

SYSTEM AND METHOD FOR MEASURING COAGULATION TIME WITHOUT THERMOSTATIC CONTROL

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Many medical problems relate to the coagulation of blood. In particular during treatment with anticoagulant medication, a patient's coagulation parameters fluctuate continuously. Such fluctuations can cause severe
20 problems. For example if a patient is treated with an anticoagulant drug such as Heparin or Marcumar, it is important that his or her coagulation parameters remain within a defined range of values to avoid complications. Only in this way it is possible to reduce effectively the
25 number of blood clots while simultaneously avoiding bleeding complications. A rapid, precise method for the continuous monitoring of blood coagulation parameters that meets all therapeutic needs is therefore required.

30 Currently, in particular three coagulation parameters are of medical interest, namely prothrombin time (PT), activated partial thromboplastin time (APTT) and activated clotting time (ACT). PT mainly serves for monitoring the effect of vitamin K antagonists on
35 coagulation (which influence factors II, V, VII and X of

the coagulation cascade). The PT test measures the activation of the extrinsic pathway by addition of tissue thromboplastin.

5 APTT is used primarily to monitor heparin therapy. The test detects factor changes in the intrinsic coagulation cascade (factors VIII, IX, XI, XII and other enzymes and factors). The test reagents for this type of test have not yet been standardized and therefore differences in
10 the heparin sensitivity of reagents from different manufacturers are considerable.

ACT is determined to monitor heparinization in situations where an APTT test cannot be performed, because the
15 patient was administered a high dose of heparin.

Traditionally, the coagulation parameters are determined by "wet chemistry" tests. An aliquot of blood sample is mixed with liquid reagents and the point of time at which
20 the blood clots is detected. The results are indicated either directly (in seconds) or in the form of derived quantities such as ratio to a respective normal value (in percent). With respect to PT further common quantities for indication of the test results are % Quick and INR
25 (International Normalized Ratio).

Since several years so-called "dry chemistry" tests of coagulation parameters have become available. They are performed by means of test systems comprising disposable
30 reagent carrier elements (often designated "test elements") and an evaluation instrument which generally is adapted for the evaluation of a particular type of test element from a particular manufacturer. The test element contains the reagent system necessary for the
35 particular test and, preferably, suitable information for

the evaluation of the test such as the test type, the lot number and the expiration date.

The invention refers to such dry chemistry tests. Each
5 test element is designed to allow a drop of a blood or plasma sample (which depending on the test may be pretreated, in particular by reaction with a preparatory anticoagulant) applied thereto to contact and dissolve a reagent system (which normally comprises a plurality of
10 reagents) present in the test element and suitable to initiate the reaction sequence of the blood coagulation path. After mixing of the sample with the reagents the resulting coagulation detection liquid is present in a coagulation detection zone of the test element. The
15 coagulation process is monitored by observing a measurable property of the coagulation detection liquid which changes in a characteristic manner when a defined reaction step of the coagulation path occurs. The system comprises means for detecting such change and generating
20 a corresponding signal by the measurement and evaluation electronics of the instrument. The measurement and evaluation electronics also includes a time measurement electronics for measuring a coagulation time required for the change to occur. This time is converted into the
25 desired coagulation parameter (in the appropriate units). To this end evaluation data stored in the instrument and/or in the test element can be used. The results are then displayed on a display of the instrument and/or forwarded to further evaluation, for example by a
30 separate computer system.

Such a system is commercially available from the applicants under the trade name CoaguChek®. Further details may be found in the appropriate literature
35 including US patent 5,789,664 and WO 01/11356. The sample

may be whole blood or plasma. Hereafter reference is made to blood as an example. This should, however, not be understood as a limitation to the general applicability of the invention.

