RESUMEN

La caracterización y tratamiento de las enfermedades cardiorrespiratorias suele ser una tarea compleja, debido a que el sistema cardiorrespiratorio de humanos y animales está influenciado por acciones reflejo, que se activan en caso de disfunción para restablecer las condiciones normales de funcionamiento. Por este motivo, la interpretación de los síntomas puede resultar contradictoria, dificultando la identificación de las causas de la enfermedad. Otro aspecto que complica el adecuado diagnóstico es que las mediciones disponibles suelen ser limitadas, ruidosas y poco confiables.

Desde hace décadas, la Ingeniería de Sistemas y Procesos, ha estado contribuyendo al modelado, optimización y control de sistemas biomédicos por entenderse que aquellos modelos matemáticos que permitan simular en forma realista estos sistemas, constituyen herramientas valiosas para asistir al personal médico a comprender los mecanismos de las enfermedades cardiovasculares y respiratorias, diagnosticar disfunciones y seleccionar tratamientos, además de representar una alternativa a la experimentación en animales.

En esta tesis se desarrolló un modelo del sistema cardiorrespiratorio humano que integra los procesos circulatorios, barorreflejo, respiratorio y de transporte de substancias así como el efecto farmacológico de drogas sobre las variables hemodinámicas. Sobre este modelo se aplicaron técnicas de optimización dinámica para calcular los perfiles temporales de drogas administradas tanto por vía intravenosa como respiratoria, a fin de optimizar ciertas funciones objetivo de interés.

Finalmente, con el propósito de desarrollar modelos “paciente-específicos”, se realizaron estudios de análisis de sensibilidad y de estimación de parámetros de los sectores circulatorio y respiratorio, a fin de caracterizar la relación entre los parámetros y las salidas de ambos sub modelos y de hallar los parámetros que mejor representen a un individuo en particular.

ABSTRACT

In general, the characterization and treatment of cardiovascular and respiratory diseases are difficult tasks because the cardio-respiratory system of humans and animals are complex processes influenced by reflex actions, which are activated to restore normal operating conditions in case of dysfunction. Therefore, the interpretation of symptoms may be contradictory, making the identification of the causes of the dysfunction a difficult activity. Another issue that complicates the proper diagnosis is that the available measurements are often limited, noisy and unreliable.

In the last decades, the Process System Engineering discipline has contributed to the modeling, optimization and control of biomedical systems, in the understanding that mathematical models that realistically simulate physiological processes can become valuable tools to assist medical staff to investigate the mechanisms of cardiovascular and respiratory diseases, diagnose dysfunctions and select treatments. Moreover, they can be an alternative to animal testing.

In this thesis, a model of the human cardio-respiratory system was developed to simulate the following processes: blood circulation, baroreflex, breathing, transport of substances and pharmacological effect of drugs on hemodynamic variables. This model was the basis of a dynamic optimization study aimed at establishing the infusion profiles of drugs, administered intravenously or via the respiratory system, in order to optimize certain objective functions of medical interest.

Finally, in order to generate "patient-specific" models a sensitivity analysis and a parameter estimation study of the circulatory and respiratory sections were performed to investigate the relationship between parameters and outputs of each sub model and to identify the parameter values that best suits a specific individual.

REFERENCIAS

Adams II T, Seider W, Practical optimization of complex chemical process with tight constraints, Computers and Chemical Engineering 32 (2008) 2099-2112.

Aittokallio T., Gyllenberg M., Polo O. Parameter estimation of a respiratory control model from noninvasive carbon dioxide measurements during sleep. Mathematical Medicine and Biology 24 (2007), 225−249

Allerød C., Rees E., Rasmussen B., Karbing D., Kjærgaard S., Thorgaard P., Andreassen S. A decision support system for suggesting ventilator settings: Retrospective evaluation in cardiac surgery patients ventilated in the ICU. Computer Method and Programs in Biomedicine 92 (2008) 205-212.

Armstrong P., Moffat J., Marks G. Arterial-Venous nitroglycerin gradient during intravenous infusion in man, Circulation 66 (1982) 1273-1276.

Ashour S., Hanna O., A New Very Simple Explicit Method for the Integration of Mildly Stiff Ordinary Differential Equations, Comp. Chem. Eng., 14 (3) (1990) 267-272.

Audoly S., Bellu G., D'Angiò L., Saccomani M. and Cobelli C. Global Identifiability of Nonlinear Models of Biological Systems. IEEE Transactions on Biomedical Engineering, Vol. 48, No 1, (2001) 55-65.

Avraam M., Shah N., Pantelides C. A Decomposition Algorithm for the Optimization of Hybrid Dynamic Processes, Computer and Chemical Engineering Suplement (1999) s451-s454.

Bahl V., Linnenger A. Hybrid simulation of continuous-discrete systems, European Symposium on Computer Aided Process Engineering – 10, Editor S. Pierucci, Elsebier, (2000) 163-168.

