Università Campus Bio-Medico di Roma

School of Engineering

PhD Course in Biomedical Engineering

(XXVII - 2012/2014)

New Tools for a Technology-aided Assessment of Newborns' Oral-Motor Behavior

Eleonora Tamilia

Coordinator

Prof. Giulio Iannello

Supervisor

Prof. Eugenio Guglielmelli

Co-Supervisor

Dott. Ing. Fabrizio Taffoni

February 2015

New Tools for a Technology-aided Assessment of Newborns' Oral-Motor Behavior

A thesis presented by

Eleonora Tamilia

in partial fulfillments of the requirements of the degree of

Doctor of Philosophy

in Biomedical Engineering

Coordinator

Prof. Giulio Iannello

Supervisor

Prof. Eugenio Guglielmelli

Co-supervisor

Dott. Ing. Fabrizio Taffoni

February 2015

Table of contents

Abstract

Thanks to technology advances, the survival of high-risk newborns is increasing, and there is a rising concern about the potential problems that this population may encounter. As a result, both medical and research communities are calling for new and more reliable tools to support health care professional in assessing the newborn's neuro-motor status, his readiness for discharge and planning for subsequent care. The newborn's oral-motor behavior during feeding is the earliest window in which care providers and parents can view and assess the well-being of the infant. One of the major developmental milestones of high-risk newborns in fact is the attainment of adequate Nutritive Sucking (NS) skills for feeding: they often show oral-motor dyscoordination and are unable to suck and feed orally. This is why the importance of monitoring newborns' oral-motor activity has been acknowledged over the years, and the need for reliable instruments has been recently stressed. Over the last decades significant advances occurred in the technology-assisted monitoring of NS disorders in newborns, however there are no accepted standards for their implementation in clinical practice, and so no objective tool is regularly and widely used.

The goal of this PhD thesis was to provide new tools for a technology-aided assessment of newborns' oral-motor behavior during feeding. The first objective has been to overcome the technological challenges emerging from the state of the art, designing a hardware platform that was suitable for a wide and regular application in both clinical (pre-discharge) and domestic (post-discharge) setting:

i) A low-cost device for monitoring sucking pressures has been designed and developed in order to be easily integrated on a typical feeding bottle: the measuring system has been experimentally validated in laboratory and then tested collecting data on newborns during the routine clinical practice.

ii) Two novel methods for the ecological estimation of nutrient consumption during bottle-feeding have been proposed and two low-cost sensor-based modules have been developed and experimentally validated in laboratory.

iii) Given the importance of oral-respiratory coordination during NS, a sensing non-invasive solution capable of monitoring the temporal breathing pattern has been designed

and developed with a completely non-invasive approach, in order to be easily embeddable on a common feeding bottle. Its laboratory validation fosters its successful application, and further work is needed to test and validate the system on newborns

The second objective of this thesis has been to develop an automated analysis system capable of quantitatively assessing oral feeding ability, in order to help clinicians in routine clinical monitoring and decision-making. The increasing need for an objective assessment tool indeed makes also increasingly important to establish quantitative and reliable measures for a proper analysis of oral-motor function. A software system to systematically treat and analyze sucking pressure data has been developed: proper algorithms for automatic segmentation and features extraction have been proposed and tested for the analysis of different experimental data. Besides, a series of measures of motor control and variability in coordination has been introduced for the analysis of oral-motor function, and the results from their analysis seemed to indicate their useful contribution to the quantitative assessment of NS skills. Experimental data have been analyzed to investigate the suitability of the assessment system to the evaluation of the newborn's maturational course, as well as to quantify the deviation from a typical behavior. The results obtained are promising and further work is now dedicated to the collection of a larger longitudinal set of data from both high-risk and healthy infants, in order to support the reported findings and also define normative data.

List of figures

List of tables

I. INTRODUCTION

International data indicate that the prevalence of preterm birth is increasing worldwide [1]. There is concern around these rising trends because prematurity is the leading cause of death in children under the age of 5, and also a leading cause of later long-term neurological disabilities in children. As technology advances, these high-risk infants have a better chance of postnatal survival; however, the outcome and the potential problems these infants may encounter must be carefully considered and monitored.

The American Academy of Pediatrics (AAP) has recently reported as, with increased survival of very preterm newborns, many infants are discharged with unresolved medical issues that may complicate their subsequent care [2]. Today, in fact, infants are often discharged requiring more care and closer follow-up than was typical in the past. In addition, societal and economic forces have come to bear on the timing and process of discharge and follow-up care, even because the prolonged convalescent stage of hospitalization may result in: i) increased risk to the infant for iatrogenic injury or infection, ii) separation-related effects on the parental relationship, iii) increased financial cost to the health care system. As a result, both medical and research communities are calling for data on developmental issues of this population, as well as for new and more reliable tools to support health care professional in assessing readiness for discharge and planning for subsequent care.

Many developmental milestones must be attained by these infants during hospitalization. After physiologic stability, a major developmental task is the attainment of adequate oral-motor skills for feeding by breast or bottle. Oral feeding is the most complex sensorimotor process the newborn undertakes in the first months of life. The AAP recognizes oral feeding mastery an essential criterion for discharge, and this is often the last task infants master in their NICU course prior to safe discharge home. Unlike the majority of healthy full term infants, who are born with adequate skills to coordinate suck, swallow and respiration that allow safe oral feeding, preterm infants need time to develop these skills gradually. They often demonstrate oral-motor dyscoordination and are unable to suck and feed orally [12], representing a frequent and serious challenge both to the newborn and the physician-provider-parent team.

Coordination between sucking, swallowing, and breathing during feeding depends on intact brainstem pathways and cranial nerves: the immaturity of the Central Nervous System (CNS) in fact can affect oral motor functions [6] and cause the inability to successfully perform oral feeding [7–10]. Infancy indeed is a crucial period for the establishment of fundamental neural circuits that are necessary for the development of normal motor function. Perinatal brain lesions, that may follow preterm birth, are one of the main causes of injury to the developing brain that result in later motor impairments, usually referred to as cerebral palsy. As neural plasticity is highly malleable during early infancy, the identification of motor dysfunction at this stage of life should provide an increased potential to compensate for neural damage through interventional strategies and also ensure efficient long-term healthcare resources and support. Nutritive Sucking (NS) is one of the earliest goal-directed action evident in a newborn's movement repertoire, so it may also provide an early opportunity to investigate mechanisms of fine motor control [11]. For these reasons, oral-motor behavior can provide valuable insights into the infant's neuro-motor status and future development [12–16], allowing the early identification of abnormal behaviors: deviations from the norm may cue the candidates for later impairments which appropriate care must be ensured to. From an anatomical point of view, sucking control involves similar oral motor structures to those required for coherent speech production; thus early sucking problems have been also suggested as predictors of significant delays in the emergence or development of speech-language skills [17,18].

Abnormalities in the integration of respiration into feeding bursts may correlate with abnormalities in brainstem centers involved in control of breathing and rhythmic suck, and may be predictive of longer-term subtle neurological and feeding problems [33].

Given all these factors, the benefits of monitoring newborns' oral-motor activity while feeding have been acknowledged over the years, and the need for reliable instruments for neonatal sucking assessment has been stressed in several works [2,4,15,19]. Clinicians would benefit from specifically designed devices to assess oral feeding ability in their routine clinical monitoring and decision-making process. Nevertheless, no objective reliable assessment tools are widely and regularly used as yet. The assessment of NS competency in fact is part of the clinical evaluation, but it is not carried out objectively. This underscores the urgency of effective objective tools and techniques for monitoring and assessment, even because the attainment of safe oral feeding is one of the most challenging prerequisites for hospital discharge of the preterm infant, and then an important contributor to the length of hospital stay and to the extent of hospital costs.

The need for a reliable instrument for the assessment of oral-motor feeding competency is also highlighted by the fact that one of the most common reason for hospital readmission in the 2 weeks after NICU discharge is feeding problems, as reported in [66]: a tool to objectively assess feeding competency on the day of discharge does not exist, and strict adherence to purely physiologic criteria may lead to the discharge of asymptomatic infants at risk of developing feeding difficulties later.

The definition of the optimal timing of the introduction of suck feeds is also vital to ensure that the commencement of feeding is beneficial rather than detrimental to the health of the infant [3]. As a matter of fact, the most common clinical problem, also manifested in moderately (31 to 33.6 weeks of gestational age, GA) and late preterm infants (34 to 36.6 weeks of GA), who are generally considered to be low-risk premature infants and whose medical complications and risks are often underestimated, is feeding difficulty [68,71]. Fig. 1 shows some results from a recent work on medical and developmental outcomes of late preterm birth. Despite its importance, the optimal timing of the introduction of suck feeds is still unclear in both the literature and in practice.

Introducing suck feeds as soon as the neurologic development and physical condition of the infant permits, has been reported to have several advantages, such as shorter transition time to all suck feeds, greater maternal satisfaction, and shorter hospital stay [5]. However, on the other hand, feeding infants who are unable to safely commence feeding may lead to problems with respiration, growth and nutritional status [85].

All these problems can be minimized by using reliable instruments for monitoring and establishing objective measures for a careful discharge planning and close follow-up: with few objective criteria for the assessment of its progress in the hospital, and no organized follow-up care, poor feeding skills and abnormal motor behavior may go undetected for too long. Notwithstanding the ongoing development of tools for the assessment of NS, there is not a common approach to this issue, thus causing problems of variability of the measurements, as highlighted by several authors [9,15,19]. Such heterogeneity represents also one of the causes of the discrepant and scattered findings reported in literature, and a major challenge in implementing them in clinical practice, as reported by Slattery *et al*. in 2012 [15]. As a matter of fact, although oral-motor behavior of infants is described in multiple sources, there is a need for objectivity with well-defined meaningful quantitative measures, that can aid clinicians in decision making processes for management of infants and young children with feeding disorders [9,75].

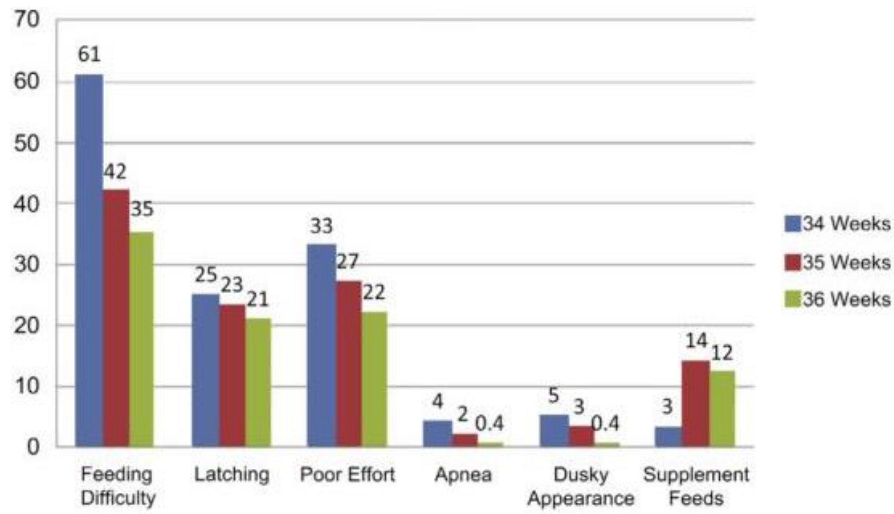


Fig. 1 Distribution of feeding difficulties among late preterm infants in a report of the Association of Women's Health, Obstetric and Neonatal Nursing (AWHONN). The cohort represents 802 infants from 34 to 36.6 weeks from 14 hospitals (as reported in [68]).

I.1. Objectives of the work

This thesis work arose from the context detailed above and aimed at fulfilling the extant needs, providing new tools and methods for a technology-aided assessment of newborns' oral-feeding behavior.

There is a pressing need today for novel technology-assisted solutions for the early assessment of infants' sensorimotor function [86]. Such solutions may provide sensitive and accurate information at an early developmental stage, with the potential to integrate on the currently available clinical assessment tools, enhancing diagnostic and prognostic power.

A technology-assisted tool for the assessment of newborns' oral-motor function while feeding has the potential benefit of:

- removing the subjectivity issue from the assessment procedure, and so providing quantitative objective measures, usable for robust intra-subject and inter-subject comparisons. This means that they might allow evaluating the patient's maturational course (intra-subject), and also the patient's displacement from normative behaviors (inter-subject).

