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ChemBook

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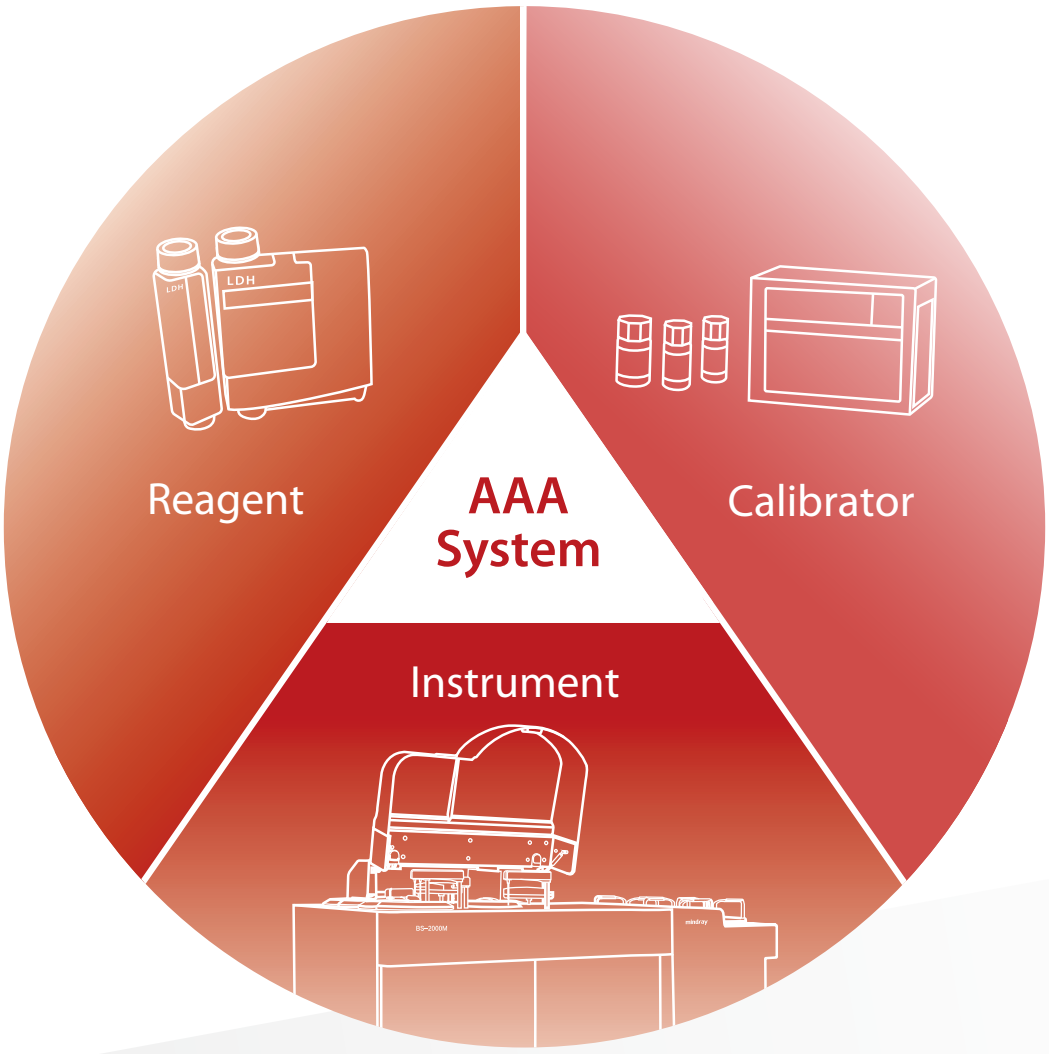