5

Known coagulation test systems differ inter alia with respect to the measurable property of the coagulation detection liquid which is used to measure the coagulation time and with respect to the arrangement by which the
10 contacting of the sample with the reagents is achieved as well as by the design of the detection zone:

- In some tests the measurable property of the liquid is its viscosity which can be detected e.g. by including magnetic particles into the reagent system. The
15 moveability of these particles can be detected by means of an alternating magnetic field. In such systems the increase of the viscosity caused by the onset of coagulation is the change marking the end of the coagulation time.
- 20 - Alternatively a chemical constituent, the concentration of which changes at a defined point of the coagulation path, can be used to mark the end of the coagulation time. In particular the enzyme thrombin, the final protease for both plasmatic
25 coagulation pathways, can be monitored by known means, including a reagent present in the reagent system of the test element which is suitable to generate an electrical or optical signal which can be measured by the evaluation instrument (see e.g. WO 01/63271).
- 30 - With respect to the physical arrangement of the test element it has been proposed to use a single permeable porous membrane which is fastened to a plastic handle similar as with traditional test strips (US patent 5,580,744). In such test elements the sample is

directly applied to the membrane in which the reagent system is contained.

- In an alternative arrangement the sample application point of the test element is located at a distance
5 from the coagulation detection zone and the transport of the sample liquid from the former to the latter is accomplished by a capillary channel (see US patent 5,789,664).

10 While tests for coagulation parameters have become relatively simple, in particular due to the introduction of dry chemistry tests, it remains an important task to further simplify the design and thus reduce the cost without sacrificing accuracy. For example, if a person
15 received a replacement cardiac valve his or her long-term health highly depends on the fact that the coagulation status remains reliably between certain boundaries. To this end inexpensive small battery-operated instruments should be available to be used by the patients themselves
20 in order to monitor their blood coagulation status. Similar requirements apply to "point of care (POC)" testing by the medical profession.

Therefore the invention addresses the task to simplify
25 the design of systems for determining coagulation parameters while simultaneously maintaining the required degree of accuracy.

This task is achieved by a system for the determination
30 of a coagulation parameter of blood or plasma samples of patients, said system comprising a disposable test element including a reagent system to be mixed with the sample, thereby forming a coagulation detection liquid, and a coagulation detection zone where the coagulation
35 detection liquid is contained for monitoring a measurable

property of the coagulation detection liquid, said measurable property changing during coagulation, and an instrument with a holder for holding said disposable test element inserted therein and with a measurement and
5 evaluation electronics adapted for detecting a signal which corresponds to the measurable property of the coagulation detection liquid and including a time measurement electronics for measuring a coagulation time required for said change to occur for deriving the
10 desired coagulation parameter therefrom, wherein the coagulation time is determined at a non-standard temperature of the coagulation detection liquid different from a standard temperature for the respective coagulation parameter, said non-standard temperature
15 being measured by a temperature measurement device, the instrument has a non-volatile memory containing data which define a mathematical relationship of coagulation time versus temperature which relationship is independent of the individual patient whose blood is examined, and
20 the coagulation parameter for the standard temperature is calculated from the coagulation time measured at said non-standard temperature, using said mathematical relationship.

25 Known systems for the determination of coagulation parameters generally comprise some kind of thermostating device designed to maintain during the coagulation measurement a defined standard temperature, usually 37°C. This requires an electric heater and an electronic
30 temperature control system. Based on the invention such a thermostating device is not necessary. Rather the coagulation measurement can be made at a convenient temperature (e.g. room temperature). Nevertheless accurate values of the desired coagulation parameter can be deter-
35 mined which are directly comparable to those determined

at the standard temperature. This leads to a plurality of advantages:

- For small portable battery operated coagulation instruments the heating system is expensive and consumes more battery energy than all other components combined. The volume, weight and cost of the instruments can be reduced substantially if no heating system and a smaller battery are required.
- In order to secure an exact control of the desired standard temperature test elements of known dry chemistry systems often have a long capillary for guiding the sample liquid from the point of sample application (outside the instrument) into the interior of the instrument where the thermostating device is located. If no such long capillary is necessary the sample volume can be reduced.
- The warm up time required with known instruments before testing is eliminated or reduced. This simplifies the use of the system, in particular in home monitoring or POC applications.
- For INR calibration a manual technique is generally used which causes difficulties in controlling the standard (37°C) temperature. Errors due to temperature deviations can be reduced if the technique can be performed at room temperature.