- providing detailed measurements of some aspects that could not be perceived by a human examiner, thanks to the instrumented equipment;

- saving time for both assessment and training, and allowing the use in a domestic setting for post-discharge follow-up.

As section I.3 will describe, over the last decades significant advances occurred in the sensor-based analysis of feeding disorders in newborns: several instrumented devices have been used to measure oral-motor behavior with promising results. However, currently there are no accepted standards for their implementation in clinical practice and so no sensor-based tool is regularly and widely used. As a matter of fact, unmet needs (UN), along with concomitant challenges, still emerge.

UN1 First of all, the need remains for an objective reliable instrument for monitoring infant's feeding ability that is suitable for a wide and regular application in both clinical (pre-discharge) and domestic (post-discharge) setting.

In response to this, this work aimed at developing a technology-assisted tool adopting a strategy that can be referred to as *problem-focused* rather than *platform-focused*, as the focus has been on the design of a platform that was optimized to solve the specific problem/need. The goal was to develop an hardware platform that addressed the following key design points:

· *Safeness* – It must ensure electrical safety and the absence of any possible adverse consequence for the infant's well-being due to the device usage.

- *Non-Obtrusion / Non-Invasiveness* - It must minimize any invasiveness and be unobtrusive in order to not alter the infant's natural behavior, as well as to not generate any skepticism about its use.

- *Ease-of-use / Portability* - It must be easy to use and portable so that it can be made regularly used in different settings and by different, also untrained, users.

- *Cost* - It must be low-cost in order to be made widely available in different settings.

Therefore, given the State of the Art (SoA) regarding the sensor-based solutions already proposed for oral feeding measurement, we identified the technological challenges to overcome for the development of a platform that meets these requirements (see Section I.3 for a detailed discussion of the SoA). These challenges translate into the following specific technological objectives of this work:

OB1.1 Development of a smart module for sucking pressures monitoring that may fit any typical feeding apparatus (Section II.3).

OB1.2 Development of a reliable and sensitive module for the estimation of nutrient consumption during bottle-feeding (Section II.2).

OB1.3 Development of a sensing solution for breathing recording that can be integrated on a feeding apparatus (Section III).

UN2 Further, with the growing need for an objective assessment tool, it has become increasingly important to establish and define quantitative and reliable measures for a proper analysis of oral-motor function. The progress on this direction has been slow (see Section I.3.1) and needs further efforts.

Hence, this work aimed at developing an automated analysis system capable to quantitatively assess oral feeding ability, then helping clinicians in routine clinical monitoring and decision-making. An automated software system would minimize the need for specialized training in test delivery and interpretation, thus positively affecting the cost and ease-of-use factors of the whole assessment system.

The second goal of this work was to develop a software platform to systematically treat and analyze the data. This final objective has been pursued addressing at the following specific points:

OB2.1 Implementation of proper methods for signal processing and segmentation (Section IV.1).

OB2.2 Identification and implementation of quantitative methods for the analysis of oral-motor ability and coordination (algorithms for features extraction, Section IV.2).

OB2.3 Investigation of data analysis strategies capable of monitoring typical development and of discriminating typical versus atypical behavior (analysis of experimental data, Section IV.3).

This dissertation will describe the achievements accomplished in the design and development of both hardware (UN1) and software (UN2) platforms for the early quantitative assessment of infants' oral-motor function while feeding.

The first focus of the work has been on the development of the hardware modules, starting from the design of a sucking monitoring platform (Section II):

- Sections II.1 and II.2 will describe the design and development of sensor-based solutions for the estimation of nutrient consumption during bottle-feeding (*Module A* and *Module B*)

- Section II.3 will describe the design and development of a sensor-based solution for suction and expression monitoring (*Suction/Expression Monitoring Device*).

Then the design of another hardware module has been addressed: a breathing monitoring module has been designed and developed (Section III), and its suitability to be embedded on a typical feeding bottle has been validated.

Afterward, the focus of this work has shifted towards the development of a software system capable of a systematic signal analysis (Section IV):

- Section IV.1 will describe the algorithms implemented in order to process and segment the signals acquired by the hardware

- Section IV.2 will present the different methods investigated for a quantitative analysis of the signal, and will describe their implementation on the signals of interests.

- Section IV.3 will show the results obtained from the analysis of experimental data. Strategies of data analysis for the discrimination of healthy versus risky behavior will be described and experimented.

I.2. Oral-Motor Behavior in the Neonate

Sucking is the first oral-motor function to occur in the womb: it is a precocious oral-rhythmic motor behavior in humans, which is then integral to competent oral feeds. There are two basic forms of sucking: Non-Nutritive Sucking (NNS) when no nutrient is involved, and Nutritive Sucking when a nutrient such as milk is ingested from a bottle or breast. Infants are usually able to produce normal NNS patterns in the first hour after birth, but it may take several hours or days before breast or bottle feeding becomes well established. Coordination demands may make NS challenging for immature infants. NS behavior is composed of a complex pattern of activity involving the tongue, lips and jaw that results in the extraction of liquid nutrient from a feeding nipple. In addition, successful feeding requires complementary coordination between sucking (Sk), swallowing (Sw) and breathing (B) systems: safety in NS implies first of all a proper coordination of sucking and swallowing movements with breathing to avoid aspiration, as the anatomical pathways for air and nutrients share the same pharyngeal tract.

A nutritive suck is characterized by the rhythmic alternation of *Suction* (S), i.e., creation of a negative Intraoral Pressure (IP) through the depression of jaw and tongue, and *Expression* (E), i.e., the generation of positive Expression Pressure (EP) through the compression of the nipple between the tongue and the hard palate. This S/E alternation allows the infant to create the extraction pressure over the fluid contained in a vessel towards the oral cavity. Sucking effectiveness depends on an appropriate integration and synchronization of the structures in lips, cheeks, tongue and palate:

- *Expression* is achieved by contraction of orbicularis oris muscle and closure of the jaw in the antero-superior direction by contraction of temporal and masseter muscles. During this phase the medial portion of the tongue is elevated. This compression generates a positive pressure over the teat, producing expression of flow towards the mouth.

- *Suction* is generated by lowering (or opening) of the jaw in the postero-inferior direction, by contraction of the suprahyoid muscles, and by posterior displacement of the tongue elevation followed by tongue depression that coincides with maximum negative pressure.

The temporal sequencing and coordination of the articulators into a cycle of expression and suction is fundamental for NS. This pattern of activity demonstrates a coordination between different muscle groups in their respective roles [87]. Considering neuromuscular relations, the jaw-closing muscles (temporal and masseter), the orbicular muscle and the suprahyoid group are controlled by the trigeminal, facial and hypoglossal nerves, respectively. This pattern of activity, as reported in [87], suggests that if the sucking center in the brainstem is adequately developed, the neural regulation of movements during sucking is well coordinated.

Fig. 2 shows a typical S/E pattern during NS from experimental data acquired on a healthy term infant (data collection is described in IV.3.2).

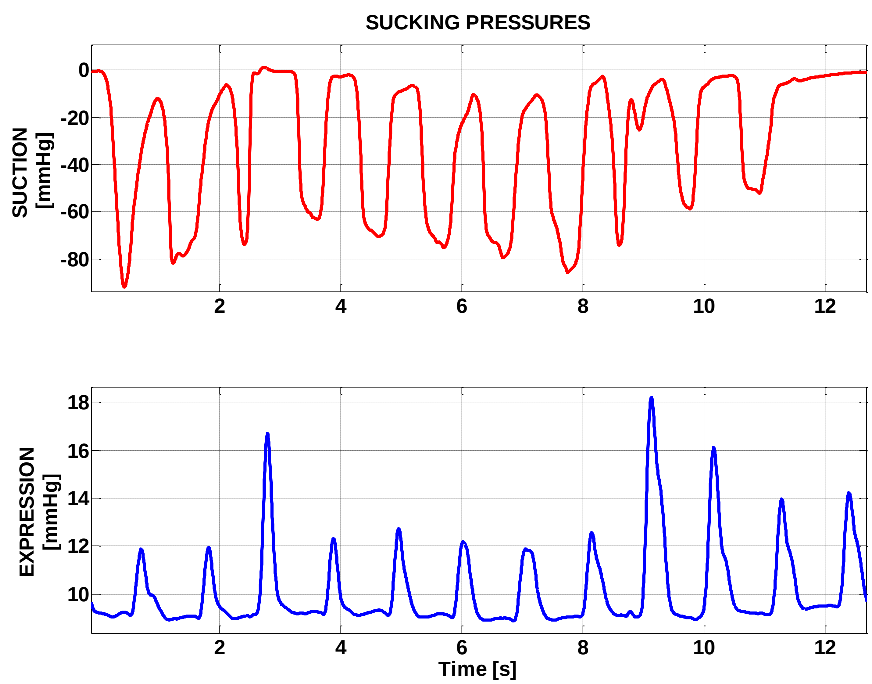


Fig. 2 Suction/Expression pattern. During suction a negative intraoral pressure is generated by a backwards tongue movement: a decrease in the pressure waveform (top, red) represents a suction event. During expression of nipple, positive pressure is created: an increase in the pressure waveform (bottom, blue) represents an expression event.

In full-term healthy infants, the NS process is characterized by a burst-pause sucking pattern, where a burst consists of a series of suck events, occurring with a typical frequency of 1 Hz [21], and a pause is a period of at least 2 s without sucking events. This burst-pause pattern evolves during feeding in three stages: continuous, intermittent and paused [24]. At the beginning of a feeding period, infants suck vigorously and continuously with a stable rhythm and long bursts (continuous sucking phase). This phase is generally followed by an intermittent phase in which sucks are less vigorous, bursts are shorter and pauses are longer (intermittent sucking phase). The final paused phase is characterized by weak sucks and very short sporadic bursts.

Moreover, in a safe and efficient cycle of NS, a safe coordination pattern between sucking (S/E), and breathing (B) is required [22]. Breathing in fact does not stop during NS. The suction force for liquid extraction is caused by movements of the oral structures, not by the stomach as adults do: the cyclic movement of the oral apparatus allows breathing to integrate with no interruption in either processes. Coordination by the CNS is essential for integration of breathing with sucking and swallowing to facilitate safe oral feeding. Premature infants, in fact, not only may have difficulty breathing following birth, but also have to progress through a protracted period of learning to coordinate sucking and breathing as they are breast or bottle fed. Respiration must accommodate to the S/E cycle, without resulting in choking, aspiration or excessive decrease in minute ventilation.

Oral Behavior as a Dynamical System

Several studies in the past have documented that behavioral rhythms, such as sucking and breathing, have an endogenous origin [21]. However, to understand how infants' behavioral rhythms influence and coordinate each other, a perspective on spontaneous pattern formation in physical and biological systems has been used in several studies, referred to as dynamical systems. Over the past decades, a dynamical systems approach to infant development has suggested new concepts and mathematical tools to analyze the emergency of coordination patterns during infancy [69,70]. This approach may allow specifying how the different parts of a system (as the components involved in oral feeding behavior) interact establishing coordinated functional units, called synergies [72].

One aspect of this approach is to identify macroscopic quantities, or order parameters, which describe the cooperation of the individual components of a complex system. Considering the oral feeding as a complex dynamical system, we can consider:

- *Suction/Expression synergy*: coupling between oscillators involved in expression and oscillators involved in suction. It involves the cooperation between oral, labial, mandibular, and lingual-pharyngeal muscle groups, as previously described.

- *Sucking/Breathing synergy*: the coupling between oscillators involved in breathing and the ones involved in sucking, The respiration indeed must also accommodate to the S/E cycle, involving airway, lingual-pharyngeal and intercostal muscles groups.

By using the tools of a dynamical systems approach to examine coordination, feeding disorders may be approached as a problem of competition between system components: it may be possible to address why some infants have difficulty sustaining NS (namely the S/E rhythmic alternation), and/or why they cannot sustain safe and efficient breathing while feeding.

In [73] and [74], analytical tools motivated by a dynamical systems perspective on coordination are used to analyze the dynamics of jaw oscillation during sucking (coordination between expression and suction), and the dynamics of sucking and breathing. These studies proved as oral feeding behavior exhibits the properties of a motor synergy, as also reported in [49]. Moreover, they proved the sensitivity of the inherent measures of oral and oral-respiratory coordination in discriminating high risk preterm infants from healthy full term infant. This suggests and fosters that the application of the quantitative methods for investigating coordination and its variability, that are based on such a dynamical perspective and operate for other modes of action [76,84], may hold for to the quantitative analysis of infant feeding problems.

