaktif bir yaklaşım getirebilir, düzenleyici kurumların gereksinimlerini karşılayabilir ve dolayısıyla daha doğru ve güvenilir hasta sonuçları sağlayabilir. PQCA tabanlı İKK, geleneksel yöntemlerin eksikliklerinin üstesinden gelen tek bir algoritma kullanarak analitik değişkenliğin kontrolünü sağlayabilir. Gelecekte, yeni kullanılabilir hesaplama modelleri, İKK için daha karmaşık, tahmine dayalı matematiksel çerçeveleri mümkün kılacaktır.

INTRODUCTION

Laboratory tests play a main role in the diagnosis, treatment, and prognosis and constitute a principal part of electronic patient records. For this reason, accuracy and repeatability, two basic parameters that demonstrate the performance of laboratory tests, should be guaranteed. When the accuracy and repeatability of a measurement system do not change, or the range of the measurement series is called "analytical run" according to the Clinical & Laboratory Standards Institute guideline C24-A2 (1). It is the utmost 24 hours for biochemical tests as declared by Clinical Laboratory Improvement Advisory Committee (CLIA)(2).

Internal Quality Control (IQC) is an evaluation process of the laboratory's reliability using quality control materials with different levels of analyte concentrations before running patient samples, i.e. before each run, and whether the result is within the acceptable range. In particular, it aims at controlling the analytical processes in use. In the process, "quality control charts" used, which are historically similar to those employed in the industry. The most well-known charts are Levey-Jennings control charts, with mean target and standard deviation (SD) limits. In routine, IQC result from each run are marked on the charts, at how many SDs from the target value. Westgard multi-rules are most often used in medical laboratories to evaluate the IQC results (3). For tests with different analytical performance, it is not very practical to use the fixed rules. Therefore, it is recommended using "individualized quality control rules" according to the analytical performance of each test. To prevent non-standardized IQC assessment of laboratory staff from these assessment challenges, many laboratories prefer to use the a few of Westgard multiple rules rather than all.

IQC is based on the acceptance or rejection of the distance (bias) of the control results in the run; however the power to show repeatability is somewhat weaker. For this reason, in addition to IQC applications, total analytical error (TAE) is monitored to determine analytical performance in clinical laboratories (4). TAE is the combination of bias and precision, and is calculated by the formula as bias ± 1.65 CV%. Therefore, it is a common practice to use as a quality indicator for test performance (4). It has also become the focus of routine IQC work conducted regularly at many clinical laboratories.

TAE is primarily used to characterize the past analytical performance of clinical laboratories by regulatory bodies. Laboratories need to ensure the future performance of their analytical systems so that future analytical errors lie within Total Allowable Error (TEa). TAE's current formulations do

not adequately mitigate these two diverging needs. In particular, the following issues need to address:

a. Current methods used in practice to compute TAE summarize the past performance of analytical systems. They do not offer any formal inference procedures for predicting the performance of analytical systems for a specific point in the future.

b. In theory, TAE might exceed the allowable limit at any time point. That is called an out-of-control event (OOCE). In cases an OOCE has been identified to occur at a control measurement point, the current IQC procedures do not offer any support to determine the certain moment when this OOCE might have started.

c. In Levey-Jennings chart, as one of the most widely used IQC tools, the acceptable limits are usually defined as two SDs, in each direction. Manufacturer based SD limits are often wider than the TEa limits currently used in practice (5). Consequently, control results accepted in routine practice, based on Levey-Jennings charts, may be classified as unacceptable based on TEa.

In the 1970s, Westgard used power-function curves when defining rules that set OOCEs. However, high-capacity central processors, graphics processors, and artificial intelligence software tools were not available in those years. However, we have high-capacity hardware and software support with artificial intelligence today. In the study, we aimed to propose a computational framework, "Predictive Quality Control Algorithm (PQCA)", which is a generalization of TAE and captures the temporal aspects of the data, to overcome all of the above shortcomings of the current approaches. This new algorithm is designed to enable laboratories to take corrective actions in case of past OOCEs and to take preventative actions in case of future OOCEs through predictive capabilities and, hence a heightened level of readiness, and a new problem-solving capability are provided to laboratories.

