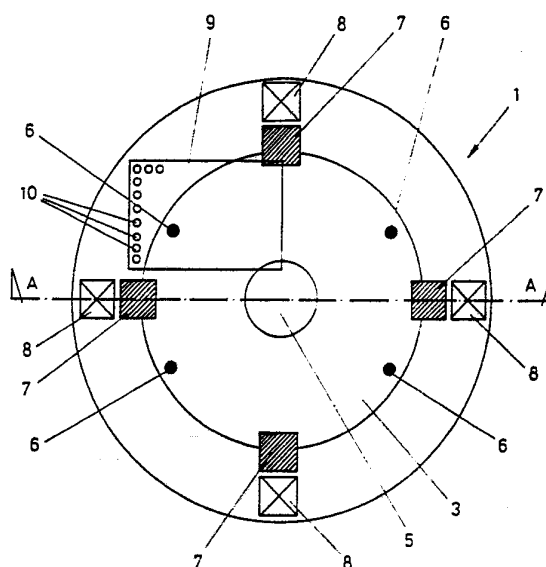




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : G01N 33/48, B01F 11/00	A1	(11) International Publication Number: WO 92/10754 (43) International Publication Date: 25 June 1992 (25.06.92)
(21) International Application Number: PCT/GB91/02181 (22) International Filing Date: 9 December 1991 (09.12.91) (30) Priority data: 9026706.3 7 December 1990 (07.12.90) GB 9122053.3 17 October 1991 (17.10.91) GB (71) Applicant (for all designated States except US): EURO/DPC LIMITED [GB/GB]; 31 Station Lane, Witney, Oxfordshire OX8 6AN (GB). (72) Inventor; and (75) Inventor/Applicant (for US only) : WILLIAMS, Aled [GB/GB]; Gorwel, Llanfairfechan, Gwynedd LL56 3JQ (GB). (74) Agent: AUSTIN, Hedley, William; Urquhart-Dykes & Lord, Alexandra House, Alexandra Road, Swansea, West Glamorgan SA1 5ED (GB).		(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>

(54) Title: ANALYTICAL APPARATUS AND METHOD**(57) Abstract**

The apparatus comprises: a) a reagent package comprising at least one open topped receptacle; b) a support structure for the package comprising a platform having a plurality of magnetisable elements arranged around its edge; c) a plurality of electromagnets, each being spaced from and adjacent to a corresponding magnetisable element, and being arranged to produce controlled oscillatory movement of the support structure so as to induce circulation in a reaction mixture present in the or each receptacle; and d) a device such as a video camera for monitoring the extent of reaction (such as coagulation reaction) during induction of the circulation. The method comprises locating a reaction mixture within the or each receptacle, electromagnetically inducing circulation of the reaction mixture and monitoring the extent of the reaction during induction of the circulation.

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Analytical Apparatus and Method

The present invention is concerned with an analytical method and apparatus, useful, inter alia, for inducing and monitoring coagulation and other reactions.

The apparatus according to the present invention is particularly applicable for studying the coagulation of human blood (although it can be used for any other reaction involving viscosity change or where thorough circulation and mixing is required in an open-topped receptacle). It is often necessary to detect the precise time at which coagulation occurs following the addition of certain substances to blood. The analysis generally comprises agitation of the sample whilst simultaneously monitoring its viscosity. It is known to shake reaction vessels (such as microplates) during an analytical procedure and subsequently monitor the extent of the reaction. However, with such apparatus it is difficult, or impossible, to carry out reproducible sample agitation.

There is now provided by the present invention an analytical method and apparatus capable of simultaneously agitating and monitoring one or more samples, such that the agitation is carried out in a controlled and reproducible manner. According to the present invention, therefore, there is provided analytical apparatus comprising:

- a) a reagent package comprising at least one open-topped receptacle arranged for the reaction therein of a sample and a reagent;
- b) support means for said package comprising a platform having, around a peripheral region thereof, a plurality of magnetisable elements;

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- c) a plurality of electromagnets, each being spaced from and adjacent to a corresponding magnetisable element, and being arranged to produce controlled oscillatory movement of said support means and thereby inducing circulation in a liquid present in the or each said receptacle about a respective vertical axis in the or each said receptacle; and
- d) means for monitoring the extent of reaction between said sample and said reagent during induction of said circulation.