Dynamical Systems Approach

Although humans are able to move in an apparently effortless and graceful way, motor control is an extraordinary complex task: even the simplest movement requires that thousands of neurons coordinate their activity to control hundreds of motor units, belonging to dozens of different muscles. This is due to a highly non-linear and extremely redundant dynamic system, physically interacting with a changing and not always predictable environment.

Dynamical systems approaches to movement analysis have gained support in past years because they provide a theoretical framework for simplifying and working with complex systems [77]. Even if physical systems can be composed of many parts interacting, their behavior may often be described by a single low-dimensional term or measure. Most human movements involve a great number of moving parts, all coordinated together, explaining why so many researchers and clinicians have put such effort into modeling the human movement as a dynamical system (e.g. [78,79]).

A central goal in dynamical systems theory is to identify the attractors, or stable states, of the system: analysis of the variability of coordination allows investigating the stability of the system, or its resiliency to perturbation. Human movement is inherently variable. When a motion is performed repeatedly, even when the goal remains constant, repetitions will vary if compared each other. A traditional perspective [80] argues that variability is synonymous with "noise" arising from errors, either in the performance of the movement or in the recording and treatment of the data [81,82]. Alternatively, dynamical systems theory argues that variability is not inherently good or bad, but reflects the variety of coordination patterns used to complete the task [83].

Researchers have used different techniques of nonlinear dynamics to study variability. Two main approaches have been used in the dynamical systems perspective to address movement coordination between two bio-physical oscillators. The first one is referred to as *discrete methods*. These methods are point estimate approaches that illustrate the relative timing of key events in a movement cycle. The second approach is referred to as *continuous methods*, which involve the evaluation of movement coordination over the entire period of time referred to as a cycle.

Section IV.2.2 will describe these techniques and the relative measures of coordination and variability, and their specific application to the dynamics of the oral-motor coordination will be proposed (IV.3.2). Through the analysis of experimental data, collected from healthy and low-birth weight infants, we will investigate whether perinatal problems of high risk premature infants emerge using such dynamical model and its concomitant observables. Positive results might suggest that it may be useful to incorporate measures of the rhythmic character of newborns' oral-motor behavior into standardized assessments of neurobehavioral function.

I.3. State-of-the-Art (SoA)

The state of the art regarding the technology-assisted tools used for measurement and assessment of neonatal oral feeding behavior will be described in this section that will provide:

1. a detailed overview of the main quantities and measures used to quantitatively analyze oral-feeding behavior and its development,

2. a review of the sensor-based solutions used to measure the previously identified quantities and indices,

3. a discussion about the main functional specifications required to a proper device for assessment, and the main advantages and weaknesses of the illustrated sensing systems, taking into consideration the application to clinical practice or domestic use.

I.3.1. SoA: Quantitative Analysis of Oral-Motor Behavior In Newborns

The ability to nutritively suck is not always completely mature in infants at birth and may require time to develop or to mature. For immature infants, the developmental complexity of the feeding process can cause a series of difficulties associated with the initiation and progression of feeding from a bottle, which is in fact the most frequent indicator of the discharge readiness adopted by healthcare personnel [24]. Bottle feeding behavior indeed has been widely investigated because of this reason, and because it allows standardization or control of some feeding characteristics across infants (e.g., liquid composition, nipple hole size, and hydrostatic pressure of milk) [25]. The adoption of evaluative measures given by technology-assisted methods (in opposition to observational methods) is increasing, because of the growing interest in reliable, valid quantitative measures of oral sensorimotor function in infancy [9]. Indeed, instrumental quantitative measures of early oral feeding ability have been reported to be more sensitive and specific to predict later neurodevelopment outcomes, compared to non-instrumental observational tools [15], whose psychometric properties are still debated [26].

The identification of the most significant measures of oral feeding ability may be important to lead future research to focus on their investigation and on the establishment of normative data necessary for the identification of deviations from the norm. Table 1 reports an overview of the most significant indices reported in literature resulting from the instrumental assessment of infants' NS behavior during bottle feeding. The indices have been grouped according to the final goal of the assessment: (i) evaluation of the level of maturation of oral feeding skills in preterm infants; (ii) evaluation or characterization of the level of maturation of oral feeding skills in term infants; and (iii) early detection of later neurodevelopmental outcomes. Table 2 lists the different physical quantities that have been measured to monitor the NS process and from which the evaluation indices have been extracted. Both tables are organized in order to separate the different components of the oral feeding behavior that can be monitored, with focus on sucking, breathing, and nutrient consumption.

Preterm infants' maturation has been assessed in terms of sucking skills during bottle feeding using several indices. The organization into bursts and the establishment of a stable temporal pattern are important developmental steps in the maturation process of the sucking component [30]. Some descriptive parameters represent important indices for the evaluation of this maturation, *i.e.*, the number of sucks per burst and the percentage of sucks in bursts. In addition to these descriptive parameters, several temporal parameters appear to be consistent indicators of preterm infants' maturation, such as: sucking frequency (sucks per min), burst duration, inter-burst width, inter-suck width, and an index of rhythmic stability referred to as Coefficient of Variation of the sucking process (COV_{Sk}). This index is used in several studies to assess the maturational patterns in terms of rhythmicity [29,30,31], and it is defined as follows:

$$COV_X := \frac{SD\ (I)}{mean\ (I)}$$

where *SD* is the standard deviation, and *I* represents the time interval between two consecutive events of the considered *X* process (e.g., the interval between consecutive sucks).

Application	**Significant Indices**			
	Sucking	***Breathing***	***Consumption***	***Ref***
Assessment of oral feeding maturation in preterm infants	Sk frequency Sucks per burst Percent sucks in burst COV_{Sk} Burst duration Inter-bursts width Inter-suck width S amplitude E amplitude S:E ratio S-E interval S-E Relative Phase S/E rhythmicity	COV_B Sk:B ratio Sk-B Weighted Coherence	Efficiency Nutrient intake rate Bolus size	[25,27–36,73]
Assessment of the oral feeding maturation in term infants	Sk frequency Sucks per burst Percent sucks in burst COV_{Sk} Burst duration Inter-bursts width Inter-suck width Inconsistency	Sk:B ratio Sk-B interface	Efficiency Nutrient intake rate Bolus size	[37–43]
Assessment of oral feeding for prediction of later neurodevelopment	Sucks per burst IP amplitude EP amplitude		Nutrient intake rate	[13,14, 36,44]

Table 1 Overview of the most significant indices used for the technology-aided assessment of infants' NS behavior during bottle feeding.

All these indices can be calculated measuring any quantity that allows the identification and the temporal characterization of sucking events, without distinction between suction and expression components (e.g., through measures of intra-nipple pressure or chin movements, as in [30,31]). Furthermore, the maturational process of preterm infants' oral-motor skills has been proven to be characterized by some developmental stages defined through indices of both expression and suction [28]. Preterm infants seem to develop and establish first the expression component, then suction, and finally the S/E rhythmic alternation. Hence, measures of both sucking pressures (IP/EP) are needed to estimate some significant indicators of this maturational progress [28,29]: S and E rhythmicity, the S:E ratio, the time lag between S and E (S-E interval), S and E amplitude. Moreover, in [73] a dynamical system approach to the analysis of oral-motor coordination has been proposed: the relative phase between S and E is calculated between peaks of expression and suction, providing a measure of the timing of suction relative to the opening and closing of the jaw.

Sucking	Breathing	Nutrient Consumption
IP [25,27,37–39,41]	Nasal airflow/ Thoracic movements [30,25]	Total transferred nutrient [25,28,35,40,41]
EP/IP [14,28,29,32,35]	Thoracic movements [29,32,33,41]	Minute transferred volume [32,36,39]
Intranipple pressure [30,40]		Transferred milk weight [29]
Chin movements [31]		
Throat-eye (S) and jaw-eye (E) distance [44]		

Table 2 Overview of the physical quantities measured to monitor the NS process.

Regarding the maturational level of sucking skills in term infants, it appears to be completely assessable through a set of descriptive and temporal indices, that do not require the measurement of both sucking pressures [37–42]. Almost all of these indices have been already mentioned, except for a measure of *inconsistency* introduced in [37] to quantify the sucking variability. The authors define it as the SD of the ratios of amplitudes of successive sucks within bursts (measure of the suck-to-suck fluctuation in amplitude).

Immature NS does not only reflect sucking ability, but also the coordination of suck with respiration. Table 1 also reports the principal indices adopted to investigate oral-respiratory coordination skills. The COV calculated from the breath-breath intervals (COV_B) has been used to analyze the feeding-related respiratory rhythms [33]; while for the oral-respiratory coordination, the phase of the respiration cycle where sucking occurs (i.e. Sk-B interface) seems to characterize an unsafe versus a safe well-coordinated feeding pattern [41]. Analyzing the oral-respiratory coordination from a dynamical perspective, the following analytical tools have been proposed [49,73,74]: the ratio of sucking to breathing frequency and the bilateral weighted coherence of the coupling between Sk and B.

For both preterm and term infants, oral feeding performance is usually assessed through indices of sucking efficiency (usually defined as the nutrient volume per suck) and the rate of nutrient intake (intake volume divided by feeding duration), calculated using the different measures of nutrient consumption adopted and reported in Table 2. An alternative definition of the sucking efficiency that has been adopted is the average milk intake per suck divided by average effect (pressure · duration) per suck [41]. The bolus size (volume per swallow) is another index of nutrient consumption that allows to assess feeding performance in relation to the swallowing pattern.

Nutritive sucking has also been considered as an early motor marker for the prediction of later neurodevelopmental outcomes in infants [15]. Some already mentioned sucking indices (Sk frequency, number of sucks per burst, IP amplitude) have turned out to be predictors of later neurological outcomes [13]. Moreover, the newborn's sucking pattern has been classified according to the rhythmicity and amplitude of S and E components, inferring prediction of later neurological development [14]. In [44] S and E have also been assessed, through measurements of throat and jaw movements (see Section I.3.2 for details), and the eye-jaw and eye-throat distances have demonstrated to be useful to identify the differences in feeding performance between healthy infants and infants with neurological disorders. Nutrient consumption is another important factor whose monitoring can allow the estimation of significant indices with predictive value. The newborn's feeding behavior, assessed through the milk intake rate (mL/min), has demonstrated to be correlated with future neurodevelopment assessment [36]. No measurements of breathing have been carried out to this specific aim. Such predictive potential of sucking assessment is also confirmed by other authors [6,45,46] whose studies are not included here since they used non-instrumental tools for the assessment that are not of interest for the specific aim of this work.

The importance of the instrumental monitoring of NS has also been demonstrated in the case of neurodisabled infants with Down's syndrome, as reported in [35]: the use of sucking pressure waveforms (IP and EP) seems to be helpful in the examination of the development of sucking behavior, intraoral movements and for therapeutic effects. Moreover, problems with sucking and swallowing can be observed in children with cerebral palsy (CP) within the first 12 months of life, which often precede the diagnosis [6,47]. These observations emphasize the importance of monitoring feeding behavior, also at home, and taking a careful feeding history.

I.3.2. SoA: Sensor-Based Tools to Measure Oral-Feeding Behavior In Newborns

In the previous section an overview of the wide set of indices and quantities, used to objectively assess infant oral feeding, has been reported. The measurement of such a heterogeneous set of indices has implied in literature the use of several technology-assisted solutions, that can be grouped into three categories: (i) sensing systems to monitor sucking process (Table 3); (ii) sensing systems to monitor breathing process while feeding (Table 4), and (iii) sensing systems to monitor nutrient consumption (Table 5).

Sensing Systems to Monitor Sucking Process

The literature suggests several methods to monitor the Sk process. Such methods rely on Pressure Transducers (PTs), optical motion capture systems, and resistive strain gauges to monitor EP and IP, chin, throat, and jaw movements (see Table 3).

PTs are usually adopted to measure both IP and EP. In particular, the measurement of IP is always performed using PTs, but adopting two different nutrient delivery systems. In the first one, a common bottle nipple is used (Fig. 3): a catheter is applied to the tip of the nipple for IP measurement, while the nutrient flows from the lumen of nipple to the infant's mouth through the orifice normally present on the nipple tip. This configuration has been adopted in several studies, that used two different sensing solutions for IP measurement, depending on the position of the transducer and on its type, as illustrated in Fig. 3: a small pressure catheter (e.g., Millar Mikro-Tip SPR-524) is used and directly placed at the nipple tip [28,29,32,34,48], or a semiconductor PT is connected to the end of a uncompressible catheter whose tip is placed into the oral cavity [10,14,16,25,35,41,44,49-51].