MATERIALS AND METHODS

Routine IQC data from the database of the clinical laboratories at XXX Training and Research Hospital were retrospectively used in the study. No patient data was reported based on the findings of this study. The study was conducted by following the Helsinki Declaration, and the approval of the local ethics committee of XXX Training and Research Hospital (Decision No: 14/20, 2017) has been obtained.

A total of 10 analytes included in this work: aspartate aminotransferase, calcium, creatinine, glucose, sodium, CA 15.3, cortisol, follicle-stimulating hormone (FSH), insulin, testosterone, thyroid stimulating hormone, and vitamin B12 (see Table 1). These analytes have been chosen for the following reasons; a) to represent photometric, potentiometric, and immune-chemical assays, b) because they are common and easily recognizable. Each collected data was evaluated by two medical biochemistry specialists, one for each biochemical and immunochemical test group. IQC data was normally checked against non-analytical errors, e.g., human errors, marked if found to be erroneous and the control measurement was repeated. Data marked as erroneous were not included in the study. TAE is the combination of bias and precision, and is calculated by the formula as bias ± 1.65 CV% (4).

Table 1. Analytes evaluated within the scope of the study.

Analyte	Units	Analyzer	Method	IQC Product Specifications
AST Ca CREA Glc	U/L mg/dL mg/dL mg/dL	AU 5800 Beckman Coulter Inc., CA, USA	Spectrophotometric	Beckman Coulter Control Serum Level 1 and 2, Catalogue Number ODC0003-ODC0004, Lot Number 0037-0038
Na	mmol/L	AU 5800 Beckman Coulter Inc., CA, USA	Indirect potentiometric	Beckman Coulter Control Serum Level 1 and 2, Catalogue Number ODC0003-ODC0004, Lot Number 0037-0038
CA 15.3	U/mL	UniCel DxI 800 Beckman Coulter Inc., CA, USA	Chemiluminescence	MAS T-Marker Liquid Assayed Immunoassay Control Level I and II, Catalogue Number TUM-101- TUM-202, Lot Number TM19061- TM19062, Thermo Fischer Scienfic Inc., MA, USA
Cortisol Insulin Testosteron TSH Vitamin B12	µg/dL µIU/mL ng/dL µU/mL pg/mL	UniCel DxI 800 Beckman Coulter Inc., CA, USA	Chemiluminescence	MAS Liquimmune Liquid Assayed Immunoassay Control Level I and II, Catalogue Number LIG-101- LIG-202, Lot Number LIA20041- LIA 20042, Thermo Fischer Scienfic Inc., MA, USA

AST: aspartate aminotransferase; Ca: calcium; CREA: creatinine; Glc: Glucose; IQC: internal quality control; Na: sodium; TSH: thyroid stimulating hormone.

Gaussian Process for Machine Learning (GPML) (6) was used as the formal basis of the predictive model proposed in this work. GPML's computational implementation was performed using Python 3.6.2 and Sci-Kit Learn Library 0.19.1 (7). A 64-bit Windows 10 machine (Intel i5 5200-U, 12 GB RAM) was used to run experiments reported in this article. Gaussian Process For Machine Learning

GPML is an extensive machine-learning algorithm for solving time-series-based medical problems (8-10). GPML is proposed as a probabilistic model to capture the generative process of control measurement variability. The selection of GPML is justified based on the fact that clinical laboratory control measurements are widely assumed to be normally distributed (1). This makes GPML an ideal candidate for our purposes as it is generalized by a multivariate Gaussian. The mean vector and the covariance matrix K together define multivariate Gaussian, uniquely. In GPML, the covariance between two points in the time series of control measurements is defined by a positive definite kernel function k. For two output-input pairs, (y, t) and (y′, t′), the kernel function defines K (y, y′) = k (t, t′). Given a set of training observations y, t the distribution of test points y*, t* is

p(y*|y) ~ N(*, Σ), (Equation 1)

such that

* =K (t*, t) K (t, t)−1y, (Equation 2a)

Σ = K (t*, t*) − K (t*, t) K (t, t)−1K (t*, t)T (Equation 2b)

The kernel k is a function whose behavior is governed by a set of hyper-parameters.

A kernel function is used to compute the covariance matrix. Thus, it plays a major role in the success of the GPML model. Although mathematically a vast number of kernel functions can be defined, the kernel function to be used for a specific analytical method needs to be consistent with the data observed. In Figure 2, PQCA output was shown for the same data as in Figure 1 except that the kernel function is chosen to be Matern instead of Radial Basis Function (RBF) (11). A close look at the two figures could show differences in details.

