Review: Intelligent Modeling and Control in Anesthesia

Jheng-Yan Lan\textsuperscript{1,2} Maysam F. Abbod\textsuperscript{3} Rong-Guan Yeh\textsuperscript{2}
Shou-Zen Fan\textsuperscript{4} Jiann-Shing Shieh\textsuperscript{2,5,*}

\textsuperscript{1}Department of Anesthesiology, National Taiwan University Hospital in Yuan Lin Branch, Yuanlin 640, Taiwan, ROC
\textsuperscript{2}Department of Mechanical Engineering, Yuan Ze University, Chungli 320, Taiwan, ROC
\textsuperscript{3}School of Engineering and Design, Brunel University, London UB8 3PH, United Kingdom
\textsuperscript{4}Department of Anesthesiology, College of Medicine, National Taiwan University, Taipei 106, Taiwan, ROC
\textsuperscript{5}Center for Dynamical Biomarkers and Translational Medicine, National Central University, Chungli 320, Taiwan, ROC

Received 5 Sep 2011; Accepted 17 Feb 2012; doi: 10.5405/jmbe.1014

Abstract

This paper provides a detailed review of the clinical aspect and engineering view of how to measure, interpret, model, and control general anesthesia. The mechanisms of anesthesia in terms of unconsciousness, amnesia, analgesia, and akinesia in modern balanced anesthesia are reviewed. The assessment and interpretation of anesthesia according to clinical signs (i.e., lacrimation, sweating, papillary dilatation), physiological monitors (i.e., electromyography, electrocardiography, blood pressure, electroencephalography, oxyhemoglobin saturation), and evaluation indices (i.e., bispectral index scale, entropy, auditory evoked potentials, and surgical stress index) are reviewed in order to define the objectives of general anesthesia. Finally, the intelligent modeling and control of anesthesia are thoroughly reviewed. Modern general anesthesia is moving towards the monitoring, interpretation, modeling, and control of multi-outputs from quantitative and qualitative nonlinear physiological signals and multi-outputs for drug control of unconsciousness, amnesia, analgesia, and akinesia. A multistage hierarchical system should thus be developed for the modeling and control of general anesthesia in the future.

Keywords: General anesthesia, Unconsciousness, Amnesia, Analgesia, Akinesia, Intelligent systems, Modeling and control

1. Introduction

General anesthesia is a reversible change that includes unconsciousness, amnesia, analgesia, and akinesia, with concomitant stability of the cardiorespiratory and autonomic systems [1-5]. In order to reach the proper anesthetic state for surgery, hypnotic and analgesic effects are considered as major fundamental pharmacologic components. Under general anesthesia, memory and awareness are critical components of the depth of anesthesia (DOA). However, anesthesiologists have multiple inconsistent definitions of the anesthetic state and have no standard measurement to assess it. Analgesia is an important aspect of balanced anesthesia, but there is no commercially available monitor for its evaluation. Therefore, in clinical practice, anesthesiologists must provide specific care during surgical procedures, including neuromuscular relaxation or paralysis, adequate DOA, and analgesia. These interacting requirements necessitate a balanced administration of suitable drugs.

Direct measurements of blood pressure (BP), respiratory parameters, temperature, blood oxygen saturation, and other related vital signs are feasible. The patient can be controlled by manipulating the monitored values, but the response is often delayed. For example, when tachycardia and hypotension occur, the total amount of blood loss is large and the hypoperfusion continues for a period of time. Furthermore, direct measurements cannot provide sufficient information of the autonomic nervous system (ANS) and central nervous system (CNS), which are related to the DOA, level of surgical stress, and nociceptive changes. Biological systems are spatially and temporally complex systems connected by dynamic interconnected feedback loops. Thus, although direct measurements of vital signs are available, precise modeling and anesthesia control are very challenging for anesthesiologists.

Quantitative modeling approaches are being replaced by qualitative techniques, especially in the artificial intelligence field. Hybrid models (quantitative/qualitative) and hybrid intelligent algorithms (neural networks, fuzzy logic, evolutionary computing) have been applied to anesthesia [6]. This review is divided into two sections. The first section reviews the mechanisms and effects of anesthetics and how to assess the anesthesia. The second section reviews intelligent modeling and control systems for anesthesia.
2. Mechanisms of anesthesia

The most commonly used inhaled anesthetics in modern anesthesia are a single gas (i.e., nitrous oxide) and volatile liquids (i.e., halothane, enflurane, isoflurane, desflurane, and sevoflurane). The immobilizing and hypnosis/amnesia effect of inhaled anesthetics involves sites of action in the spinal cord and supraspinal mechanism, respectively. Each agent has a complicated molecular mechanism and multiple targets contribute to the effects. Nonopoid intravenous anesthetics such as barbiturates (i.e., thiopental, methohexital), benzodiazepines (i.e., midazolam), propofol, ketamine, and etomidate, have an important role in modern anesthesia practice. They are widely used to facilitate the rapid induction of anesthesia or to provide sedation during monitored anesthesia care. With the introduction of propofol, intravenous anesthesia has become more popular as a component of anesthesia maintenance. However, currently available intravenous anesthetics are not ideal anesthetic drugs in the sense of producing all and only desired effects (hypnosis, amnesia, analgesia, immobility). Therefore, balanced anesthesia with multiple drugs (neuromuscular-blocking drugs, inhaled anesthetics, and opioids) is generally used.

2.1 Mechanisms of unconsciousness

Most anesthetics induce unconsciousness by changing neurotransmission, either increasing the primary inhibitory neurotransmitter gamma-aminobutyric acid (GABA) or decreasing the activation of the primary excitatory N-methyl-D-aspartate (NMDA) receptors [7,8] at multiple sites in the cerebral cortex [9-11], thalamus, and brain stem [12]. A positron-emission tomographic study showed that cortical metabolic activity is decreased after general anesthesia [13], and functional magnetic resonance imaging showed evidence of unconsciousness in the cerebral cortex [10]. Hypnotic drugs administered during induction rapidly reach brain-stem arousal centers and contribute to unconsciousness. Furthermore, the drugs act on several nuclei in the area, resulting in impaired brain-stem function which is manifested as apnea [14], atonia [15], and loss of normal reflexes, such as oculocephalic and corneal reflexes [16]. In the central thalamus, anesthetics control the normal arousal system [17].