Content

Analysis of the False Low Result for Abnormally High Triglyceride Sample

by Dr. Jiang Xiaojun
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Due to the changing diet structure and unhealthy lifestyle, hyperlipidemia has become a common phenomenon in today's society among patients, particularly those who show high triglycerides (TG) and chylomicrons (CM). This also brings considerable interference to biochemistry testing. In clinical practice, the interference of lipemia can be evaluated by serum index and TG concentration. In this case, the sample was sent to the laboratory for detecting the cause of abdominal pain of the patient and the system gave an alarm on abnormal absorbance. The TG result was only 3.75mmol/L, which was inconsistent with the sample status that was already marked as severe lipemia. We checked the reaction curve of TG and found that the optical density (OD) value of the reaction quickly rose to the top and then began to decrease. When the reaction reached the end, the OD value was only one sixth of its peak value, and that caused the false low result. After manual sample dilution, the result was 67.2 mmol/L, which was much higher than the linearity upper limit 20mmol/L of TG. We also rerun this sample on another detection system, the testing result was still much lower than the actual concentration.

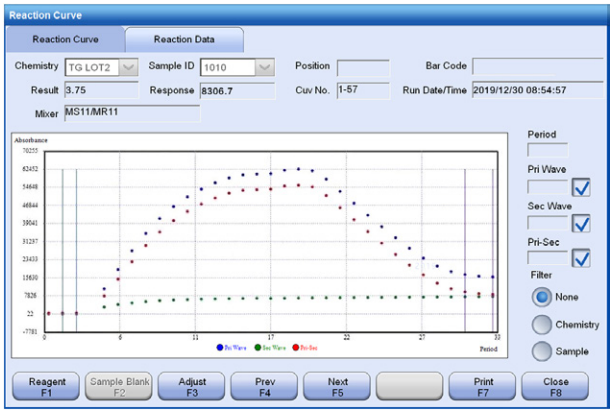

Figure 1: Abnormal TG reaction curve

Endpoint colorimetric method is used for TG assay. When the reaction equivalence point is reached, all the analytes convert into products, and the absorbance no longer rises or falls.The measuring principle showed in the TG reagent instruction manual is oxidase method involving "Trinder" color reaction (Figure 2).

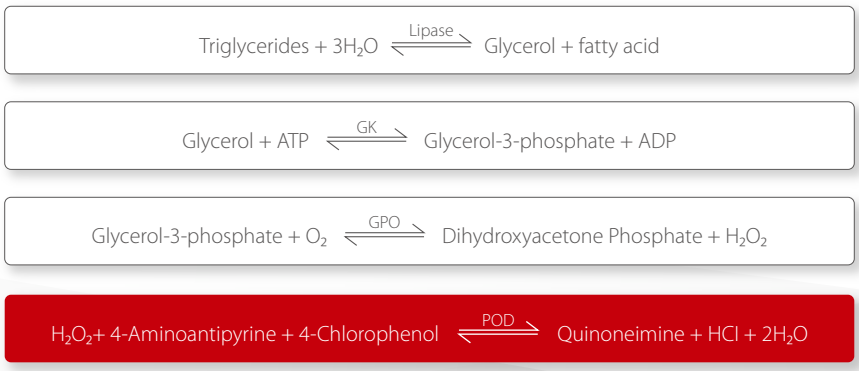

Figure 2: Reaction princible

Due to the extremely high TG concentration in the sample, the reaction speed will be very fast. The oxygen in the reaction solution is quickly exhausted and new oxygen fails to be dissolved into solution and join the reaction timely. Under such circumstance, the reaction will be stagnated or even reversed, which will lead to an inaccurate result (usually lower than actual concentration). Mindray integrated chemistry system can monitor the reaction curve in the real time, and give an intelligent alarm flag when it finds abnormal absorbance characteristics. After the identification, the system will trigger the auto-dilution function, and produce more reliable results.

High TG concentration cases are quite common in clinical practice. If the laboratory technician fails to find the abnormalities in time, wrong results may be reported. Even if the abnormal reaction curve can be detected by experienced person, repeated review and manual rerun with dilution will lower the work efficiency. So the intelligent alarm flag plus auto rerun function in the integrated testing system is of great benefit to result reliability and laboratory efficiency.

For the integrated close chemistry system, some indexes have been inbuilt in the software, which can help the system monitor the reaction curve and give an assessment for abnormal reaction. In the software interface in figure 3, P1 and P2 refer to sequence number of absorbance points on the reaction curve. The software can automatically calculate the value of P2 minus P1 (P2-P1). M and N respectively refer to the minimum and maximum of the value (P2-P1) for identifying the existence of abnormalities in the reaction process.