Baker C., Bocharov G., Paul C. and Rihan F. Computational modelling with functional differential equations: Identification, selection, and sensitivity. Applied Numerical Mathematics 53 (2005) 107–129.

Balsa-Canto E, Vassiliadis V, Banga J, Dynamic Optimization of Single- and Multi-Stage Systems Using a Hybrid Stochastic-Deterministic Method, Industrial & Engineering Chemistry Research 44 (2005) 1514-23.

Banga J., Balsa-Canto E., Moles C., Alonso A. Dynamic optimization of bioprocesses: Efficient and robust numerical strategies. Journal of Biotechnology 117 (2005) 407-419.

Bardoczky G., de Vries J., Meriläinen P., Schofield J. Tuomaala L. Side stream spirometry. Datex Division Instrumentarium Corp., Helsinki. Finland. 1996.

Barón-Esquivias G., Martínez-Rubio A., Tilt Table Test: State of The Art. Indian Pacing and Electrophysiology Journal 3 (2003) 239-252.

Barton P., Allgor R., Feehery W., Galán S. Dynamic Optimization in a Discontinuous World, Industrial & Engineering Chemistry Research 37 (1998) 966-81.

Barton P., Banga J., Galán S. Optimization of hybrid discrete/continuous dynamic systems. Computer and Chemical Engineering 24 (2000) 2171-82.

Blanco P., Feijóo R. A 3D-1D-0D Computational Model for the Entire Cardiovascular System. Mecánica Computacional Vol. XXIX, págs. 5887-5911.

Blomhøj M., Kjeldsen T., Ottesen J. Compartment models, 2005. Disponible en http://www4.ncsu.edu/~msolufse/Compartmentmodels.pdf

Boender C., Rinnooy Kan A., Timmer G. A stochastic Method for Global Optimization. Mathematical Progralmming 22 (1982) 125-140.

Breslin D., Mirakhur R., Reid J., Kyle A. Manual versus target-controlled infusions of propofol. Anaesthesia 59 (2004) 1059-1063.

Brown A. Receptors under pressure. An update on baroreceptors, Circ Res.46 (1980) 1-10.

Cagnina Leticia Cecilia. Optimización Mono y Multiobjetivo a través de una Heurística de Inteligencia Colectiva. Tesis Doctoral, 2010.

Campolongo F., Cariboni J., Saltelli A. An effective screening design for sensitivity analysis of large models. Environmental Modelling & Software 22 (2007) 1509-1518.

Carrasco E., Banga J. Dynamic Optimization of Batch Reactors Using Adaptive Stochastic Algorithms. Industrial & Engineering Chemistry Research 36 (1997).

Carson E., Cobelli C. Modelling Methodology for Physiology and Medicine. Biomedical Engineering. Academic Press, 2000

Chachuat B. Nonlinear and Dynamic Optimization: From Theory to Practice. Automatic Control Laboratory, EPFL, Switzerland. 2007.

Chang P., Matson G., Kendrick J., Rideout V. Parameter Estimation in the Canine Cardiovascular System IEEE Transactions on Automatic Control, VOL. AC-19, NO. 6, (1974).

Christiansen T., Dræby C. Modelling the respiratory system Technical report IMFUFA Roskilde University Denmark Text No 318, 1996.

Clerc M., Kennedy J. The Particle Swarm—Explosion, Stability, and Convergence in a Multidimensional Complex Space, IEEE Transactions on Evolutionary Computation Vol. 6 Nº 1 (2000)

Conn A., Gould N., Toint P. Trust-Region Methods, Society for industrial and Applied Mathematics, Philadelphia, PA, (2000)

Cooke C., Wall B., Huch K., Mangold T. Cardiovascular effects of vasopressing following V1 receptor blockade compared to effects of nitroglycerin. Am. J. Physiol. Regulatory Integrative Comp. Physiol. 281 (2001) R 887-893.

Cooper V., Hainsworth R. Effects of head-up tilting on baroreceptor control in subjects with different tolerances to orthostatic stress. Clinical Science 103 (2002), 221–226.

Coronel J., Buschiazzo H., Cañás M., Mordujovich P., Klyver B., Valsecia M., Rodríguez Echandía E., Aguirre J., Armando Meuli M. F.T.N Formulario Terapéutico Nacional. 11ava Edición. COMRA. Período 2008-2011.

Costa E., Lage Jr. P., Biscaia Jr. E. On the numerical solution and optimization of styrene polymerization in tubular reactors. Computers and Chemical Engineering 27 (2003) 1591-1604.

Csendes T. Nonlinear Parameter Estimation by Global Optimization: Efficiency and Reliability. (2005) Disponible en: http://www.researchgate.net/publication/220123651_Nonlinear_Parameter_Estimation_by_Global_Opitmization_-_Efficiency_and_reliability/file/32bfe50da030078cee.pdf

Cukier R., Fortuin C., Schuler K., Petschek A., Schaibly J. Study of the sensitivity of coupled reaction systems to uncertainties in rate coefficients, I theory, The Journal of Chemical Physics 59 (1973) 3873-78.