During the experimental work on which the invention is based it has been determined that the change of coagulation time parameters versus temperature can be described by a functional relationship which is specific for a particular instrument and a particular reagent system but surprisingly is independent on the sample. Therefore the same functional relationship $f(T)$ (which may e.g. be a linear function or a polynomial) describes the tempera-

ture dependence no matter whose blood is being examined. Taking PT as an example this may be expressed mathematically:

5 (1) $PT^{37} = f(T) * PT^T$

where

PT^{37} : PT value for the standard temperature of 37°C

PT^T : PT value for a (lower) non-standard temperature.

- 10 Generally in the field of clinical chemistry it is not unusual to perform a temperature correction calculation if a test is temperature dependent and the actual test temperature differs from a desired standard test temperature. For example tests for determining the concentration of glucose in blood are temperature dependent and
15 it has been proposed to eliminate errors caused by temperature variations by an appropriate correction calculation (see e.g. US patents 5,405,511 and 5,972,715).
- 20 Coagulation detection is, however, fundamentally different from the detection of the concentration of an analyte such as glucose. The temperature dependence of glucose tests is caused by influencing factors which are independent of the individual sample which is tested. In
25 particular the enzymatic reaction on which the test is based depends on the temperature. A coagulation test is fundamentally different since it is essentially an experimental model of the natural coagulation process which - as is well known - involves a highly complicated
30 reaction of more than ten factors and enzymes in the blood of the particular patient. The fact that the coagulation behaviour of blood is different for every individual is also apparent from the fact that the dosage

of corresponding medication (e.g. Heparin or Marcumar) has to be individually adapted.

Therefore in coagulation testing the quantity which is
5 measured depends on the particular individual sample,
i.e. the individual whose blood is tested and the status
of his or her coagulation system. Regarding the
temperature dependence the same had to be assumed.
Therefore it could not be expected that, by examining the
10 blood of a limited number of patients at different
temperatures with the same test system (same type of
instrument and same reagent system, preferably of the
same manufacturing lot) a universal $f(T)$ -curve could be
generated which allows calculation of PT^{37} from PT^T values
15 determined at a non-standard temperature for additional
patients with quite different blood.

In the prior art PT and APTT tests have generally not
been performed at temperatures outside the standard range
20 at about 37°C. An exception is described in

A. Uldall: "Prothrombin time standardization and
temperature problems", Clinica Chimica Acta, 1980,
39-44.

25 This publication refers to PT tests performed in a glass
tube which are immersed into a water bath to allow exact
control of the temperature. The author refers to problems
caused by deviations from the standard temperature of
37°C, e.g. in case the glass tube is not immersed
30 sufficiently deeply and by the fact that the tube has to
be withdrawn from the water bath repeatedly in order to
check the coagulation status. In order to reduce these
problems a lowering of the generally accepted standard
temperature from 37°C to 30°C is considered.

US-patent 5,031,619 refers to a Bleeding Time Test. In such tests an incision of predetermined dimensions is applied to the skin of a patient and the time is measured from a moment that bleeding through the incision begins to the moment coagulation appears to occur. Such bleeding time measurements are used as screening tests for evaluation of the hemostatic adequacy of platelets which depends on platelet number and platelet function. It is a qualitative (or at most semi-quantitative) test allowing screening for certain disorders (e.g. Glanzmann's thrombasthenia). The patent refers to the earlier known fact that the rate at which external bleeding occurs is roughly inversely proportional to the temperature of the subject's skin and suggests to use a fixed factor of 0.05 per degree in order to compensate for variations of the temperature of the subject.

Above identified US patent 5,580,744 describes a large number of experiments all of which are performed at a constant standard temperature. As a theoretical alternative the possibility is mentioned to perform coagulation detection reactions at a deviating temperature such as room temperature. An equation for a possible correction calculation is given but the patent contains no explanation how this should be accomplished in practice. Nothing is mentioned about the problems caused by the fact that the coagulation path way is different for each individual. Evidently the author did not address this question in view of the fact that his system is specifically designed to be used by a single person.

