Bull’s Multirule Algorithm, \( \bar{x}_M \), An Excellent Means of Internal Quality Control for Hematology Analyzers

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Abstract

Automated Hematology cell counters are extensively used in hematology laboratories and their functional accuracy is monitored using expensive commercial controls and retained specimens. In this present study we have tried to implement a computational method based on Bull’s Multirule Algorithm \( \bar{x}_M \) along with the existing quality control method. The Algorithm works on the principle that mean of red cell indices - MCV, MCH, MCHC remain stable for any particular hospital population over a number of years. This mean can be used to check accuracy and calibration of the hematology analyzer. A batch of 20 blood samples is used to derive means of red cell indices and is compared to \( \pm 3\% \) and \( \pm 2\% \) action limits of the computed Bull’s mean. The batch is re-analysed if it fails Bull’s Multirule criteria; that is if (1) the mean is outside \( \pm 3\% \) action limit (2) mean of three consecutive batches is outside \( \pm 2\% \) action limit.

In the current study we could identify calibration anomalies in the analyzer using this criteria in spite of following NABL and CAP recommendations on use of commercial controls. Thus we emphasize, that commercial controls within acceptable limits are not the surest way to know proper functioning of the analyzer and recommend \( \bar{x}_M \) should be incorporated in the daily quality control regimen

Introduction

The term quality control has been described, as a method of repeated assays of known standard materials and monitoring reaction parameters, to ensure precision and accuracy\(^1\) and taking necessary corrective measures to bring it in conformance with the specification.

Traditionally, quality control in hematology consisted of (1) analyzing stabilized control material with known manufacturer’s means and limits,(2) between run controls - where recently analyzed patient samples were reanalyzed at designated time intervals and (3) Bull’s moving average \( \bar{x}_M \), using patient data as a means of quality control\(^2\). Bull’s moving average \( \bar{x}_M \) was first proposed by Dr Brian S Bull, Loma Linda University in 1974. It was subsequently refined by Korpman and Bull in 1976 known as Bull’s Multirule Algorithm \( \bar{x}_M \), as a means of internal quality control using red cell indices - Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Hemoglobin Concentration (MCHC)\(^2\). \( \bar{x}_M \) works on the principle that red cell indices are known to be stable blood parameters. Hence, the mean of red cell indices of a given patient population would not vary more than \( 0.5\% \) from day to day or year, to year provided the population does not change\(^4\). Therefore, if the mean of
red cell indices is known, patient blood sample can be used to check calibration and drift of the hematology analyzer. The algorithm involved extensive calculation and hence was difficult for implementation, but in the later years its importance was established and $\overline{X}_B$ was incorporated in the hematology analyzers, although publications on specific $\overline{X}_M$ use in hematology analyzers are not readily available. The algorithm analyses the patient’s red cell indices through instrument in batches of twenty. The mean of each batch is compared to Bull’s mean and its action limits, i.e. the percent deviation of Bull’s mean. The batch is rejected if either of the two Bull’s Multirule criteria is satisfied (1) the mean of one of the batches is outside its ±3% action limit or (2) the mean of three consecutive batches is outside its ±2% action limit. The standard data established by Dr Bull obtained from 1,767 hospitals, yielded the following mean values MCV - 89.9 fl, MCH - 30.5 pg and MCHC- 33.9 g/dl.

In the present study, similar attempts have been made to study Bull’s Multirule Algorithm using patient’s data from BARC hospital. The population taken for sampling purpose comprises of general Indian population of different ethnicities including men, women and children. This patient population would remain constant for a number of years since it involves people who are beneficiaries of the Contributory Health Service Scheme of Department of Atomic Energy.

**Materials and Method**

Patient’s blood collected in EDTA vactutainers was processed on well calibrated five-part differential haematology cell counter, SYMEX XS 1000i. Complete data of thousand patients was retrieved from the analyzer using Sysmex software and MCV, MCH and MCHC required for computing Bull’s mean was exported to excel sheets. Standard deviation (SD) was calculated and ±3SD limits were applied to the patient data and five percent grossly abnormal samples were rejected. Moving averages for forty seven batches, of twenty patients, each was obtained. ±2% and ±3% action limit was applied to Bull’s mean, $\overline{X}_M$, the weighted moving average of forty seven moving averages. Bull’s mean, $\overline{X}_M$, function in the analyzer was activated with this range. Thereafter the analyzer automatically plotted the Levy-Jennings (L-J) graph using MCV, MCH and MCHC data, obtained after processing the patient’s sample. A single point on the graph corresponded to a batch of twenty processed patients’ samples. The graph was studied prior to release of the reports for online viewing by the clinicians. Subsequently a graph with ±3% action limits as the criteria and also ±2% action limit was documented.

**Observation and Results**

As seen in Table 1, the computer simulation generated the above values for Bull’s mean standard deviation and coefficient of variation and action limits of MCV, MCH, and MCHC. The graph so obtained from the analyzer...
using ±2% and ±3% action limits was well within the range. MCHC being the most stable parameter, followed a straight line graph whereas MCV and MCH were found to be scattered around the mean. A graph using the above data was also plotted manually with the help of Excel sheets and was found to be comparable with the analyzer graph. This further indicated the accuracy and proper functioning of the analyzer.

It was further observed that the standard data for MCV, MCH and MCHC obtained by Dr Bull was not in agreement with our data, which could be probably due to lower hemoglobin standards in Indian population. A study comprising data of 1000 patients was also done, to find out the MCV, MCH and MCHC values of the same population in three different seasons of the year. First thousand patient’s data processed on well calibrated 3-part differential hematology analyzer Sysmex - KX 21 was retrieved from our database and Bull’s mean for each season was computed, the results of which are as shown in Table 2. Hence it should be noted that although there were variations between the data obtained in the present study and those obtained by Dr Bull, the data obeyed Bull’s Multirule Algorithm and hence was acceptable.