Cukier R., Levine H., Shuler K. Nonlinear sensitivity analysis of multiparameter model systems. Journal of Computational Physics 26 (1978) 1-42.

Deswysen B., Charlier A., Gevers M. Quantitative evaluation of the systemic arterial bed by parameter estimation of a simple model. Med. & Biol. Eng. & Comput. 18 (1980) 153-166.

Deswysen B. Parameter Estimation of a Simple Model of the Left Ventricle and of the Systemic Vascular Bed, with Particular Attention to the physical Meaning of the Left Ventricular Parameters. IEEE Transactions on Biomedical Engineering, Vol. BME-24, NO. 1, 1977

Doi M., Gajraj R., Mantzaridis H., Kenny G.: Relationship between calculated blood concentration of propofol and electrophysiological variables during emergence from anaesthesia: a comparison of bispectral index, spectral edge frequency, median frequency and auditory evoked potential index. Br J Anaesthesia 78 (1997) 180-184.

Dokos S., Lovell N. Parameter estimation in cardiac ionic models. Progress in Biophysics & Molecular Biology 85 (2004) 407–431.

Domach M. Introduction to biomedical engineering Introduction to Biomedical Engineering. Carnegie Mellon University. Prentice Hall. Second Edition. 2004.

Dua P., Pistikopulos E. Modelling and control of drug delivery systems. Comp. Chem. Eng. 29 (2005) 2290-96.

Dua P., Pistikopoulos E. Modelling and mult-parametric control for delivery of anaesthetic agents. Med. Biol. Eng. Comput. 48 (2010) 543-53.

Eberhart R., Shi Y. Particle swarm optimization: Developments, applications and resources. Proceedings of the IEEE Congress on Evolutionary Computation, IEEE Press (2001), Seoul, Korea.

Efron B., Tibshirani R. An Introduction to the Bootstrap. Chapman and Hall, New York, NY, 1993.

Eftaxias A., Font J, Fortuny A., Fabregat A., F. Stüber. Nonlinear kinetic parameter estimation using simulated annealing. Computers and Chemical Engineering 26 (2002) 1725-33

Ellwein L., Tran H., Zapata C., Novak V., Olufsen M. Sensitivity Analysis and Model Assessment: Mathematical Models for Arterial Blood Flow and Blood Pressure. Cardiovasc Eng 8 (2008) 94–108.

Ellwein L., Pope S., Xie A., Batzel J., Kelley C., Olufsen M. Modeling cardiovascular and respiratory dynamics in congestive heart failure. Descargado en el año 2012.

Fecha del paper más reciente citado en este trabajo: 2009 Disponible en: http://www4.ncsu.edu/~msolufse/OlufsenAmJPhysiolSubmitted.pdf

Faller D., Klingmüller U. and Timmer J. Simulation Methods for Optimal Experimental Design in Systems Biology. Simulation, Vol. 79, Issue 12, (2003) 717-725

Ferrari A., Gutierrez S., Biscaia Jr E., Development of an Optimal Operation Strategy in a Sequential Batch Reactor (SBR) through Mixed Integer Particle Swarm Dynamic Optimization (PSO), Computers and Chemical Engineering (2010).

Fink M., Batzel J., Tran H. A Respiratory System Model: Parameter Estimation and Sensitivity Analysis Cardiovasc Eng 8 (2008) 120–134.

Franz, G. Nonlinear rate sensitivity of the carotid sinus reflex as a consequence os static and dynamic nonliearities in baroreceptor behavior. Annals of the New York Academy of Sciences, 156 (1969) 811–824.

Galán S., Barton P. Dynamic Optimization of Hybrid Systems, Computers Chem. Engng. 22 Suppl (1998) s183-s190.

Gentilini, A., C. Frei, A. Glattfedler, M. Morari, T. Sierber, R. Wymann, T. Schnider and A. Zbinden, Multitasked closed-loop control in anesthesia, IEEE Engineering in Medicine and Biology 20 (2001) 29-53.

Ghouri A., Monk T., White P. Electroencephalogram spectral edge frequency, lower esophageal contractility, and autonomic responsiveness during general anesthesia. J. Clin. Monit. 9 (1993) 176-185.

Glass P., Bloom M., Kearse L., Rosow C., Sebel P., Manberg P. Bispectral analysis measures sedation and memory effects of Propofol, Midazolam, Isoflurane and Alfentanil in healthy volunteers. Anesthesiology 86 (1997) 836-847.

Gómez Pérez K., Dalessandro Martínez A. Modelos de sistemas fisiológicos: Sistema cardiovascular. Revista de la Facultad de Ingeniería de la U.C.V., Vol. 21, N° 3 (2006) pp. 145–161.