The invention will be further described hereafter with reference to the figures wherein

- Fig. 1 shows a crosssectional view of a coagulation test system with the test element inserted into the evaluation instrument;
- Fig. 2 shows a schematic design diagram of a preferred system according to the invention;
- Fig. 3 shows an enlarged view of an element temperature sensor shown in fig. 2;
- Fig. 4 shows a graphical representation of the ratio PT^{37}/PT^T vs. $T[^\circ C]/37$ for a series of experiments performed in the context of the invention;
- Fig. 5 shows a graphical representation of experimental results comparing the invention with a conventional determination of INR values;
- Figs. 6 to 10 show results corresponding to figure 4 performed with different coagulation parameter tests.

Figure 1 is a crosssectional schematic representation of a coagulation test system comprising an evaluation instrument 1 and a disposable test element 2. The test element has a sample application opening 3, a capillary channel 4 and a space 5 which serves as reaction chamber and coagulation detection zone 6. The channel 4 is very short and can even be omitted because with a system according to the invention coagulation detection zone 6 need not be thermostated and is, when test element 2 is inserted in a holder 8 of instrument 1, preferably located outside the housing of the instrument 1 close to sample application opening 3.

In prior art devices easy application of the sample required that the sample application opening is outside of the instrument whereas thermostating required that the

coagulation detection zone of the test element is inside the instrument housing. The sample was transported from the former to the latter by a long capillary path. This again required a large sample volume not only because of
5 the length of the path but also because of a sufficiently large capillary path cross-section required for adequate speed of liquid transport. In contrast the invention allows a very short transport distance (of preferably less than 1 cm or even less than 0,5 cm) and an extremely
10 small sample volume (preferably less than 5 μ l, most preferably less than 2 μ l).

Space 5 receives the coagulation detection liquid which is formed by mixing of a sample applied to the sample
15 application field 3 and a reagent system (not shown). Coagulation detection is performed in the coagulation detection zone 6 by detecting a change of a coagulation-related measurement quantity of the liquid contained therein. The resulting signals are transmitted via lines
20 9 to a measurement and evaluation unit 13 which controls the operation of the instrument. Coagulation detection can be performed by any of the methods known from the prior art, in particular by optical or electrochemical means, see e.g. US patent 5,789,664 and WO 01/11356.
25 Details of a preferred embodiment will be described below.

The system of the invention comprises a temperature measuring device 7 which is suitable for measuring the
30 temperature of the coagulation detection zone 6. For example infrared temperature detection can be used as described in WO 01/33214. Preferably, however, a temperature measurement sensor, in particular a thermistor, is integrated as element temperature sensor
35 14 into test element 2 and connected by plug-in contacts

to the electronics of the instrument. Additionally a instrument temperature sensor 15 may be provided and used as will be described in more detail below.

- 5 Test element 2 carries information relating to test type and reagent lot in an information field 10 which is evaluated by an element information reader 11. The detected information signal is transmitted via lines (not shown) to the measurement and evaluation unit 13.
- 10 Information field 10 and information reader 11 are shown only schematically. A barcode and an appropriate barcode detector can be used as a preferred example.

- A ROM key 16 sits exchangeably in a ROM key holder 17 and is connected to the central measurement and evaluation unit 13 for data exchange therewith. It includes a memory 18 in which data required for evaluation of the test are stored. These data may depend on the manufacturing lot of the test element. Preferably information field 10
- 20 contains identification data which are specific for the manufacturing lot of the particular test element 2. This information is read by information reader 11 and compared with lot identification data stored in ROM key 16 in order to make sure that the ROM key inserted into the
- 25 instrument corresponds to the manufacturing lot of the test element 2.

- Memory 18 of ROM key 16 also includes data describing the mathematical relationship of coagulation time versus
- 30 temperature which is used for calculating the desired coagulation parameter for a standard temperature from the coagulation time measured at a non-standard temperature. Alternatively these data may also be contained in a permanent memory of instrument 1.

