Non-invasive Pain Sensor Development for Advanced Control Strategy of Anesthesia
A Conceptual Study

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Abstract: This paper introduces the mechanisms of pain perception in the human body in order to start the challenging task of controlling analgesia as part of general anesthesia. This research proposes a pain sensor, which measures analgesia levels. For control purpose, a prediction model is needed in order to obtain a model-based predictive control (MPC) strategy. This paper proposes to employ a compartmental fractional-order derivative model as a prediction model for the diffusion process that occurs when a drug is taken up by the human body. Simulations are preformed to investigate the effect of the fractional order on the diffusion of Propofol in the human body.

1 INTRODUCTION

The main objective of a drug delivery system is to provide effective therapy by minimizing the side effects and reducing deviation from the desired state of the patient. To develop an advanced drug delivery system, there is a need for a mathematical model, which takes pharmacodynamic and pharmacokinetic effects of the drugs into account.

Nowadays, the applications of control theory rely mostly on deterministic assumptions where the general approach of open-loop configuration assumes that the pharmacokinetic relations can be modeled by a linear system with known parameters (Wagner, 1976). Nevertheless, these assumptions do not take into account the individuality of each patient. Furthermore, is the model optimization procedure based on the average of a population which results in suboptimal solutions. Therefore, the challenge is to use a closed-loop configuration in order to formalize the process of observation and intervention to provide a better and more accurate control.

Moreover, some computer-control systems try to predict the future drug effect in order to adjust the parameters in advance (Absalom et al., 2011). As anesthesia is neither a simple process nor a well-understood process, it is a very challenging system to control. Taking into account the difficulty in modeling consciousness, the mechanism of anesthetic-induced loss of consciousness is nowadays still confounding scientists. Current models for anesthesia are mean field models of drug action (Absalom et al., 2011), which describe anesthetic phenomena based on the electroencephalogram (EEG) and associated with different brain states. A relationship between changes in EEG signals and depth of anesthesia was developed in order to control the delivery of intravenous drugs. Afterwards, this relationship was used to inject liquid ether into an anesthetic circuit. The first main impulse was given in the early 70s with the introduction of physiology-based compartment-models of uptake and action of anesthetic drugs (Zwart et al., 1972).

The advantage of automated closed loop control of anesthesia is a continuous drug delivery contrary to intermittent control, which is nowadays standard practice. By having a continuous drug delivery, overdose or under-dose of hypnotic or analgesic drugs can be avoided. Under-dosing patients can result in sensing pain during the surgery without being able to move. However, feedback information currently presents a major problem for control algorithms because of the presence of artifacts (e.g. eye movement, leg movement, etc.) or by patient mismatch, which results in erroneous signals. Consequently, the quality of measured signals decreases, leading to complex

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numerical filtering.

The paper is structured as follows: in section II, we describe how pain is perceived and transmitted during anesthesia. The challenges coinciding the automated control of anesthesia are discussed in section III, followed by the discussion of the proposed sensor. Section IV shows the simulations and results. In the last section conclusions are formulated.

2 PAIN PERCEPTION AND TRANSMISSION DURING ANESTHESIA

Anesthesia is the process of having sensation (including the feeling of pain) blocked or temporarily taken away. Adequate anesthesia can be defined as a reversible pharmacological state where the three main parts of anesthesia (muscle relaxation, hypnosis and analgesia) are guaranteed. Good monitoring of anesthesia includes an attentive observation of the patient during critical phases. There are several kinds of general anesthetics, but those most commonly used enhance or mimic the action of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (Garcia et al., 2010).

The main components of anesthesia are: (1) muscle relaxation, which is induced to prevent unwanted movement or muscle tone and causes paralysis during surgical procedures. EMG signals are used to quantify the level of muscle relaxation. (2) hypnosis, which is a general term indicating unconsciousness and absence of post operative recall of events occurred during surgery (Kuizenga et al., 2001). Level of hypnosis is related with the infusion of drugs and can be monitored by a BIS monitor (based on EEG) and (3) analgesia (pain relief) which is an insensibility to pain without loss of consciousness i.e. a state in which painful stimuli are not perceived or not interpreted as pain. It is usually induced by an analgesic drug, although trauma or a disease may produce a general or regional analgesia. Figure 1 shows the input-output variables of anesthesia. Notice, that the three main parts of anesthesia are unmeasurable up until now. However, relationships have been defined between unmeasurable and measurable outputs in order quantify the levels of hypnosis and relaxation. For analgesia levels ,however, these methods are insufficient.