Gopal V., Biegler L. Nonsmooth dynamic simulation with linear programming based methods, Comp. and Chem. Engng. 21 (7) (1997) 675-689.

Gopinath R., Bequette B., Roy R., Kaufman H. Issues in the design of a multirate model- based controller for a nonlinear drug infusion system, Biotechnol. Prog. 11 (3) (1995) 318–32.

Guyton A., Coleman T., Granger H. Circulation: Overall regulation; Annu. Rev. Physiol. 34 (1972) 13-46.

Hann C., Chase J., Desaive T., Froissart C., Revie J., Steveneson D., Lambermont B., Ghuysen A., Kolh P., Shaw G. Unique parameter identification for model-based cardiac diagnosis in critical care. Proceedings of the 7th IFAC Symposium on Modelling and Control in Biomedical Systems, Aalborg, Denmark, 2009.

Hann C., Chase J., Shaw G. Integral-based identification of patient specific parameters for a minimal cardiac model. Computer Methods and Programs in Biomedicine 81 (2006) 181-192.

Harada T., Kubo H., Mori T., Sato T. Screening Parameters of Pulmonary and Cardiovascular Integrated Model with Sensitivity Analysis. Proceedings of the 28th IEEE EMBS Annual International Conference New York City, USA, Aug 30-Sept 3, 2006.

Held C., Roy R. Multiple Drug Hemodynamic Control by Means of a Supervisory-Fuzzy Rule-Based Adaptive Control System: Validation on a Model. IEEE Transactions on Biomedical Engineering Vol. 42, NO. 4. (1995).

Hengl S., Kreutz C., Timmer J. and Maiwald T. Data-based identifiability analysis of non-linear dynamical models. Bioinformatics Vol. 23 no. 19 (2007) 2612–18.

Hengstmann J., Goronzy J. Pharmacokinetics of ^{3}H-Phenylephrine in man. Eur. J. Pharmacol. 21 (1982) 335-341.

Homma T., Saltelli A. Importance measures in global sensitivity analysis of nonlinear models. Reliability Engineering and System Safety 52 (1996) 1-17.

Hosomi H., Sagawa K. Effect of pentobarbital anesthesia on hypotension after 10% hemorrhage in the dog. Am. J. Physiol 236 (1979) H607-H612.

Huang J., Roy R. Multiple-Drug Hemodynamic Control Using Fuzzy Decision Theory. IEEE Transactions on Biomedical Engineering. Vol. 45, NO. 2, (1998).

Hunter P., Borg T. Integration from proteins to organs: the Physiome Project, Nature reviews, Molecular cell biology 4 (3) (2003) 237–243.

Hvala N., Strmčnik S., Šel D., Milanič S., Banko B. Influence of model validation on proper selection of process models – an industrial case study. Computer and Chemical Engineering 29 (2005) 1507-1522.

Ichise M., Toyama H., Innis R., Carson R. Strategies to Improve Neuroreceptor Parameter Estimation by Linear Regression Analysis Journal of Cerebral Blood Flow & Metabolism 22:1271–1281 (2002).

Isaka S., Sebald A. Control Strategies for Arterial Blood Pressure Regulation, IEEE Transactions on Biomedical Engineering 40 (1993) 353-63.

ITFoM - Information Technology Future of Medicine. Future and Emerging Technologies Flagship Initiatives. http://www.itfom.eu/. 2011

Jaramillo-Magaña J. Interrelaciones entre el Sevorano y el Índice Biespectral. Anestesia en México, Suplemento 1, 2004.

Katare S., Kalos A., West D. A Hybrid Swarm Optimizer for Efficient Parameter Estimation. Evolutionary Computation Vol 1 (2004) 309-315.

Kearse L., Manberg P., Chamoun N., deBors F., Zaslavsky A. Bispectral Analysis of the Electroencephalogram Correlates with Patients Movements to Skin Incisions during Propofol/Nitrous Oxide Anesthesia. Anesthesiology 81 (1994) 1365-1370.

Kennedy J., Eberhart R. The Particle Swarm Optimization. Proceedings of the IEEE international conference on neural networks (1995) 39-43.

Kirby R., Colaw J., Douglas S. Death from Propofol: Accident, Suicide, or Murder? Anesthesia and Analgesia 108 (4) (2009) 1182-1184.

Korakianitis T., Shi Y. A concentrated parameter model for the human cardiovascular system including heart valve dynamics and atrioventricular interaction. Medical Engineering and Physics 28 (2006) 613-28.

Korner P. Integrative neural cardiovascular control. Physiological Reviews. Vol. 51, NO 2. (1971).

Kwok K., Shah S., Finegan B., Kwong G. An Observational Trial of a Computerized Drug Delivery System on Two Patients. IEEE Transactions on Control Systems Technology. Vol. 5, NO. 4, (1997).

