

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 August 2006 (24.08.2006)

PCT

(10) International Publication Number
WO 2006/089086 A3

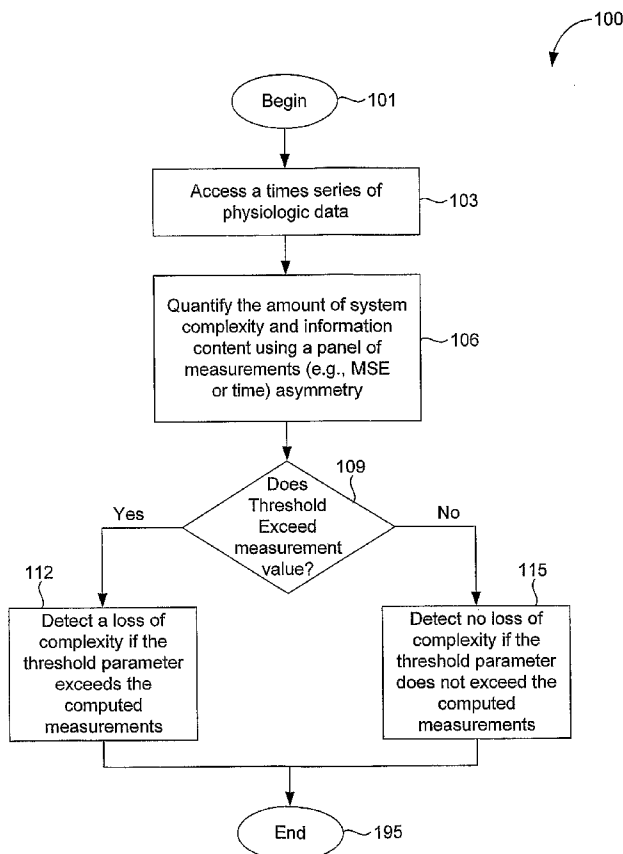
- (51) International Patent Classification:
A61B 5/00 (2006.01)
- (21) International Application Number:
PCT/US2006/005581
- (22) International Filing Date:
17 February 2006 (17.02.2006)
- (25) Filing Language:
English
- (26) Publication Language:
English
- (30) Priority Data:
60/654,079 18 February 2005 (18.02.2005) US

- (71) Applicants and
- (72) Inventors: GOLDBERGER, Ary L. [US/US]; 39 Spaulding Lane, Newton Centre, Massachusetts 02459 (US). PENG, Chung-Kang [US/US]; 40 Spring Lane, Sharon, Massachusetts 02067 (US). COSTA, Madalena [PT/US]; 121 Park Drive, Apt. 22, Boston, Massachusetts 02215 (US).
- (74) Agents: RAY, MICHAEL, B. et al.; STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C., 1100 New York Avenue, N.W., Washington, District Of Columbia 20005 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(71) Applicant (for all designated States except US): BETH ISRAEL DEACONESS MEDICAL CENTER, INC. [US/US]; 330 Brookline Avenue, Boston, Massachusetts 02215 (US).

[Continued on next page]

(54) Title: COMPLEXITY-BASED DYNAMICAL ASSAY FOR ASSESSING THE TOXICITY AND EFFICACY OF PHARMACEUTICAL AND OTHER THERAPEUTIC INTERVENTIONS



(57) Abstract: In a subject undergoing therapeutic intervention, efficacy of the therapeutic intervention is assessed based on a series of physiologic data associated with the subject. The series of physiologic data is analyzed to produce a measure of complexity. The complexity measure is then compared to a control. The efficacy of the therapeutic intervention is assessed based on the comparison of the complexity measure to the control. The control may be, for example, a complexity measure taken prior to initiation of the therapeutic intervention, a complexity measure taken from a different subject, or a predetermined threshold value. The measure of complexity is generated using, for example, a multiscale entropy measurement (MSE), a time asymmetry measurement, and/or an information-based similarity measurement. An increase in complexity indicates a positive effect of the therapeutic intervention, while a decrease in complexity indicates a negative effect of the therapeutic intervention.

WO 2006/089086 A3



(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
25 October 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/05581

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61B 5/00 (2007.01) USPC - 600/301 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) IPC(8) - (2007.01) USPC - 600/301		
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) USPTO EAST System (US, USPG-PUB, EPO, DERWENT), MicroPatent, IP.com, google Scholar, google		
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 6,631,291 B2 (VIERTIO-OJA et al) 21 November 2002 (21.11.2002) entire document	1-4, 7-9, 14-15, 17-18, 23-24, 26-27
Y	US 6,490,478 B1 (ZHANG et al) 25 September 2000 (25.09.2000) entire document	5-6, 10-13, 16, 19-22, 25, 28-31
Y	Suder et al. One-dimensional, nonlinear determinism characterizes heart rate pattern during paced respiration. Am J Physiol Heart Circ Physiol. 1998, vol. 275, pages 1092-1102, [retrieved on 2007-05-10].	5
Y	Suder et al. One-dimensional, nonlinear determinism characterizes heart rate pattern during paced respiration. Am J Physiol Heart Circ Physiol. 1998, vol. 275, pages 1092-1102, [retrieved on 2007-05-10].	6, 16, 25
Y	Hoekstra et al. Non-linear time series analysis: methods and applications to atrial fibrillation. Ann. Ist. Super. Sanità. 2001, vol. 37, n. 3, pp. 325-333, [retrieved on 2007-05-10].	10-11, 19-20, 28-29
Y	Yang et al. Information-Based Similarity Index. 2004-10-27, [retrieved on 2007-05-11].	12-13, 21-22, 30-31
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>		
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>		
Date of the actual completion of the international search 12 May 2007	Date of mailing of the international search report 05 SEP 2007	
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774	