Moving average quality control of routine chemistry and hematology parameters: a toolbox for implementation

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Moving average quality control of routine chemistry and hematology parameters – a toolbox for implementation

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Abstract

Objectives: Moving average quality control (MA QC) is a patient-based real-time quality control system. Advantages compared to conventional periodic internal quality control (IQC) include absence of commutability problems and continuous monitoring of performance. We implemented MA QC for multiple routine hematology and chemistry parameters. We describe the evaluation process and provide practical tools to aid MA QC implementation.

Methods: Nine parameters (serum sodium, calcium, bicarbonate and free thyroxine, hemoglobin [Hb], mean corpuscular volume, mean corpuscular hemoglobin concentration [MCHC], reticulocyte count and erythrocyte sedimentation rate [ESR]) were chosen for initial consideration. Using data extractions from the laboratory information system (LIS; General Laboratory Information Management System), evaluation of usefulness and optimization of MA QC settings was performed using bias detection curves. After this, MA QC settings were incorporated in our LIS for further evaluation and implementation in routine care.

Results: Three out of nine parameters (Hb, ESR, and sodium) were excluded from MA QC implementation due to high variation and technical issues in the LIS. For the six remaining parameters, MA QC showed added value to IQC and was therefore implemented in the LIS. For three parameters a direct MA alarm work-up method was set up, including newly developed built-in features in the LIS. For the other parameters, we identified MA utilization beyond real-time monitoring.

Conclusions: Implementation of MA QC has added value for our laboratory setting. Additional utilization beyond real-time QC monitoring was identified. We find MA QC especially useful for trend monitoring, detection of small shifts after maintenance and inter-analyzer comparisons.

Keywords: moving average; patient-based real-time quality control (PBRTQC); quality assurance; quality control.

Introduction

Analysis of internal quality control (IQC) is an important ingredient of analytical quality control in medical laboratories. However, traditional IQC is inherently associated with several limitations, including its non-continuous character and the potential non-commutability of control materials. The non-continuous character of IQC is due to the periodical (e.g., daily) scheduling of IQC analysis and non-commutability is caused by the fact that traditional IQC materials are often freeze-dried with added stabilizers, resulting in matrix changes [1–4]. Moving average quality control (MA QC) is an alternative to traditional IQC.

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MA QC, also known as patient-based real-time quality control (PBRTQC), is a mathematical procedure that averages real-time patient results of an assay and uses the obtained mean values for QC purposes [5]. The principle of MA QC is depicted in Figure 1. Patient-based QC generally uses the mean, but other algorithms have also been developed and evaluated, including the median, exponentially weighted moving average, and Xbar/Bulls methods [4, 5]. Several settings in MA QC can be adjusted to obtain optimal conditions for specific laboratory tests, analyzers or patient populations. These include the window (the number of patient results that is used to calculate a MA value), alarm limits (upper and lower MA limits that generate an alarm), and settings to exclude specific patient results. The latter can be achieved using truncation limits (upper or lower thresholds that exclude patient results from the MA calculation), using patient-specific filtering criteria (e.g., hospital department or patients' age), or using statistical methods such as additional regression adjustment [6].

Potential advantages of MA QC compared to internal QC are the absence of commutability problems, absence of sensitivity to pre-analytical errors, and, above all, continuous monitoring of performance. Furthermore, no control materials and additional analyses are required, which potentially results in cost-reductions. For example, Fleming et al. showed that implementation of MA QC for 28 routine chemistry tests throughout regional laboratories in the United States could reduce IQC material usage by 75–85% [2, 7].

Despite its advantages and first description several decades ago, MA QC is often not used in daily practice due to the complexity to obtain optimal settings (which can be specific to a laboratory and/or patient population) and difficulties to integrate MA QC within laboratory information systems (LIS) [1, 8].

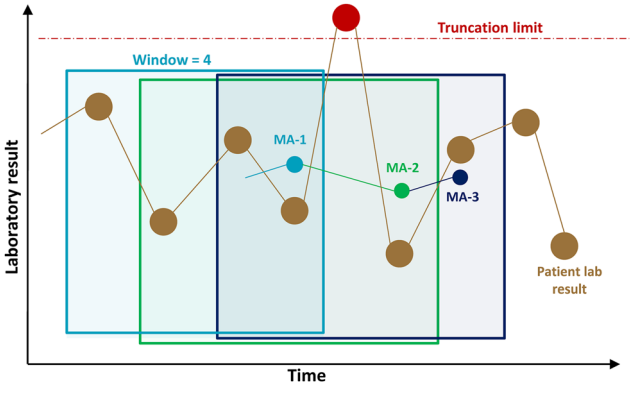

Figure 1: The principle of moving average quality control (MA QC). The average of a specific number of patient results is continuously calculated (in this example the four most recent patient results, as the window is set on 4). Each time a new patient result is generated, a new moving average value is calculated (depicted as MA-1, MA-2, and MA-3). Patient results above the truncation limit are excluded from the moving average calculation (depicted in red).

