Prediction and Analysis of Weaning Results of Ventilator-Dependent Patients with an Artificial Neuromolecular System

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Abstract. We have developed a vertical information processing model, motivated from physiological evidence, which integrates intra- and interneuronal information processing. Information processing at the intraneuronal levels is to create a repertoire of pattern processing neurons. Information processing at the interneuronal levels is to group appropriate pattern processing neurons to constitute an effective pattern processing system. The system was applied to a database of the weaning results of ventilator-dependent patients. Ventilator has been used to support the breathing need of patients, and weaning is the gradual process of removing it from ventilator-dependent patients. Experiments with the model show that the integrated system is able to learn to differentiate data in an autonomous manner, separating those patients who have successful weaning results from those who do not. Our parameter analysis shows that most of the parameters identified as significant by the system are the same as those by physicians, but some are not.

Keywords: Weaning, Evolutionary Learning, Artificial Neural Networks.

1 Introduction

People are in great danger when they have difficulty in breathing, especially if they have chronic pulmonary disease or neuromuscular problems. Ventilator has been commonly used to support their breathing needs. Statistics show that most people in intensive care unit (ICU) are in critical conditions and around 40% of them need ventilator to support their breathing [1], [18]. When patients are no longer in critical conditions, they will be transferred to respiratory care center (RCC) for further care.

Removing ventilator from patients too early could put them in dangerous situation. However, for those patients who can breathe naturally, placing ventilator on them may be of little help. When to remove a ventilator from a patient is sometimes a tough question. Statistics show that the successful weaning rate is between 35% and 60% [16], [17]. The decision is usually based on the subjective assessments of physicians. The parameters that the physician takes in accounts are physiological factors, including maximal inspiratory pressure (Pimax)[10], [20], vital capacity

(VC)[20], rapid shallow breathing index (RSBI)[23], minute ventilation (VE)[10], [21], pH and PCO₂[2], [16], APACHE II score, and blood urine nitrogen (BUN).

The above studies are related to what parameters to consider when the physician tries to wean ventilator off patients in ICU. However, there are limited studies regarding weaning in RCC, where one of the major tasks is to help patients to progress from mechanical ventilation to spontaneous breathing as early as possible. At present, there are 27 parameters used to determine whether weaning is successful or not for ventilator-dependent patients in RCC. These parameters are divided into four categories. The first category includes gender and age. The second category comprises physiological parameters. These are APACHE II score and coma scale at admission time, blood urine nitrogen (BUN), creatinin (Cr), albumin (Alb), hemoglobine (Hb), the ratio of respiratory frequency to tidal volume (RSBI) and coma scale before removing ventilator. The third category of parameters is related to the diseases carried by patients. These include chronic obstructive pulmonary disease, cardiovascular disease, cerebral vascular disease, other internal factors, septic syndrome with multiple organ failure, respiratory tract disease, trauma, acute respiratory distress syndrome, brain surgery, and other surgeries. The fourth category of parameters is regarding the treatment and complication occurring during the patient's admission time. These include the length of time staying in ICU, the length of time using ventilator, and tracheostomy, respiratory tract infection, blood stream infection, urinary tract infection, and other infection.

Successfully weaning patients off ventilator requires careful assessments. It may be helpful if we develop an intelligent system to assist physicians in making such a decision. In this study, we apply an artificial neuromolecular system (ANM), a biologically motivated model that integrates intra- and inter-neuronal information processing, to differentiate a database of ventilator-dependent patients. The system has two hypotheses. The first is that some neurons in the brain have significant intra-neuronal information processing, which might directly or indirectly relate to their firing behavior [14], [13], [15]. Neurons of this type will be called cytoskeletal neurons or enzymatic neurons[4], [6]. They combine, or integrate, input signals in space and time to yield temporally patterned output signals to control other neurons. The second hypothesis is that some neurons in the brain serve as pointers to other neurons in a way that allows for memory manipulation. Neuron of this type is called reference neurons [6-7]. Reference neurons are used to select appropriate subsets of cytoskeletal neurons, which then control the manner in which input patterns are transduced to output patterns.

2 The Architecture

The ANM system as currently implemented comprises eight competing subnets, each consisting of 30 cytoskeletal neurons. Cytoskeletal neurons are manipulated by two levels of reference neurons. Low-level reference neurons select comparable cytoskeletal neurons in each subnet (i.e., neurons that have similar cytoskeletal structures). High-level reference neurons select different combinations of the low-level reference neurons. Fig. 1 provides a simplified picture (only two of the competing subnets were shown, each consisting of only four cytoskeletal neurons). In Fig. 1, the intraneuronal

Fig. 1. Connections between reference and cytoskeletal neuron layers. When Ra fires, it will fire $r1$ and $r4$. Similarly, the firing of Rb will cause $r3$ and $r4$ to fire, which in turn fires $E3$ and $E4$ in each subnet. (E_i stands for cytoskeletal neuron i).

structures of $E1, E2, E3,$ and $E4$ in subnet 1 are similar to those of $E1, E2, E3,$ and $E4$ in subnet 2, respectively.