Through the reaction curve monitoring and algorithm function, the analyzer can automatically identify the abnormalities and give an "RE" flag, and subsequently trigger the auto-dilution function. After automatic dilution and rerun, the reaction curve returned to normal and the test result was 68.4 mmol/L, which is in line with the result obtained from manual dilution (Figure 4).

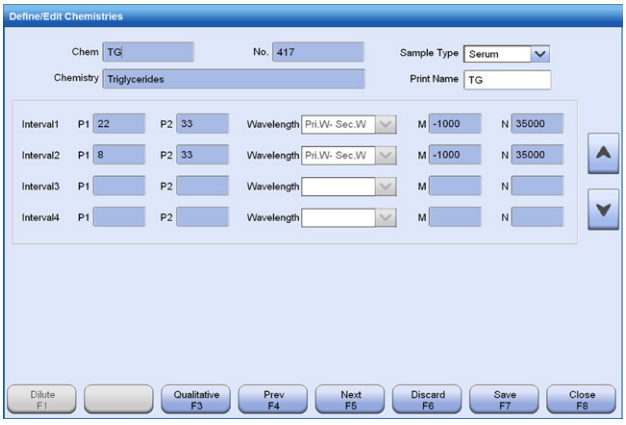

Figure 3: Index setting for abnormal reaction curve alarm

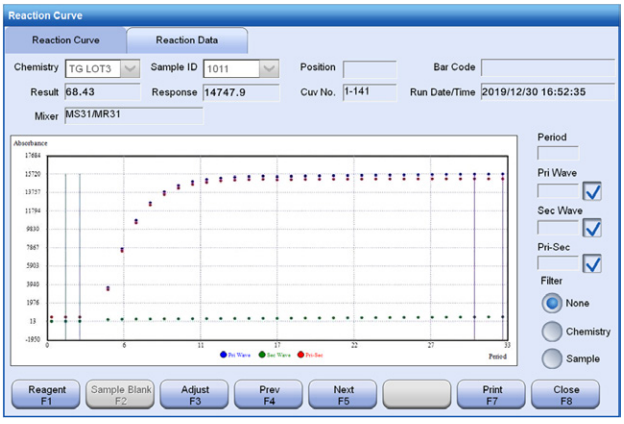

Figure 4: Normal reaction curve after sample auto-dilution

The integrated AAA testing system has inbuilt a powerful testing database in the software. For example, application data (R1/R2/S volume, reaction time, Pri./Sec. wavelength, linearity range, rerun rule) and reaction monitoring data (carry-over pairs, substrate depletion check rule, Trinder reaction check rule, and Hook effect check rule). The powerful database can make the testing system more efficient and intelligent, and more user-friendly. Taken together, the integrated AAA chemistry system can greatly improve the efficiency, shorten the TAT time, reduce potential risk of errors and increase both clinical and patient satisfaction.

Intelligent Identification of Hook Effect to Avoid False Low Result

by Bigang Zhou; Hu Wang; Nancy JI
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A bunch of clinical biochemistry items are tested by immunoturbidimetric method which measures the turbidity of an immune complex formed from antibody-antigen reaction. It is inevitable that there will be Hook effect created in an antigen-antibody reaction when concentration of analyte (antigen) begins to exceed amount of antibody present in reagent. If not well treated as to this condition, wrong reading results may be obtained. This short case-based article aims to get a closer look at how modern biochemical analysis technology effectively avoid the false result caused by Hook effect.

A 60-year-old female patient received a routine urinalysis on chemistry test paper and a microalbumin (mALB) urine test on chemistry analyzer. The urine paper test showed a high level of protein in urine (3+) with an estimated concentration of more than 300 mg/dl, while the biochemical test for mALB obtained a value of 34.62 mg/dl. There is a significant difference between the two results. Is the result of urine paper test abnormal or is there something wrong with urine biochemical results?