The central measurement and evaluation unit 13 may consist of conventional electronic circuitry including an ASIC 20 and a circuit board 21. It comprises a programmable microprocessor for controlling the instrument functions and performing the required calculations. In particular it combines the signal information received from coagulation detection device 6, element information device 11, non-volatile memory 18 and temperature measuring device 7 to derive the desired coagulation parameter. This result is transmitted to a display (not shown) of instrument 1. Power for the instrument operation is provided by a battery 22.

Most parts of the system shown in figure 1 are conventional and no further details need to be described. Deviating from the prior art, however, instrument 1 must not be equipped with a thermostating system including a heater and electric heating control. Rather it uses a temperature measuring device 7 for measuring (directly or indirectly) the temperature of the coagulation detection liquid in the coagulation detection area and the mathematical relationship stored in memory 18 to calculate the coagulation parameter for the standard temperature.

During experimental evaluation of the invention it has been adequately demonstrated that measuring the temperature adjacent to the space in which the coagulation detection liquid is contained is sufficient to allow accurate calculation of a desired standard coagulation parameter (which would have been obtained at a controlled temperature of approximately 37°C) from measurements performed at a deviating (generally substantially lower) temperature using a mathematical relationship which is independent of the respective

sample and can therefore be stored in a non-volatile memory of the instrument and repeatedly used for a plurality of different individuals (patients). The measurement and evaluation unit 13 is adapted to perform
5 the required calculations.

Figures 2 and 3 show important design features of a preferred embodiment of a coagulation test system partly as top view showing a preferred layout of test element
10 layers and partly as block diagram of the electronics. This preferred embodiment is in particular characterized by two aspects:

- Coagulation detection is performed by an arrangement of reagents and electrodes as shown in the upper part
15 of figure 2.
- The required accurate measurement of the temperature of the coagulation detection zone is achieved by the combined use of an element temperature sensor 14 integrated into the test element and an instrument
20 temperature sensor 15 located at the instrument (relatively remote from the coagulation detection zone 6).

Both these aspects can be combined. In this case the test
25 element preferably has two layers of electric leads such as layers A and B shown in figure 2. Such layers can be applied in known manner onto a non-conducting (plastic) carrier foil and separated by an isolating layer. Electrical contact between the electrode arrangement
30 provided by the leads of the layers and the instrument is achieved by element contact pads 25 and 26 respectively which provide electrical connection with corresponding instrument contacts 27 (figure 1). In order to provide transport of the sample liquid from a sample application
35 opening 3 to a coagulation detection zone 6 a capillary

channel 4 is provided on top of layer A. All these design elements can be embodied by known means therefore no further description thereof is required.

5 Electrode arrangement A of figure 2 comprises five electrodes including a first counter electrode 30, a drop detection electrode 31, a working electrode 32, a second counter electrode 33 with two fingers 34 surrounding the working electrode 32 and a stirrup-shaped fill detection
10 electrode 35. The electrode structure may be produced e.g. by laser ablation techniques out of gold layers of about 50 μm thickness.

Counter electrode 30 is located close to fill opening 3
15 and is covered by a reference reagent layer 37 containing e.g. Ag/AgCl. Working electrode 32 and second counter electrode 2 are covered by a coagulation detection reagent 38 which includes the required reagent system to start the reactions of the coagulation path. Reagent
20 layer 38 also contains any reagents required for detection of the appropriate measurable property, in particular in the preferred case of enzymatic detection of coagulation a substrate of the respective enzyme, for example the substrate electrozyme TH of the enzyme
25 thrombin.

A test protocol performed with the system shown in figure 2 may include the following steps:

- The instrument is switched on automatically by
30 inserting a test element and usual operation checks are performed.
- When a sample drop is applied to sample opening 3 of capillary channel 4 and the liquid bridges first counter electrode 30 and drop detection electrode 31
35 this may be detected by applying a suitable AC-

potential to these electrodes and detecting a sharp drop of the impedance when both electrodes are contacted by the liquid.