	Measurand	Measuring Transducer	Measurement Procedure	Ref.
Suction	Intraoral Pressure	PT	PT embedded into a catheter and placed at the tip of the nipple	[28,29,32, 34,48]
			PT connected to a catheter, whose opposite tip ends into the oral cavity lumen	[10,14,16, 25,35, 41,44,49–51]
			PT placed between the nipple and a flow limiting device (restriction orifice or a capillary tube)	[37,39]
	Throat movements	Videocamera and markers	Digital video camera at 1 m from the infant's face; markers placed on the lateral angle of the eye and on the throat	[44]
Expression	Expression Pressure	PT	PT connected to a polyethylene catheter, connected to a catheter of compressible silicone rubber, placed on the nipple	[27,29,32, 34,48]
			PT connected to the lumen of the nipple by means of a silicone catheter; one-way valve placed between the nipple chamber and the nutrient reservoir.	[14,35,49]
	Jaw movements	Videocamera and markers	Digital video camera at 1 m from the infant's face; markers placed on the lateral angle of the eye and on the tip of the jaw.	[44]
		Strain gauge Transducer	Strain gauge transducer attached between the infant's forehead and the chin	[10]
Sucking events (no S/E distinction)	Intranipple pressure	PT	PT connected to the lumen of the nipple by means of a silicone catheter	[30,33,40, 51,52]
	Chin movements	Strain-gauge	Stretch-sensitive strain gauge placed under the infant's chin and secured over the zygomatic bones; its wire connector inserted into a plethysmograph	[31,53]

Table 3 Overview of the measuring systems used to monitor sucking process: measurands, sensors and measurement procedures.

Some studies [16,50,51] using the first configuration specify that the catheter used is filled with fluid for a more robust pressure measurement, less sensitive to artifacts; some others, using the same configuration, do not specify. The nipple can be also standardized and calibrated so that it responds to a certain differential pressure (difference between intra-nipple and intraoral pressure) with a known and acceptable milk flow rate, as in [14,25,35,57]. In the second configuration (see Fig. 4), the nipple is modified to embed a tube for nutrient delivery within the nipple tip, and a second tube is connected to a PT to measure IP pressure. The properties of the nipple in this case do not completely resemble an ordinary nipple: it is not filled with fluid, so expression movements cannot influence the nutrient's release, and nutrient flows only when the infant develops an appropriate IP.

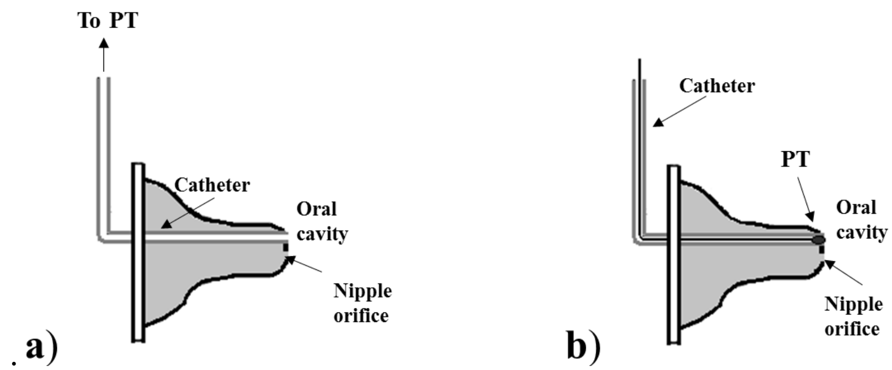


Fig. 3 Schematic diagrams of a nipple designed for nutrient delivery and IP monitoring: (a) PT connected to an end of a catheter whose other end is connected to the oral cavity; (b) PT inserted in the catheter and directly flushing in the oral cavity

One of the earliest works measuring sucking behavior describes the use of a capillary tube as flow meter [39]: the system is composed of a stoppered burette connected to a capillary tube and then to a nipple. To guarantee a constant delivery pressure equal to the atmospheric one, an opening is placed to a side arm of the burette and always kept at the same height as the nipple. The flow-limiting capillary tube allows to regulate the flow of nutrient introducing a known linear relation between IP and flow throughout the range of infant sucking pressures (considered as 0 to −300 mmHg). Since such arrangement may be considered a closed hydraulic system, any increase or decrease of pressure applied to the nipple is transmitted to every part of the connected system. In particular, since the capillary can be considered as a concentrated resistance, it is possible to measure the main pressure drop along it, and a pressure equal to the desired IP in the part after it. Fig. 4a shows the described configuration where the PT is placed between the capillary and the nipple.

A similar capillary system has also been used in later studies [8,13,27], where the PT is specified to be connected to the oral cavity by means of a second catheter inserted within the nipple, as Fig. 4b illustrates. The nipple is stiffened with the use of a silicone rubber, in order to prevent nutrient delivery through expression movements, in both systems. With this arrangement, the nutrient flow rate through the tube can be calibrated, so that a certain IP provides a known flow rate, and the consumption is proportional to the pressure-time integral. This calibration is allowed thanks to a proper configuration of the feeding system which eliminates two influencing factors: the hydrostatic pressure caused by the height of the level of nutrient over the infant's mouth, and the gradual vacuum increase inside a sealed nutrient reservoir as the milk flows out. Particular attention in fact has to be paid in order to limit the effects of these two factors, which influence the net pressure forcing the liquid into the mouth thus hampering the feeding performance [28].

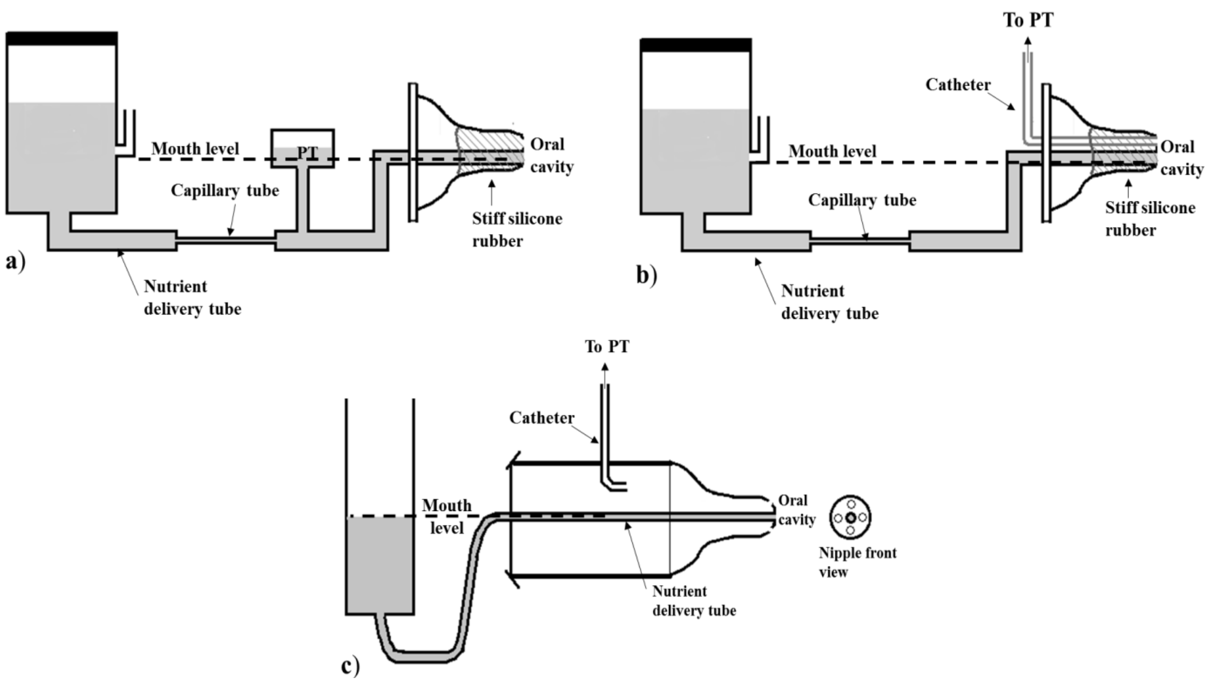


Fig. 4 Schematic diagrams of feeding apparatuses designed for nutrient delivery and IP monitoring: (a–b) configurations including a capillary tube, where a PT measures pressure changes between the nipple and the capillary tube (a), or in the oral cavity through a second catheter inserted into the nipple (b); (c) a PT measures the pressure changes in a chamber directly communicating with the oral cavity, and the nutrient is delivered from an open reservoir through a catheter into the mouth.

In Fig. 4c another feeding apparatus adopting such expedients is shown. An opened reservoir is used to avoid vacuum creation, and the level of the nutrient is constantly maintained at the level of the catheter tip to eliminate any hydrostatic pressure. This measuring system, adopted in [54], embeds two catheters: one for nutrient delivery into the oral cavity, and a second one ending into the same chamber as the nipple which is in direct communication with the oral cavity thanks to some holes in the nipple tip.

Lang and colleagues in [37] developed a solution, which is very similar to an ordinary feeding bottle, embedding a nutrient delivery tube and enabling a higher level of portability (see Fig. 5a).

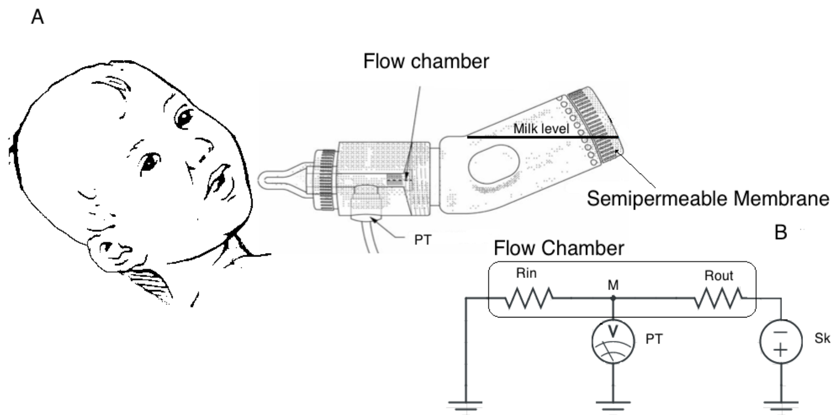


Fig. 5 (a) Portable sensing feeding apparatus for IP monitoring: the milk is released into the infant's mouth through a tube connected to a common nutrient reservoir. The tube has an orifice restriction at the beginning and a PT for IP measurement before the nipple; (b) Equivalent electronic circuit.

They use a modified commercial bottle (VentAire feeding bottle, produced by Platex) where a flow chamber is inserted between the milk reservoir and the outlet. The chamber has an inlet flow restriction orifice and an anti-backflow valve. The inlet chamber diameter is very small with respect to the outlet, offering a higher resistance to milk flow. The pressure inside the milk reservoir is maintained at the atmospheric value thanks to a gas permeable, fluid impermeable membrane. The shape of the bottle reduces the effect of the hydrostatic pressure allowing for an easy adjustment of the level of milk to that of the infant's mouth. Such system allows monitoring the suction pressure by measuring the pressure changes inside the chamber. The system may be modeled by the equivalent electronic circuit reported in Fig. 5b. The inlet and outlet diameter are represented by two electrical resistances, R_{IN} and R_{OUT} respectively; the PT measuring the pressure (voltage) inside the flow chamber with respect to the atmospheric pressure (GND) is modeled by a voltmeter connected to the measuring node M; finally, sucking pressure is represented by a voltage generator (Sk). The voltage measured at node M will be:

$$V_M = \frac{R_{in}}{R_{in} + R_{out}} V_{Sk} \cong V_{Sk}$$

since $R_{in} >> R_{out}$ (due to the geometry), V_M may be reasonably assumed as equal to V_{Sk}.