Most anesthetics interact with various molecular sites of neuronal action via ligand-gated or voltage-gated channels on the main targets and cause hyperpolarization of neurons in thalamocortical loops, disrupting the connectivity in the cortex [18]. In the mammalian CNS, GABA is the main inhibitory neurotransmitter and its fast inhibitory effects are controlled through GABA\textsubscript{A} receptors. Barbiturates, etomidate, propofol, sevoflurane, enflurane, desflurane, and isoflurane are GABA-agonist agents [9], which increase the sensitivity of receptors to GABA, prolong the inhibitory post-synaptic effect after a GABA release, and increase the inhibition of postsynaptic neuronal excitability [18] at clinically effective concentrations.

Glutamate is the major excitatory neurotransmitter in the CNS. Ketamine, nitrous oxide, and xenon can inhibit glutamate effects through the NMDA receptor [18-20]. Most hypnotic agents produce low electroencephalography (EEG) patterns under unconsciousness conditions, whereas NMDA antagonists, such as ketamine, are associated with active EEG patterns. When ketamine is used with propofol, an additive anesthetic interaction occurs that is not reflected in the bispectral index scale (BIS) [21]. Thus, the addition of ketamine to an anesthetic complicates the interpretation of the processed EEG again emphasizing the need to consider the clinical circumstances and drugs used when interpreting a DOA index.

2.2 Mechanisms of analgesia induced by general anesthesia

Intravenous or inhalational anesthetics are used for hypnotic effects, but are ineffective at eliminating the hemodynamic response to high-stress stimuli even with large doses [22,23]. Opioids are typically combined with hypnotic drugs to create a state of nonresponsiveness. Opioids are unique in producing analgesia without loss of touch, proprioception, or consciousness. Opioids suppress pain by their action in the brain, spinal cord, and peripheral nervous system through agonists, partial agonists, and mixed agonists-antagonists, with opioid receptors (\(\mu\)-, \(\delta\)-, \(\kappa\)-opioid receptors). The principal effect of opioid receptor activation is a decrease in neurotransmission, which results mostly from presynaptic inhibition of neurotransmitter release (e.g., acetylcholine, dopamine, norepinephrine, substance P) [24] and increased potassium conductance, leading to hyperpolarization of cellular membranes. Opioids produce analgesic effects by directly inhibiting the ascending transmission of nociceptive stimulation from the spinal cord dorsal horn and activate pain control circuits via the descending transmission of the rostral ventromedial medulla.

Opioids affect many organ systems, including the respiratory and cardiovascular systems, and can cause a variety of adverse effects. The pharmacokinetic and pharmacodynamic properties of opioids are affected by a variety of factors, such as age, body weight, organ failure, and shock. Proper dosing and monitoring allow the adverse effects to be minimized. Increasing the concentration of inhaled anesthetics produces a continuum of changes in the EEG and eventually results in burst suppression and a flat EEG. In contrast, a ceiling is reached with opioids. Once the opioid dosage is increased to a critical level, further increases will not affect the EEG [25]. Problems with signal processing need to be resolved before analysis of the EEG can be used as a routine parameter of DOA.

2.3 Mechanisms of akinesia induced by general anesthesia

Neuromuscular blockers are used to facilitate endotracheal intubation and maintain neuromuscular blockade during surgical procedures. Neuromuscular-blocking drugs interrupt the transmission of nerve impulses at the neuromuscular junction and thereby produce paresis or paralysis of skeletal muscles. Non-depolarizing muscle relaxants produce a neuromuscular blockade by competing with acetylcholine for postsynaptic \(\alpha\)-subunits. In contrast, succinylcholine, a depolarizing neuromuscular blocker, produces prolonged depolarization that results in decreased sensitivity of the
Table I. Clinical sign features, power spectra, and entropy analysis evaluation indices for inadequate general anesthesia conditions (EMG: electromyography; EEG: electroencephalography; ECG: electrocardiography; SpO$_2$: oxyhemoglobin saturation; BP: blood pressure; HRV: heart rate variability; RRI: R peak interval; FFT: fast Fourier transform; LFP: low-frequency power; HFP: high-frequency power; PPGA: plethysmograph amplitude; BPV: blood pressure variability; BIS: bispectral index; AEP: auditory evoked potentials; CPC: cardiopulmonary coupling; LHR: low/high frequency ratio; DFA: detrended fluctuation algorithm; MSE: multi-scale entropy; CI: complex index; SSI: surgical stress index; and PVI: pleth variability index).

<table>
<thead>
<tr>
<th>Clinical signs of inadequate general anesthesia</th>
<th>Monitors</th>
<th>Signal processing</th>
<th>Evaluation indices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic responses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td>Movement</td>
<td>EMG, EEG, Observation;</td>
<td>Power spectral analysis, BIS, Entropy</td>
</tr>
<tr>
<td>Withdrawal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consciousness</td>
<td>Awareness, Pain</td>
<td>EEG, Observation; Subjective experience;</td>
<td>BIS, Entropy AEP</td>
</tr>
<tr>
<td>Nociception</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic responses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breathing</td>
<td>Breathing pattern change</td>
<td>Observation; Respiration rate, volume</td>
<td>Coherence and Cross-power Spectrum</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td>Tachycardia</td>
<td>ECG</td>
<td>HRV, RRI, FFT, LFP, HFP</td>
</tr>
<tr>
<td>Volume</td>
<td>SpO$_2$</td>
<td>FPPA</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>BP</td>
<td>BPV</td>
<td></td>
</tr>
<tr>
<td>Sudomotor</td>
<td>Sweating</td>
<td>Skin conductivity</td>
<td></td>
</tr>
<tr>
<td>Papillary dilatation</td>
<td>Pupillometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacrimation</td>
<td>Observation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal</td>
<td>Catecholamines, Corticosteroids</td>
<td>Blood drawing and lab analysis</td>
<td></td>
</tr>
</tbody>
</table>

Postsynaptic nicotinic acetylcholine receptor and inactivation of sodium channels, inhibiting propagation of the action potential across the muscle membrane.