We recently implemented MA QC for six routine clinical chemistry and hematology parameters (out of nine candidates) in a university medical center in The Netherlands. This manuscript describes the process of evaluation and implementation and includes a toolbox with practical means that can be helpful in implementation of MA QC in medical laboratories.

Materials and methods

Test candidates for MA QC

Nine laboratory parameters were investigated: sodium, calcium, bicarbonate and free thyroxine (FT4) in serum, and hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), erythrocyte sedimentation rate (ESR), and absolute reticulocyte count in whole blood. In our laboratory, chemistry assays are performed on the Cobas 8000 system (Roche), hematology parameters are determined on the XN9000 (Sysmex) and ESR is measured on the Starrsed (Mechatronics/Sysmex).

Evaluation and implementation of MA QC

The evaluation and implementation of MA QC consisted of the following steps:

(1) Preparation: each parameter was assessed using the MA Generator application (Huvaros, versions used between 2019 and 2021) [1]. Comma-separated values files were extracted from the LIS (GLIMS, General Laboratory Information Management System, version 9.5.18 or 9.5.25) with all anonymous patient results of a specific laboratory parameter, including date and time of analysis and name of the module/analyzer, over a period of one year (Jan–Dec 2018). Results from QC materials, test patients and studies, and non-numerical values were excluded from the exported files using pre-set filters. Files were divided into periods of 3 months (as the MA Generator program has a maximum number of 20,000 results to be processed per analyzer) and were uploaded into the MA Generator application. Using this application, it was evaluated if MA QC could have a potential value for each individual parameter, and if so, the optimal MA settings (window, alarm limits, and truncation limit) were determined for each parameter. For this optimization, graphical comparison of bias detection curves was performed, and validation charts were used to determine the final MA settings [9, 10].

(2) Evaluation: after establishing the optimal settings, MA QC was incorporated in the LIS. The same settings were used as for the extraction files (i.e., no results from QC or studies, or non-numerical results). During the one-year evaluation period, no actions were taken if MA QC alarms occurred. We monitored how many MA QC alarms occurred and assessed their underlying

reasons. During the evaluation period, settings were adjusted and optimized, and the effects of truncation limits and excluding certain departments or patient categories were evaluated.

(3) Implementation: after the evaluation period, MA QC was implemented in routine care. All laboratory technicians were informed about and trained on the new procedures for MA QC alarm work-up. The following parameters were selected for implementation: calcium, bicarbonate, FT4, MCV, MCHC, and reticulocytes.

MA alarm work-up

Two features were built into the LIS in order to assist MA alarm work-up:

(1) A pre-programmed query to assess the cause of a generated MA alarm. A button was built into the LIS that opens a pre-set query window. The operator specifies the parameter, the analyzer and the time frame, yielding an Excel file containing the following information: analysis date and time, sample number, patient identifier, clinical department, analyzer, test result, and whether this result is within or outside reference values. In addition, the MA value and whether it was outside the MA alarm limits are also provided per test result.

(2) An automated direct comparison between bicarbonate test results in serum (measured on Cobas 8000, Roche) and bicarbonate measured in arterial blood gas samples (RAPIDPoint 500, Siemens) from the same patient laboratory order. This feature generates an Excel file with test results from the last 30 days, containing order number, date, the test results, and the automated calculated difference between the two methods (in %, with the blood gas value taken as the reference). The last row provides the average of the arterial blood gas results, the serum results, and the average difference between the two.

Results

Selecting test candidates for MA QC and determining the initial MA settings

To evaluate the potential of MA QC in an academic hospital, test parameters were strategically chosen. First, analytes were selected that are measured on different (modules of) analyzers (i.e., sodium using an ion selective electrode unit, calcium and bicarbonate on a photometric, and FT4 on an immunochemistry module). MA QC can thus be used strategically to get quickly alarmed when major analyzer problems occur. The variation of the test results was also taken into account, selecting parameters with a small range in laboratory values (e.g., sodium and calcium) as well as tests with a larger range of possible values (ESR and FT4). Besides that, parameters were selected (e.g., serum bicarbonate and FT4) that had shown more assay problems in the past (relative to other tests) and hence had the highest chance of benefitting from MA QC. The hematology parameters were also selected because of the possibility to easily perform between-analyzer comparisons. The selected parameters were sodium, calcium, bicarbonate and FT4 in serum, and Hb, MCV, MCHC, ESR, and reticulocyte count in whole blood.