For the EP measurement, a rubber silicon tube can be placed on the outer surface of the nipple of a feeding bottle [27,29,32,34,48] (see Fig. 6a). One end of the catheter (the one inside the mouth) is closed, while the other end is connected to a PT by means of a polyethylene catheter. This monitoring system is reported in [28] as having a limitation due to the rapid reaching of a plateau corresponding to the catheter's full compression. Otherwise, a PT can be connected to the lumen of the nipple by a polyethylene catheter to measure EP. In particular, EP is measured using this configuration and adding a one-way valve between the nipple chamber and the nutrient reservoir [14,35,49] (see Fig. 6b). Such a valve allows to isolate the interior of the nipple from the milk reservoir during the expression phase, in order to ensure that the nipple is always full. The same configuration without the valve allows monitoring the intra-nipple pressure changes due to the sucking events with no S/E distinction [30,33,40,52]. McGowan et al. [51] adopted this configuration also to estimate the net pressure forcing the nutrient out of the nipple given by the difference between intra-nipple pressure and negative IP measured outside the nipple (see Fig. 7).

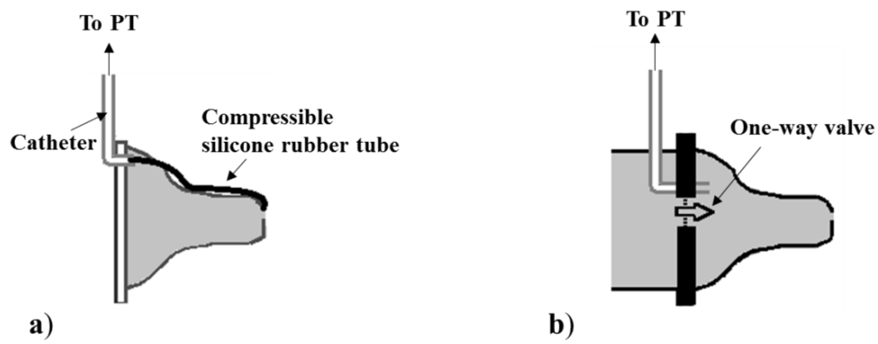


Fig. 6 Sensing solutions for EP measurement: (a) a PT measures EP by means of the compression of a silicone tube inserted into the catheter connected to the transducer; (b) a PT is connected via a catheter to the lumen of the nipple (continuously filled with liquid); a one-way valve between the nutrient chamber and the nipple is applied.

The two different sucking components can be also monitored through the measurement of throat and jaw movements. Such movements have been measured adopting two different technological solutions in [10,44]. One includes the use of a strain-gauge transducer attached between the infant's forehead and the chin [10], to measure jaw movements associated with mouthing movements. The other one uses a 1 meter distant camera placed at 90° with respect to the front of the baby's face, and three markers placed on the infant' s face (see Fig. 8) [44]: one on the lateral Eye Angle (EA), one on the Tip of the Jaw (TJ), and the last one on the Throat (T). To estimate the distance of the marker in the object plane, the Direct Linear Transformation (DLT) method is used. Authors simultaneously recorded IP, EP and two anatomical distances, *i.e.*, the eye-throat and the eye-jaw distance, and proved their correlation with suction and expression pressures respectively.

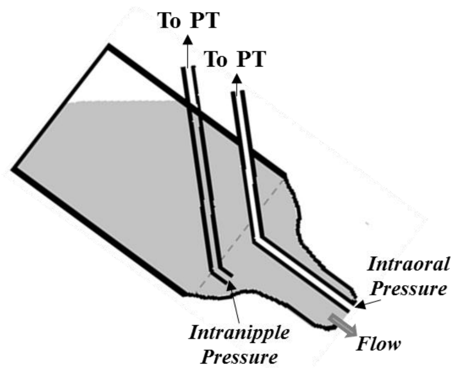


Fig. 7 Sensing solutions for the measurement of the net pressure forcing the nutrient out of the nipple chamber. Two PTs are adopted to measure intra-nipple and intraoral pressure, and calculate the pressure gradient causing the nutrient to flow out.

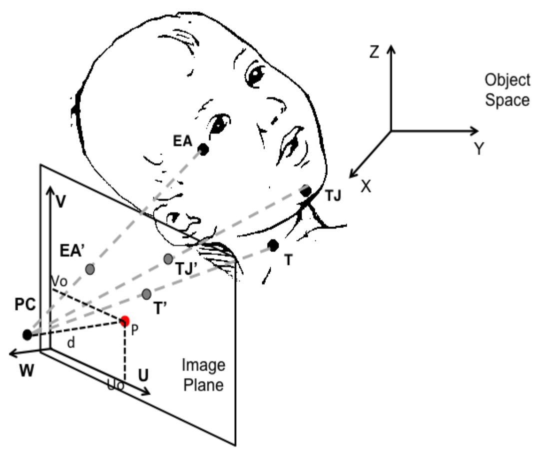


Fig. 8 Position of the marker on the throat region, for DLT method application, is determined by first locating three facial markers: the external eye angle (EA), the tip of the jaw (TJ) and the throat region (T).

In other works [31,53], mercury-in-rubber strain gauges are used to monitor chin movements. Such sensors are connected to a plethysmograph that detects changes in electrical resistance of the gages as they are stretched with sucking activity. Strain gage is kept under tension during measurements, stretching it by at least 10% to 20% beyond its resting length before application. Such set up demonstrates reliability in sucking monitoring, even distinguishing chewing on the nipple and other non-sucking activity from true sucking [58].

Sensing Systems to Monitor Breathing Process

The evaluation indices of breathing concern rhythmicity and its interface with sucking, rather than its "extent" (see Table 1). Different solutions in terms of complexity have been adopted to monitor this process and they are shown in Fig. 9.

	Measurand	Measuring Transducer	Measurement Procedure	Ref.
Breathing flow	Nasal air-flow	Thermistor/ Termocouples	Sensor placed below the nostrils	[10,25,30, 40,49]
		Pneumotachograph and PT	Sensor placed in a nostril	[43]
		PT	PT connected to a catheter inserted just into the nares (information about direction only)	[10]
Breathing movements	Thoracic movements	Strain-gauge	Respiratory band around the infant's chest	[25,30,33,4 1,50]
		PT	Pressure drum placed below the chest	[29,32]

Table 4 Overview of the measuring systems used to monitor breathing process: measurands, sensors and measurement procedures.

Nasal thermistors or thermocouples below the nostrils are used to measure air flow. However, they are not sufficient to distinguish between inspiration and expiration. To clearly identify flow direction, a PT connected to the nostrils by a soft catheter can be used [10]. Catheter and thermistor are embedded into a rigid tool (see Fig. 9b), which is kept in the infant's nostrils during feeding, capable of recording very low airflows (discrimination threshold less than 0.5 L/min), without adding any significant resistance to the flow. Another solution that allows measuring both the airflow and its direction is the use of a miniaturized pneumotachograph connected to a pressure transducer, placed in a nostril. Such nasal flowmeter has turned out to be suitable for preterm infants [43], because of its low dead space (less than 0.11 mL), low resistance (0.1 mm $H_2O/mL \cdot s$), light weight (0.2 g) and compact design.

Airflow monitoring is also widely performed by thermistors because of their rapid response to flow changes [10,25,30,40,49]; however, they are prone to artifact caused by temperature equilibration when airflow stops [62]. To avoid such problem, many authors monitor breathing by measuring thoracic movements (see Fig. 9a). Such measures pertain to changes in lung inflation measured by chest and abdominal movements, and enable to determine the precise timing of the end of inspiration and expiration, not allowing for quantitative measures such as tidal volume or minute ventilation. Mercury-in-rubber or piezo-resistive strain gauges (respiratory bands) have been used to measure chest movements [25,30,33,41,50], as well as PTs, connected to a drum taped at the thoraco-abdominal junction [29,32].

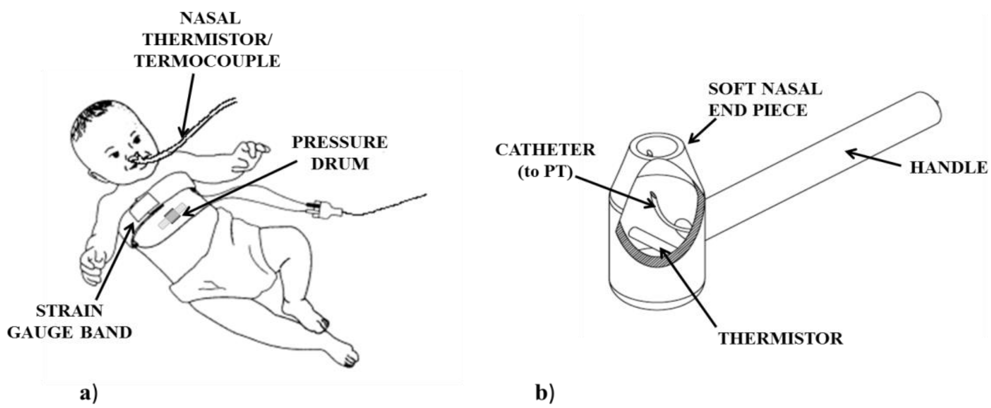


Fig. 9 Devices used for breathing monitoring. (a) Nasal thermistor or thermocouple applied below the nostrils for nasal airflow measurement; pressure drum or strain gauge band on the chest for respiratory movements measurement; (b) Rigid tool applied into the nostrils: the thermistor and the PT are used respectively to assess air flow and its versus.

Sensing Systems to Monitor Nutrient Consumption

Nutrient consumption is often estimated measuring the residual nutrient volume at the end of the feeding session (total consumption) or at variable time intervals. This measure is frequently performed observing the liquid level in a graduated reservoir [28,32,39] or using a balance [29,48]. Many authors do not even mention this measure, despite reporting consideration about the total ingested nutrient volume [25,40,41]. Measurements of the nutrient consumption at very close intervals of time have also been used [23,50,56]. In [50] a PT is used to measure the hydrostatic pressure of the remaining liquid column in a cylindrical reservoir in order to estimate the residual volume of liquid: here the authors measure the hydrostatic pressure of the milk contained in a fixed reservoir, that cannot be tilted, while a tube connects it to the feeding bottle. Such approach enables to measure the residual nutrient volume in the bottle at variable temporal intervals, when sucking activity is absent.

Measures of the flow of nutrient have been performed using particular flow meters [10,54,55]. In [55], the authors use an ultrasonic flow transducer to measure the liquid flow between the feeding bottle and the tip of the feeding nipple. In the other two studies the milk flow is estimated from the measurements of airflow entering the reservoir to fill the void left by the milk, using a pneumotachometer [54], or a thermistor [10]. In addition to all these methods, many studies, as already described before, estimated the milk flow rate using a calibration of the nutrient delivery system.

	Measurand	Measuring Transducer	Measurement Procedure	Ref.
Nutrient flow	Air flow into the bottle	Thermistor	Sensor fixed to the lumen of a rigid tube inserted into the reservoir bung	[10]
		Pneumotachometer	Inserted at the top of the nutrient reservoir	[54]
	Milk flow	Ultrasonic flow transducer	Placed between the nipple and the bottle	[55]
Nutrient volume	Nutrient weight	Balance	Residual milk weighted continuously or at intervals	[29,48]
	Nutrient volume	Graduated reservoir	Residual milk volume measured from the graduated reservoir	[27,32,39]
	Hydrostatic Pressure	PT	PT connected to a catheter placed at the base of the residual liquid column	[50]

Table 5 Overview of the measuring systems used to monitor the nutrient consumption: measurands, sensors and measurement procedures.

I.3.3. SoA: Discussion

Oral feeding is a complex process requiring a mature sucking ability and a mature coordination of sucking with breathing. The proposed overview of scientific literature about this topic highlighted the absence of a unique technological sensing solution to assess such skills. Oral feeding behavior is assessed in literature, monitoring sucking, breathing, and nutrient consumption, through a wide set of quantities and indices. Notwithstanding such heterogeneity, reflecting the absence of a shared theoretical model, the monitoring of oral feeding, has resulted potentially useful for the assessment of oral-motor pattern maturation in preterm and term infants, and as prognostic tool for predicting later neurodevelopmental outcomes.

Intraoral and expression pressures have been proven to be two fundamental quantities to study preterm infants' feeding behavior. In particular, S/E coordination and rhythmicity have been principally investigated, demonstrating to be significant to characterize and assess the development of sucking skills and, possibly, their immaturity. Besides, the importance of these two components has also been confirmed in the case of neuro-disabled infants, confirming the importance of S/E monitoring for the assessment of immature sucking patterns.