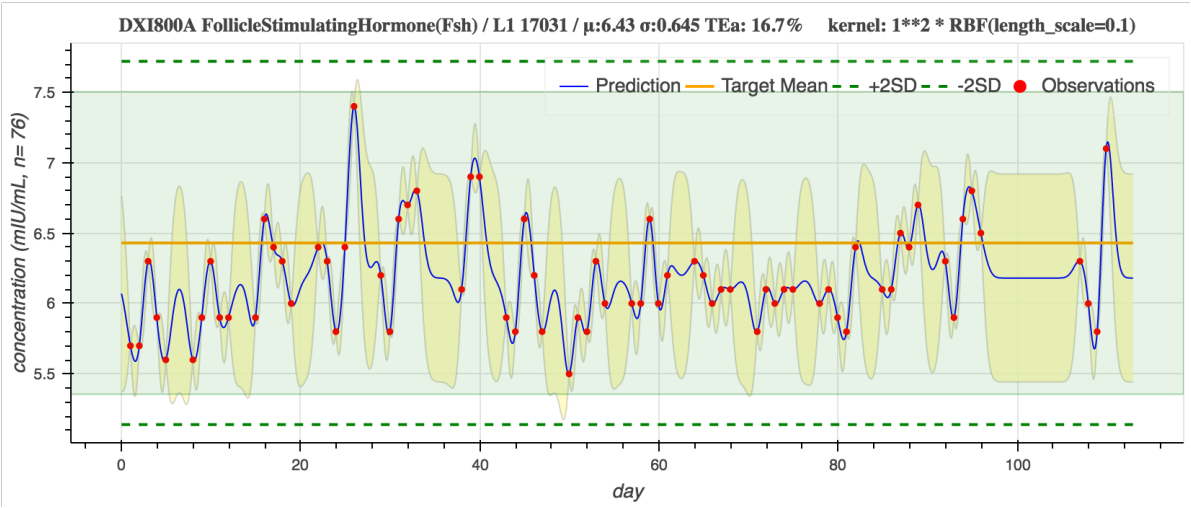

Figure 1. A Digital control chart for FSH level 1 control data

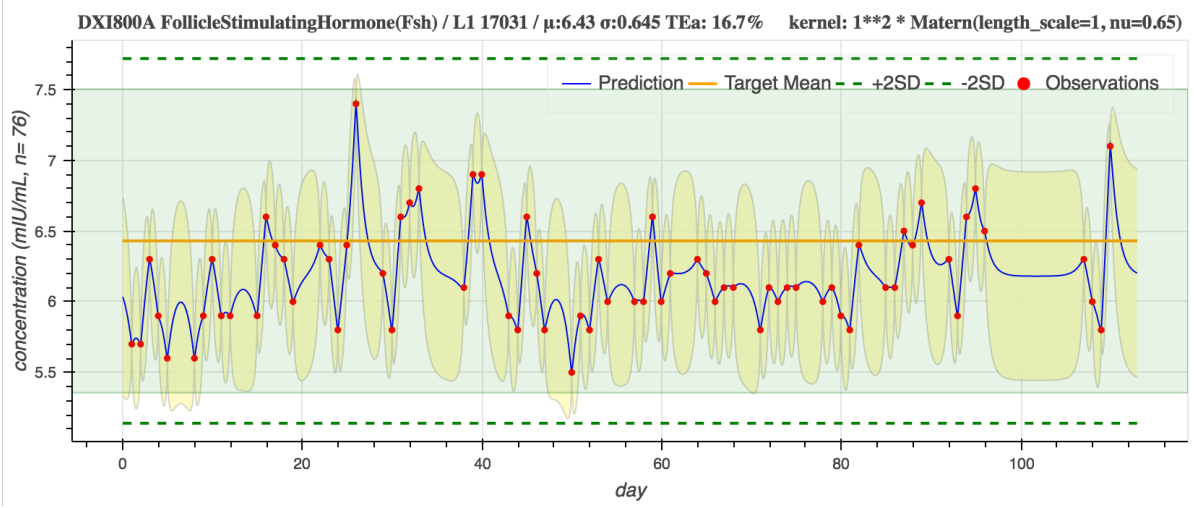

Figure 2. FSH level 1 control data processed using Matern kernel function

In control measurement time-series data, systematic errors in the analytical processes may cause bias or drift. GPML natively supports tracking of bias or drift in the mathematical model.

