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(54) Title: CHARGE PERTURBATION DETECTION SYSTEM FOR DNA AND OTHER MOLECULES

(57) Abstract: Methods and apparatus for direct detection of chemical reactions are provided. In a preferred embodiment, electric charge perturbations of the local environment during enzyme-catalyzed reactions are sensed by an electrode system with an immobilized target molecule. The target molecule is preferably DNA. The charge perturbation caused by the polymerase reaction can uniquely identify a DNA sequence. The polymerization process generates local perturbations of charge in the solution near the electrode surface and induces a charge in a polarazible gold electrode. This event is detected as a transient current by a voltage clamp amplifier. Detection of single nucleotides in a sequence can be determined by dispensing individual dNTPs to the electrode solution and detecting the charge perturbations. Alternatively, multiple bases can be determined at the same time.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/40558

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **C12M l/34(** 2006.01);C12N **11/16(** 2006.01);G01N 15/06(2006.01)

USPC: 435/6,283. l,287.2;422/68. 1,82.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 283. 1, 287.2; 422/68. 1, 82.01

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,164,3 19 A (HAFEMAN et al) 17 November 1992 (17.1 1.1992) columsn 5-8, 20 and fig. 1.	1-5, 8-1 1, 13-17 ---------- 6-8, 12, 18-19
X --- Y	US 2002/0123048 A1 (GAU) 05 September 2002 (05.09.2002) paragraphs 58-78, 110, 181.	1-3, 6-10, 13 ---------- 4-5, 11-12, 14-19
Y	US 2004/0197793 A1 (HASSIBI et al) 7 October 2002 (07 10.2004) paragraph 180.	12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categones of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent 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 pπor to the international filing date but later than the pnoπty 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 when the document is taken alone

"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

"&" document member of the same patent family

Date of the actual completion of the international search

05 November 2007 (05. 11.2007)

Date of mailing of the international search report

20 DEC 2007

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/40558

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. Ill Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-19

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-19, drawn to a device for detecting a reaction.

Group 2, claim(s) 20-32, drawn to a method for detecting a chemical reaction.

The inventions listed as Groups 1 & 2 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking Groups 1 & 2 appears to be that both groups relate to a polarizable electrode adjacent to molecules in a container having a reaction medium.

However, Hafeman et al (U.S. Patent No. 5,164,319) teach the device fore detecting charge perturbation, the device comprising a container for containing reaction medium having reactant and targets (i.e. channel, #16), a polarizable electrode in the container (#14, counter electrode, Column 2) an amplifying circuit for maintaining a potential in the electrode and generating a signal in response to perturbation (Column 20, lines 17-61) and a detector for detecting the signal (Column 20, line 17-Column 21, line 2).

Therefore, the technical feature linking Groups 1 & 2 do not constitute a special technical feature as defined under PCT Rule 13.2 because it does not define a contribution over the prior art.