- 5 - When the blood sample is further drawn into capillary channel 4 (by capillary action) its arrival at working electrode 32 and second counter electrode 34 can again be detected by applying a suitable AC-potential to these electrodes. The wetting of working electrode 32 is also a suitable starting point for the coagulation time measurement as it coincides with dissolving of reagent layer 38 and therefor with the start of the coagulation reaction sequence.
- 10 - Complete fill of capillary 4 is detected by a current flowing between fill detection electrode 34 and second counter electrode 33.
- 15 - An enzyme activity is detected as measurable property of the coagulation detection liquid by electrochemical means. To this end after complete fill of capillary 4 a suitable constant DC-potential is applied to working electrode 32 with reference to first counter electrode 30. Thereafter current measurements are taken at suitable intervals (e.g. 0.1 seconds). When at the end of the coagulation path the enzyme Thrombin is formed it cleaves an electrochemically active group from the substrate contained in reagent layer 38 thereby causing an increase of the current which is characteristic of the enzyme formation. This change defines the end of the coagulation time which is used for deriving the desired coagulation parameter in known manner.
- 20
- 25
- 30

Layer B shown in figure 2 is an example of electric leads suitable as element temperature sensor 14. Its temperature sensitive range 40 is defined by the area in

which a very thin and narrow electric thermistor-conductor runs, typically in a meandering manner as shown in more detail in figure 3. Conductor 41 can be made from typical thermistor material with a large dependence of resistance versus temperature. However, also materials more common for test element manufacturing including a gold layer of sufficiently small thickness (less than 100 μm) has been found suitable.

10 The resistance of the thermistor-conductor 41 is measured by a four-terminal arrangement where two terminals 42,43 are used for feeding a constant current into thermistor-conductor 41 and two separate terminals 44,45 are used to measure the resistance in current-free manner.

15 During operation of the system the temperature signal generated by element temperature sensor 14 is used in combination with the signal generated by instrument sensor 15 to determine a reliable temperature value of high accuracy to be used for calculation of the coagulation parameter for the standard temperature from a measurement performed at a (lower) non-standard temperature:

- 25 - The element temperature sensor 14 is only used to provide information about temperature changes in close proximity of the coagulation detection zone 6. It is therefore not necessary for this sensor and the temperature measurement electronics 46 (which is part of measurement and evaluation electronics 13) to allow temperature measurement in absolute quantities.
- 30 - Instrument temperature sensor 15 is used to provide temperature information relative to the standard temperature. This temperature information has to be absolute in the sense that the measured difference from the standard temperature is (with a high degree
- 35

of accuracy) the same for all instruments which is a necessary requirement for using the same mathematical relationship of coagulation time versus temperature for the temperature conversion of all instruments.

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In practical use after insertion of a test element 2 into instrument 1 the temperature of element temperature sensor 14 is monitored to derive an information about the change of the element temperature versus time or in other words the speed of element temperature change. Only when this speed of change falls below an acceptable value (in other words only when the temperature of the element 2 is sufficiently constant) a signal is given that a drop of a sample may be applied to the test element to perform a determination of coagulation parameter. If this condition is met the temperature value of instrument temperature sensor 15 is used as "true" temperature for the conversion.

20 Preferably not only the temperature change of element temperature sensor 14 but also the temperature change of instrument temperature sensor 15 is monitored. Even better results are achieved if a coagulation determination takes place only when the speed of change of both temperature sensors is below a suitable limit (which may be different for both sensors) indicating a highly constant temperature environment.

During experimental evaluation of the invention it has been found that by these means a temperature measurement is possible which fulfills even the extremely high requirements of coagulation tests. Simultaneously due to the fact that the test element temperature sensor need not provide absolute temperature values it can be incorporated relatively inexpensively into the disposable

test elements. The instrument temperature sensor 15 needs not be located inside the instrument. Rather it can be even advantageous to locate sensor 15 at the outside of the instrument in a position where the environmental temperature is measured.

Figure 4 shows experimental results which were generated as follows:

- 10 - Samples from 27 different patients and four standard liquids ("normals ") were taken, each separated in multiple aliquots.
- 15 - From each sample four measurements of PT^T -values were made at four non-standard temperatures between 16° and 32°C (using four aliquots). These measurements were performed with a CoaguCheck®S instrument as manufactured by the applicant which was modified by disabling its thermostating system. Temperature variation was provided by positioning the instrument in a temperature chamber.
- 20 - In order to improve the precision and increase the data base each of these measurements was performed with four different instruments.
- Simultaneously for each sample PT^{37} was determined using a conventional CoaguCheck®S system with
25 thermostating.