It is preferred that the magnetisable elements are located at substantially equi-distant positions around the peripheral region of the platform. Typically the magnetisable elements are of mild steel or other ferromagnetic material.

In use of apparatus according to the invention each electromagnet is preferably switched sequentially (using known stepper motor technology) so as to cause attraction between a respective electromagnet and its corresponding adjacent magnetisable element. The frequency, amplitude and direction of this sequential "attraction process" can be varied and thus a vortex can be induced in the liquid in each receptacle, rotating around a vertical axis.

Typically, the monitoring means can be arranged to follow separately the reaction within a single receptacle or simultaneously the reactions within a plurality of receptacles.

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A floating object is often included in each receptacle and the monitoring means follows the movement characteristics of this object. This gives a measure of the sample viscosity and hence an indication of the extent of the reaction. Suitable monitoring means include any one of the following:-

- a) a video camera arranged to view a plurality of receptacles simultaneously;
- b) an optical device such as a photodiode arranged to view each receptacle individually;
- c) a scanning device arranged to view receptacles in turn (e.g. using optical fibres or a beam splitter); or
- d) electromagnetic means to detect a change in flux linkage with said object.

There is further provided a method comprising:-

- a) locating within at least one open topped receptacle, disposed on a platform; a reaction mixture comprising a sample and reagent capable of undergoing a coagulation reaction with said sample;
- b) electromagnetically inducing circulation of said reaction mixture in the or each said receptacle about a respective vertical axis by controlled oscillatory movement of said platform; and
- c) monitoring the extent of reaction between said sample and said reagent during induction of said circulation.

The invention will now be further illustrated, by way of example only, with reference to the accompanying drawings wherein:-

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Figure 1 is a plan view of apparatus according to the invention; Figure 2 is a vertical section along plane A-A of Figure 1; and Figure 3 is an enlarged plan view of a single receptacle used in the apparatus of Figure 1.

Referring to Figures 1 and 2 there is shown apparatus generally designated 1 comprising a base portion 2, a movable support 3 and an uppermost platform 4. Central axis 5 attaches the upper face of base portion 2 to support 3, whereas support legs 6 attach the upper face of support 3 to the lower face of platform 4. Fixed to platform 4, at substantially equi-distant positions, are four magnetisable elements 7. In the illustrated embodiment, these extend outwards beyond the outer circumference of support 3. Support legs 6 and magnetisable elements 7 occupy alternating positions around the periphery of support 3. Remote from support 3 and adjacent to each element 7 are separate electromagnets 8. Each electromagnet 8 sequentially attracts the corresponding adjacent magnetisable element 7 to produce oscillatory vibrational movement of platform 4. Microplate 9 lies on the surface of platform 4 and comprises an array (such as an 8 x 12 array) of open-topped microwells 10.

Referring to Figure 3 there is shown the circulation of the reagents within each microwell 10 as a result of the oscillatory movement of platform 4; this is anticlockwise in the illustrated embodiment, but it is of course possible to arrange for the circulation to be clockwise.

Claims:

1. Analytical analysis comprising:
 - a) a reagent package comprising at least one open-topped receptacle arranged for the reaction therein of a sample and a reagent;
 - b) support means for said package comprising a platform having, around a peripheral region thereof, a plurality of magnetisable elements;
 - c) a plurality of electromagnets, each being spaced from and adjacent to a corresponding magnetisable element, and being arranged to produce controlled oscillatory movement of said support means and thereby inducing circulation in a liquid present in the or each said receptacle about a respective vertical axis in the or each said receptacle; and
 - d) means for monitoring the extent of reaction between said sample and said reagent during induction of said circulation.
2. Apparatus according to claim 1, wherein said magnetisable elements are located at substantially equi-distant positions around the peripheral region of said platform.
3. Apparatus according to claim 1 or 2, wherein said magnetisable elements comprise mild steel.
4. Apparatus according to any of claims 1 to 3, wherein the monitoring means is arranged to follow separately the reaction within a single receptacle or simultaneously the reactions within a plurality of receptacles.
5. Apparatus according to any of claims 1 to 4, wherein said monitoring means comprises a video camera arranged to view a plurality of receptacles simultaneously; an optical device arranged to view each receptacle individually; a scanning device arranged to view receptacles in turn; or electromagnetic means arranged to detect a change in flux linkage with a floating object included in each receptacle.