Doctors often use a peripheral nerve stimulator to titrate the dose to produce the desired pharmacologic effect. At the conclusion of surgery, the responses evoked by the nerve stimulator are used to judge spontaneous recovery from neuromuscular blockade, which is facilitated by the administration of anticholinesterase drugs. Muscle relaxants may confound the accuracy of devices in relation to the DOA. Fluctuating muscle tension and tonic input from muscle spindles contribute to CNS arousal. As a result, muscle relaxants may deepen anesthesia [26-29] by reducing neural traffic [30]. The reversal of muscle relaxation can also change the amount of electromyography (EMG) activity and influence the anesthesia monitor [31].

3. Assessment and interpretation of anesthesia

Inadequate general anesthesia and pain control may cause side effects and lead to increased morbidity. Although the assessment of awareness and pain is always based on patients’ subjective reports, there are clinical signs (i.e., lacrimation, sweating, papillary dilatation), physiological monitors (i.e., EMG, electrocardiography (ECG), BP, EEG, oxyhemoglobin saturation (SpO$_2$)), and evaluation indices (i.e., BIS, entropy, auditory evoked potential (AEP), surgical stress index (SSI)) that can help give objective reports of general anesthesia. Table I shows clinical sign features and their correlation to power spectral and entropy analysis evaluation indices (e.g., BIS and AEP) for inadequate general anesthesia conditions.

The assessment and interpretation of general anesthesia are introduced in the following subsections.

3.1 Clinical signs

There are three periods of general anesthesia: induction, maintenance, and recovery. Different clinical signs can be observed in the individual stages. When a small dose of a hypnotic drug such as propofol or a barbiturate is administered, the patient is in the sedation state and easily arousable. As the dose is increased, a state of paradoxical excitation is observed, which is characterized by incoherent speech or purposeless movements. As the concentration is further increased, an irregular respiratory pattern develops, which may progress to apnea. At the same time, muscle tone and response to oral commands obviously decrease. The corneal and eyelash reflexes are lost. Tracheal intubation is usually performed at this state.

A combination of inhalational agents, hypnotic agents, opioids, and muscle relaxants is used to maintain anesthesia. In the maintenance period, anesthesiologists use heart rate (HR) and BP to monitor the level of anesthesia because the clinical signs are difficult to access. When the HR and BP increase dramatically, it means that the state of anesthesia is inadequate for the patient. Other clinical signs that indicate inadequate general anesthesia are sweating, papillary dilatation, the return of muscle tone, movement, lacrimation [32], and the hormonal response [33,34] (i.e., catecholamines, corticosteroids). PRST (blood pressure, heart rate, sweat, and tear formation) is used to assess responsiveness. It is used as a standard measure of autonomic reactions in clinical practice [32].

The return of spontaneous respiration and muscle tone,
HR and BP increases, salivation and tearing, and grimacing, swallowing, coughing, and defensive movements are the behavioral and physiological signs of recovery from general anesthesia. At this point, there is sufficient return of brain-stem reflexes to maintain spontaneous respiration and airway protection, and thus the anesthesiologist performs extubation.

3.2 Electrophysiologic monitoring

The EEG represents electrical activity of the cerebral cortex derived from summated inhibitory and excitatory post-synaptic activity, which in turn is the result of subcortical events, including those that pass through subcortical thalamic nuclei. Anesthetic drugs affect cerebral blood flow, metabolism, and EEG patterns, which are related to the degree of EEG activity [30]. For an awake state with closed eyes, EEG is active and normally shows prominent alpha activity (10 Hz). After the administration of a hypnotic drug, the patient enters the sedation state and the EEG shows an increase in beta activity (13-25 Hz) [5]. In the maintenance period, there are four phases of EEG. Phase 1 is a light state of general anesthesia with decreased EEG beta activity (13-30 Hz), and increased alpha activity (8-12 Hz) and delta activity (0-4 Hz) [31]. In phase 2, an intermediate state, beta activity decreases and alpha and delta activities increase [31,32]. During phase 3, a deeper state, the EEG is characterized by burst suppression [33]. Surgery is often performed in phases 2 and 3. Phase 4 is the most profound state, during which the EEG is isoelectric.

EEG patterns were initially used as a measure of the DOA to define the anesthetic state but a discrepancy seemed to exist between the clinical signs and EEG patterns, especially during induction and recovery [35]. Because the effects of the interactions of several administered anesthetic drugs on EEG patterns are not known, there is no standard method for choosing an optimal EEG parameter, and there is no clear definition for the assessment of clinical DOA, it is difficult to apply EEG to measure clinical DOA.

3.3 Quantitative EEG-derived indices and monitors

Power spectral analysis, a frequency analysis method that decomposes an EEG signal into a series of sine waves, is a traditional method for the quantification of EEG and reflects the amount of activity in the frequency bands of the EEG signal. Bispectral analysis was applied to EEG signals to describe the states of awake and sleeping subjects by Barnett et al. [36] and Dumermuth et al. [37]. Numerous methods for processing EEG signals, such as entropy, the patient state index, narcotrend, and evoked responses, have been evaluated for monitoring DOA.

3.3.1 Bispectral index scale

The BIS value is calculated from a multivariate logistic regression analysis from a collected database of EEG recordings from adult volunteers with hypnotic drug concentrations, behavioral assessments, and clinically important endpoints [38,39]. The BIS, scaled from 0 to 100, creates a dimensionless number. Zero represents complete electrical silence of the cerebral cortex, and 100 represents an alert state. A BIS value of less than 55 is acceptable during general anesthesia, and that between 50-60 is associated with low probability of response to verbal command.

In a prospective cohort study [40], 4945 surgical patients monitored with the BIS were compared with 7826 similar cases in a previous study where no cerebral monitoring was used. In the BIS-monitored group, 0.04% had explicit recall compared with 0.18% in the control group (p<0.038). BIS values between 40 and 60 have been recommended. Hence, this cohort study and similarly other studies have shown that the incidence of awareness decreasing from 0.18% to 0.04% is associated with the use of BIS monitoring [41,42]. However, in some studies, there was no difference in the incidence of awareness and volatile anesthetic consumption between BIS-monitored and routine care patients [43]. In addition, the BIS has been applied to pediatric anesthesia [44,45], the detection of brain death [46], the prediction of neurological prognosis after trauma and cerebral ischemia [47], and as a monitor of the sedation level in intensive care units [48].

The BIS is used as a DOA monitor during propofol anesthesia, but it has some limitations for sevoflurane and enfurane anesthesia. During ketamine, dexmedetomidine, N₂O, and xenon anesthesia, the BIS does not perform well [49].