From the results PT-ratios $Y=PT^{37}/PT^T$ were calculated. These PT-ratios are shown in figure 2 relative to a temperature ratio X calculated by dividing the respective
30 measurement temperature T (in °C) by 37.

Figure 4 shows that all data are very close to a curve $Y=f(X)$ determined by regression analysis therefrom. In this case the curve is a second order polynomial as shown

in figure 4. This proves the surprising fact that the temperature dependence can be described by a single functional relationship independent on the source of the samples used.

5

With respect to the temperature it was convenient during the practical experiments to use temperature ratios (as shown in place of the absolute temperatures). Evidently $Y=f(X)$ can be easily transformed to $Y=PT^{37}/PT^T=f(T)$.

10 Furthermore an equation for calculating PT^{37} is easily found by solving this equation for PT^{37} :

$$PT^{37} = f(T) * PT^T$$

Figure 5 shows a comparison of INR-values determined according to the invention (designated INR_{INV}) with
15 corresponding data determined by a reference method (INR_{CKS}). INR values are calculated by forming a ratio between PT and a Median Normal PT (MNPT) as is well known in the art. The figure shows that the results generated
20 by both methods are in excellent agreement with a Mean Relative Deviation (MRD) of 3,74%. It should be noted that the values of INR_{INV} were determined with ambient temperature measurements between about 16°C and 32°C whereas the reference values INR_{CKS} were determined at the
25 standard temperature of 37°C.

Figures 6 to 10 show the results of experiments performed with a smaller number of samples but a plurality of different methods. In each case a ratio of a coagulation
30 parameter at a standard temperature and the same parameter at the respective non-standard temperature (designated Y for PT-ratios, Z for INR-ratios and V for APTT-ratios) is plotted against the temperature ratio X. The individual figures are based on experiments using the
35 following coagulation test systems:

Figure 6:

CoaguCheck® S Low ISI PT Strips. These tests use dry Low ISI thromboplastin derived from human recombinant tissue factor requiring non-anticoagulated fresh venous or capillary blood. The samples were from patients on oral anticoagulant treatment.

Figure 7:

CoaguCheck® S Low Volume PT Strips. These strips contain High ISI thromboplastin derived from rabbit brains requiring non-anticoagulated fresh venous or capillary blood.

Figure 8:

Amelung 4 Channel Lab Analyzer with Low ISI Lab reagent. This reagent contains Ortho Recombiplastin PT derived from human recombinant tissue factor requiring citrated plasma.

Figure 9:

Amelung 4 Channel Lab Analyzer with High ISI Lab reagent. This reagent includes Dade C Plus PT derived from rabbit brains requiring citrated plasma.

Figure 10:

Amelung 4 Channel Lab Analyzer with Ortho Auto APTT Lab reagent requiring citrated plasma.

In each case the resulting data can be described for all samples by a single functional relationship as shown in the figures. Thus the invention is applicable to different types of coagulation tests including both "dry chemistry" and "wet chemistry" test.

Patent Claims

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1. System for the determination of a coagulation parameter of blood or plasma samples of patients, said system comprising

10 a disposable test element (2) including a reagent system (38) to be mixed with the sample, thereby forming a coagulation detection liquid, and a coagulation detection zone (5) where the coagulation detection liquid is contained for monitoring a measurable property of the coagulation detection
15 liquid, said measurable property changing during coagulation, and

an instrument (1) with a holder (8) for holding said disposable test element (2) inserted therein and with a measurement and evaluation electronics (13) adapted
20 for detecting a signal which corresponds to the measurable property of the coagulation detection liquid and including a time measurement electronics for measuring a coagulation time required for said change to occur for deriving the desired coagulation
25 parameter therefrom,

wherein

the coagulation time is determined at a non-standard temperature of the coagulation detection liquid different from a standard temperature for the
30 respective coagulation parameter, said non-standard temperature being measured by a temperature measurement device (7),

the instrument (1) has a non-volatile memory (18) containing data which define a mathematical

relationship of coagulation time versus temperature which relationship is independent of the individual patient whose blood is examined, and

the coagulation parameter for the standard

5 temperature is calculated from the coagulation time measured at said non-standard temperature, using said mathematical relationship.