The quality control for qualitative urine paper test and mALB urine chemistry test on that day received a re-check, and the quality control of both two methods were normal. There was a "PRO" flag (Hook effect alarm) for the mALB first measuring result and the reaction curve was abnormal. Then the lab technician rerun the sample after diluting 20 times and got the result 847.7 mg/dL; but there was still an alarm flag, "RRN" flag which indicated that the sample reaction degree was exceeded the highest level calibrator reaction degree. Subsequently, the mALB result 1082.8 mg/dL was obtained after diluting 30 times, and there was no alarm. The evidently big difference between the initial result and later test results after dilution, and along with the low serum Alb result (15.1 g/L) and clinical diagnosis of nephrotic syndrome, can sufficiently prove that the initial chemistry test result for mALB (34.62 mg/dL) was wrong.

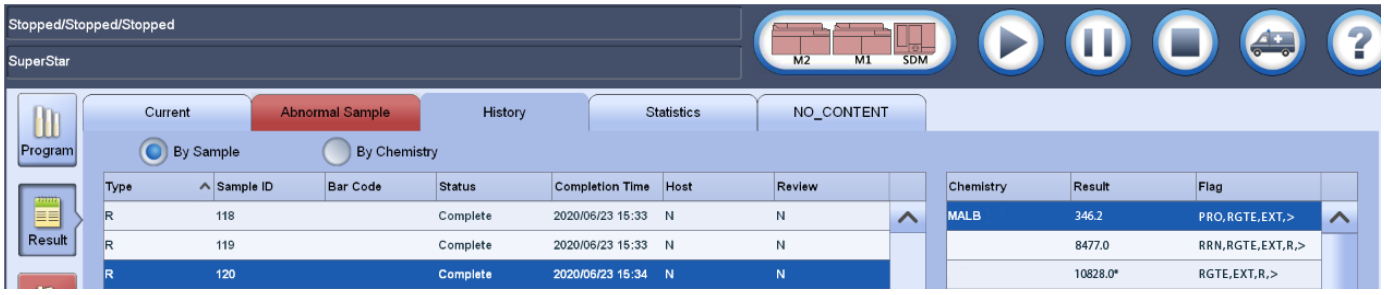
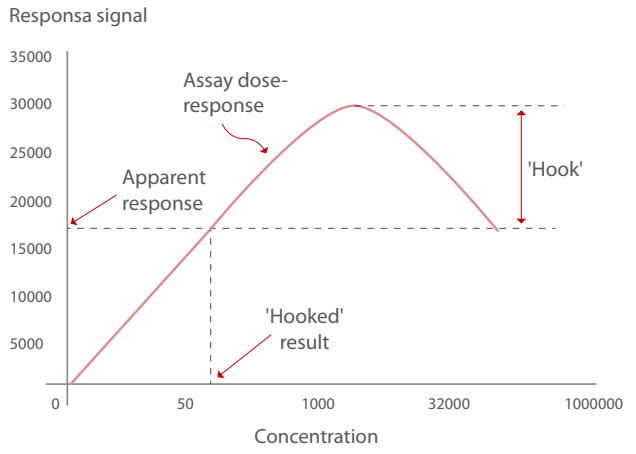


Figure 1: mALB testing results

Urine mALB is one of the sensitive and reliable index to detect kidney dysfunction in the early stage. Continuous monitoring of mALB level presents important clinical significance for screening of early kidney injury, early therapeutic intervention and prognosis evaluation of a nephropathy. Accurate test results from laboratories are of great benefit for clinical diagnosis and treatment. So how to avoid false low results similar to this case? In order to improve the accuracy of clinical biochemical assay, two dimensions should be considered, that is, optimization of reagent reaction system for extending reagent linearity, and integration of measurement systems for improving identification ability of abnormal test results.

What is Hook Effect?

Hook effect can occur when presenting inappropriate ratio of antigen to antibody and bring falsely low results. The numbers of antigen-antibody complexes formed by two samples with vastly different concentrations could be equal, which contributes the error of the result. In this case, the hooked result occurred in mALB urine test.



Diagrammatic representation of the 'hook' effect. resulting in an artefactually low concentration reading.