3.3.2 Entropy

Approximate entropy, which measures the logarithmic likelihood of patterns, has been used to analyze physiological signals and EEG for short time series [50-53]. Although there are multiple entropy algorithms, only spectral entropy has been used in a commercially available device, the GE Healthcare Entropy Module (formerly Datex-Ohmeda M-Entropy), which was commercially released in 2003. The algorithm uses the time-domain and frequency-domain data from Fourier analysis and then applies the Shannon function to the frequency data. Spectral entropy, termed time-frequency balanced spectral entropy, depends on the sampling frequency and windowing [54], but is independent of the frequency components of the signal [55]. Both approximate and spectral entropy decrease during general anesthesia [54].

Facial EMG has a frequency range that overlaps with traditional EEG (0.8-32 Hz), thereby confounding the analysis of cortical activity. Facial EMG changes with the level of consciousness and the use of neuromuscular-blocking drugs. When original EEG signals are analyzed, the response entropy (RE) and state entropy (SE) indices are obtained. SE is computed from the EEG across the 0.8 to 32 Hz range and should encompass mainly the hypnotic elements of the EEG, whereas RE is computed from 0.8 to 47 Hz, which includes a significant amount of facial EMG [56]. The displayed SE range is 0 (isoelectric EEG) to 91 (fully awake), and the RE range is 0 to 100. The anesthetic range is 40 to 60. The manufacturer recommends that SE values outside this range may require a change in hypnotic dosing. If the SE value is in this range but the RE is more than 10 above the SE, more analgesic may be required.

3.3.3 Evoked potentials

Sensory, including visual, somatosensory, and auditory, stimulation produces an evoked response between the sensory
receptor and neural generator within the functional integrity pathway in the CNS. The evoked response can be separated from the underlying, spontaneous EEG by signal-averaging techniques. Because auditory evoked responses are sensitive to anesthetic drugs and their signal represents the conduction of the peripheral nerve to the brain stem, which is the major control system of the ANS, AEP has been used as a measure of the anesthetic effect and DOA [57].

Many investigations associated with evoked potentials have focused on mid-latency auditory evoked potentials (MLAEPS) [57-59]. Hypnotic anesthetic drugs increase the latencies and decrease the amplitudes of waves Pu and Nb. In contrast, opioids produce minimal changes in MLAEPs [60] in a clinically effective concentration. There are some limitations of MLAEPs, such as complex setup, need for intact hearing, and considerable time needed to produce a response. Therefore, the AEP index, based on a proprietary algorithm, was introduced [61,62]. The AEP index simplifies the interpretation of MLAEP waveforms, but it still requires an adaptive technique for extracting the MLAEP from the original EEG signal. The process involves an autoregressive method and an exogenous input (ARX) to allow the extraction of the AEP signal within 15-25 sweeps of 110-ms duration [63]. This concept has been incorporated into a commercial device that calculates the A-Line ARX Index (AAI), which was derived from the fast-extracted MLAEP waveform analysis and ranges from 0 (deep hypnotic effect) to 100 (awake). The recommended surgical anesthesia range is 15-25. In clinical studies, the A-Line performed comparably to the BIS and other EEG-based monitors but did not demonstrate advantages that would outweigh the nuisance of ear plugs and continuous high-frequency clicking sounds in patients' ears [64-66].

3.3.4 Clinical interpretation and effects of drug effects in EEG

Studies of all currently available devices show a good relationship with the Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) scale for commonly used hypnotics such as midazolam [67], propofol [66,68-72], isoflurane, sevoflurane [64,73], and desflurane. The relationship between sedation and the derived electrophysiologic index does not seem to be influenced by age in adults [74]. Although the average index tracks the sedation scale well at the steady state, there is huge inter-individual variation, particularly during non-steady-state conditions such as induction and recovery [75]. Thus, inter-subject variability in the EEG requires the assessment of the awake values before titration of a hypnotic to a given target EEG index.

The dissociative anesthetic ketamine, an NMDA antagonist, produces excitatory effects in the EEG. Ketamine doses that create unresponsiveness do not change the BIS [76]. When ketamine is used with propofol, an additive anesthetic interaction occurs [77] that is not reflected in the BIS [21]. Thus, the addition of ketamine to an anesthetic complicates the interpretation of the processed EEG.

Nitrous oxide (N₂O), an NMDA antagonist, has a sympatholytic effect. Most studies suggest that nitrous oxide given in concentrations of up to 70% has minimal effect on the BIS [78,79] and have found that the effect of nitrous oxide appears to depend on the monitor used.

3.4 Neuromuscular monitoring

Neuromuscular function is monitored by evaluating the muscular response to supramaximal stimulation of a peripheral motor nerve [80,81]. After the administration of a neuromuscular-blocking drug, the decrease of muscle response reflects the degree of fiber blockade [82,83]. There are several patterns of nerve stimulation. The most commonly used patterns of electrical nerve stimulation are single-twitch, train of four (TOF), titanic count, post-tetanic count (PTC), and double-burst stimulation (DBS). Moreover, it has been possible to measure movement (i.e., degree of muscle relaxation) since the commercial product the Datex EMG machine (Datex NMT-221 monitor, Datex Instrumentarium, Helsinki, Finland) launched in the market in 1980. Therefore, it is easy to monitor neuromuscular function in general anesthesia.

3.5 Measurements of analgesia during general anesthesia

Pain is a subjective conscious experience derived from internal or external stimuli. During general anesthesia, consciousness vanishes and the experience of pain disappears. The term nociception is used to describe the consequences of surgical stimulus on system function. Several indicators, including heart rate variability (HRV) [32], changes of the photoplethysmographic pulse wave amplitude [84,85], facial muscle activity [86], changes in skin conductivity [87], pupillometry [88], ocular microtremors [89], and EEG-based monitoring [86], have been proposed to assess the degree of nociception.

Photoplethysmography (PPG) gives the concentration of oxyhemoglobin in the blood and its waveform can be used to estimate volume changes. Changes in PPG amplitude (PPGA) correlate with perfusion and reflect the relation of the left ventricular volume and the peripheral vascular bed [90,91]. Under general anesthesia, increased PPGA response [92] and skin vasomotor response [93] have been related to nociception. However, several factors may easily cause noise in PPGA measurements, such as the movement of the detector, physiological factors, and pharmacological factors.