The analysis of literature has also highlighted how the coordination with breathing represents a challenging milestone to attain in development of feeding skills both for preterm and term infants. This consideration suggests the importance of measuring systems for the detection B events and their temporal pattern, rather than for their quantitative characterization. Regarding the prognostic value of infants' oral feeding skills, it seems that the assessment of the only sucking skills is sufficient to predict later neurodevelopmental outcomes. However, the reported studies [13,14,43], dealing with the issue, are rather recent and encourage further research investigating also sucking-breathing coordination [36].

The quantitative analysis of oral-motor coordination from a dynamical perspective seems to be provide a comprehensive theoretical framework to model this skill. It has been proposed to study the complex transition from immature to mature oral feeding [74]: thus, further research is encouraged in this field, in order to identify and establish sensitive and objective measure of coordination between the components of the oral feeding behavior. Despite the possibility of considering a common theoretical framework offered by the dynamical approach, further effort is needed to unify the technological approach.

The heterogeneity in the measures used for analysis represents a cause of discrepant findings reported in literature, and a major challenge in applying them to clinical practice, as reported by Slattery *et al*. in 2012 [15]. Such heterogeneous set of quantities and indices has been assessed with different technological solutions. Due to the differences related to the application field (preterm assessment; term assessment; prognostic tool), each solution should be carefully assessed according to the specific application requirements, which should always aim at a balanced compromise between reliability, invasiveness and practicability. In the following, a discussion of what emerged from the analysis of the SoA is reported.

The distinction between suction and expression components of sucking seems to be a characteristic specific of the assessment of preterm infants. PTs are the most commonly adopted sensing solution for the measurement of intraoral and expression pressures. However, the simultaneous monitoring of both sucking components imposes special constraints. In particular, the measuring configuration including a tube for nutrient delivery (Fig. 4 and Fig. 5) removes the contribution of the expression component on the extraction of nutrient, and it drives infants to modify their sucking response [63] forcing a higher IP. This solution can be adopted if the only goal is to investigate suction ability, since it forces the newborn to rely on it.

Moreover, the specific application to preterm infants imposes additional constraints, due to the weakness of this population. The presence of an additional resistance to the nutrient flow, caused by the tube restriction (see configuration in Fig. 4a,b and Fig. 5), makes such measuring solutions unsuitable when applied to preterm infants: additional resistance implies additional sucking efforts to extract the same amount of nutrient from the bottle.

The acceptability of the feeding apparatus is essential for every application. A nutrient delivery tube within the nipple tip may compromise the nipple's mouth feel, even for full-term and/or healthy infants accustomed to feeding from standard nipples on commercial bottles: they often refuse anything other than their usual nipple style [57]. For such reason, the relative simplicity of the common orifice nipples adapted for IP monitoring, as shown in Fig. 3, may be more advantageous. With such a configuration, infants' expression movements can alter flow rate through the nipple, and so the simultaneous measurement of EP, which is fundamental for preterm infants' assessment, makes sense. Both sensing solutions, illustrated in Fig. 3, are applicable on every feeding apparatus and nipple, not requiring a particular design: they can be embedded in both a clinical and a portable domestic assessment tool. Besides, they can be also adopted for sucking monitoring during breastfeeding [42,64]. The PT directly placed into the infants' mouth (see Fig. 3b) is reported as being more advantageous than the solution where the pressure waveform is directed to the PT by means of a catheter (Fig. 3a and Fig. 4) for aspects of higher accuracy, no time delay, no motion artifacts; however, it implies costs that are decisively higher, and higher invasiveness.

Regarding the measurement of EP using PTs, both reported methods (Fig. 6) appear to be suitable for clinical and domestic use, as they can be incorporated in a standard feeding apparatus. However, the configuration including the unidirectional valve (Fig. 6b), may alter the normal infant's feeding dynamics.

Optical motion capture systems may be also considered for E and S monitoring through jaw and throat movements. The advantage of such monitoring approach is its complete non-invasiveness: any feeding apparatus can be adopted (depending on clinicians' or parents' decision), as no sensing elements are required (it can be even adopted for breastfeeding monitoring [64]). Notwithstanding such advantage, the practicability is very low, as it would require specialized personnel, a structured environment, precise calibration procedure and it would be time consuming and expensive. These reasons make this kind of monitoring system not easily practicable both for clinical and domestic post-discharge application. Moreover, mouthing movements (jaw movements) are not directly linked to the effective nutrient expression, as infants could have an ineffective seal around the teat, which would prevent them from feeding properly. Fig. 10 summarizes the critical analysis of the sensor-based solutions proposed in literature for the distinct measurement of Suction and Expression.

If no S/E distinction is necessary, sucking events can be monitored. The intra-nipple pressure can be easily recorded adopting a non-invasive and practical sensing solution, even embeddable in a common feeding apparatus. Sucking movements can also be recorded, adopting mercury-in-rubber strain-gauges on the infant's chin. The advantages of this latter solution is the fact that it does not require any special sensors to be applied on the feeding apparatus, which can consequently be freely selected by the user (it could be also used for breastfeeding monitoring). However, it is moderately invasive as the sensing element has to be placed on the infant's face. This may produce additional stress to the preterm newborn who often shows hypersensitivity of the facial area due to frequent necessary aversive oral and/or nasal procedures [29].

		No alteration of the process dynamics	Adaptation to any feeding solution	Low-Cost	Acceptability	Domestic Setting	Clinical Setting
SUCTION	PT + Catheter	✓	✓	✓	✓	✓	✓
SUCTION	PT in the mouth	✓	✓	X	✓	✓	✓
SUCTION	Optical Motion Capture	✓	✓	X	X	X	X
EXPRESSION	PT + Silicone Catheter	✓	✓	✓	✓	✓	✓
EXPRESSION	PT in the lumen + Valve	X	X	✓	✓	✓	✓
EXPRESSION	Optical Motion Capture	✓	✓	X	X	X	X

Fig. 10 Critical analysis of the characteristics of the sensor-based solutions proposed in literature for the distinct measurement of Suction and Expression.

The coordination with respiration is a challenging milestone in term and even more in preterm infants, given their greater immaturity and risky condition. Therefore, its careful assessment at the discharge of NICUs is strongly suggested. Respiratory monitoring during feeding is quite thorny because of the high response time required to the sensors (breathing events are faster during NS), and because of the movement artifacts. Moreover, it is essential, particularly in premature infants, that any respiratory measurement be acceptable to the subject without imposing additional stress. The main techniques to record respiratory events in a clinical environment during feeding, were critically compared and analyzed in [62], even taking into consideration the above-mentioned issues. The use of a PT in a nasal cannula just inside the nostrils, as shown in Fig. 9b, and of an abdominal PT (Fig. 9a), can be considered suitable for clinical monitoring of respiratory events, because of their minimal invasiveness. The latter can be considered preferable in NICU where the subject may also receive oxygen via a nasal cannula, so any measure relying on nasal airflow would result useless. Quantitative information can be obtained using a nasal thermistor, embedded into a tube where the flow stream has to be canalized. However, it does not provide information about the airflow direction and it may also impose additional stress especially to a hypersensitive premature infant. A preferable solution can be the use of a pneumotachograph connected to a PT placed in a miniaturized cannula to be inserted in a nostril: it can measure both airflow and direction. However, as already said, these sensing solutions (measuring nasal airflow) may turn out to be impracticable in NICU applications.

Considering a domestic post-discharge application requiring high easiness to use and portability, none of the respiratory monitoring solutions, reported before, would be easily practicable: none of them is embedded in the feeding apparatus, but they all imply the use of an additional dedicated apparatus. In a post-discharge setting, this may stress the user that is generally less inclined than a clinician to the application of any additional element on the infant's body.

Volume consumption was monitored in most of the studies, and it appears to provide important indices to evaluate the changing feeding performances in both preterm and term infants. The nutrient consumption is mainly recorded at the beginning and at the end of feeding (or at specific time intervals), by weighing the bottle or verifying the level of the nutrient on the graduated reservoir. Even if such methods are quite simple and not invasive, their main drawback is that they enable a global estimation of the ingested volume, but they do not allow for continuous monitoring of milk volume intake, preventing from the energetic analysis of sucking process. Moreover, as the rate of milk flow during bottle feeding plays a crucial role in feeding-related ventilator changes of both term and preterm infants [34], its assessment through reliable measures appears to be important both for infants' clinical evaluation and post-discharge monitoring. To this aim, the use of air-flow sensors (thermistors or pneumotachometers) mounted on the top of the inverted nutrient reservoir, may represent a practicable sensing solution to be further investigated to increase the level of integration and develop a portable feeding tool (it also implies the resolution of the vacuum build-up problem). The solution using PTs to measure nutrient consumption, as presented in literature, implies a bulky and little practical solution, unsuitable for domestic daily use. Portability can be obtained adopting an ultrasonic flow sensor, as in [55], but it represents an expensive solution. As previously described, several systems used a calibration procedure in order to obtain a linear relation between the suction pressure and the consequent flow. However, they imply some particular expedients to eliminate hydrostatic pressure and vacuum in the nutrient reservoir, in order to make the flow solely depending on suction (see configurations in Fig. 4). This affects the easiness to use and portability of the system, and it also does not represent a recommended solution when both sucking components (S/E) need to be monitored, as already discussed.

II. SENSOR-BASED SOLUTIONS FOR NUTRITIVE SUCKING MONITORING

The importance of monitoring NS ability of newborns has been largely discussed in the previous section: the quantitative analysis of the sucking pressures (Suction and Expression), generated and controlled by the infant while feeding, provides a sensitive means of assessing early oral-motor function and neuro-developmental status. These two pressures are controlled by the infant pursuing a specific goal that is getting nutrient. NS in fact, contrary to NNS, is a goal-directed behavior. All newborns are able to suck on a pacifier within a few minutes after birth, however they may show difficulties to suck from a bottle in order to get milk into the mouth and feed. Hence, along with sucking pressures, the simultaneous measurement of the volume of extracted milk (namely, of the "attained goal") is fundamental, as it may allow quantification of the efficiency and energy expenditure, for a better and more complete assessment of NS skills.

This chapter will describe the sensor-based solutions designed and developed in order to monitor NS, in terms of volume of taken milk and sucking pressures, in an ecological unobtrusive way. With the term "ecological" we mean a methodology and/or an instrumentation that does not modify the environment and/or the observed task. Emphasis on ecological nature of data collection is common in behavioral studies, and becomes particularly important when dealing with newborns who may already be distressed and not cooperative with experimenters or clinicians, who therefore are not inclined to additional, complex and time-consuming settings and procedures.

In particular, this chapter will describe the technological solutions designed to address two of the three technological objectives described in the previous chapter: Section II.1 and Section II.2 will describe two modules for the estimation of nutrient consumption during bottle-feeding (OB1.2); Section II.3 will describe a smart module for sucking pressures monitoring that may fit any typical feeding apparatus (OB1.1).

Sucking Efficiency (SEF)

The estimation of the volume of milk delivered to the infant during each sucking act is particularly important because it allows quantification of the effectiveness of NS activity. Sucking Efficiency (SEF) in fact is usually expressed in literature as the volume of milk taken by the infant per suck cycle, and it represents one of the most important parameters for the assessment of the sucking pattern developmental course [40].

It is very common in pediatric practice to weigh the bottle at the beginning and at the end of the feeding to obtain a raw estimation of the overall amount of milk delivered to the child. Most of the studies in literature also estimate the milk volume intake by weighing the bottle and/or surveying the milk residual, at the end or during the feeding (see I.3.2). This implies some obvious drawbacks such as the measure coarseness and feeding interruption. These approaches in fact allow a global estimation of the extracted nutrient, preventing though from any energetic analysis of sucking. On the other hand, some technology-based solutions have been proposed in literature to refine this technique: they are based on complex technologies, that are either expensive or non-portable and awkward to implement in a clinical and even more in a domestic setting. Hence, they have remained restricted to small-scale research studies and do not allow for extended application to large-scale studies or implementation in everyday domestic or clinical settings. Such implementation is desirable in order to obtain methodological and analytical improvements that may ultimately provide significant new data to clinical assessment of infant neurophysiological health. This work addresses this issue proposing two novel low-cost practical methods to estimate the volume of milk delivered to the newborn, based on two different pressure measurements (as shown in II.1 and II.2).

II.1. Module A: SEF Estimation

The goal of the first module designed was to test a new ecological method for the estimation of the volume of liquid delivered to the newborn during a burst. The method is based on a non-invasive measure of hydrostatic pressure exerted at the base of a teat. Integrating this methodology with an ecological measure of intraoral pressure that provides the number of sucks per burst (as the ones that will be proposed in II.2 or in II.3), it will be also possible to estimate the SEF (volume of ingested milk per suck).