Measurement of serum ferritin by a two-site immunoradiometric assay, Anal Biochem 1974; 61: 209-24 Interference in immunoassay. Ann Clin Biochem 1999; 36: 704-721

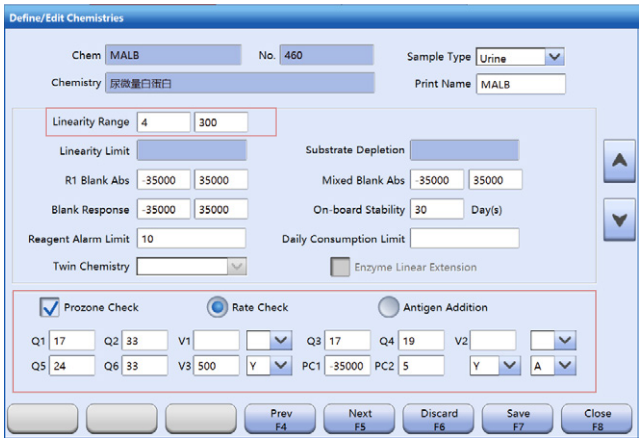


Figure 2: Inbuilt Index of mALB Item in Software

How to Identify Hook Effect?

Special attention should be paid to the abnormality identification function as to modern chemistry analyzers. Currently, Mindray's integrated AAA chemistry testing system has built many powerful testing database in the software (For example reagent application parameter, reagent linear range and reaction check rule, rerun rule, etc.). Figure 2 shows the linearity range and Hook effect check rule for mALB item. The intelligent algorithm of Mindray AAA close chemistry system can provide automatic identification and alarming of Hook effect, thus improving the accuracy of test results.

Let’ s look at how does Mindray chemistry system help the lab provide more reliable result for mALB test. If the measuring result is higher than Mindray reagent linearity upper limit 300 mg/L, then the software will give a “>”flag, and trigger a dilution and rerun. If the measuring result is lower than linearity upper limit, the software will check if the result is true or false low result according to the inbuilt pre-zone check rule. If the software judge this is a false low result, it will give a “PRO” flag, then subsequently trigger a default 20 times dilution and rerun. The reaction curve check-up function and intelligent flag alarm function can bring more reliable results, and the auto-dilution can largely bring less manual operation and longer walk-away time.

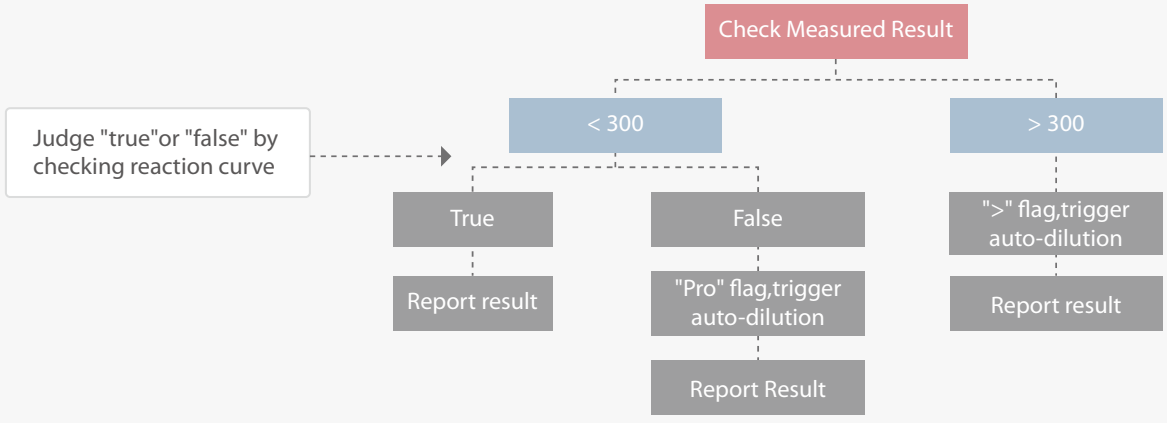


Figure 3: Result Check and Rerun Rule of mALB Test

A series of refined parameters built into the system, thus make the system more intelligent and more efficient. It can improve system’ s ability to support clinical diagnosis and treatment, especially the identification ability of abnormal results of high-concentration samples. So the integrated AAA chemistry system can greatly improve the laboratory efficiency, shorten the TAT time, reduce potential risk of errors and increase both clinical and patient satisfaction.