Larsen R., Rathgeber J., Bagdhan A., Lange H., Rieke H. Effects of propofol on cardiovascular dynamics and coronary blood flow in geriatric patients. A comparison with etomidate, Anaesthesia 43 (Supplement) (1988) 25-31.

Lauzon A., Bates J. Estimation of time-varying respiratory mechanical parameters by recursive least squares. The American Physiological Society (1991).

Leier C., Heban P., Huss P., Bush C., Lewis R. Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. Circulation 58 (1978) 466-75.

Lerou J., Dirksen R., Kolmer H., Booij L., Borm G. A system Model for Closed-circuit Inhalation Anesthesia. Anesthesiology 75 (1991) 230-237.

Lewis R. (Ed.). Sax's Dangerous Properties of Industrial Materials, 11th Ed., p. 1552, Wiley & Sons, Hoboken, NJ, 2004

Liang F., Takagi S. Multi-scale modeling of the human cardiovascular system with applications to aortic valvular and arterial stenoses. Med. Biol. Eng. Comput., 47 (2009) 743–755, 2009.

Liu F., Walmsley J., Burrage K. Parameter estimation for a phenomenological model of the cardiac action potential. 2010. Disponible en: http://conferences.science.unsw.edu.au/CTAC2010/FawangLiuCTAC10.pdf

Lorandi L., Diong B., Nava P., Solis F., Menendez R., Ortiz G., Nazerad H. Parametric Sensitivity Analysis of Human Respiraitory Impedance. Proceedings of the 25 Annual International Conference of the IEEE Cancun, Mexico September 17-2 I , 2003.

Lutchen K. Sensitivity analysis of respiratory parameter uncertainties: impact of criterion function form and constraints. American Physiological Society (1990) 765-775.

Luyben W. Process modeling, simulation, and control for chemical engineers. McGraw-Hill. Second Edition. 1990.

Malan T., DiNardo J., Isner R., Frink E., Goldberg M., Fenster P. Cardiovascular effects of Sevoflurane compared with those of Isoflurane in Volunteers. Anesthesiology 83 (1995) 918-28.

Malpas. S. Editorial comment: Montani versus Osborn exchange of views, Exp. Physiol. 94 (4) (2009) 381-97.

Mao, G., L. R. Petzold, Efficient integration over discontinuities for differential-algebraic systems, Computers and Mathematics with Applications 43 (2002) 65-79.

Marseguerra M., Zio E., Podofillini L. Model parameters estimation and sensitivity by genetic algorithms. Annals of Nuclear Energy 30 (2003) 1437–56.

McNames J., Aboy M. Statistical Modeling of Cardiovascular Signals and Parameter Estimation Based on the Extended Kalman Filter. IEEE Transactions on Biomedical Engineering, Vol. 55, NO. 1, 2008

Myles P., Leslie K., McNeil J., Forbes A., Chan M. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial The Lancet Vol. 363 (2004).

Monti A., Médigue C., Mangin L. Instantaneous Parameter Estimation in Cardiovascular Time Series by Harmonic and Time-Frequency Analysis IEEE Transaction on Biomedical Engineering, Vol. 49, NO. 12, December 2002

Montier E., Struys M., De Smet T., Versichelen L., Rolly G. Closed-loop controlled administration of propofol using bispectral analysis. Anaesthesia 53 (1998) 749-754.

Olufsen M., Ottesen J., Tran H., Ellwein L., Lipsitz L., Novak V. Blood pressure and blood flow variation during postural change from sitting to standing: model development and validation. Journal of Applied Physiology 99 (2005) 1523-37.

Ottesen J., Olufsen M., Larsen J. "Applied Mathematical Models in Human Physiology", Philadelphia: Editorial Siam, 2004.

Ottesen J. The Mathematical Microscope Making the inaccessible accessible, in: BetaSys: Systems Biology of Regulated Exocytosis in Pancreatic ß-Cells, Systems Biology, Volume 2 (2011) Chapter 6, 97-121.

Ottesen J. Modelling of the baroreflex-feedback mechanism with time-delay. Journal of Mathematical Biology. Volume 36, Issue 1 (1997a) pp 41-63.

Ottesen J. Nonlinearity of baroreceptor nerves. Surv. Math. Ind. 7 (1997b) 187-201.

Pantelides C. SpeedUp - Recent advances in process simulation, Comp. Chem. Engng., Vol.12 no.7 (1988) 745-755.

Park T., Barton P. State event location in differential-algebraic models. ACM Transactions on Modeling and Computer Simulation. Vol. 6 No. 2 (1996) 137–165.

Peslin R., Papon J., Duvivier C., Richalet J. Frequency response of the chest: modeling and parameter estimation. Journal of Applied Physiology Vol. 39, No. 4, October 1975.

Prata D., Schwaab M., Lima E., Pinto J. Nonlinear dynamic data reconciliation and parameter estimation through particle swarm optimization: Application for an industrial polypropylene reactor. Chemical Engineering Science. 64 (2009) 3953-3967.