The selected candidates were first assessed using the Huvaros MA Generator application. This tool generates bias detection curves and MA validation charts [9], providing information on how many patient results are needed to be able to detect a certain amount of bias. First, the window, MA alarm limits, and potential truncation limits (used to exclude patient results above or below a set threshold) were evaluated and selected for each of the nine parameters. We found that using patient data from a long time period (e.g., 12 months) is best when evaluating the optimal MA settings, as it comprises lot number changes, analyzer maintenance, etc., and thereby prevents that alarm limits are set too strict. In general, the bigger the window the smaller the bias that can be detected. However, this is at the expense of how long it takes (i.e., how many patient results are needed) to detect that bias. For each parameter one should decide the best balance between small bias and fast detection, which also depends on the intended use of MA QC for that particular analyte (see below). Noteworthy, selecting a large window that provides the lowest bias detection might be of very limited practical use when the test volume per day is very small. Analytes that show small analytical and/or biological variation are generally best suited for MA QC [11]. Sodium is therefore inherently a good candidate for MA QC, as can be seen in Figure 2A. The MA validation chart provided by the MA Generator application shows the number of tests needed (y-axis) to detect a certain amount of bias (x-axis). From this it can be concluded that a bias of >5% should be detectable within measuring <10 sodium results. On the other hand, we found that there is, in our setting and for our intended use, too much variation within the patient samples to detect reasonable biases for ESR and Hb, even when using truncation limits. Figure 2B shows that a large bias of 40% cannot be detected even after a high number of ESR measurements. However, it was previously shown that implementation of MA QC for Hb is possible [12]. Whether MA QC is considered useful for a particular analyte, is hospital/laboratory-specific (e.g., based on production volume), dependent on the intended use (e.g., direct alarm work-up vs. trend monitoring), and based on expert opinion. For sodium, calcium, MCV, MCHC, and reticulocytes, only a window and alarm limits were selected (see Table 1). For FT4, we concluded that a truncation limit of >30 pmol/L was necessary. Although evaluations were performed per analyzer, for simplicity and the possibility of inter-analyzer comparisons, we decided to use the same LIS settings per analyte among the different analyzers. However, MA QC was monitored for each analyzer individually [13].