3 Pattern Processing Neurons

Cytoskeletal neurons are the major pattern processing neurons in the ANM system. Information processing sketched in cytoskeletal neurons is motivated from some physiological evidence that the internal dynamics of a neuron control its firing behaviors [13], [14], [15]. Our hypothesis is that the cytoskeleton plays the role of signal integration. That is, it is capable of integrating signals in space and time to yield spatiotemporal output signals. The dynamics of cytoskeletal neurons are simulated with 2-D cellular automata [22].

Our implementation (Fig. 2) in the cytoskeletal neuron is to capture the signal integration capability (to be described below). When an external signal impinges on the membrane of a cytoskeletal neuron, a readin enzyme sharing at the same site is activated. The activated readin enzyme will then activate the cytoskeletal component sharing at the same site, which in turn activates its neighboring component of the same type, and so on. Thus, the activation of a readin enzyme will in turn activate a chain of neighboring components of the same type (i.e., initiate a unidirectional signal flow). As to a neighboring component of different type, an activated component will affect its state when there is an MAP (microtubule associated protein) linking them together. The interactions between two different types of neighboring components are assumed to be asymmetric.

For example, in Fig. 3a, the activation of the readin enzyme at location (2,2) will trigger a cytoskeletal signal flow along the C2 components of the second column, starting from location (2,2) and running to location (8,2). When the signal arrives at location (8,2), the C2 component sharing at the same site will be activated, which in turn stimulates its neighboring C1 component at location (8,1) to a more exciting state (but is not sufficient to activate it). A counter example (Fig. 3b) is that the activation of the readin enzyme at location (4,1) will trigger a cytoskeletal signal flow along the C1 components of the first column, starting from location (4,1) and running to

location (8,1). The activation of the C1 component at location (8,1) will activate its neighboring C2 component at location (8,2). The activation of the latter will in turn activate the C2 component at location (7,2), its next neighboring component at location (6,2), and so on. Thus, it will trigger a signal flow on the second column, starting from location (8,2) and running to location (2,2).

Fig. 2. Cytoskeletal neurons. Each grid location has at most one of three types of components: C1, C2, or C3. Some sites may not have any component at all. Readin enzymes could reside at the same site as any one of the above components. Readout enzymes are only allowed to reside at the site of a C1 component. Each site has eight neighboring sites. The neighbors of an edge site are determined in a wrap-around fashion. Two neighboring components of different types may be linked by an MAP (microtubule associated protein).

We have described the feature that different types of components interact with each other in an asymmetric manner. The other feature is that different types of components transmit signals at different speeds. The summary of the above two features is that C1 components transmit signals at the slowest speed, but with the highest activating value, and that C3 components transmit signals at the fastest speed, but with the lowest activating value. The activation value of C2 components and their transmitting speed are intermediate between those of C1 and C3 components.

When the spatiotemporal combination of cytoskeletal signals arriving at a site of readout enzyme is suitable, the readout will be activated and then the neuron will fire. Fig. 4 shows that there are three possible cytoskeletal signal flows, initiated by external signals, to activate the readout enzyme at location (8,3). One is a signal flow on the second column, the other on the third column, and another on the fourth column. Any two of the above three signal flows might activate the readout enzyme at location (8,3), which in turn will cause the neuron to fire. Nevertheless, the neuron might fire at different times in response to different combinations of signal flows along these fibers. One is that different types of components transmit signals at

different speeds. The other is that signals may be initiated by different readin enzymes. For example, the signal flow on the second column may be initiated either by the readin enzyme at location (2,2) or by the readin enzyme at location (3,2). Similarly, the signal flow on the fourth column may be initiated either by the readin enzyme at location (1,4) or by the enzyme at location (2,4). A signal initiated by different enzymes will integrate with another signal at different times. All of these will affect the temporal firing behaviors of a neuron.

Fig. 3. Interaction between different types of component via an MAP. (a) An external signal will trigger a signal flow on the second column, starting from location (2,2) and running to location (2,8). When this signal arrives at location (8,2), it will affect its neighboring C1 component at location (8,1) to a more exciting (i.e., a state that is much easier to be activated later). (b) An external signal will trigger a signal flow on the first column, starting from location (4,1) to running to location (8,1). The activation of the C1 component at location (8,1) will in turn activate the C2 component at location (8,2) via the MAP, which in turn will trigger a signal flow on the second column, starting from location (8,2) and running to location (2,2).