The proposed method does not produce a systematic under or over estimation, however the measurement errors depend on the bottle inclination. The lowest errors are obtained for a high tilt angle (70°), when the relative error in the estimation of the minimum volume of interest is within the 3%. However the method enables to estimate the same volume at the lowest likely inclination of the bottle (30°) with a relative error within the 7%.

II.1.1. Algorithm Definition

This method is based on the measurement of the hydrostatic pressure of the liquid column inside the bottle at the base of the teat. During feeding, the level of the liquid inside the bottle decreases at each suck, so at the end of each burst of sucks, when the infant ceases its sucking activity for at least 2 s, the liquid level variation may be estimated through the pressure trace offset, measured at the base of the bottle teat before and after the burst.

According to the Stevin's law, this offset is due to the height (h) of the liquid above the point where the pressure is measured. Given the density (ρ) of the liquid, this pressure may be expressed as:

$$P = h \cdot g \cdot \rho + P_t \qquad (1)$$

where g is the acceleration of gravity and P_t is the pressure at the top of the column, maintained equal to the atmospheric pressure (P_{atm}) in order to eliminate the vacuum build-up within the bottle during the feeding session.

The height of the liquid along the vertical axis depends on the bottle tilt angle (θ). So, at the beginning (t_i) of a burst, considering θ with respect to a horizontal axis (see Fig. 11) the liquid height h_i is

$$h_i = l_i \cdot \sin \theta_i \qquad (2)$$

where l represents the level of liquid along the axis of the bottle, that coincides with h when the bottle is vertically tilted.

At the end of a burst, at time t_{i+1}, the liquid volume inside the reservoir is reduced by the amount corresponding to the volume taken by the infant (ΔV_{i+1}), causing a lowering of the liquid column ($h_{i+1} < h_i$) and a consequent decrease of the hydrostatic pressure

$$\Delta P_{i+1} = P_{i+1} - P_i \, . \tag{3}$$

Thus, from the previous relations, considering ρ as constant, the variation of the liquid level l, at time t_{i+1}, can be expressed as

$$\Delta l_{i+1} = \left(\frac{P_{i+1}}{\sin\theta_{i+1}} - \frac{P_i}{\sin\theta_i}\right) \cdot \frac{1}{g \cdot \rho} \tag{4}$$

Since the generic variation of the volume of liquid (ΔV) inside a constant section reservoir is given by the product of the liquid level variation (Δl) and the reservoir section (S), we can obtain the following relation from (4):

$$\Delta V_{i+1} = \left(\frac{P_{i+1}}{\sin\theta_{i+1}} - \frac{P_i}{\sin\theta_i}\right) \cdot \frac{S}{g \cdot \rho} \tag{5}$$

which enables to estimate the liquid volume variation in a burst, through the measure of the hydrostatic pressure before (t_i) and after (t_{i+1}) the burst, together with the measure of the reservoir inclination (θ_i and θ_{i+1}).

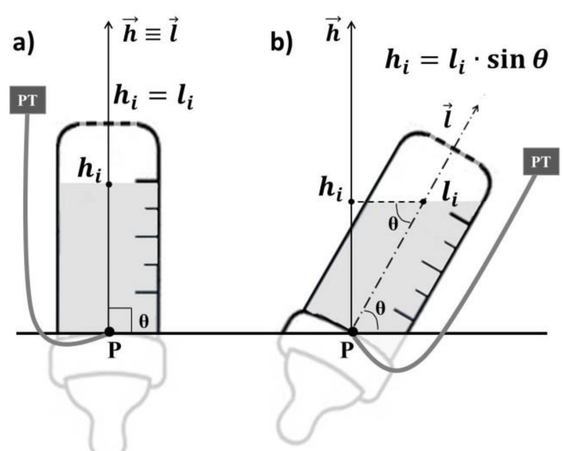


Fig. 11 Liquid column height depending on the bottle tilt angle (θ). a) at time t_i the pressure transducer (PT) measures the pressure exerted at the point P by the liquid column height h_i. b) When θ differs from 90°, the liquid column height h_i does not coincide with the liquid level l_i (taken along the bottle axis).

II.1.2. Experimental Setup

Experimental validation of the method for liquid volume estimation has been carried out as described below.

An open reservoir, with a constant circular section (d=27 mm, S=550 mm^2), was fastened on a vertical support allowing the orientation of the reservoir at different inclinations. The reservoir is open so that the liquid surface was always at the atmospheric pressure, as assumed in section II.1.1. This experimental condition can be then easily fulfilled in a real application as well, by means of a venting system that vents air at the back of the feeding bottle, maintaining the air pressure constant at 1 atm regardless of suction, as the bottle used to test the module later described in section II.2.

The hydrostatic pressure was measured by a low cost integrated silicon pressure sensor (MPX70002, Freescale Semiconductor: range of 2 kPa, sensibility of 1V/kPa and accuracy of ±0.1 V). The sensor was connected to a non-compliant catheter (1.2 mm of internal diameter), inserted at the base of the reservoir, and it was placed over the top of the reservoir, in order to separate the liquid media from the sensor by a column of air, that is compatible with the sensor unlike liquid media.

The inclination was estimated by a 3-axis accelerometer (ADXL330, MEMS made by Analog Devices) fixed on the reservoir, which measures acceleration with a minimum full-scale range of ±3 g and allows a static tilt estimation with a maximum error of ± 1°.

II.1.3. Measurements and Results

The performances of the proposed method have been assessed through a set of measurements of the minimum volume of interest at 3 different reservoir inclinations.

The open reservoir is filled with 50 mL of water at room temperature with a known density (ρ) equal to 1 g/cm3. A pipette (capacity=8 mL, resolution 0.1 mL) is used to withdraw the amount of liquid corresponding to a single burst, through an electronic pipette dispenser, in order to simulate the sucking act.

The minimum volume of milk an infant ingests during a burst has been considered equal to 4 mL, according to the recent study of Taki et al. [20], that reports this value for newborns at 1 month of age, and greater volumes at 3 and 6 months. A set of measurements were performed to verify if the proposed method enables to discriminate the minimum value of volume of interest. Hence, a volume of 4 mL of water was subtracted to the reservoir and the corresponding pressures at the beginning and at the end of the withdrawal were measured by the pressure sensor, in order to estimate the subtracted volume via the algorithm described before. Fig. 12 shows the pressure signal during 4 consecutive trials performed with the reservoir tilted of 70°.

Such measurements were repeated at 3 different inclinations (70°, 50°, 30°) to cover the range of the possible bottle tilt angles during a feeding session. A total amount of 16 withdrawals were performed for each inclination.

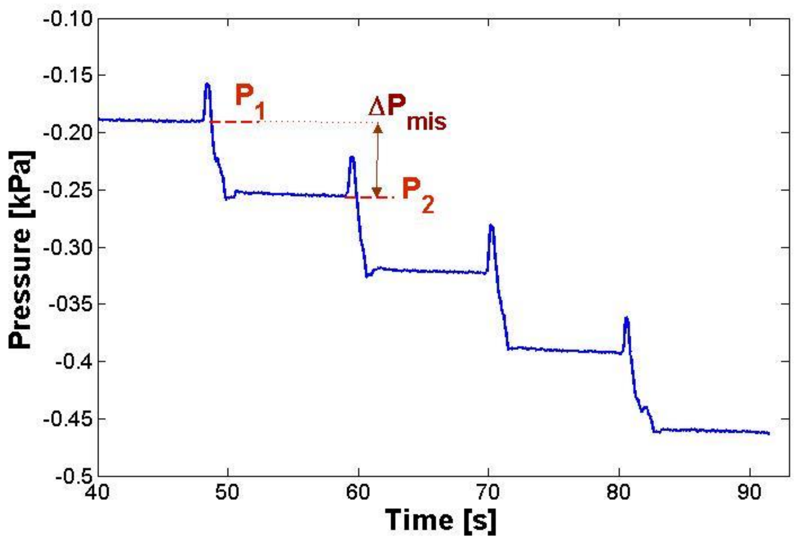


Fig. 12 Pressure signal during 4 withdrawals of 4mL of water. The reservoir tilt angle during the trials was maintained fixed at 70° and estimated by the accelerometer output. P_1 and P_2 are the pressure values at the beginning and the end of the first withdrawal and ΔP_{mis} is the measured pressure variation. The visible peaks in the pressure trace correspond to the insertion of the pipette in the liquid.

Since the tilt angle of the reservoir is maintained constant during each liquid subtraction, the volume variation, expressed in (5), is estimated as follows

$$\Delta V = \frac{\Delta P \cdot S}{g\rho} \cdot \frac{1}{\sin\theta} . \tag{6}$$

Experimental validation was performed with water because its density is known and is lower than the milk density, whose range is [1.02-1.04] g/cm3. Therefore, if the system results able to discriminate the ΔP generated by the subtraction of the minimum volume of water, it will be suitable also for the same application with a liquid of higher density, since the ΔP generated by the latter will be higher.

Table 6 reports the mean values of the measurement errors calculated as: (i) Absolute Error (AE), i.e., the absolute value of the difference between the estimated volume and the subtracted volume (4 mL); (ii) Relative Error (RE), i.e., the AE divided by the subtracted volume value. These errors have been calculated for all the measurements and the RE mean values with their uncertainty (U) are reported in Fig. 13.b.

It must be considered that the resolution of the pipette used to take the liquid volume determines an uncertainty U_{ref} in the reference volume (4 mL), that is equal to 0.048 mL (calculated with a confidence level of 95%). Thus, this uncertainty implies a minimum AE in the measurements equal to 0.048 mL (see Fig. 13.a) and a minimum RE of 1.2%.

One-way ANOVA, or the non-parametric Kruskal-Wallis test when appropriate, was performed with Tukey-Kramer post hoc test to verify the differences between errors at different tilt angles, and it demonstrates that estimated volumes obtained at the highest inclination of 70° present lower AE than the others (p=0.0002), as reported by Table 6.

Inclination	**Mean AE (mean ± U[a]) [mL]**	**Mean RE (mean ± U[a]) [%]**
70°	0.08[b] ± 0.04	2.1[b] ± 0.9
50°	0.19 ± 0.07	4.9 ± 1.7
30°	0.23 ± 0.04	5.7 ± 1.1

[a.] The reported uncertainty (U) is the *expanded uncertainty* calculated using a Student reference distribution and a level of confidence of 95%.

[b.] p<0.01 vs. 30° and 50° (One-way ANOVA or Kruskal-Wallis test on ranks, as appropriate, with Tukey-Kramer post hoc)

Table 6 Measurement Errors at different inclinations

The better volume estimation performances at higher inclinations are consistent with the algorithm definition which implies that a given error in the tilt angle (θ) estimate is more influential at lower inclinations.

In fact, following the algorithm defined in II.1.1, if an error (θ_{err}) occurs, it determinates an error ($\Delta\theta_{err}$) in the volume estimation as well,

$$\Delta V_{err} = \Delta V_{\theta+\theta err} - \Delta V_{\theta} \,. \tag{7}$$

Considering $\Delta\theta$ equal to the subtracted volume

$$\Delta V_{\theta} = \frac{\Delta P \cdot S}{g\rho} \cdot \frac{1}{\sin\theta} = 4, \tag{8}$$

the error in the volume estimation can be expressed as follows,

$$\Delta V_{err} = 4 \cdot \left(\frac{\sin\theta}{\sin\theta + \theta_{err}} - 1\right), \tag{9}$$

and it decreases with increasing tilt angle.

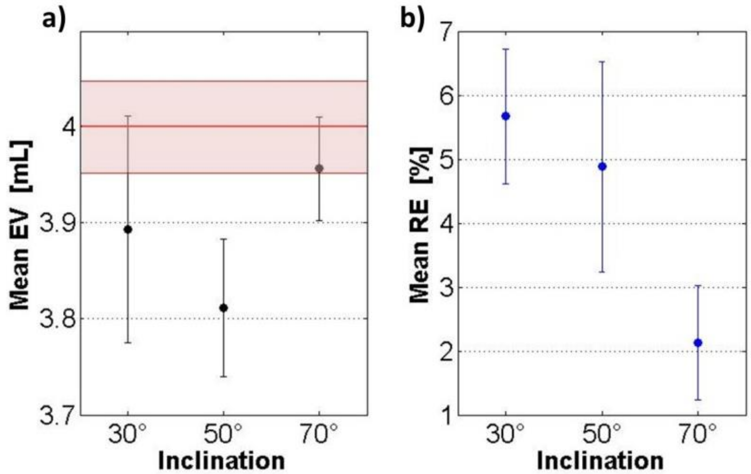


Fig. 13 a) Mean values of the Estimated Volumes (EV) with their uncertainty bars at 3 tilt angles of the reservoir. The red area marks the subtracted volume with its uncertainty U_{ref} due to the pipette resolution; b) Mean values of the Relative Errors (RE) and their uncertainty U at 3 tilt angles.