Equations 2a and 2b form the basis of GPML inference which enables the prediction of y* after observing data (t, y), thus updating prior beliefs about points t*. As the GPML enables us to predict complete functions over the space of t, it also provides us both with mean predictions and with associated measures of uncertainty. In many cases of analytical methods, though, we observe some noise-corrupted versions of data. In other cases, where GPML over-fits the data, we might want to introduce some terms into the predictive equations to condition the data. Although in this article we will not be diving into these issues to keep our argument focused on the core issues, GPMLs can easily be extended to allow for Gaussian noise models of various sorts.

A digital control chart was prepared for each control material and was presented to the user through a computer (Figure 1). The chart displayed measured concentration on the vertical y-axis vs. time on the horizontal x–axis (x–the axis was the time axis and was denoted as ' t-axis' where time values were given relative to the start date which was the origin of the t-axis). The target mean value, provided by the manufacturer of the IQC material, was drawn as a solid (orange-) horizontal line. Dashed (green-) horizontal lines, also provided by the manufacturer, represented two SDs (1.96 to be exact) from the target mean value in each direction. The shaded (light green) area in the middle marked the TEa. TEa value was set at 21.19% (5) above and below the target mean s which the current approach is based on a control limit. Prediction point using all data observed and predicted (TAEp) value, referred to in this article as upper and lower control limits, for the control material which in this case was FSH, level 1. At the top of Figure 1 were the name, the kit number, the numerical values for the target mean, the target SD, and the TEa set for the control material. Kernel information was placed at the top right and will be reviewed in detail in the following section.

Measured control results were called observations, whereas data predicted were called predictions. Observations were marked as solid (red-) dots on the chart. The continuous solid (blue-) curve consists of the predictions made. Symmetrically shaded (yellow-) areas on each side of the blue curve showed 95% confidence intervals (CI)s of predictions. 95% CI limits permit the use of simple decision criteria as will be presented later.

Prediction curves and 95% CIs were graphed on the digital control chart. OOCE's were defined to be those points where 95% CI limits overflow the control limits. Predictions and CI limits can help identification of TEa violations (OOCE's) which may be in the past or the future of the analytical process under study. An OOCE occurred when CI limits exceeded control limits (TEa lines) in any direction. OOCEs that fall on the right-hand side of the current observation point were called future OOCEs and OOCEs that fall on the left-hand side of the current observation point were called past OOCEs. In Figure 1, one example of an OOCE could be observed between the 5th and the 6th observations (days 4–8) where CI limits go below the lower control limit and another one could be observed after the 20th observation (days 24-28).

In the case of OOCE's in the past, points that lie on the left side of the active point, of the analytical process under study, recovery and correction procedures were recommended to be started. In the case of future OOCE points, points that lie on the right side of the current observation time, either a new observation was planned for just before the first future OOCE or immediate corrective action was started.

PQCA presented below was activated each time a control result is observed, per control material. The definition of PQCA:

1. Is the current observation corrupted by non-analytical causes, e.g., using the wrong vial? If yes, reject the current observation and repeat the control measurement.
2. Run the GPML algorithm to generate a control chart using all data accumulated so far for the control material. The output of GPML is an entire prediction function for the specified range of time. Also in the output are the associated 95% CIs for predictions.
3. Note on the chart, periods where 95% CI limits are not contained fully within upper and lower control limits. Call these periods OOCE.
4. For OOCE's with time periods smaller than the time of the current observation, which is OOCE's in the past of the analytical process, start the laboratory's review procedure (not described in this article) for patient results generated during these OOCE periods.
5. For predicted OOCE's, which are in the future of the process, either start corrective action immediately or schedule another control measurement for a time point well before the first OOCE is predicted to occur.

RESULTS

The PQCA algorithm is defined and a digital control chart is introduced in the materials and methods section. PQCA is applied to each control level of 10 analytes chosen for this work. Similar conclusions are reached for the other analytes included in the study. Results are presented for FSH as a representative.