Press W., Teukolsky S., Vetterling W. and Flannery B. Numerical Recipes in Fortran 77 The Art of Scientific Computing Second Edition Volume 1 of Fortran Numerical Recipes. 1996.

Puttick R., Diedericks J., Sear J., Glen J., Foex P., Ryder W. Effect of Graded Infusion Rates of Propofol on Regional and Global Left Ventricular Function in the Dog. British Journal of Anaesthesia 69 (1992) 375-381.

Quarteroni A., Ragni S., Veneziani A. Coupling between lumped and distributed models for blood flow problems. Comput Visual Sci 4: 111–124 (2001).

Ramsay J., Hooker G., Campbell D., Cao J. Parameter estimation for differential equations: a generalized smoothing approach. J. R. Statist. Soc. B (2007) 69, Part 5, pp. 741–796.

Rampil I. A primer for EEG signal processing analysis. Anesthesiology 89 (1998) 980-1002.

Rao R., Bequette B., Roy R. Simultaneous regulation of hemodynamic and anesthetic states: a simulation study. Annals of Biomedical Engineering 28 (2000) 71-84.

Rao R., Huang J., Bequette B., Kaufman H. Control of a Nonsquare Drug Infusion System: A Simulation Study. Biotechnol. Prog. 15 (1999) 556-564.

Rees E. The Intelligent Ventilator (INVENT) project: The role of mathematical models in translating physiological knowledge into clinical practice. Computer Methods and Programs in Biomedicine 104s (2011) s1-s29.

Rees E., Allerød C., Murley D., Zhao Y., Smith B., Kjærgaard S., Thorgaard P., Andreassen S. Using Physiological Models and Decision Theory for Selecting Appropiate Ventilator Settings. Journal of Clinical Monitoring and Computing 20 (2006) 421-429.

Reyes-Sierra M., Coello Coello C. Multi-Objective Particle Swarm Optimizers: A Survey of the State-of-the-Art. International Journal of Computational intelligence Research 2 (3) (2006) 287-308.

Richardson A., Hollinger D. Statistical modeling of ecosystem respiration using eddy covariance data: Maximum likelihood parameter estimation, and Monte Carlo simulation of model and parameter uncertainty, applied to three simple models. Agricultural and Forest Meteorology 131 (2005) 191–208.

Rittner F., Döring M., "Curvas y bucles en la ventilación mecánica", Dräger. 2005. Disponible en www.respira.com.mx/docs/f1280259197-0.pdf

Rodriguez-Fernandez M., Mendes P., Banga J. A hybrid approach for efficient and robust parameter estimation in biochemical pathways. BioSystems 83 (2006a) 248-65.

Rodriguez-Fernandez M., Egea J., Banga J. Novel metaheuristic for parameter estimation in nonlinear dynamic biological systems. BMC Bioinformatics 7 (2006b).

Rosow C., Manberg P. Bispectral Index Monitoring. Anesthesiology Clinics of North America. Vol 19, NO 4. 2001.

Sacks J., Welch W., Mitchell T., Wynn H. Design and analysis of computer experiments, Statical Science 4 (1989) 409-35.

Sáez-Pérez J. Distensibilidad arterial: un parámetro más para valorar el riesgo cardiovascular, SEMERGEN - Medicina de Familia, Volume 34, Issue 6, (2008) 284–290.

Saltelli A., Chan K., Scott E. "Sensitivity Analysis". Chichester: Editorial John Wiley & Sons, 2000.

Saltelli A., Ratto M., Andres T., Campolongo F., Cariboni J., Gatelli D., Saisana M., Tarantola S. "Global Sensitivity Analysis. The Primer". Chichester: Editorial John Wiley & Sons, 2008.

Saltelli A., Ratto M., Tarantola S., Campolongo F. Sensitivity analysis practices: Strategies for model-based inference. Reliability Engineering and System Safety 91 (2006) 1109–1125.

Samar Z. Cardiovascular Parameter Estimation using a Computational Model, MSc Thesis, Massachusetts Institute of Technology, 2005.

Schlegel M., Stockmann K.; Binder T.; Marquardt W. Dynamic optimization using adaptive control vector parameterization, Computers and Chemical Engineering 29 (2005) 1731–1751.

Schlüter M., Egea J., Antelo L., Alonso A., Banga J. An Extended Ant Colony Optimization Algorithm for Integrated Process and Control System Design. Ind. Eng. Chem. Res. 48 (2009) 6723-6738.

Schnider T., Minto C., Shafer S., Gambus P., Andresen C., Goodale D., Youngs E. The Influence of Age on Propofol Pharmacodynamics. Anesthesiology 90 (1999) 1502-16.

Schwaab M., Pinto J. Análise de Dados Experimentais I. Fundamentos de Estatística e Estimação de Parâmetros. 1° edição, 2007.