Role of Substrate Depletion Limit Parameters Built in the Mindray Automatic Chemistry System

Author: Gong Xiaolin, Shanghai Center for Clinical Laboratory

When the liver, heart and other organs of the human body are critically damaged, a large quantity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK) and other enzymes will be released, which greatly increases their concentration in the peripheral blood. Under such circumstances, these enzymes' concentration far exceeds the linear range of reagent. It is very likely that the substrates in the reagent would be consumed very fast, and lead to that the reaction is no longer at zero-order and cause the report results far below actual concentration.

Mindray BS series chemistry analyzers with built-in substrate depletion limit parameters can provide an alarm flag for substrate depletion. When the device detects the depletion of substrate during reaction, it will start the linearity extension function, and use photometric points with linear change in default reaction time (or in lag time) to calculate ΔA/min ratio and report its corresponding results.

The BS-2000M2 automatic biochemical analyzing system is a modular biochemical analyzing device independently developed by Shenzhen Mindray Medical Bioelectronics Co., Ltd. Using BS-2000M2, this study will do a series of routine chemistry tests such as ALT, AST, ALP, GGT, LDH, α-HBDH, CK, CK-MB, α-AMY and UREA tests, all with high-concentration of analytes, so as to give a general assessment on BS-2000M2 about its enzyme linear extension function in clinical practice.

Material and Method

▸ Source of Samples

The research team collected serum samples, from both outpatient and inpatient departments, from the Xuhui Hospital of Fudan Zhongshan Hospital. A total of 63 samples, all with a high concentration of analytes such as ALT, AST, ALP, GGT, LDH, α-HBDH, CK, CK-MB, α-AMY and UREA. The concentration of these analytes falls into three categories: within the linear up-limit, around the linear up-limit and exceeding the linear up-limit. All samples were free of visible hemolysis and lipidemia.

▸ Device and Reagents

BS-2000M2 and the original reagent kits, calibrators and quality control products for testing ALT, AST, ALP, GGT, LDH, α-HBDH, CK, CK-MB, α-AMY and UREA were all purchased from Shenzhen Mindray Medical Bioelectronics Co., Ltd.

▸ Methodology

First, perform calibration and maintenance of the device according to recommended methods from the manufacturer. Ensure that all testing items are within the effective calibration period and quality control is under control.

The basic principle of enzyme linear extension function is that when the reaction is over, the system will search for the absorbance points with linear change during the reaction time according to substrate depletion limit. If the number of absorbance points with linear change in reaction time (N) is 1 or 0, the system will start linear extension function and find the linear absorbance points without substrate depletion in lag time period, then calculate △A/min of these points and report calculated result (Figure 1). If this calculated result exceeds reagent linearity upper limit, a ">" mark will be given. If the number of absorbance points with linear change in lag time (N) is still 1 or 0, the result cannot be calculated and an "ENC" mark will be given to indicate this error. Then the system will trigger auto-dilution and rerun the sample to report a normal result.