4 Evolutionary Learning

Six levels of evolutionary variation are possible in the system: at the level of readin enzymes (initiating signal flows), at the level of readout enzymes (responding signal flows), at the level of MAPs (modulating signal flows), at the level of cytoskeletal components (transmitting signal flows), at the level of connections among receptor neurons and cytoskeletal neurons, and at the level of reference neurons. In the current implementation we allow variation-selection operators to act on only one level at a time. One level, or aspect, is open to evolution for sixteen cycles. During this time all the other levels are held constant. The levels of evolutionary changes are turned on in the sequence of reference neuron, readin enzyme, reference neuron, connection among receptor neurons and cytoskeletal neurons, reference neuron, cytoskeletal component, reference neuron, readout enzyme, reference neuron, and MAP.

Fig. 4. Different combinations of cytoskeletal signals to fire the neuron. The figure demonstrates that the readout enzyme at location (8,3) might be activated by any two of signal flows along C1, C2, and C3 components.

Evolutionary learning at cytoskeletal neuron level has three steps:

1. Each subnet is activated in turn for evaluating its performance.
2. The pattern of readout enzymes, readin enzymes, MAPs, connectivities, and other components of best-performing subnets is copied to lesser-performing subnets, depending on which level of evolution is operative.
3. The pattern of readout enzymes, readin enzymes, MAPs, connectivities, and other components of lesser-performing subnets is slightly varied.

Evolutionary learning at reference neuron level has three steps:

1. Cytoskeletal neurons controlled by each reference neuron are activated for evaluating their performance.
2. The pattern of neural activities controlled by best-performing reference neurons is copied to lesser-performing reference neurons.
3. Lesser-performing reference neurons control a slight variation of the neural grouping controlled by best-performing reference neurons.

5 Application Domains

In this study, the ANM system was employed to differentiate a clinical database of ventilator-dependent patients. In total, there were 189 records, of which 84 patients had successfully weaned from ventilators while the remaining 105 failed. The following procedure described how to link the ANM system with the database. Note that in this model the cytoskeletal neurons served as the major components responsible for information processing. We first explained how to set up the connections between these 27 parameters and cytoskeletal neurons. Then we described how to map each parameter value to an external signal for cytoskeletal neurons. At last, we explained how to evaluate the system's performances.

We note that the connections between the parameter layer and cytoskeletal neuron layer were only partial. That is, each of these neurons was responsible for processing only a small subset of stimuli generated from these 27 parameters (through evolutionary learning). However, it should be noted that all cytoskeletal neurons that had connections with a parameter would receive the same pattern of stimuli. The initial connections between these 27 parameters and cytoskeletal neurons were randomly decided, but subject to change as learning continued. Through evolutionary learning, each cytoskeletal neuron would be trained to be a specific input-output pattern transducer.

Each parameter was encoded with a 5-bit pattern. In total, there were 135 bits required to encode all of these 27 parameters. For each parameter, the minimal and maximal values of these 189 records were determined (to be denoted by MIN and MAX, respectively). The difference between these two values was equally divided into 5 increments (denoted by INCRs). The transformation of each actual parameter value (to be denoted by ACTUAL) into the corresponding 5-bit pattern was shown to be

$$= \begin{cases} 00001, & \text{if } \text{MIN} \leq \text{ACTUAL} < (\text{MIN} + \text{INCR}) \\ 00010, & \text{if } (\text{MIN} + \text{INCR}) \leq \text{ACTUAL} < (\text{MIN} + \text{INCR} \times 2) \\ 00100, & \text{if } (\text{MIN} + \text{INCR} \times 2) \leq \text{ACTUAL} < (\text{MIN} + \text{INCR} \times 3) \\ 01000, & \text{if } (\text{MIN} + \text{INCR} \times 3) \leq \text{ACTUAL} < (\text{MIN} + \text{INCR} \times 4) \\ 10000, & \text{if } (\text{MIN} + \text{INCR} \times 4) \leq \text{ACTUAL} \leq \text{MAX} \end{cases}$$

Each bit with value '1' represented a specific set of stimuli to a cytoskeletal neuron. When a readin enzyme received an external stimulus, a cytoskeletal signal was initiated. As to which readin enzymes of a neuron would receive the stimuli from a parameter, it was randomly decided in the beginning and subject to change during the course of learning. For each record, all stimuli were sent to cytoskeletal neurons simultaneously. This means that all cytoskeletal signals were initiated at the same time. The cytoskeleton integrated these signals in space and time. For each input record, the class of the first firing cytoskeletal neuron was assigned as its output (to be described below).