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6. An analytical method which comprises:-
 - a) locating within at least one open topped receptacle, disposed on a platform; a reaction mixture comprising a sample and a reagent capable of reacting with said sample;
 - b) electromagnetically inducing circulation of said reaction mixture in the or each said receptacle about a respective vertical axis by controlled oscillatory movement of said platform; and
 - c) monitoring the extent of reaction between said sample and said reagent during induction of said circulation.
7. A method according to claim 6, which is carried out in apparatus according to any of claims 1 to 5.

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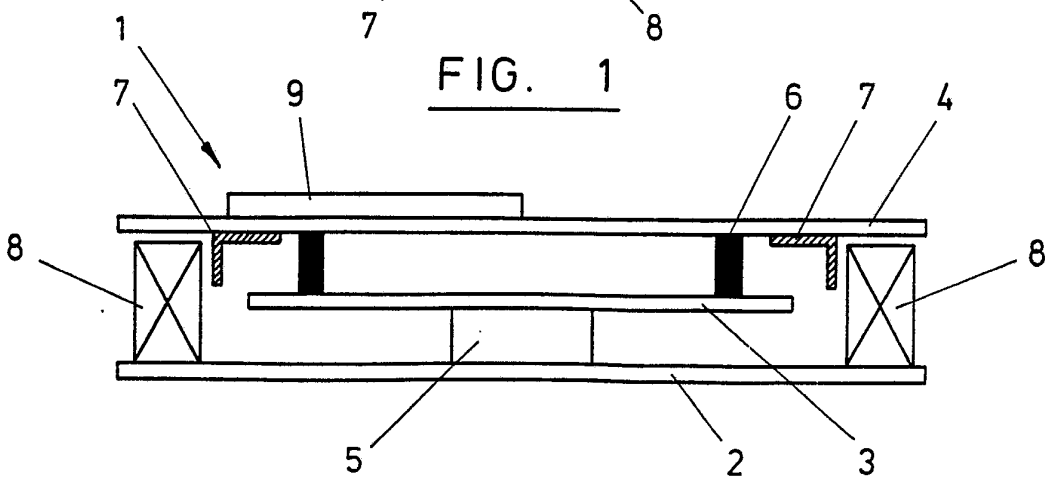
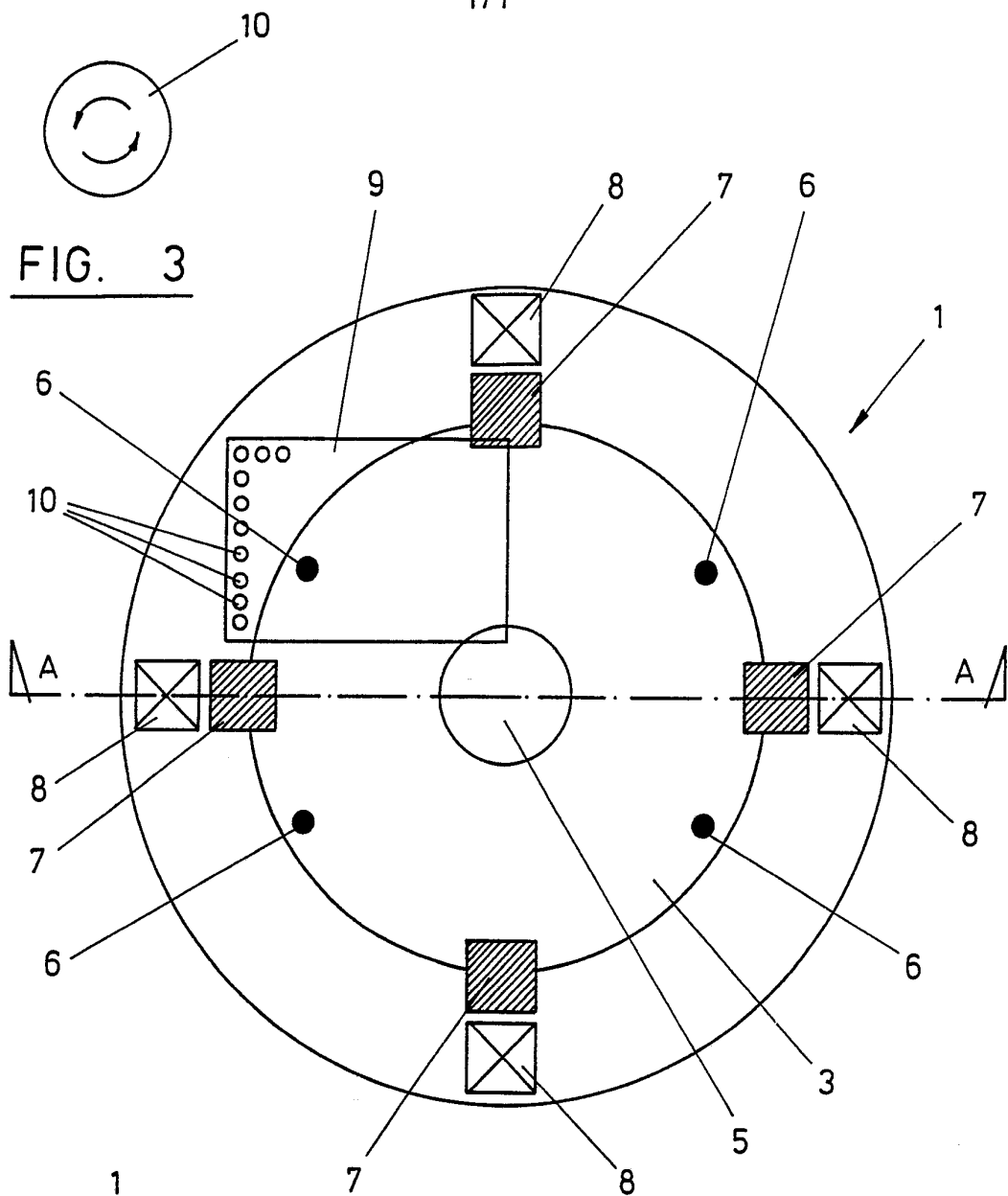