Schwaab M., Biscaia E., Monteiro J., Pinto J. Nonlinear parameter estimation through particle swarm optimization. Chemical Engineering Science 63 (2008) 1542-52.

Schwender D., Daunderer M., Mulzer S., Klasing S., Finsterer U., Peter K. Spectral edge frequency of the electroencephalogram to monitor "depth" of anaesthesia with isoflurane or propofol. British Journal of Anaesthesia 77 (1996) 179-184.

Schwilden H., Stoeckel H., Schüttler J. Closed-loop feedback control of Propofol anaesthesia by quantitative EEG analysis in humans. Br. J. Anaesthesia 62 (1989) 290-296.

Sebel P., Bowles S., Chamoun N. EEG Bispectrum Predicts Movement during Thiopental /Isoflurane Anesthesia. J. Clin. Monit. 11 (1995) 83-91.

Secher A., Young A. Servoanalysis of carotid sinus reflex effects on peripheral resistance. Circ. Res, 12 (1973) 152-162.

Sher A., Cooling M., Bethwaite B., Tan J., Peachey T., Enticott C., Garic S., Gavaghan D., Noble D., Abramson D., Crampin E. A Global Sensitivity Tool for Cardiac Cell Modelling: Application to Ionic Current Balance and Hypertrophic Signaling. 32nd Annual International Conference of the IEEE EMBS Buenos Aires, Argentina, August 31 - September 4, 2010.

Shi Y., Eberhart R. A modified particle swarm optimizer, Proceedings of the IEEE Congress on Evolutionary Computation 1998, Piscataway, USA, pp. 69–73.

Siggaard-Andersen O., Wimberley P., Fogh-Andersen N., Gøthgen I. Measured and derived quantities with modern pH and blood gas equipment: Calculation algorithms with 54 equations. Scan. J. Lab. Invest. 48 (1988) 7-15.

Smith B. Minimal Hemodynamic Modelling of the Heart & Circulation for Clinical Application, PhD Thesis, Mechanical Engineering Department, Canterbury University, New Zealand, 2003.

Smith B., Chase J., Shaw G., Nokes R. Simulating transient ventricular interaction using a minimal cardiovascular system model; Physol. Meas., 27 (2006) pp. 165-179.

Soares R., Secchi A. A new environment for modelling, simulation and optimisation. Computer Aided Chemical Engineering 14 (2003): 947-952.

Sobol I. Sensitivity analysis for non-linear mathematical models. Mathematical Modelling and Computational Experiment 1 (1993) 407-414.

Spickler J., Kezdi P. Dynamic response characteristics of carotid sinus baroreceptors. Am. J. Physiol 212 (1967) 472-476.

Sreenivas Y., Lakshminarayanan S., Rangaiah G. Advanced Control Strategies for the Regulation of Hypnosis with Propofol. Ind. Eng. Chem. Res. 2009a, 48, 3880-97.

Sreenivas Y., Tian Woon Yeng, Rangaiah G., Lakshminarayanan S. A comprehensive Evaluation of PID, Cascade, Model-Predictive, and RTDA Controllers for Regulation of Hypnosis. Ind. Eng. Chem. Res. 2009b, 48, 5719-30.

Srinivas Y., Timmons W., Durkin J. A comparative study of three expert system for blood pressure control. Expert System with Applications 20 (2001) 267-274.

Srinivasan R. Nudelman H. Modeling the carotid sinus baroreceptor. Biophys. J. 12 (1972) 1171-1182.

Struys M., Smet T., Versichelen L., Van de Velde S., Van den Broecke R., Mortier E. Comparison of Closed-loop Controlled Administrationof Propofol Using Bispectral Index as the Controlled Variable versus “Standard Practice” Controlled Administration. Anesthesiology 95 (2001) 6-17.

Summers R., Ward K., Witten T., Convertino V., Ryan K., Coleman T., Hester R. Validation of a computational platform for the analysis of physiologic mechanisms of a human experimental model of hemorrhage. Resuscitation 80 (2009) 1405-10.

Sun Fan, Du Wenli, Qi Rongbin, Qian Feng, Zhong Weimin. A Hybrid Improved Genetic Algorithm and Its Application in Dynamic Optimization Problems of Chemical Processes. Chinese Journal of Chemical Engineering, 21(2) (2013) 144−154

Tackley R., Lewis G., Prys-Roberts C., Boaden R., Dixon J., Harvey J. Computer Controlled Infusion of Propofol. Br. J. Anaesth. 62 (1989) 46-53.

Taher M., Cecchini A., Allen M., Gobran S., Gorman R., Guthrie B., Lingenfelter K., Rabbany S., Rolchigo P. Baroreceptor responses derived from a fundamental concept. Annals of Biomedical Engineering Volume 16, (1988) 429-443.

Tashkova K., Silk J., Atanasova N., Dzeroski S. Parameter estimation in a nonlinear dynamic model of an aquatic ecosystem with meta-heuristic optimization. Ecological Modelling 226 (2012) 36-61.