Understanding pain perception and transmission is necessary in order to measure analgesia during general anesthesia. Pain receptors are distributed in the superficial layers of the skin (Figure 2) or in some

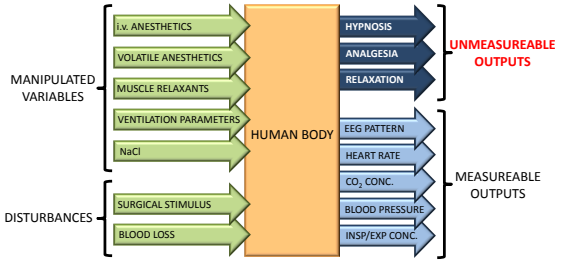

Figure 1: Schematic of input/output variables of anesthesia.

internal tissues. Five different types of receptors exist: (1) *mechanoreceptors*, which detect mechanical deformation of the receptor or its adjacent cells; (2) *thermoreceptors*, which detect changes in temperature; (3) *nociceptors*, which detect the damage of the tissues, whether it be physical or chemical damage; (4) *electromagnetic receptors*, which detect light on the retina of the eye and (5) *chemoreceptors*, which detect the taste in the mouth, smell in the nose, oxygen levels in the arterial blood, carbon dioxide concentration and other factors that make up the chemistry of the body. Pain receptors are activated by extremes of pressure and temperature or as a veritable soup of chemicals released from injured tissue. Histamine, K^+, ATP (AdenasineTriPhosphate), acids and bradykinin are among the most potent pain producing chemicals (Keele, 1970).

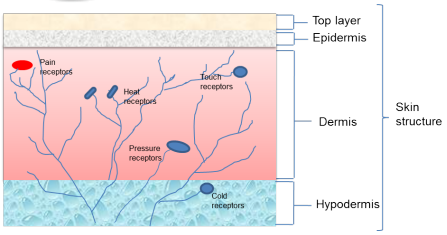

Figure 2: Schematic overview of pain receptors in the skin (Marieb and Hoehn, 2011).

Pain perception has three stages: (1) a peripheral stage peripheral tissue sensitization, (2) a transmission stage - by specialized structures and (3) an integration of pain - can be conscious or not and involves functions such as: attention, concentration, memory, affect.

Peripheral stage - in this first stage tissues are damaged due to chemical, mechanical or thermal stimuli followed by stimulation of pain receptor and activation of the receptors by noxious stimuli. When an inflammation appears the pain fibers are subdued to chemical aggression. Once the tissue is damaged, the release of chemical substances (e.g. bardykinin) takes place. This leads to a sensitization of nerve endings that results in a pain signal and an increase in local temperature (Marieb and Hoehn, 2011).