FIG. 2

INTERNATIONAL SEARCH REPORT

PCT/GB 91/02181

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 G01N33/48; B01F11/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	G01N ; B01F ; B01L	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 325 874 (SERBIO) 2 August 1989 see abstract see claim 19; figure 1 ---	1,3,6,7
A	Dynatech Laboratories Ltd product information see the whole document ---	1,4,7
A	US,A,3 650 698 (TECHNICON CORPORATION) 21 March 1972 see abstract; figures 1,3 ---	1,3,6,7
A	EP,A,0 063 744 (KERNFORSCHUNGSANLAGE JULICH) 3 November 1982 see abstract; figure 1 ---	1,4,7

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¹⁰ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "A" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
19 MARCH 1992	31. 03. 92	
International Searching Authority	Signature of Authorized Officer	
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0 308 994 (GOROG,PETER) 29 March 1989 see abstract see column 3, line 56 - column 4, line 1; figure 1 ---	1,5

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. GB 9102181
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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0325874	02-08-89	FR-A- 2625564	07-07-89
		FR-A- 2634020	12-01-90
		JP-A- 1213572	28-08-89
		US-A- 4918984	24-04-90

US-A-3650698	21-03-72	BE-A- 759811	03-06-71
		CA-A- 959741	24-12-74
		CA-A- 944266	26-03-74
		CH-A- 561422	30-04-75
		DE-A, B, C 2058973	16-06-71
		FR-A- 2072819	24-09-71
		GB-A- 1325730	08-08-73
		GB-A- 1340829	19-12-73
		NL-A- 7016252	08-06-71
		US-E- RE27866	01-01-74
		SE-B- 366121	08-04-74
		SE-B- 403937	11-09-78

EP-A-0063744	03-11-82	DE-A- 3115745	25-11-82

EP-A-0308994	29-03-89	EP-A, B 0129425	27-12-84