Cytoskeletal neurons were equally divided into two classes, corresponding to two different groups of records. One class of neurons represented the group of patients who have successful weaning while the other unsuccessful weaning. For each record (input pattern), we defined that the system made a correct response when the class of the first firing neuron was in accordance with the group shown in the database. The ANM system was tested with each of these 189 records in sequence. The greater the number of correct responses made by the system, the higher its fitness was.

6 Experimental Results

Two experiments were performed. The first was to apply the system to the RCC database. For comparison, we also tested the database with two other artificial neural networks (the back-propagation neural network and support vector machine) and one tree-based decision algorithm (Waikato Environment for Knowledge Analysis). In the second experiment, we examined the effectiveness of each parameter in determining weaning results.

6.1 Data Differentiation

These 189 records were divided into two sets: training and testing. The training set consisted of 120 records, about two thirds of the database. The testing set consisted of 69 records, about one third of the database. Ten runs were performed. For each run, 120 out of these 189 records were selected at random as the training set whereas the remaining 69 records were grouped as the test set.

The experimental result showed that the number of records recognized by the ANM system increased continuously during the course of learning. The average differentiation rate was 91%. Then, the system after substantial learning was tested. The average differentiation rate on these ten test sets was 71.0%, implying that it possessed a certain degree of differentiation capability.

For comparison, we first tested the database with the Weka tool, a collection of data mining algorithms that employed tree-based classifications. The best result that we obtained with this tool was collected. The average differentiation rate of 10 runs on the testing set was 63.2%. We then tested it with the support vector machine. The average differentiation rate on the testing set was 69.9%. Lastly, we employed the back-propagation neural network to the database. Several combinations of the numbers of hidden layers (including nodes) and transferring functions were tested. The ten best results were collected. The average differentiation rate on the testing set was 70.9%.

6.2 Parameter Analysis

In this experiment, we investigated the effectiveness of each parameter in determining the weaning results of ventilator-dependent patients. We noted that the system learned to treat a particular parameter as rather significant when it could always be used to give a correct response to all training records. In other words, altering the values of this parameter might lead to a completely different result. By contrast, the system tended to ignore those parameters with insignificant values. In other words, for an insignificant parameter, any alteration of its values had no effect on the response. To generate a test set, we copied the training set and varied a specific parameter of each of the training patterns. The variation was made by setting a parameter at a specific value, starting from 0.1 to 1 (with an increment of 0.1). Thus, there were eleven testing sets generated for each of these 27 parameters. In total, there were 297 testing sets. For each testing set, we set a parameter at a specific value but kept the values of other 26 parameters unchanged. For example, the first testing set was identical to the training set except the value of the first parameter of each record was set to be 0.1. The second testing set was generated in a similar manner, but the value of the first parameter was set to be 0.2.

The system after substantial learning was employed. The experimental results showed that there were almost no changes on the system's outputs when the values of these 7 parameters (Cr, respiratory tract disease, cardiovascular disease, and chronic obstructive pulmonary disease, septic syndrome with multiple organ failure, other surgeries, and the length of time staying in ICU) were altered. That is, altering the values of these parameters had no significant effect on the system's outputs. This implied that there was essentially no direct relationship between these parameters and

patients' weaning results. By contrast, the outputs were quite different when the following 10 parameters (age, Alb, BUN, Hb, cerebral vascular disease, coma scale before removing ventilator, RSBI, respiratory tract infection, urinary tract infection, other infection) were set at different values, illustrating that they played a vital role in affecting patients' weaning results. Among these 10 parameters, age and coma scale before removing ventilator are two most important parameters. For the remaining 10 parameters, the result showed that the changes of the system's outputs fell within a certain range, suggesting that to some extent they were important parameters.

We were particular interested in those parameters identified as very important by one side but as insignificant by other side. Our experimental result showed that there were four parameters identified by the physician as very significant but by the ANM system as almost insignificant. These included respiratory tract disease, cardiovascular disease, chronic obstructive pulmonary disease, and septic syndrome with multiple organ failure. All of these parameters were related to the disease carried by the patients. Even though the result was not quite the same as that of the physicians; however, in some senses it should provide another dimension of information to physicians. It implied that some important parameters that the physician had in mind might not be that critical.

7 Conclusions

The experimental result with the RCC database is consistent with our previous result that the system demonstrates a high differentiation capability. Finally, we note that a parameter is significant if it can be used to effectively differentiate data and to make it redundant if it cannot. The significance of each parameter is dependent upon the structure of a data set. Different sets possess different significant parameters. The parameter analysis result has some implications for clinical studies. It provides physicians with information about the effectiveness of each parameter in determining weaning for patients. Our experimental result shows that some of these significant parameters are the same as those recognized by physicians whereas some are not. The finding of those significant parameters not previously recognized by physicians may provide them another dimension of information, which in turn may open up a possibility of exploring some unknown phenomena.

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