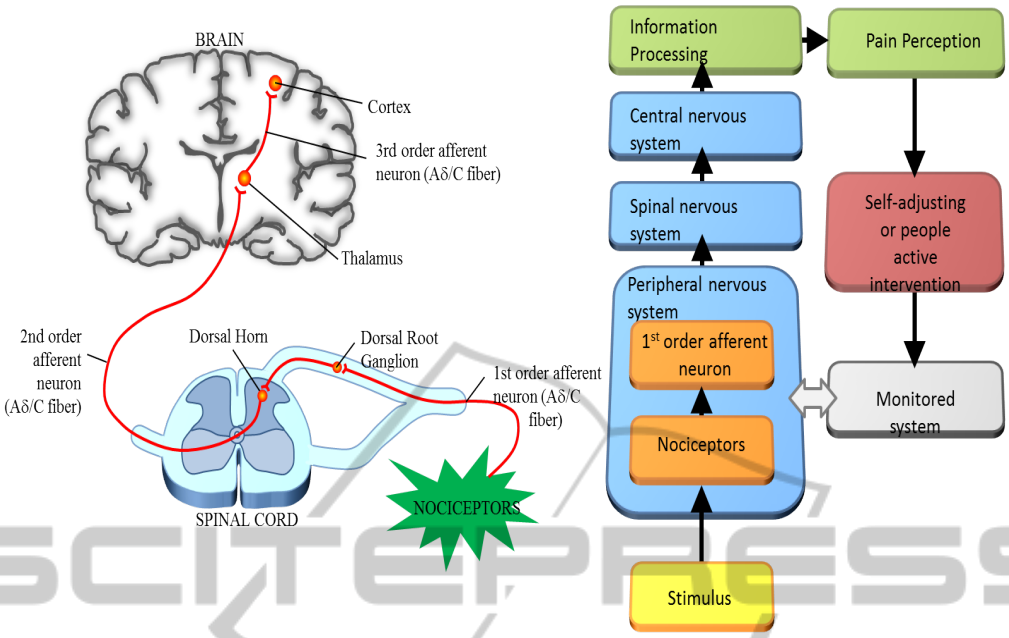

Figure 3: Schematic representation of a biological pain pathway (right side) and general flow chart of the pain perception process (left side).

Transmission stage - the second stage includes: peripheral receptors, nervous tracts, spinal mechanisms, ascending and descending pathways, brainstem, thalamus and the cortex. According to control theory of pain (Melzack, 2011), the mechanism in the brain acts as a gate to increase/decrease the flow of nerve signals from the peripheral receptors to the central nervous system. Pain transmission is influenced by many factors such as: (a) a continuous increase of duration and amplitude of the action potentials in the dorsal horn, this phenomenon is named *wind-up phenomenon*, (b) a correlation of the amplification phenomenon according to the stimulation of fibers. Clinically, this results in hyperalgesia or secondary pain and the phenomenon is described as a *temporal summation* and (c) a *central hypersensitivation*, this represents the pathophysiological mechanism of chronic pain.

Integration stage - the last stage involves components such as brainstem, thalamus, hypothalamus, subcortical nuclei and brain cortex. These structures take care of flexion reflexes, pain sensation and its perception, responses, etc. Pain control depends on the thalamus and the gate system.

A schematic representation of the pain pathway is presented in figure 3. The incoming pain fibers excite second-order neurons that send long fibers to the opposite side of the cord and then upward to the brain as can be observed in figure 3 (right hand side). Figure 3 (left hand side) shows a general flow chart that describes the pain perception process.

3 CHALLENGES FOR AUTOMATED CONTROL OF ANESTHESIA

The development of a pain sensor to measure analgesia levels during general anesthesia has several challenges.

- The first step is to obtain a suitable patient model. Taking into account the individuality of each patient the identification is very challenging.
- The second challenge of this research is that this model has to be generalized.

To control the depth of the anesthesia, there is a need for a sensor that can measure the level of analgesia. The degree to which a person reacts to pain varies tremendously. A robust controller should handle the nonlinear response profile and inter- and intra-patient variation of the patient's analgesic state to infusion of an analgesic drug (e.g. Reminfetanil, Propofol). An ideal controller guides the induction of anesthesia in order to reach the target as fast as possible without initial overshoot and maintains the desired target. Therefore, from control engineering viewpoint, model-based predictive control (MPC) plays a crucial role in solving such complex problems.

One proposed benefit of automated, closed-loop drug delivery systems is that continuous, responsive control of the clinical and therapeutic effect may improve quality of care compared to intermittent control.

3.1 Non-invasive Pain Sensor Development

Pain is a complex response to the interaction of multiple inflammatory mediators that are released at the point of injury. Clinical assessment of pain is necessary to diagnose, manage and choose treatment options, as well as for the evaluation of the most efficient treatment. Current methods of assessing pain include visual analog, Wong-Baker faces and verbal numeric scales (Hemmerling et al., 2007). However, studies have shown that these methods may be subjective and discrepancies are likely to be recorded for similar pain intensity measurements. Hence, there is a need to develop a more objective scale that relies on the fundamentals of biochemical mechanisms of pain transduction.

General anesthesia consists of three components acting simultaneously on the patient's vital signs: hypnosis, analgesia and neuromuscular blockade. Hypnosis and neuromuscular blockade are relatively well-characterized and can be quantified by respectively electroencephalogram (EEG) and electromyogram (EMG) data. By contrast, analgesia is far from being well-characterized and no sensor is available for measuring the pain relief levels that the patient experiences during general anesthesia. The challenge originates from unavailability of models that characterize pain perception in the neural dynamics. Unlike the well-understood dose-response relationship for the hypnotic component of sedation, the dose-response relationship for the analgesic component of sedation needs further study.