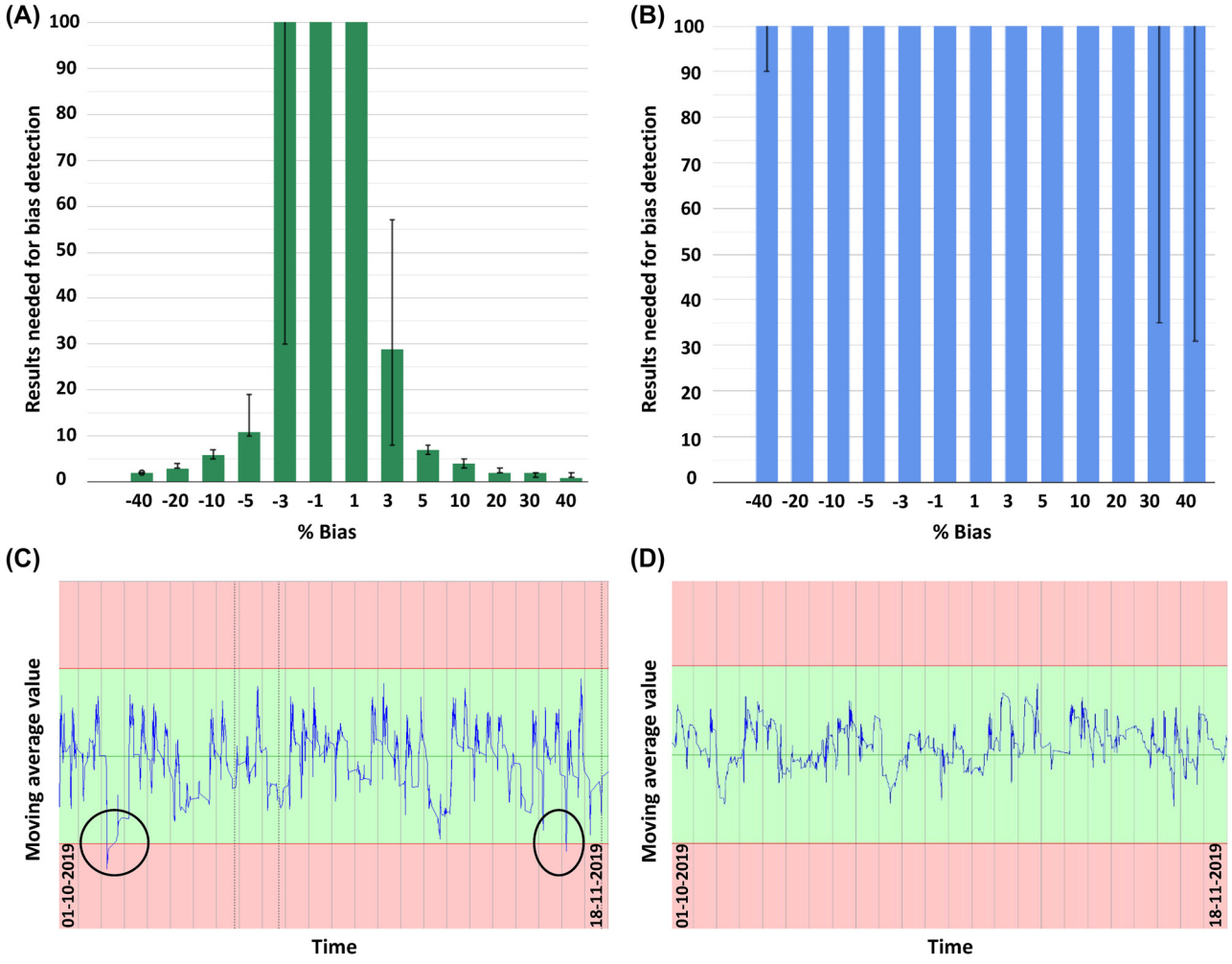

Figure 2: Evaluation of moving average quality control (MA QC) settings.
(A) MA validation chart of sodium with window of 10. (B) MA validation of erythrocyte sedimentation rate with window of 50. (C) MA QC of calcium, black circles indicate false MA alarms. (D) MA QC of calcium with same settings as (C) but excluding data from the following departments: intensive care, acute internal medicine, emergency room, and transplantation unit. Initially two false alarms were obtained, excluding data from the mentioned departments resulted in zero MA alarms.

Evaluation of MA QC within the laboratory information system

Once the initial settings per parameter were established (see Table 1), the LIS test environment was used to check for potential technical restrictions. Due to the high number of sodium test results it took a significant amount of time to load the MA plots, and the QC graphs used for interpretation of IQC became overcrowded. Therefore, sodium was excluded from the list of parameters to be incorporated into the 9.5 version of GLIMS present at that time. In higher versions (≥9.9.6) of GLIMS these problems do no longer occur as MA QC can be plotted separately from the IQC data. As no further technical restrictions were seen, the other parameters were directly incorporated within the LIS (production environment), yet without any triggers for alarm work-up. The incorporated parameters were evaluated for one year. It was assessed how often the set MA limits (from here on referred to as “MA alarms”) were exceeded. The MA alarms were investigated and categorized as true alarms (bias in assay, analyzer problems, IQC measurements out of range, etc.) or (apparently) false alarms (single patients with extreme results causing the MA alarm, etc.). Besides the alarms, the general stability of the MA of the different parameters was also evaluated. An iterative process of finetuning during the evaluation year resulted in the final MA settings (see Table 1).

Table 1: Parameter settings – initial and final.

Parameter	Initial settings (MA Generator)				Final settings (GLIMS)				
	Window	Lower and upper alarm limit	Other settings	n of alarms per month[a]	Window	Lower and upper alarm limit	Other settings	n of alarms per month[a]	Direct MA alarm work-up
Hemoglobin	–	–	–	–	–	–	–	–	–
ESR	–	–	–	–	–	–	–	–	–
Serum sodium	10	133.4–146.1 mmol/L	NA	–	–	–	–	–	–
Serum bicarbonate	20	20.0–29.1 mmol/L	NA	0.5	30	20.5–29.1 mmol/L	NA	0.5	No
Serum calcium	16	2.08–2.50 mmol/L	NA	22	16	2.04–2.53 mmol/L	Departments excluded: intensive care, acute internal medicine, emergency room, (kidney/liver) transplantation unit	0.7	Yes
Serum FT4	20	14.5–20.4 pmol/L	Truncation limit: >30 pmol/L	4	20	13.6–20.7 pmol/L	Truncation limit: >30 pmol/L	0.8	Yes
MCV	25	84.6–96.1 fL	NA	2.2	25	85.3–97.8 fL	NA	0.3	No
MCHC	25	19.8–21.5 mmol/L	NA	3.7	25	19.3–21.6 mmol/L	NA	0	Yes
Reticulocytes	25	52.8–127.5×10^9/L	NA	7	20	20–118×10^9/L	Patients <1 year old excluded	0.3	No

[a]Average calculated over a period of two or three months and as an average of the two or three analyzers available for each analyte in our laboratory. ESR, erythrocyte sedimentation rate; FT4, free thyroxine; MA, moving average; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; n, number; NA, not applicable.