Huiku et al. [94] proposed the SSI, which is a simple numerical measure of the surgical stress level under anesthesia. Two continuous variables, the interval between successive hearts beats (HBI) and PGA, are used to calculate SSI: 100- (0.7 × PPGAnorm + 0.3 × HBInorm), where PPGAnorm is the normalized PPGA and HBInorm is the normalized HBI. The SSI value indicates the balance between the intensity of surgical stimulus and the level of antinociception. An SSI value near 100 corresponds to a high stress level, and that near zero corresponds to a low stress level.

4. Intelligent modeling and control in anesthesia

In general anesthesia, the clinical anesthesiologists’ major challenge is to maintain the patient anesthesia via drug-induced unconsciousness, muscle relaxation, and analgesia (i.e., pain relief). The former two take place in the operating room,
whereas the latter is mainly related to postoperative conditions. In recent years, automated drug infusion has been implemented with feedback strategies to control the patient’s anesthesia. However, measurement of anesthesia is the difficult part in designing such systems. Feedback control can be used to keep the patient in a desired anesthesia state with the advantages of reduced induction time and minimum amount of drugs delivered. Feedback control has been used for BP regulation, inhalation drug concentration control, muscle relaxation control, and ventilation control [95]. The first feedback controller used in anesthesia was designed to control the delivery of intravenous (IV) drug [96]. Feedback control has become increasingly used in clinical medicine. Most investigators have used feedback control with a classical proportional, integral, and derivative (PID) control scheme. However, the human body is a highly nonlinear system. The human body during anesthesia might experience different situations, such as neural muscular blockade, BP changes, and HRV. Therefore it is quite difficult to use a traditional PID controller for monitoring anesthesia. Neural network and fuzzy logic controllers are suitable for controlling nonlinear systems [6,96,97]. Adaptive intelligent control can be used to achieve balanced anesthesia. The modeling and control of muscle relaxation, DOA, and analgesia are reviewed below.

### 4.1 Modeling and control of muscle relaxation

#### 4.1.1 Fuzzy logic

Anesthesiologists are familiar with administering bolus injections of non-depolarizing muscle relaxants for controlling the muscle relaxation at more or less regular intervals [98,99]. If the muscle relaxation is inadequate, anesthesiologist promptly administer a bolus injection. This control method is undesirable for eye or brain surgery because the slightest movement could be dangerous. The patient is always given more muscle relaxant than required, which may prolong the effect. In order to obtain the optimal drug delivery rates, on-line drug administration strategies should be developed [100]. Numerous computer control strategies for muscle relaxants have been reported [101–106]. A major problem in designing adequate feedback controllers for physiological systems is the variation in the response to external stimuli among individuals. Adaptive control schemes are considered suitable candidates to solve this clinical problem [107]. A precise model of biological systems may not exist or it may be too difficult to obtain. Knowledge-based systems (KBSs) and intelligent computing systems are used for modeling and control in medical diagnosis and treatment. A KBS uses model-based reasoning (MBR), rule-based reasoning (RBR), or case-based reasoning (CBR). Intelligent computing methods (ICMs) include fuzzy logic (FL), genetic algorithms (GAs), and artificial neural networks (ANNs). Pandey et al. conducted a survey of knowledge-based and intelligent computing systems applied to medicine, reviewing techniques such as KBS, ANN, FL, and GAs [108]. Linkens et al. implemented self-organizing fuzzy logic control (SOFLC) for automated drug delivery during muscle relaxant anesthesia [109]. The self-organization of the rule base has proven to provide a robust controller for conditions such as model uncertainty, noise contamination, and parameter changes [109]. For example, traditional type-1 fuzzy-based systems can handle slight uncertainties within a short term, such as the imprecision and slight noise associated with the inputs and outputs of fuzzy logic controllers (FLCs). However, the effectiveness of type-1-based agents deteriorates due to long-term uncertainties, such as those related to heart transplants. Type-2 fuzzy sets can be used to represent the inputs and outputs of the FLC to handle short- and long-term uncertainties [110,111]. FLCs account for the uncertainty in measured signals and can match the significantly nonlinear and variable processes commonly encountered in biomedical applications [100,112,113].

#### 4.1.2 Neural networks

Previous studies have used the pharmacokinetic/pharmacodynamic (PK/PD) model for determining the infusion scheme (e.g., for mivacurium [114], atracurium [115], and pancuronium [116]). The main drawback of this approach is the need to find proper values for the model parameters. Lendl et al. applied ANNs to adjust specific parameters without the knowledge of the inner pharmacodynamic processes [117]. Good control systems can inexpensively be designed using ANNs [118,119], which can easily be configured to approximate the desired input/output mapping when pairs of input and output values (samples) are available. Lendl et al. [117] developed a novel control system which was tested clinically on 35 patients. The system utilizes the EMG module within the Datex AS/3 monitor for monitoring the muscle blockade and a Graseby 3500 infusion pump for IV administration of mivacurium. The monitor measures the ratio of the first twitch intensity to the baseline; it decreases with increasing neuromuscular blockade. The performance of this feedback system compares favorably with that of closed-loop controllers [109]. Mendonca et al. developed an automatic system (Hipocrates) that controls the neuromuscular blockade of anesthesia by the continuous infusion of non-depolarizing muscle relaxants [120]. Hipocrates is based on adaptive, robust, and classical control strategies as well as a wide range of noise elimination techniques.

#### 4.1.3 Hybrid and other systems

The conventional method of muscle-relaxant administration is for the anesthesiologist to administer a bolus dose, the size of which is determined from experience. Supplements are given when necessary. Linkens et al. proposed a system that automatically controls the level of muscle relaxant in anesthetized patients undergoing surgery [121]. A linearized model of the patient was identified based on the pharmacokinetic and pharmacodynamic parameters. The model was utilized to develop a Smith predictor feedback controller.

Chuang et al. [122] developed a non-depolarizing neuromuscular block controller which has two rule bases to control the administration of cisatracurium. The first rule base is developed using a fuzzy modeling algorithm (FMA), while the second is developed based on experts’ clinical experience. The performance of the two rule bases was tested using disturbances such as set-point change, time delay change, noise
contamination, as well as sampling time changes. Results show that the FMA-based rule-base controller had better performance.