Figure 4 shows the three main parts proposed for a pain sensor: the role of biological recognition elements (receptors, enzymes, antibodies, etc.) is to differentiate the target molecules in the presence of various chemicals, the transducer electrochemical, optical, magnetic, etc.) converts the bio-recognition event into a measurable signal, the signal processing part converts the signal into a readable form.

3.2 A Prediction Model for Model-based Predictive Control

Model-based Predictive Control (MPC) refers to a family of control algorithms that compute a sequence of manipulated variables by solving an optimization problem, incorporating explicit knowledge of the

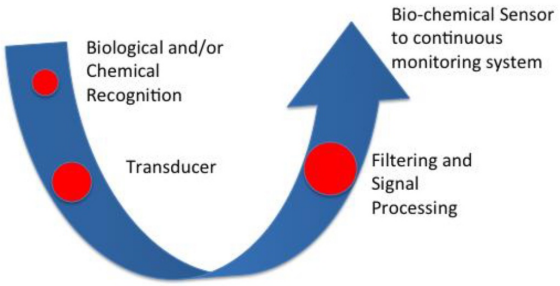

Figure 4: Three main parts of the proposed sensor.

plant model and incorporating feedback information (De Keyser, 2003). Due to the properties of MPC (its ability to handle nonlinear, constrained, and multivariable systems but also its severe computational requirements), it has primarily been used in the chemical process industries. Thus, while MPC remains an open and growing area of research in systems and control, there are somewhat limited applications reported outside the processes industries. More recently, there has been considerable interest in expanding the applicability of MPC to other domains of engineering which were traditionally considered unsuitable for MPC due to their small physical size and fast dynamics. The MPC strategy can be visualized by the block-scheme in Figure 5 (De Keyser and Van Cauwenberghe, 1981; D'hulster et al., 1983).

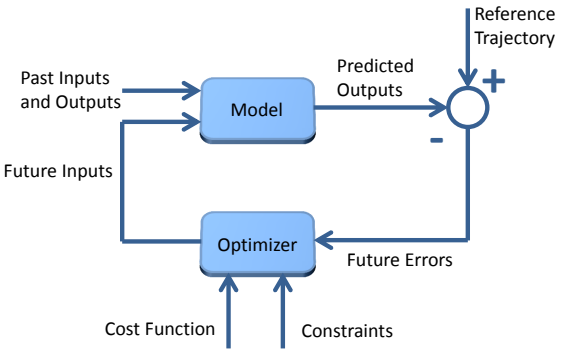

Figure 5: MPC block-scheme.

The success of MPC as a computer control paradigm can be attributed to three important factors. First and foremost is the incorporation of an explicit process model into the control calculation; this allows the controller to deal directly with all significant features of the system dynamics. Second, the MPC algorithm predicts the system behavior over a future horizon in time. This means that the effects of disturbances can be anticipated and removed, allowing the controller to drive the system more closely along the desired trajectory. Finally, the MPC controller con-

siders input, state and output constraints directly in the control calculation. This means that constraint violations are far less likely, resulting in tighter control around the optimal operating point of the system.

Standard models include step response models, transfer function models and linear state space models, however, these models do not suffice in modeling the dynamics of the diffusion processes that occur in the human body. To model the diffusion processes in the human body, we use compartmental models in combination with fractional-order derivatives i.e. Fractional Calculus (Dokomuetzidis et al., 2010). Two compartments are used in this diffusion model: plasma (blood) and muscle.