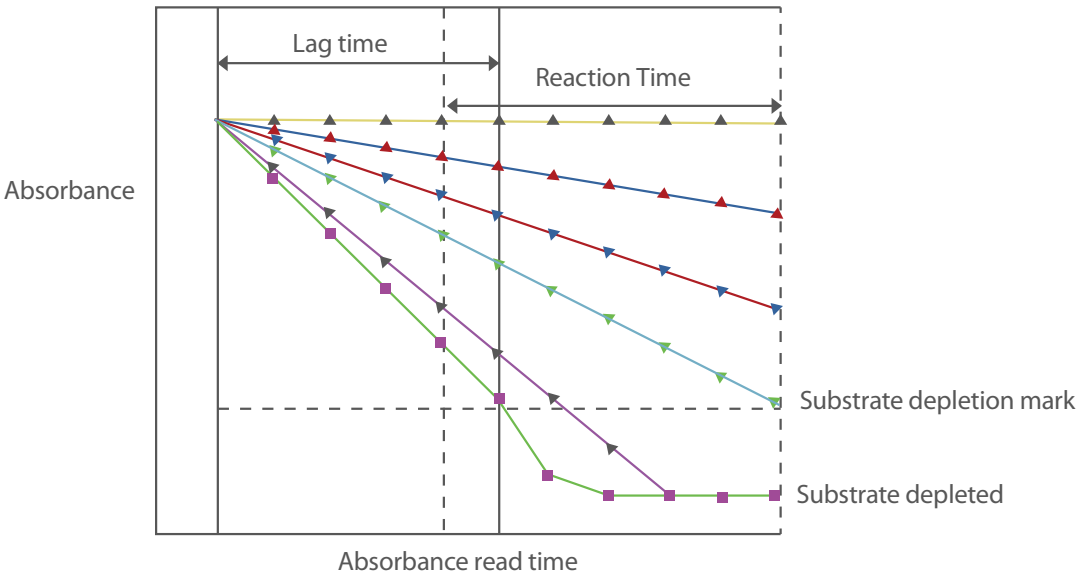


Figure 1: The principle of enzyme linear extension function

Discussion

The clinical performance of a biochemical analyzer is affected by many factors such as the device itself, reagent performance, integration application protocol, manufacturer' s traceability, daily calibration and maintenance in the laboratory etc. When choosing a biochemical analyzer, the laboratory should pay special attention to ensure that the device can do substrate depletion monitoring in kinetic-based tests.

In this study, the linear extension function of BS-2000M2 was proved to be good. The results showed that the upper limits of the reportable range of the ten tests were extended, respectively, to 3339 U/L, 7411 U/L, 3407 U/L, 3945 U/L, 7646 U /L, 9783 U/L, 14106 U/L, 3296 U/L, 9700 U/L and 54 mmol/L (Table 1). It can be inferred that in each test, when the result is lower than the maximum mentioned above, the relative deviation between the calculated result with enzyme linearity extension function and the rerun result after dilution is clinically acceptable. Besides, there is no false alarm or omission of substrate depletion during the research.

Item	Upper limit of reagent linearity range	Upper limit of reportable range with linear extension function	Highest clinically visible concentration	Sample quantity	Sample proportion within reportable range (%)
ALT(U/L)	1000	3339	1232	63946	100.00
AST(U/L)	800	7411	4708	45245	100.00
ALP(U/L)	800	3407	2338	42387	100.00
GGT(U/L)	650	3945	3464	42326	100.00
LDH(U/L)	1000	7646	6877	21161	100.00
α-HBDH(U/L)	1000	9783	4829	19497	100.00
CK(U/L)	1000	14106	30764	11097	99.96
CK-MB(U/L)	600	3296	1299	8877	100.00
α-AMY(U/L)	1500	9700	3463	8126	100.00
UREA(mmol/L)	40	54	139	45963	99.97