4.2 Modeling and control of depth of anesthesia

4.2.1 Fuzzy logic

Many techniques have been utilized for monitoring DOA based on clinical measurements such as EEG signals, BP, plasma concentration of propofol, and AEP. Other non-numerical clinical signs, such as lacrimation, pupil response, and sweating, are also used for determining DOA. Linkens et al. used a hierarchical structure based on fuzzy modeling to monitor DOA using many clinical signs in the operating theatre [123]. The first level uses numerical clinical signs, such as HR and systolic arterial pressure (SAP), via a self-organizing learning algorithm or a rule base derived from anaesthetists’ experience to interpret primary depth of anesthesia (PD OA). The second level uses non-numerical clinical signs, such as lacrimation, pupil response, and sweating, which are combined with the first level of PDOA to decide DOA. Linkens et al. also proposed a self-organizing fuzzy model (SOFM) algorithm for simulating anesthetic procedures during operation from the induction to maintenance stages.

Schaublin et al. studied the fuzzy logic control of mechanical ventilation during anesthesia [124]. This control system automatically adjusts ventilatory frequency and tidal volume to achieve and maintain the end-tidal carbon dioxide fraction at a desired level (set-point). The system can achieve and maintain a desired end-tidal carbon dioxide fraction during routine anesthesia by controlling the mechanical ventilation reliably and safely. Elkafi et al. developed an intelligent signal processing method for evoked potentials for anesthesia monitoring and control [125]. The system was validated via 21 clinical trials and was found to reliably assess DOA during anesthesia using propofol. Elkafi et al. used a SOFM to substitute an early auto-regressive technique with an exogenous input model to maintain the drug propofol for anesthesia using off-line analysis [126]. The results were sufficiently encouraging to perform on-line clinical trials using fuzzy-logic-based control and monitoring in an operating theatre.

Shieh et al. developed SOFLC and a hierarchical rule base for DOA [127], a hierarchical system of on-line advisory for controlling and monitoring DOA using self-organizing fuzzy logic [128], and genetic fuzzy modeling and control of the BIS for general intravenous anesthesia [129]. The first study proved the suitability of the SOFLC system and hierarchical rule base in clinical trials as an intelligent adviser for DOA management. After extensive validation in the second study, the system was implemented in on-line mode and was found to reduce the recovery time. In the third study, a genetic fuzzy logic controller (GFLC) and a genetic proportional integral derivative controller (GPIDC) were simulated and compared using a patient model based on the BIS value as a controlled variable. The results indicated that both GFLC and GPIDC control the BIS target better than manual control with similar drug consumption.

Simanski et al. studied automatic drug delivery in anesthesia [130]. A survey was conducted on the methods of modeling, measurement, and general progress of closed-loop control systems in anesthesia. The Rostock assistant system for anesthesia control (RAN) was discussed, which provides multiple-input/multiple-output (MIMO) control of the depth of hypnosis. The effect of the system is similar to that of neuromuscular blockade since the system controls arterial hypotension. The results of 22 patients were presented.

Chou et al. developed a multivariable fuzzy logic/self-organizing method for anesthesia control [131]. In operating theatres, anaesthesiologists usually adopt a specific regime to administer anaesthetic drugs during the different stages of the operation. Therefore, an automatic closed-loop control system cannot be realized using a fixed control system. A multi-stage controller that can change from fixed to adaptive regimes is an attractive solution. Studies have applied SOFLC to biomedical systems for muscle relaxation [109,132,133], DOA [127,128], and patient analgesia control [134]. Previous studies [135] have simulated controlling anesthesia in operating theatres using a multivariable SOFLC structure. The simulation results are sufficiently encouraging for performing clinical trials.

Abdulla and Wen developed robust internal model control for DOA [136]. The system includes a robust internal model controller (RIMC) based on the BIS. Patient dose-response models were developed to provide an adequate drug administration regimen to avoid under- or over-dosing patients. Simulation results showed that the RIMC outperformed the traditional PID controller. The controller robustness was tested by varying the patient model parameters.

4.2.2 Neural networks

No anesthesia monitoring system is considered to be uniformly applicable to anesthesia. Robert et al. [137] surveyed studies related to the monitoring of anesthesia using ANNs. It was found that neural networks have been successfully utilized to assess DOA indicators such as those based on hemodynamics, pupillary reflex, anesthetic concentration, spontaneous EEG, and AEPs.

Ortolani et al. [138] used ANNs to obtain a non-properitary index of the DOA from processed EEG data. Two hundred patients who had undergone general abdominal surgery were recruited for the trial. The results indicated that the ANN was successfully trained to predict an anesthesia depth index, ranging from 0 to 100, which correlates very well with the BIS during total IV anesthesia with propofol.

Shieh et al. [139] used ANNs to simulate an entire surgical operation during inhalational anesthesia. The patient model includes four inputs (the patient’s age, weight, gender, and anesthetic agent concentration) and four outputs (HR, SAP, end-tidal anesthetic agents (ETAA), and EEG signals (i.e., BIS)). The performance of the patient model was based on the minimum cost function and pharmacological reasoning. The results showed that the approach can provide a more robust model despite the considerable individual variation in inhalational anesthesia among patients.

4.2.3 Hybrid and other systems

Allen and Smith [140] studied the neuro-fuzzy closed-loop control of DOA. AEP measurements were utilized as a
feedback signal for the automatic closed-loop control of general anesthesia using fuzzy logic and neural networks. AEP is a signal derived from the EEG in response to auditory stimulation, which may be useful as an index of the DOA. A satisfactory input to a fuzzy logic infusion controller for the administration of anesthetic drugs can be provided through a simple back-propagation neural network for learning the AEP signal index.

Single-input/single-output (SISO) pharmacokinetic-pharmacodynamic compartment models are the standard modeling paradigm used to describe the relationship between input anesthetic agents and output patient endpoint variables. Lin et al. [141] used hybrid multivariable models for predicting human response to anesthesia. Model classes such as standard linear time invariant (LTI) multivariable models, hybrid multivariable models, nonlinear SISO PK-PD models, and uncertain systems models have been introduced [141]. In addition, hybrid multivariable models have been used to describe the relations between inputs that include anesthesia, disturbances, and surgical stimuli to a variety of patient output variables. The focus of Lin et al.’s [141] work was a comparison of hybrid multivariable models constructed using subspace identification techniques to the more commonly used SISO PK-PD models. More specifically, the hybrid models were considered as switching system models, where the underlying systems are MIMO linear state-space models over which the patients’ responses switch based on their sedative state.