Teiken P., Talsma G., Creamer K., Sutton C., Flores Y. Critical Care Medicine Services, Tripler Army Medical Center, Honolulu, HI, 2nd Edition, 2000.

Thomson A., Whiting B. Bayesian Parameter Estimation and Population. Clin. Pharmacokinet. 22 (6): 447-467, 1992.

Trelea I. The particle swarm optimization algorithm: convergence analysis and parameter selection Information Processing Letters 85 (2003) 317–325.

Tsai M., Pimmel R., Stiff E., Bromberg P., Hamlin R. Respiratory parameter estimation using forced oscillatory impedance data. J Appl Physiol (1977) 322-330.

Turner M., Mier C., Spina R., Ehsani A. Effects of Age and Gender on Cardiovascular Responses To Phenylephrine. Journal of Gerontology 54A (1999) M17-M24.

Uemura K., Kamiya A., Idaka I., Kawada T., Shimizu S., Shishido T., Yoshizawa M., Sugimachi M., Sunagawa K. Automated drug delivery system to control systemic

arterial pressure in acute decompensated heart failure. J. Appl. Physiol. 100 (2006) 1278-86.

Ursino M., Magosso E., Avanzolini G. An integrated model of the human ventilatory control system: response to hypercapnia. Clinical Physiology 21 4 (2001) 447-64.

Ursino M. A Mathematical Model of the Carotid Baroregulation in Pulsating Conditions. IEEE Transactions on Biomedical Engineering. Vol. 46 Nº 4 (1999) 382-392.

Vallverdú Ferrer M. Modelado y Simulación del Sistema Cardiovascular en Pacientes con Lesiones Coronarias, PhD Thesis, Universitat Politecnica de Catalunya, 1993.

Van den Bergh, F.; Engelbrecht, A. A study of particle swarm optimization particle trajectories. Information Sciences 176 (2006) 937–971.

Vanrollenghem P., Keesman K. Identification of biodegradation models under model and data uncertainty. Wat. Sci. Tech vol 3 No 2 (1996) 91-105.

Vassiliadis V., Sargent R., Pantelides C. Solution of a Class of Multistage Dynamic Optimization Problems. 1. Problems without Path Constraints, Industrial & Engineering Chemistry Research 3 (1994) 2111-22.

Voss G., Katona P., Chizeck H. Adpative Multivariable Drug Delivery: Control of Arterial Pressure and Cardiac Output in Anesthetized Dogs. IEEE Transactions on Biomedical Engineering Vol BME-34, NO 8, 1987.

Warner H. The frequency dependent nature of blood pressure regulation by carotid sinus studied with an electric analog. Circ. Res. 6 (1958) 35-40.

Wissing H., Kuhn I., Rietbrock S., Fuhr U. Pharmacokinetics of Inhaled Anaesthetics in a Clinical Setting: Comparison of Desflurane, Isoflurane and Sevoflurane. British Journal of Anaesthetia, 84 (4) (2000) pp. 443-449.

Yasuda N., Lockhart S., Eger II E., Weiskopf R., Liu J., Laster M., Taheri S., Peterson N. Comparison of Kinetics of Sevoflurane and Isoflurane in Humans. Anesth. Analg.72 (1991) 316-24.

Yasuda N., Lockhart S., Eger II E., Weiskopf R., Johnson B., Freire B., Fassoulaki A. Kinetics of Desflurane, Isoflurane and Halothane in Humans. Anesthesiology 74 (1991) 489-498.

Yiqing L., Xigang Y., Yongjian L., An improved PSO algorithm for solving non-convex NLP/MINLP problems with equality constraints. Computers and Chemical Engineering 31 (2007) 153-162.

Yong-Ling Zheng, Long-Hua Ma, Li-Yan Zhang, Ji-Xin Qian, On the convergence analysis and parameter selection in particle swarm optimization, Proceedings of the Second International Conference on Machine Learning and Cybernetics, Wan, (2003) 2-5.

Yu C., Roy R., Kaufman H., Bequette B. Multiple-Model Adaptive Predictive Control of Mean Arterial Pressure and Cardiac Output. IEEE Transactions on Biomedical Engineering 39 (1992) 765-78.

Yu Y., Boston R., Simaan M., Antaki J. Sensitivity analysis of Cardiovascular Models for Minimally Invasive Estimation of Systemic Vascular Parameters. Proceedings of the American Control Conference San Diego, California June 1999.

Yuan H., Suki B., Lutchen K. Sensitivity Analysis for Evaluating Nonlinear Models of Lung Mechanics. Annals of Biomedical Engineering, Vol. 26, pp. 230–241, 1998.

ZHAO Chao, XU Qiaoling, Lin Siming, Li Xuelai. Hybrid Differential Evolution for Estimation of Kinetic Parameters for Biochemical System. Chinese Journal of Chemical Engineering 21(2) (2013) 155-162.