Despite the upfront evaluation in MA Generator using data from one year, the initial settings had to be adjusted for all the tested parameters, as there were too many false alarms (see Table 1). For some parameters only the MA alarm limits were altered (bicarbonate, FT4, MCV, and MCHC), based on observations on the number of false alarms in the LIS; for other parameters (calcium and reticulocytes) the effect of excluding certain patient populations was evaluated using the MA Generator application again. Analyzing the number and cause of the calcium alarms revealed that most of the MA alarms were caused by individual patients from the intensive care unit, emergency room, acute internal medicine unit, and the transplantation unit. It was therefore decided to exclude calcium results of patients from these departments for the calculation of MA (see Figure 2C, D for the effect on MA QC). For the reticulocytes too many false alarms and too much variation within the MA were observed as well. We concluded that mainly newborns with very high reticulocyte levels were the cause of the alarms, and data from patients <1 year old were therefore excluded. Excluding patient data from MA calculations was first evaluated using the MA Generator application. The newly optimized settings were then incorporated in the LIS and monitored again.

MA alarm work-up

For our academic hospital, we decided to divide the test parameters into two categories based on the intended use of MA QC: with and without direct MA alarm work-up. Differentiation between the two groups was established within the LIS by choosing different signaling levels. Parameters with direct MA alarm work-up were calcium, FT4, and MCHC. When an alarm occurs, the test results of that particular analyte on that particular analyzer are prevented from being released to the clinic, and the laboratory technician is notified. Direct action is required; IQC measurements will be performed. When IQC requirements are met, the parameter for which the MA alarm occurred will be put back into production. On the same (week) day, the cause of the MA alarm will be investigated. The rationale behind this alarm work-up is to

prioritize patient safety (only releasing patient data when analyzer issues are ruled out) while minimizing a delay in data production at the same time. When the IQC results do not fulfill the requirements, one will follow the standard procedure for IQC exceedances including remeasuring a random sample of patient test results.

For bicarbonate, MCV and reticulocytes, a procedure without direct MA alarm work-up was chosen: for these analytes, we found MA QC especially useful for weekly trend monitoring and between-analyzer comparisons.

Figure 3 depicts three examples of the added value of MA QC as compared to regular IQC from actual practice. Figure 3A–C shows the MA of FT4, in which exceedance of the upper MA limit (indicated by the circle) can be seen. The MA alarm prevented FT4 results from being released, and prompted the laboratory technician to perform an IQC measurement, which turned out to be outside the acceptable range. The cause of the alarm was investigated: due to the COVID-19 pandemic, less FT4 results were being produced resulting in longer use of the required test reagents (even though reagents were used before expiration dates). MA QC was able to detect a drift in the FT4 results, roughly 6 h before the next scheduled IQC measurement (performed once every 24 h), potentially preventing up to ~80 erroneous patient results. Figure 3D demonstrates an example of MA QC for serum bicarbonate, in which a drift can be observed that was not visible using traditional IQC measurements (Figure 3E displays the corresponding Levey–Jennings IQC plot of the same time