Nunes et al. [142] used neural-fuzzy paradigms for modeling and multivariable control in anesthesia. The modeling of patient’s vital signs and the classification of DOA were discussed. First, a hybrid patient model using Takagi-Sugeno-Kang fuzzy models was developed. Second, a fuzzy relational classifier was developed to classify a set of wavelet-extracted features from the AEP into different levels of DOA. A comprehensive patient model that predicts the effects of the drugs propofol and remifentanil on DOA while monitoring several vital signs was obtained. The patient’s model is the basis for optimal multivariable control for administering these two drugs simultaneously.

Mahfouf et al. [143] explored the dichotomy associated with monitoring and control of DOA. The paper starts with a rather conservative (simplistic) method to closed-loop control of DOA via the monitoring of arterial BP using the clinical gold standard (CGS) method followed by feedback control techniques. The merits/limitations of each technique were identified and a list of feasible techniques for future research in monitoring and control of DOA was given.

Tan et al. [144] developed decision-oriented multi-outcome modeling for anesthesia patients. The work addressed the problem of real-time modeling for monitoring, predicting, and diagnosing multiple outcomes of anesthesia patients. They showed that the consideration of multiple outcomes is necessary and beneficial for anesthesia management. It was observed that each patient has very different dynamic responses to drugs. Even for a given patient, responses to a given drug change with time, patient conditions, and surgical conditions.

As a result, it is necessary to establish real-time MIMO models for individual patients. The SISO model structure contains only a few parameters and their values can be easily estimated in real-time. The MIMO model is simplified significantly by being split into multiple SISO models.

Dua et al. [145] studied modeling and multi-parametric control for the delivery of anesthetic agents. They proposed model predictive controllers (MPCs) and multi-parametric model-based controllers for the delivery of anesthetic agents. An MPC considers the patient’s state and the drug delivery rate for solving the optimal control signal, which is performed at regular time periods. The controller features simultaneous control of cardiac output, mean arterial pressure (MAP), and unconsciousness.

4.3 Modeling and control of analgesia

4.3.1 Fuzzy logic

Conventional patient-controlled analgesia (PCA) can reduce drug consumption and improve pain control. Shieh et al. studied a pain model and fuzzy logic patient-controlled analgesia in extracorporeal shock-wave lithotripsy (ESWL) [146]. A PCA based on a fuzzy logic system was developed for controlling alfentanil administration, where the infusion rate is adjusted using a look-up table. The look-up table is based on a history of the drug demand. The results show that a combination of PCA and fuzzy logic control outperforms conventional PCA control.

Further work on pain intensity was published by Shieh et al. [134,147], who used ESWL. A hierarchical controller whose basic level controls analgesia and whose second level is an adaptive self-learning level that improves the lower-level control rules was proposed. Results show that most patients experience a moderate level of pain when using the system [134,147]. It was found that pain relief using the hierarchical system is better than that using a conventional method. The system was further enhanced by incorporating a fuzzy logic model of the pain index that is based on the interpretation of the self-titration of the drug delivery. Such system can be used online to log the patient’s BP, temperature, pulse rate, and respiration rate (RR).

Schubert et al. [148] developed a fuzzy system for the regulation of the analgesic remifentanil during general anesthesia based on the expert knowledge of anesthesiologists. The anesthesiologists monitor vital parameters such as HR and arterial BP to apply the analgesic drug. The HRV was considered as an additional input to the fuzzy system. The final controller structure is based on two controllers. The first controller is used to regulate the remifentanil administration using the HR and MAP as feedback signals. When the HR goes higher than 90 bpm, the second controller administrs a bolus of remifentanil based on the measured HR. Both fuzzy controllers are Mamdani inference systems.

4.3.2 Neural networks

Melzack discussed the concept of pain [149]. He found that pain is not directly produced by inflammation, injury, or diseases, but instead is combined and outputted from a widely
distributed neural network of the brain. Pain has been proposed as the fifth vital sign to be entered into a patient’s chart along with temperature, BP, HR, and RR. However, there is still no objective measurement for the experience of pain. Hence, an objective and reliable interpretation of the pain pattern is important for pain measurement. Shieh et al. [150] proposed an ensembled artificial neural network (EANN) with 10 inputs and one output for the prediction of a visual analog scale (VAS) of pain intensity. The system was tested on 323 patients receiving intravenous PCA after Caesarean section. The prediction performance of the EANN model was satisfactory based on the root mean square error (RMSE) of training (1.6681) and testing (1.9900) against the linear regression (LR) model of training (1.9406) and testing (2.1617) for a VAS in the range of 0 to 10. The results suggest that the EANN model can provide a useful reference for clinical practice in acute pain service.

4.3.3 Hybrid and other systems

Jacobs et al. [151] investigated modeling and estimation for patient-controlled analgesia of chronic pain. They derived a mathematical model of PCA for the real-time prediction of the continuous infusion of an analgesic drug (morphine-6j-glucuronide). Webb et al. [152] investigated the use of a computerized cold pressure test to measure analgesia. Yeh et al. [153] investigated the pain relief demand index for postoperative pain. Although they used a complicated bio-signal processing algorithm (i.e., empirical mode decomposition) to decompose the pain relief pattern of patients, the obtained results were not close to those of a traditional clinical evaluation of pain score (i.e., VAS).

5. Discussion

The main job of anesthesiologists is to maintain the adequacy of anesthesia. Muscle relaxation, unconsciousness, and analgesia characterize modern balanced anesthesia. The responses of clinical signs to inadequate general anesthesia can be divided into somatic and autonomic responses, as shown in Table 1. Somatic responses can be further divided into sensory motor responses (withdrawal and movement), and sensory consciousness and nociception (awareness and pain). Although movement (i.e., degree of muscle relaxation) can be measured, the evaluation indices of awareness (e.g., BIS, AEP, entropy) cannot reliably predict awareness during general anesthesia. Several EEG-based monitors have been associated with a decreased incidence of consciousness [40,154], reduced administration of DOA drugs [41,42], and fast recovery from anesthesia [155,156]. A study found that patients can become aware even when BIS values are within the target range (i.e., 40 to 60), and thus concluded that the BIS monitoring should not be used as part of standard practice of anesthesia [43]. Another study has shown that the Narcotrend DOA monitor cannot reliably predict awareness during general anesthesia via the isolated forearm technique [157]. Hence, monitoring awareness is still a challenging area. The assessment of pain (i.e., analgesia) is one of the main components of balanced general anesthesia. However, pain is a very subjective experience evoked by internal or external stimuli and it is very difficult to measure via vital signs [158,159]. Currently, no commercial monitoring method is available for evaluating analgesia during general anesthesia.