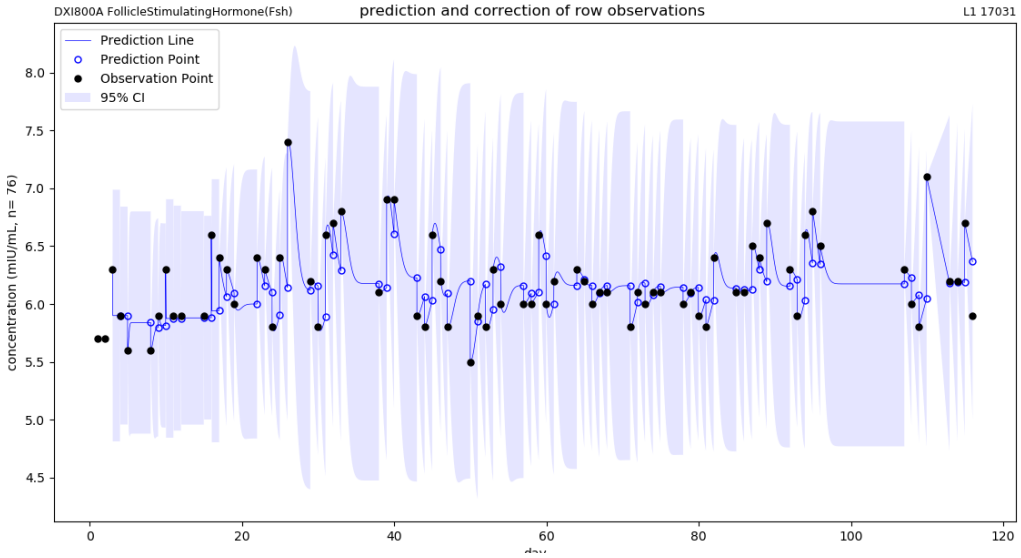

Figure 3. Prediction-observation pairs for FSH Level 1 kernel function testing

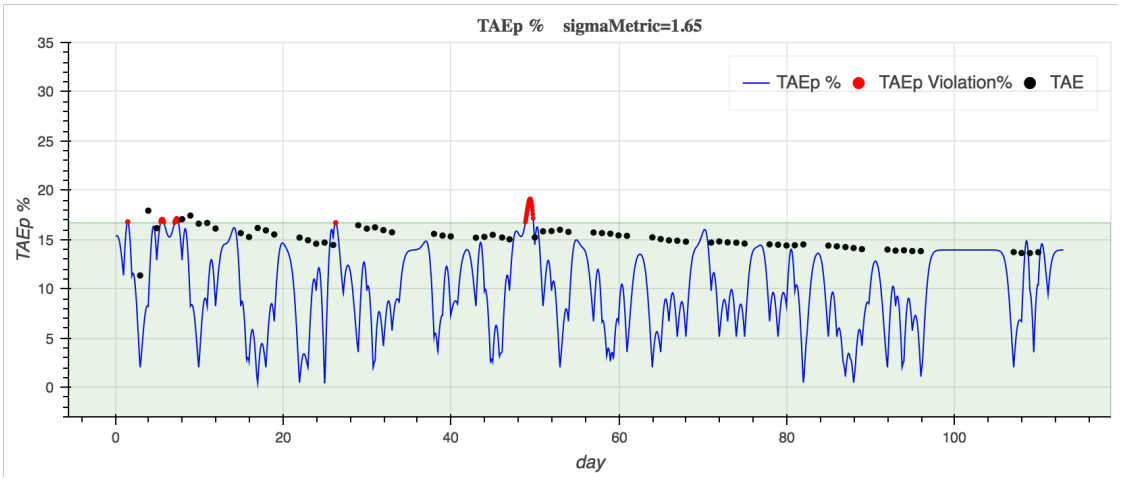

Figure 4. Comparison of TAE with TAE-predicted for FSH level 1 control data

Figure 4 presents TAE calculations using the classical formula TAE = bias% + 1.65 CV%. Solid black circles show TAE values computed as usual for each observation point. The solid blue curve shows TAE values computed for each prediction point using all data; both observed and predicted, total analytical error–predicted (TAEp). The horizontal axis shows the normalized data. TEa is set to 16.7%, which is the area shaded in the graphic. In TAE calculations, bias represents drift from the manufacturer's mean, and CV% stands for the coefficient of variation.

TAE changes very little from one observation to another whereas TAEp is wigglier. The reason for this is that TAE computes two terms related to long-term averages of observed data. Consequently, TAE and TAEp follow separate trajectories. Around day 50, TAEp exceeds the upper control limit. TAE, which is the model used in current practice, misses this OOCE. This demonstrates that the classical TAE method may miss some OOCE's.