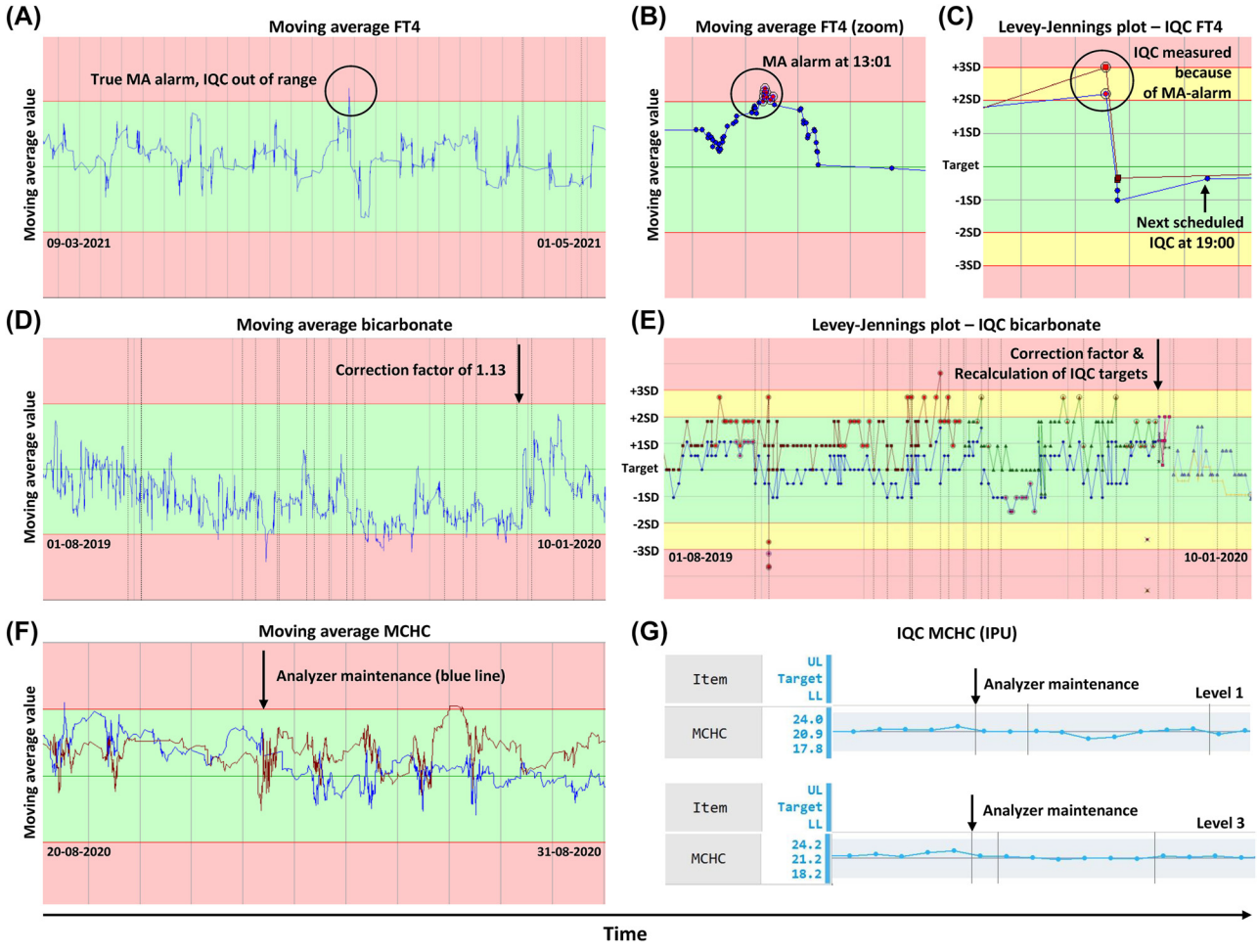

Figure 3: Examples of the added value of moving average quality control (MA QC).
(A) MA QC for free thyroxine (FT4), MA alarm prompted an internal quality control (IQC) measurement which was out of range. (B) Close-up of same MA alarm as in (A). (C) Close-up of Levey–Jennings plot of same MA alarm as in (A) and (B). (D) Trend monitoring for serum bicarbonate using MA QC, clear effect of correction factor. (E) Levey–Jennings plot of serum bicarbonate IQC of the same time period as in (D). (F) Inter-analyzer comparison and effect of analyzer maintenance on MA QC of mean corpuscular hemoglobin concentration (MCHC). (G) MCHC IQC (two levels, in mmol/L) displayed in IPU (software of the hematology XN9000-analyzer) showing no evident effect of analyzer maintenance.

(A)

Date and time	Sample number	Patient number	Department	FT4 (patient result)	FT4 (MA value)	Outside reference values?	MA alarm?
28-02-2022 09:38:14	22xxxxxxx	xxxxx	Endocrinology	26.22	19.43	Yes	No
28-02-2022 09:40:20	22xxxxxxx	xxxxx	Endocrinology	20.38	19.69	No	No
28-02-2022 09:43:09	22xxxxxxx	xxxxx	Endocrinology	26.25	20.05	Yes	No
28-02-2022 09:47:20	22xxxxxxx	xxxxx	Cardiology	17.44	20.12	No	No
28-02-2022 09:47:59	22xxxxxxx	xxxxx	Nursing ward - Psychiatry	19.85	20.58	No	No
28-02-2022 09:59:54	22xxxxxxx	xxxxx	Pulmonary medicine	27.12	20.99	Yes	Yes
28-02-2022 10:00:39	22xxxxxxx	xxxxx	Cardiology	22.82	21.15	Yes	Yes
28-02-2022 10:26:29	22xxxxxxx	xxxxx	Oncology	16.51	20.61	No	No
28-02-2022 10:27:15	22xxxxxxx	xxxxx	Cardiology	18.24	20.53	No	No

(B)