2. System according to claim 1, wherein the instrument
10 contains no device for thermostating the test element with the coagulation detection liquid contained therein, whereby the temperature of the test element and of the coagulation detection liquid depends on the temperature of the environment in which the
15 measurement is performed.

3. System according to any one of the preceding claims, wherein the instrument is battery-operated.

20 4. System according to any one of the preceding claims, wherein

the disposable test element includes an element temperature sensor (14) integrated therein,

25 the instrument includes an instrument temperature sensor (15)

the measurement and evaluation electronics (13) is adapted to derive

- from the signal of the instrument temperature sensor (15) a temperature value relative to the
30 standard temperature and
- from the signal of the element temperature sensor (14) an information about the speed of change of the element temperature versus time and

the measurement and evaluation electronics (13) uses the temperature value derived from the instrument temperature sensor for calculating the coagulation parameter for said standard temperature from the coagulation time measured at said non-standard temperature only when the speed of change of the element temperature versus time is smaller than a limiting value thereof.

5. System according to any one of the preceding claims, wherein the coagulation detection zone (6) is outside the instrument housing when the test element (2) is inserted in the holder.

6. System according to any one of the preceding claims, wherein the instrument (1) comprises an interchangeable machine readable data storage element, in particular a ROM key (16), said interchangeable data storage element including the memory (18) containing the data which define the mathematical relationship of coagulation time versus temperature.

7. System according to claim 6 wherein the test element comprises a machine readable code (10) containing identification data which are specific for the manufacturing lot of the test element (2) and the instrument has a reader (11) for reading said machine readable identification code (10) for checking by the measurement and evaluation electronics (13) that a ROM key (16) inserted into the instrument corresponds to the manufacturing lot of the test element (2).

8. Disposable test element adapted for a system according to any one of claims 1 to 7.

9. Test element according to claim 8 comprising a temperature measurement sensor (14), in particular a thermistor, and plug-in contacts allowing transfer of temperature signals of the temperature sensor to an instrument into which it is inserted.
10. Method for the determination of a coagulation parameter of a blood or plasma sample of a patient, wherein
- a reagent system (38) is mixed in a disposable test element (2) with the sample to form a coagulation detection liquid in a reaction detection zone (6) of the element (2) and a measurable property of the coagulation detection liquid is monitored, said measurable property changing during coagulation, a signal which corresponds to the measurable property of the coagulation detection liquid is detected and a time required for said change to occur is measured for deriving the desired coagulation parameter therefrom,
- wherein
- the coagulation time is determined at a non-standard temperature of the coagulation detection liquid different from a standard temperature for the respective coagulation parameter, said non-standard temperature being measured,
- data which define a mathematical relationship of coagulation time versus temperature are taken from a non-volatile memory (18) of the instrument (1), said relationship being independent of the individual patient whose blood is examined, and

the coagulation parameter for the standard temperature is calculated from the coagulation time measured at said non-standard temperature, using a mathematical relationship of coagulation time versus temperature which relationship is independent of the individual patient whose blood is examined.

11. System according to claim 1 or method according to claim 10, wherein the measurable property is the activity of an enzyme which participates in the coagulation pathway of the coagulation detection liquid.
12. System or method according to claim 11 wherein the activity of the enzyme is detected by electrochemical means.
13. System according to claim 1 or method according to claim 10, wherein the same mathematical relationship is used for all determinations of a given coagulation parameter performed with the instrument, independent of the reagent lot.
14. System according to claim 1 or method according to claim 10, wherein the mathematical relationship is determined by measuring the coagulation time for a plurality of different samples at different temperatures using the same type of instrument and reagents.