The graph shown below indicates the points plotted by the analyzer. Graph 1 has ±3% as its action limit and graph 2 has ±2% as its action limit. It is seen from the graph, that the MCHC plot followed a straight line graph whereas MCV and MCH were scattered around the mean. It is also seen, at some point during the analysis, the graph showed a sudden drift, even though two of the three QC samples analyzed after the start up procedure were within acceptable limits. According to NABL and CAP standards[6], if two out of three QC samples are within acceptable limits, the analysis can be continued. Defective QC material was thought to be the reason for the failure of one of the QC. Continuation of the drift in the graph prompted the fact that the analyzer has gone out of calibration, since more than three points in the graph were out of ±2% limits satisfying second rule of Bull’s Multirule for rejection. To confirm the calibration failure, a comparative study was done using our 3 part differential cell counter SYSMEX KX 21 and similar analyzer SYSMEX.

### Table 1: Table showing the Bull’s mean for MCV, MCH and MCHC along with std.dev, coefficient of variation and action limit.

<table>
<thead>
<tr>
<th></th>
<th>MCV</th>
<th>MCH</th>
<th>MCHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bull’s Mean</td>
<td>84.1(fl)</td>
<td>27.8 (pg)</td>
<td>33.1(g/dl)</td>
</tr>
<tr>
<td>Std. Dev.</td>
<td>0.4</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>CV %</td>
<td>0.4</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>3% Action limit</td>
<td>81.6-86.6</td>
<td>27.0-28.6</td>
<td>32.1-34.1</td>
</tr>
<tr>
<td>2% Action limit</td>
<td>82.4-85.8</td>
<td>27.2-28.4</td>
<td>32.5-33.7</td>
</tr>
</tbody>
</table>

### Table 2: Bull’s mean of first 1000 samples for 3 seasons with respect to Bull’s mean from our study and Dr. Bull’s standard mean.

<table>
<thead>
<tr>
<th></th>
<th>October ‘09</th>
<th>January ‘10</th>
<th>July ‘10</th>
<th>Bull’s Mean</th>
<th>Bull’s Standard Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCV (fl)</td>
<td>84.8</td>
<td>84.0</td>
<td>84.6</td>
<td>84.1</td>
<td>89.9</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>29.3</td>
<td>28.8</td>
<td>27.3</td>
<td>27.8</td>
<td>30.5</td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>34.6</td>
<td>34.1</td>
<td>32.7</td>
<td>33.1</td>
<td>33.9</td>
</tr>
</tbody>
</table>
XS 1000i from another hospital. The results confirmed that our 5-part differential analyzer needed recalibration. It should be emphasized here that it was only because of the $\bar{M}$, that malfunctioning of the analyzer was detected whereas the commercial QC failed to explain the reason for the drift. Thus, it is of utmost importance that the $\bar{M}$ be incorporated along with the QC practices and monitored intermittently for any drifts in the $\bar{M}$ graph.

The analyzer was monitored post calibration and Bull’s mean for the next 400 samples was computed and was found comparable with the results before the analyzer went out of calibration, as seen in Table 3.

**Conclusion and Discussion**

- It was observed from the present investigation, that the Bull’s mean obtained by Indian standards could not match those of international standards laid down by Dr Brian Bull owing to probable low hemoglobin standards. Hence, it is imperative for every laboratory to develop one’s own standard mean using one’s own patient population, as population variation is an important criterion to be considered while computing standard means.

- It is surprising to find that even though the analyzer went out of calibration at some point of time, two of the three QC values obtained, remained well within acceptable limits. However, the problem with the analyzer could be detected only with the drift in the $\bar{M}$ graph and further action with regard to corrective measures were taken and the analyzer was recalibrated. Hence, it is of utmost importance to incorporate the use of $\bar{M}$ function in the Quality control regimen, even if commercial controls and

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**Table 3: Comparison of Bull’s mean before the calibration error and after the recalibration of analyzer**

<table>
<thead>
<tr>
<th></th>
<th>Bull’s Mean before calibration error</th>
<th>Bull’s Mean after calibration</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCV (fl)</td>
<td>84.1</td>
<td>83.7</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>27.8</td>
<td>27.8</td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>33.1</td>
<td>33.2</td>
</tr>
</tbody>
</table>

**Graph 1: Levy-Jennings chart output from Sysmex XS1000i with 3% action limit (UL = Upper limit, LL = Lower limit, Target = Bull’s mean, SD = Std. Dev, CV = Coeff. Var)**
• Retained specimen are already a part of it. Moreover it also permits quality control of the analyzer during the interval when control materials are not being analyzed.

• The use of $X_m$ is advocated for the reason that in the current environment of cost restriction, multiple repeats of the commercial control can be avoided.

• It was also observed that multiple repeats of the same abnormal sample within a given batch may also cause a non random population in that batch and a shift in result. Such shifts are usually corrected in the next batch of 20 when random analysis is made.

• Shift in the results is also observed in the cases, when a batch has predominance of a particular type of patient like from the oncology, paedriatic or the dialysis unit.

• Change of reagents and their lot number also hold important significance as they too could be the reason for the shift in analyzer.

• A minimum of sixty specimens per day must be processed to yield 50% probability of detecting a 3SD shift\(^7\).

References

7. George, S Cembrowski; Quality Control in U.S. and Canadian Hematology Laboratories.