Order number	Date	Bicarbonate (arterial bloodgas)	Bicarbonate (serum)	Difference (in %)
930xxx	18-02-2022	24.2	26	7.4
930xxx	18-02-2022	17.6	19	8
930xxx	19-02-2022	26.2	29	10.7
930xxx	22-02-2022	29.6	29	-2
930xxx	22-02-2022	23.6	24	1.7
930xxx	22-02-2022	24	25	4.2
930xxx	23-02-2022	24.1	25	3.7
930xxx	24-02-2022	21.6	24	11.1
Average		24	25.13	3

Figure 4: Moving average quality control (MA QC) work-up using custom built-in features in the laboratory information system (LIS; GLIMS).
(A) Example of automatically generated Excel file that was created after a MA QC alarm for free thyroxine (FT4). For each FT4 measurement, the date, time, sample and patient number, department, and FT4 patient result is shown, as well as its corresponding MA value (both in pmol/L), whether the patient result is within or outside the reference values and whether this generated an MA alarm or not. (B) Example of an automatically generated Excel file showing bicarbonate levels (in mmol/L) measured in serum as well as in arterial blood gas samples from the same order. The difference (in %) between the individual measurements as well as the mean difference is also given. Layout of tables was adjusted for clarity, available information to be retrieved from these tables has not been changed.

period). Such additional insight by means of MA QC is highly valuable. Figure 3F shows the MA QC for MCHC on two of our XN-9000 hematology analyzers. A clear shift is seen directly after analyzer maintenance on one of the analyzers (blue line). The effect of maintenance was not observed using regular IQC (see Figure 3G) or the built-in MA option (Xbar-M) from the supplier, emphasizing the added value of MA QC as an additional quality measure. Besides that, Figure 3F demonstrates that MA QC can also be visualized for multiple analyzers within one figure, which is useful for between-analyzer comparisons.

It appeared that, next to clear instructions, additional tools enabling easy and quick MA QC work-up would be highly valuable to laboratory staff. To this end, we developed two features within our LIS. Direct access to the tools is established by buttons created within the LIS. The first feature is the MA alarm query tool used for the parameters requiring direct MA alarm work-up. The tool can be used to deduce the cause of the MA alarm: see Figure 4A for an example of its output. It provides insight into the course towards the MA alarm generated. From this, one could conclude whether the alarm is possibly caused by one single extreme test result or, for instance, a general drift. The other tool is especially designed for bicarbonate (but could potentially be applied to any test). Serum bicarbonate is a parameter for which it is challenging to maintain a stable test performance. Moreover, there is (to the best of our knowledge) no external quality assurance (EQA) program for this analyte in serum. Before implementing MA QC, we regularly performed manual comparisons between serum bicarbonate and bicarbonate levels provided by blood gas analysis (in which we assume that the latter is correct based on EQA proficiency), which is both time-consuming and reactive. We therefore developed an automated query (see Figure 4B) that performs this comparison within a few mouse clicks. By using both MA QC-based trend monitoring and the automated comparison, we are able to proactively make adjustments when needed. This led to reduction in the analytical variation for our serum bicarbonate assay. We assessed this by a

Toolbox for evaluation and implementation of moving average quality control (MA QC)

Evaluation of MA QC feasibility

- Evaluate the possibilities regarding integrating MA in the laboratory information system
- Determine for which analytes/parameters MA QC will be evaluated
  - Which parameters show analytical issues for which MA QC might be useful?
  - Does variation/range in laboratory values of the analyte allow for useful MA QC?
  - Is there a lack of proper internal and external quality control measures?
- Use the MA generator application (or similar tool) to test the feasibility of the chosen analytes and to establish the initial settings, perform finetuning of the exact alarm settings in the laboratory information system (LIS)
- Determine MA settings based on data from long months) time periods, such that lot number changes, analyzer maintenance etc. are included within the data
- Evaluate and determine intended use of MA QC per analyte *(e.g.,* acute alarm work-up, trend monitoring, comparison between analyzers)

Implementation of MA QC

- Evaluate whether the LIS allows to easily investigate which patient results cause MA alarms or find an alternative method for this
- When changing or updating MA settings within the LIS, consider creating a new QC population, as this makes it easier to monitor the effects of the update
- For each analyte, define an alarm work-up method for technicians/laboratory staff depending on the intended use of MA QC

Figure 5: Moving average quality control (MA QC) toolbox.
Recommendations for the evaluation of feasibility and implementation of MA QC within the laboratory information system.

monthly comparison between blood gas and serum bicarbonate values, showing that the mean difference between those values decreased from 14 to 6%.