DISCUSSION

The use of ML-based solutions to ease the burden of increasing test demand and to improve quality and safety in clinical laboratories has begun in recent years (12). Although clinical laboratories are health services where digitalization and automation are used extensively in daily practice, there are limited examples that exist of ML implemented into routine clinical practice (13, 14). However, publications on ML research in clinical laboratory medicine still on arise in several aspects of laboratory work including the evaluation of flow cytometry results, classification of cell morphology, interpretation of urine steroid profiles, test result interpretation, test result prediction, and the diagnosis of hematologic disorders (15-20). The model we proposed is the first study that emp-

loys a ML approach to the analytical perspective of clinical laboratory practice by predicting past and future OOCEs in IQC practice. The goal of this study is approached via the probabilistic framework of GPML.

In our study, we use the GPML approach to learn from time series control data and to predict both past and future OOCE's. In the control data vs time series, one would expect observations that stand closer to each other in time should be more similar to each other than to those that stand farther away. We can imagine two consecutive observations separated from each other by time-distance Δt. Assume Δt is made smaller and smaller approaching the limit to zero. As Δt assumes smaller and smaller values, two observations would be expected to get more and more similar to each other in magnitude. In the limit, two observations should be identical. If Δt is now moved in the reverse direction and it gets larger and larger, two observations would be less similar in magnitude. We can generalize this phenomenon so that control observations are correlated to each other in a statistical sense. The form of this correlation is important and constitutes the basis of the predictive models presented in this work.

The main outcome of this research, PQCA, has several attractive characteristics in comparison to classical rule-based quality control procedures:

1. PQCA enables proactive control of analytical methods' performance. It is capable of predicting future OOCE's. In case of a future OOCE either a new observation is planned for just before the OOCE or immediate corrective action is started.
2. PQCA can predict past OOCE's. In the case of OOCE's in the past, recovery and correction procedures are recommended to be started.
3. PQCA is a simple control procedure with a single rule. PQCA links raw control measurements and OOCE easy-use, obvious, and direct.
4. PQCA can easily model shifts in expected values of control measurements, i.e., systematic errors.
5. Laboratories wishing to meet different quality goals may set CI accordingly. Larger CI values would indicate tighter quality goals.
6. PQCA can start making accurate predictions with as few as one observation. Classical rule-based control procedures require a minimum number of observations, e.g., 20, to generate valid results.
7. PQCA can easily work with a non-deterministic target mean, e.g., peer group means.

Figure 3 is intended to justify the use of the RBF kernel for FSH control data. PQCA is applied to each prefix of the time series data and a prediction is made for the next observation point. Predictions are marked as hollow blue circles and the corresponding observations are marked as solid black circles. All observations fall within the 95% CI of their respective predictions. This process might constitute the basis for choosing the appropriate kernel function for controlling data. To make the kernel selection process more principled, cosine similarity between the observation and prediction vectors may be used, e.g., a cosine value of 0.99 or greater may be deemed to indicate a good kernel for the analyte under study.

There are a few limitations to the study. PQCA is not tested in real-time in routine IQC procedures. IQC data used in the study is evaluated retrospectively. The number and types of analytes included in the study are limited to a small group used in clinical laboratory routines.

Classical TAE calculation model, such as that proposed by Westgard (4), is based on a univariate Gaussian model (21). GPML, which the current approach is based on, is generalized by a multivariate Gaussian. In this respect, the computational view proposed in this work, PQCA, is a generalization of the classical IQC model.

CONCLUSIONS

The model we proposed is the first study that employs a ML approach to the analytical perspective of clinical laboratory practice by predicting past and future OOCEs in IQC practice. PQCA empowers clinical laboratories to evaluate the past, present, and future of the IQC data, collectively. The use of PQCA can improve the quality of laboratory service delivery, especially by enabling earlier detection of systematic errors. In this way, faster and more effective delivery of health services can be possible. Although it is possible to use it as a separate application, the integration of the PQCA into laboratory information systems may be a more accurate approach in terms of ease of use. This work might pioneer computational and laboratory sciences cooperation in quality management giving way to a new area of study, computational laboratory medicine. We believe that it will contribute significantly to the improvement of laboratory processes of the present as well as the future of laboratory medicine in general.

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