3.2.1 Fractional Calculus Principles

Fractional Calculus is a generalization of integration and derivation to non-integer (fractional) order operators (West, 1990). At first, we generalize the differential and integral operators into one fundamental operator D_t^n (n is the operation order) which is known as fractional calculus. Several definitions of this operator have been proposed. All of them generalize the standard differentialintegral operator in two main groups: (a) they become the standard differential integral operator of any order when n is an integer; (b) the Laplace transform of the operator D_t^n is s^n (provided zero initial conditions), and hence the frequency characteristic of this operator is $(j\omega)^n$. The latter is very appealing for the design of parametric modeling and control algorithms by using specifications in the frequency domain. A fundamental D_t^n operator, a generalization of integral and differential operators (*differintegration* operator), as shown in equation (1).

$$D_t^n = \begin{cases} \frac{d^n}{dt^n}, & n > 0 \\ 1, & n = 0 \\ \int_0^t (d\alpha)^{-n}, & n < 0 \end{cases} \quad (1)$$

In this equation n is the fractional order (FO) and $d\alpha$ is the derivative function. Since the entire research will focus on the frequency domain approach for fractional order derivatives and integrals, we shall not introduce the complex mathematics for time domain analysis. The Laplace transform for integral and derivative order n are, respectively:

$$L\{D_t^{-n} f(t)\} = s^{-n} F(s) \quad (2)$$

$$L\{D_t^n f(t)\} = s^n F(s) \quad (3)$$

where $F(s) = L\{f(t)\}$ and s is the Laplace complex variable. The Fourier transform can be obtained by replacing s by $j\omega$ in the Laplace transform and the equivalent frequency-domain expressions are:

$$\frac{1}{(j\omega)^n} = \frac{1}{\omega^n}\left(\cos\frac{n\pi}{2} - j\sin\frac{n\pi}{2}\right) \quad (4)$$

$$(j\omega)^n = \omega^n\left(\cos\frac{n\pi}{2} + j\sin\frac{n\pi}{2}\right) \quad (5)$$

Thus, the modulus and the argument of the FO terms are given by:

$$Modulus(\text{dB}) = 20\log\left|(j\omega)^{\mp n}\right| = \mp 20n\log|\omega| \quad (6)$$

$$Phase(\text{rad}) = \arg\left((j\omega)^{\mp n}\right) = \mp n\frac{\pi}{2} \quad (7)$$

resulting in a straight line with a slope of $\mp 20n$ passing through 0 dB for $\omega = 1$ for the magnitude (dB *vs.* log-frequency), respectively a horizontal line, thus independent with frequency, with value $\mp n\frac{\pi}{2}$ for the phase (rad *vs.* log-frequency). The respective sketches are given in figure 6.

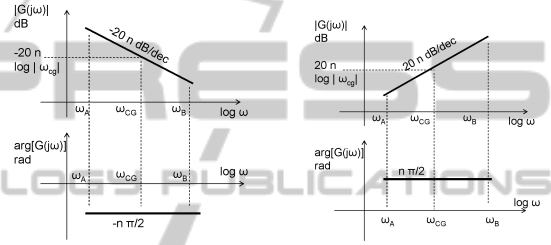

Figure 6: Sketch representation of the FO integral and derivator operators in frequency domain, by means of the Bode plots (magnitude above and phase below).

3.2.2 Principles of Compartmental Fractional Derivative Models

A two-compartmental fractional derivative model can be used to model the diffusion process in the human body (Popovic et al., 2010; Beneken and van Oostrom, 1998). The model is formulated so that the mass balance is preserved. In figure 7, we see a conceptual schematic of a model.

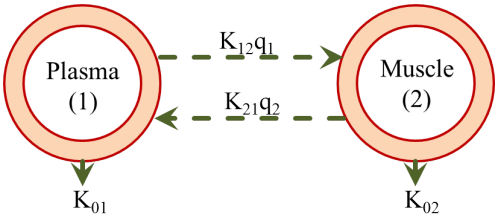

Figure 7: Conceptual schematic of a two compartment model.

The first compartment represents the plasma or any other region in the body where the kinetics of the drug are uniform. The second compartment represents the place where the drug is applied i.e. muscle, subcutaneous tissue or digestive tract. Traditionally,

the two compartments are described by a system of differential equations of integer order.

$$\dot{q}_1(t) = -K_{12}q_1(t) \tag{8}$$

$$\dot{q}_2(t) = K_{12}q_1(t) - K_{02}q_2(t) \tag{9}$$

Recently, the fractional-order models seem to better suit the dynamics of biological systems than the integer one (Magin, 2010). A simple model of a two-compartmental system is then given by the following equations:

$$\tau_1^{\alpha_1-1}\,{}_0D_t^{\alpha_1}q_1(t) = -K_{12}q_1(t), \tag{10}$$

$$\tau_2^{\alpha_2-1}\,{}_0D_t^{\alpha_2}q_2(t) = K_{12}q_1(t) - K_{02}q_2(t), \tag{11}$$

where we assumed $K_{01} = 0$, $K_{21} = 0$ and with the initial conditions $q_1(0) = \text{dose}$, and $q_2(0) = 0$. In these equations τ_1 and τ_2 are time constants which represent the speed of diffusion, while n_1 and n_2 represent a non-integer between 0 and 1 and characterize the type of diffusion (sub-, super-, etc).