Discussion

In this article, we describe the evaluation and implementation of MA QC in our academic hospital. For initial evaluation, the MA Generator tool was used. In general, we found that the MA Generator application provides a quick and easy tool to evaluate whether a parameter is suitable for MA QC, as well as to determine the initial settings for the window and alarm limits. Finetuning is a very important part of evaluation before implementation in daily practice. It is essential to evaluate the initial settings derived from the MA Generator tool within the LIS, after which adjustments can be made. The final MA settings are primarily based on expert opinion. To enable the use of MA QC in routine practice, it is also important that the available LIS supports integration of MA QC [8, 14] and has the capacity to calculate and display MA QC for the number of generated results, which was not the case for sodium in GLIMS 9.5. Also, it should be checked, when implementing new versions of a LIS, that transferring MA QC and its settings is possible. It should be noted that only an average-based calculation is possible within our current LIS, with the inherent disadvantage that it is more prone to outliers than calculations based on median or Xbar/Bulls methods [4, 5].

Although the increase in speed of error detection is highly dependent on the analyte, MA QC settings, production volume, and IQC measurement frequency, it is possible to get an upfront estimate on how many measurements it would take for MA QC to detect a certain amount of bias (per analyte) using the MA Generator tool. For example, in Figure 2A it can be seen that (for each analyzer) a bias >5% can be detected within <10 sodium results. If one would perform IQC once every 12 h, and an average of 160 sodium results would (for instance) be generated within these 12 h, it would take approximately 45 min to detect the error. This is up to about 11 h earlier than the next IQC measurement. Although this type of information is very valuable in the evaluation of the usefulness of MA QC for a certain analyte, such simulations are, obviously, theoretical: the numbers of results generated are not evenly distributed

over the day, the exact time of the error determines how much faster the error is detected than by IQC measurement, etc., meaning that such estimates do not always directly translate into daily practice.

The main advantage of MA QC is that it is continuous, and hence provides the possibility to detect analyzer/assay problems immediately (or at least faster), especially during intervals between IQC measurements, as described in multiple studies [1, 2, 5, 14, 15]. When MA QC is used with this intention, the added value to IQC alone is two-fold: earlier detection of analyzer/assay issues as well as preventing the production of inaccurate test results. Our initial goal of implementing MA QC was based on this idea. For the parameters calcium, FT4 and MCHC, we incorporated MA QC in the LIS to this end. Out of these three parameters, MA QC was most beneficial for FT4, as MA alarms prevented erroneous reporting on several occasions. Using MA QC in this way has been described previously [1, 2, 14]. During our evaluation and implementation process, however, we experienced that MA QC was also useful for trend monitoring and the comparison between analyzers. In our view, the great potential of MA QC for these purposes is underexposed. Using MA QC we were able to detect shifts (after maintenance or reagent lot changes) that were not detected using regular IQC. The most likely explanation is that MA QC lacks the commutability issues potentially related to traditional IQC. The workflow that we have set up for serum bicarbonate MA QC (i.e., trend monitoring combined with automated data comparisons with other analyzers) can be applied to other parameters to improve long-term method stability. Moreover, this strategy could be used to substitute the periodically scheduled inter-analyzer comparisons using IQC/EQA or selected patient samples, to save time, costs, eliminate commutability issues, and shift from intermittent to continuous comparisons. We are currently further exploring its possibilities. Taken together, we conclude that MA QC can also be useful beyond its "traditional" use as real-time QC monitoring.

The process of implementing MA QC in a laboratory is not a one-size-fits-all-concept; it needs a considerate amount of finetuning and optimizing the alarm settings. In our setting, the evaluation period before implementation lasted a year, but resulted in a significant reduction of alarms (Table 1). The need to optimize the MA settings was possibly partly due to changes in patient populations due to the COVID-19 pandemic. We expect that the evaluation can be done faster for new parameters, using the experience gained. The work-up by laboratory staff upon the emergence of MA QC alarms should be thoroughly assessed, as it should be feasible to carry out in daily practice. Our considerations on the process are hopefully useful for other laboratories who want to implement MA QC. The Toolbox (Figure 5) provides some practical recommendations, based on our experience and previous findings by others [1, 5, 8, 14], that can be considered when evaluating and implementing MA QC. Our newly designed features in the LIS, aiding the MA-alarm work-up and inter-analyzer comparisons, are new additions to the toolbox that hopefully inspire to explore the full potential of MA QC and the LIS.

In conclusion, although implementing MA QC can be labor-intensive, we believe it has clear added value when used wisely. MA QC has the ability to improve patient safety by using it as a continuous system control (on top of periodic IQC monitoring) that prevents erroneous results from being released to the clinic or reduces the response time to such results. Besides that, we demonstrate that MA QC can be a highly valuable tool for inter-analyzer comparisons and trend monitoring to improve long-term test stability.

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