Autonomic responses, which are more complicated, can be classified into four types depending on the system: breathing, hemodynamic, sudomotor, and hormonal. For the breathing system, the breathing pattern can be monitored by RR. For the hemodynamic system, the tachycardia, blood volume change, and hypertension can be monitored by ECG, SpO$_2$, and BP. ECG and BP have been used to analyze the HRV and blood pressure variability (BPV) in terms of sympathetic and parasympathetic nerves using the fast Fourier transform (FFT) to calculate the low/high frequency power ratio (LHR), which is strongly related to the ANS. Several studies [160-164] have used nonlinear algorithms (e.g., detrended fluctuation algorithm (DFA) based on the α index and multi-scale entropy (MSE) based on the complex index (CI)) to analyze RR intervals of ECG signals in terms of fractal characteristics and the complexity index of subjects. Although these studies focused on cardiovascular diseases (e.g., congestive heart failure (CHF) and atrial fibrillation (AF)), the DFA and MSE algorithms can be applied to general anesthesia. Studies [165,166] have calculated the cardiopulmonary coupling (CPC) via the product of the coherence and cross-power of the ECG interval and RR signals that are applied for the measurement of sleep quality. Moreover, Hui et al. [94] developed the SSI, which may be applied to the measurement of analgesia. SSI has been clinically validated [167,168], and will become commercially available in the near future.

The third type, namely sudomotor innervations, may be related to the cholinergic innervations of the ANS (i.e., sympathetic nerve) prominent in sweat glands, which causes perspiration via the activation of muscarinic acetylcholine receptors. Linkens et al. and Shieh et al. [123,127,128] investigated the second level of the DOA via fuzzy logic to combine the evaluation of sweat, lacrimation, and pupil responses to anesthetic light. They combined this with PDDA, which uses the HR and BP, to determine a confidence of the depth of anesthesia. The final type, namely hormonal responses (i.e., catecholamines, corticosteroids) are affected by the DOA [169,170]. Hormonal responses can be accurately detected by analyzing a blood sample via high-performance liquid chromatography; however, they are not strongly related to the DOA. In addition, hormonal measurements are expensive, invasive, and time-consuming; therefore, the measurements cannot be made in real-time and are not considered a major parameter for determining adequate general anesthesia. Table 1 summarizes the use of clinical signs for adequate general anesthesia. Multiple parameters should be considered for deciding adequate general anesthesia.

Because it is difficult to interpret adequate general anesthesia and the physiological signals and responses are time-variant, the precise modeling and control of general
anesthesia is challenging. Quantitative approaches were initially used but they have been found to be too complicated for interpreting general anesthesia. Qualitative techniques, particularly artificial intelligent approaches, have thus become commonly used. Hybrid models (quantitative and qualitative approaches) and hybrid intelligent algorithms (fuzzy logic, neural networks, and genetic algorithms) have been applied to general anesthesia. The intelligent modeling and control of general anesthesia has been applied to different types of anesthesia parameter (i.e., muscle relaxation, DOA, and analgesia), as shown in Table 2. Most studies have focused on how to interpret the DOA using expert systems, intelligent systems (fuzzy logic and neural networks), or hybrid models (genetic-fuzzy and neural-fuzzy paradigms). Muscle relaxation and DOA can be measured directly and fed back for regulation purposes, whereas analgesia cannot be directly measured. Because of the difficulty of measuring pain, studies have evaluated pain using PCA for ESWL and post-operation. Patients in an ESWL operation are conscious, so they can feel their pain intensity. The patients push a button when they require pain relief. Similarly, patients start to feel pain after an operation. It is thus convenient to use PCA for post-operation patients.

Table 3 lists research work related to anesthesia published in the last two decades classified based on the type of intelligent system algorithm. Most studies used fuzzy logic because it can be applied to anesthesiologists’ decision-making. However, complicated and high-dimensional MIMO systems are not easy to model using fuzzy logic. The imprecision and instability of fuzzy logic are disadvantages for general anesthesia. Hence, ANNs have become used to solve imprecise problems if learning data are sufficient. However, ANNs use hidden layers, which hide a lot of information. Neuro-fuzzy modeling [171-173] is an alternate form of artificial intelligence that combines the transparency of fuzzy logic and the learning ability of ANNs, which allow the understanding, validation, and interpretation of the model produced by the rule base. Hybrid approaches have received increasing attention because many parameters are difficult to determine during the modeling or control of general anesthesia. Future developments should consider neuro-fuzzy, genetic-fuzzy, genetic-neuro, and genetic-neuro-fuzzy approaches for the modeling or control of general anesthesia.

6. Conclusion and future developments

This paper provided a detailed review of the clinical and engineering aspects of how to measure, interpret, model, and control general anesthesia. Determining adequate general anesthesia is very difficult due to the complicated mechanisms of anesthesia, namely unconsciousness, amnesia, analgesia, and akinesia. High-performance parallel computing and embedded systems have been applied to biomedical engineering applications, allowing complicated signal processing algorithms to be implemented for general anesthesia. EMG, ECG, BP, EEG, and SpO2 are good candidates for representing general anesthesia. Therefore, a multistage hierarchical system for the modeling and control of general anesthesia should be developed.
Acknowledgements

This research was financially supported by the National Science Council (NSC) of Taiwan (NSC 99-2221-E-155-046-MY3) and the Center for Dynamical Biomarkers and Translational Medicine, which is sponsored by the NSC (NSC 100-2911-I-008-001).

References


“Spectral entropy monitoring is associated with reduced propofol use and faster emergence in propofol-nitrous oxide-alfentanil anaesthesia,” Anesthesiology, 103: 274-279, 2005.