4 SIMULATIONS AND RESULTS

In this section we presents a first attempt in using the fractional order derivatives in modelling Propofol concentration. Based on the fractional-order two-compartmental model mentioned in the previous section, simulations are performed. In our simulations, the anesthetic drug is Propofol. The objective of this simulations is to investigate the influence of the fractional-order derivatives on the Propofol concentration in a target organ i.e. the muscle.

We simulate the diffusion of Propofol in a patient of 45 years old that weighs 90 kg and has a height of 184 m. We take a bolus injection of 3.33 mg/s during a period of 15 seconds, which corresponds with an injected amount of drug of 50 mg.

The values of K_{12} and K_{02} are dependent on the age of the patient and are calculated as follows:

$$K_{02} = 1.29 - 0.024 * (age - 53) \tag{12}$$

$$K_{12} = \frac{K_{02}}{v_1} \tag{13}$$

with v_1 the volume of blood in liters ($v_1 = 4,27\ell$).

Figure 8 shows the amount of Propofol in compartment 1, i.e. the bloodstream, as a function of time and the fractional order α. In figure 9 we see the amount of drug for compartment 2, i.e. the muscle, in function of time at distinct values of α. From figure 8 we can conclude that the decay of the numerical solution changes in function of α. For lower values of α, we observe higher decay rates, which show that fractional-order models can capture inter-patient variability. In figure 9 we can see that the higher values of α will result in higher amounts of drug taken up by the muscle. This can be explained by the slower decay rates in the bloodstream resulting in more time for the drug to diffuse through the membrane.

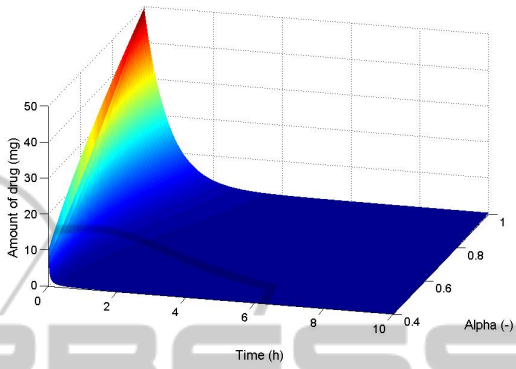

Figure 8: Amount of drug in compartment 1 as a function of α and time.

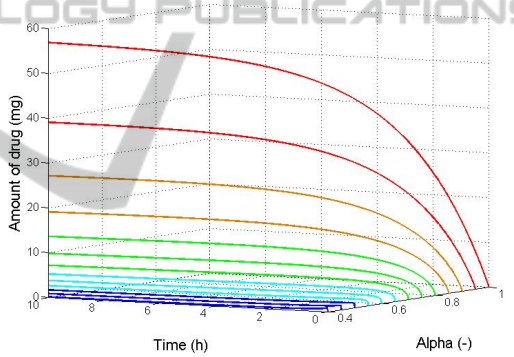

Figure 9: Amount of drug in compartment 2 as a function of α and time.

5 CONCLUSIONS

Controlling analgesia levels during general anesthesia is of great importance for the patient's quality of treatment. This research gives a overview of the complexity of the neurophysiological pain perception process needed to understand analgesia. A non-invasive pain sensor has to be developed to ensure feedback in the analgesia control strategy. The main challenges in this development is the patient model. A model-based predictive control strategy is proposed for the analgesia process based on a two-compartmental fractional derivative model. Simulations show the effect of the fractional order on the concentration of Propofol in a patient. We conclude that different values for the fractional order of the model can capture inter-patient variability, making compartmental fractional deriva-

tive models suitable to model the diffusion process in the human body.

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