Table1: The reportable range of 10 chemistry items with kinetic reaction method

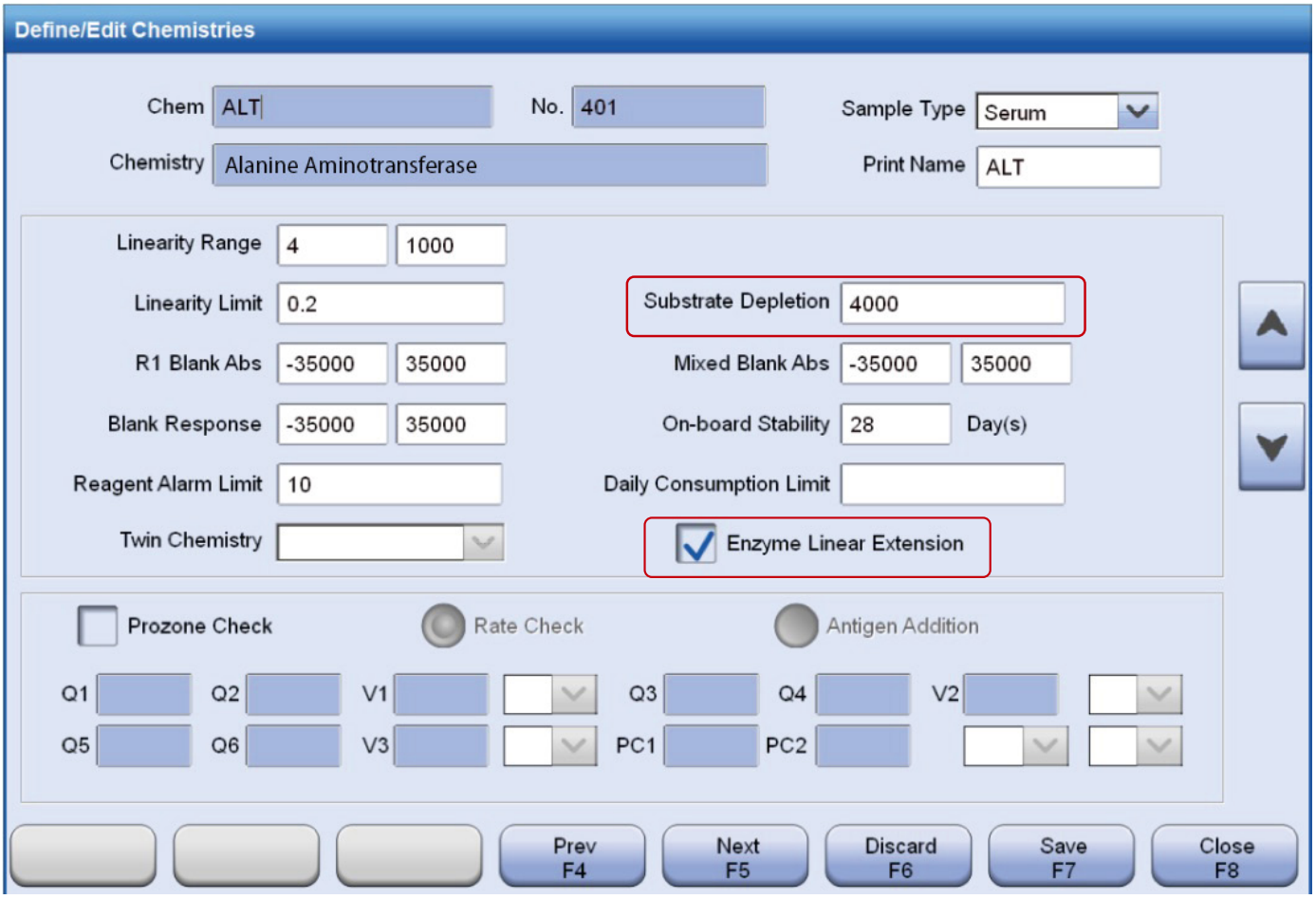


Figure 2: Inbuilt Index of Substrate Depletion Mark of ALT and Optional Enzyme Linear Extension function in software

Conclusion

In summary, the linear extension function for enzyme parameters on BS-2000M2 greatly extends the reportable range, which effectively reduces the risk of false negative results of high-concentration samples, lowers down the frequency of retesting, and shortens the sample turn-around time

Acknowledgement

Special appreciation goes to Song Yunxiao from the Department of Laboratory at the Xuhui Hospital of Fudan Zhongshan Hospital for his assistance in collecting the samples for this study.

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Original Title: Substrate Depletion Limit Parameters: Role of substrate depletion limit parameters in BS-2000M2 automatic chemistry analysis system

This article is only part of the original text. For the relevant data and complete content, see the original text.

Conclusion

Mindray chemistry AAA close systems with original reagent can help laboratories achieve reliable results and quality of care.

The integrated AAA system with powerful inbuilt software algorithm can monitor the reaction curves and give remind flags for abnormal reactions. This intelligent alarming and auto-rerun function can minimize the abnormal results and make clinical results more secure and reliable.

Mindray AAA chemistry system can offer more additional value to our customers. Mindray is also constantly striving for the excellent advanced system and want to provide more satisfactory systemic solution to our customers.

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