Furthermore the error values, expressed as the differences between the estimated and the subtracted volume, including the sign, can be analyzed in order to assess the presence or not of an under or over estimation of the volume, that could induce to reflect on the presence of a systematic error.

Fig. 14.a reports the values of the volume errors obtained in all the measurements at the worst condition, i.e., at the lowest tilt angle of 30°. A systematic error is not observed since the mean value is not significantly different from zero, as demonstrated by the Wilcoxon signed-rank test ($p>0.05$), a non-parametric alternative to the t-test, as well as at the highest inclination of 70° ($p>0.05$). Fig. 14.b shows how several measurements at 70° of inclination in fact fall within or strictly close to the minimum error range introduced by the pipette resolution.

A future development of the implemented algorithm will be the inclusion of a method to take account of the milk or formula density ρ which should be estimated as well, since it can be unknown and can actually vary from infant to infant. Furthermore a 9-axis magneto-inertial sensor will be integrated in the presented sensing core for a dynamic estimation of the bottle orientation. The final release of the electronics will be embedded on a custom-made feeding bottle to allow the test on a sample of newborns through a common objective tool.

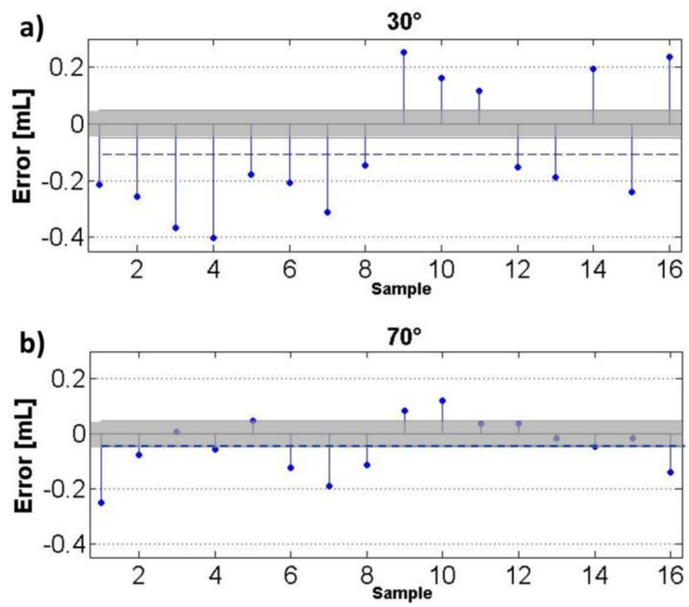


Fig. 14 Measurement errors, reported as the difference between the estimated volume and the subtracted volume (*Error=estimated volume–4mL*), are plotted separately for the lowest (a) and the highest (b) reservoir tilt angle (16 measurements each one). The blue dashed line marks the mean value, whereas the grey zone points out the minimum error (±0.048 mL) due to the pipette resolution.

II.2. Module B: Monitoring of Sucking Pressure and SEF

In this section, a new methodological advance for newborn sucking monitoring will be presented together with the results of its experimental validation. The solution proposed consists in a sensor-based module capable of monitoring intraoral pressure and SEF in an ecological, unobtrusive way.

A low-cost hardware module has been designed and integrated into a commercially available bottle. The prototype instrument allows continuous measurement of intraoral pressure and estimation of volume of milk delivered to the newborn during feeding, within a 2% margin of error (results will be showed in II.2.5). Volume estimation is based on measuring the air pressure decrease inside the feeding bottle while nutrient flows out. Moreover, volume estimation is independent from the tilt of the bottle with respect to gravity, so that it is not needed any orientation monitoring, or keeping the bottle at a specific angle to obtain good volume estimations (as for the previous method proposed and implemented on *Module A*). Since the use of this device does not modify the bottle feeding procedure, and since it does not need complex calibration procedures, this new approach may be used by untrained personnel in everyday domestic and clinical settings. Thus, it may represent an ecologically valid, cost-effective, and accessible approach enabling large scale quantitative monitoring of infants' NS.

II.2.1. Functional and Technical Specifications

In order to define the specifications of the device that should simultaneously measure intra-oral pressure and extracted milk volume, pressure range and bandwidth have been investigated through a preliminary analysis on some IP data. The collection of these data has not been part of this work: the pressure data have been granted us thanks to the collaboration with the University of Edinburgh & Early Years, where they have been collected.

Data from eight term-birth healthy infants have been used. They were recorded while feeding shortly after birth (2.6±1.5 days, mean±std) and then approximately 8 weeks later (55±15 days) for four subjects. IP was measured by inserting an umbilical catheter (length: 40 cm; internal diameter: 1.0 mm; external diameter: 1.7 mm) through the standard teat (Standard Teat, Cow & Gate, UK) of a feeding bottle, so that it protruded about 2 mm from its tip into the infant's oral cavity. The catheter had been primed with distilled water and connected to a pressure transducer (TranStar, Medex, UK/France/Italy/Germany) and medical physiology monitor (Datex-Ohmeda Light, Finland). Data were captured to a laptop PC using proprietary software (Collect4, General Electric Healthcare, Finland). Fig. 15 reports a typical 10 seconds pressure burst from the data. These data will be also used during software development, to test signal analysis algorithms and to identify sensitive measures of development (see Section IV.3.1).

Given this dataset the maximum value of intraoral negative pressure can be considered equal to -320 mmHg. The frequency bandwidth of the pressure signal has been estimated calculating its Power Spectral Density (PSD) by means of the Welch's averaged modified periodogram method. This method is based on the overlapped segmented averaging of modified periodograms: a *periodogram* means the discrete Fourier transform (DFT) of a segment of the time series, while *modified* refers to the application of a time-domain window function and *averaging* is used to reduce the variance of the spectral estimates. The frequency bandwidth has been taken analyzing of the 95% spectral edge frequency, that is the frequency below which 95% of the signal spectral power resides. As also shown by Fig. 15, the bandwidth may be considered below 10 Hz, which has been taken as the required bandwidth of our device.

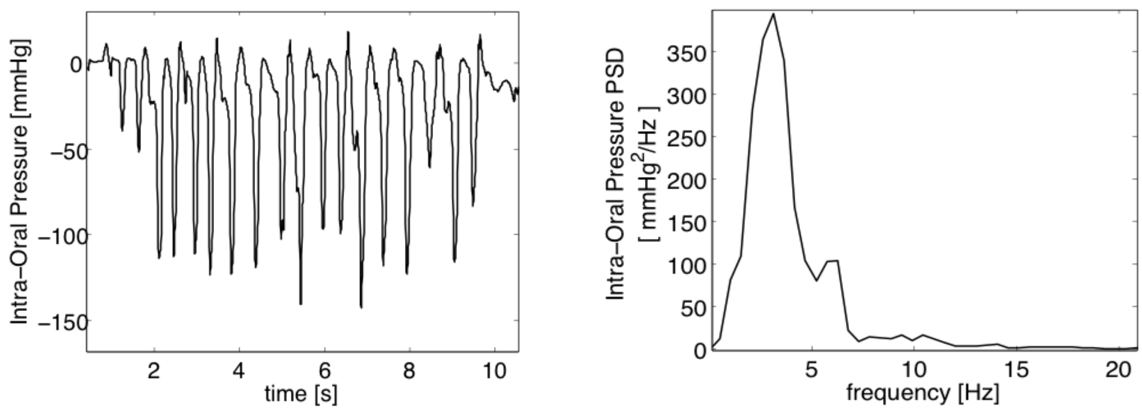


Fig. 15 Intra-oral pressure of a 1 week newborn recorded during a feeding task (on the right). ii) Power Spectral Density of IP during sucking is below 20 Hz.

The range of volume of milk extracted by an infant during each suck or burst may depend on several factors, e.g., the infant's age, weight, postconceptional age (PCA) at birth. Table 7 reports the values obtained during different studies. The values reported by Taki et al. in their recent study [42] have been considered in this work because they report both the volume of a single suck and the volume of an entire burst, unlike Fadavi's [55] and Lang's [37] works, and because they also report on longitudinal sucking performance, allowing for consideration of differences from 1 to 6 months of age. According to [42], a bottle-fed infant ingests 0.28 ± 0.13 mL per suck at the postnatal age of 1 month. This value slightly increases with the age, reaching 0.30 ± 0.24 mL at 3 months and 0.40 ± 0.20 mL at 6 months. These values, together with the number of sucks per burst, allow estimation of the minimum volume of milk an infant takes in a suck or a burst. During the first 6 months of life the average value of 0.2 mL has been considered as the minimum volume per suck.

First Author	PCA at birth week (M±SD)	PNA [days]	Sucks/ min (M±SD)	Vol/suck [mL] (M±SD)	Sucks/burst (M±SD)
Fadavi 1997 [55]	*Term*	2	73±14 65±9 72±8 71±9	0.056±0.016 0.113±0.039 0.067±0.031 0.077±0.024*	---
Qureshi 2002 [40]	39.2±1.1 43.2±1.1	1-4 30	55 70	0.235±0.102 0.343±0.123	10±9 21±22
Taki 2010 [42]	39.9 ± 1.1	30 90 120	---	0.28 ± 0.16 0.30 ± 0.07 0.40 ± 0.24	38 ± 12.2 43 ± 7 82 ± 22
Macìas 2011 [22]	*Full-term*	---	55 (18-100)	0.8-1.2	20-30 10-20 3-10
Lang 2011 [37]	*Full-term*	38-47 PMA	1.143/s 1.132 1.17 1.195	---	122 107 88 78

*Different values obtained with different nipple

Table 7 Values of parameters related to sucking and milk volume: review of the main studies

II.2.2. General Architecture

A smart module was designed and developed in order to be integrated into a commercial infant feeding bottle. Fig. 16 reports the general architecture of the module. A key idea was to physically decouple the sensing electrical part from the milk reservoir. To this end the electronics was separated from the milk reservoir by a semipermeable membrane (allowing air flow, but blocking liquid) placed between the reservoir and the electronics: direct contact between the milk and the electronics was avoided, solving both important problems of contamination and electrical safety.

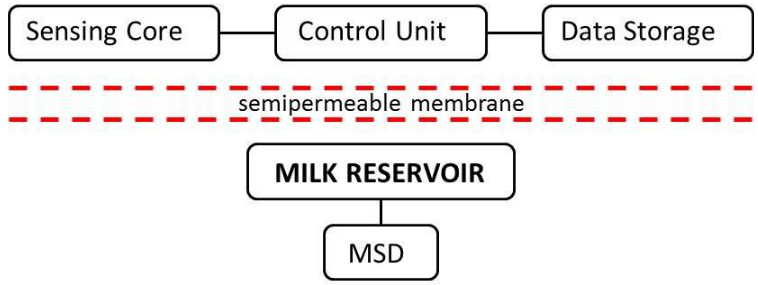


Fig. 16 The general architecture of the device. Electronic components are separated from the milk reservoir thanks to a membrane. A Mechanical Safety Device (MSD) is added to the milk reservoir to avoid the creation of excessive negative pressures inside the bottle beyond a threshold level.

The sensing core integrates sensors allowing measurement of intra-oral pressure and volume of ingested milk. The components of the sensing core will be discussed in detail in the following section. Data coming from the sensing core needed to be acquired by the control unit and stored on a suitable support. To allow portability, robustness and guarantee long duration monitoring, a micro SD support was chosen. For this reason the control unit was required have the RAM necessary for writing/reading operations on a micro SD: for FAT16 micro-SD, 512 MB RAM memory was deemed as necessary and a PIC18F46J50 chosen to be used.

Finally, a mechanical safety device was provided on the bottom of the bottle in order to avoid conditions of excessive vacuum built-up that may hinder the infant's sucking.

II.2.3. Sensing Core

IP is measured with a modified disposable teat connected via a non-compliant catheter (1.2 mm of internal diameter) to a low cost integrated silicon pressure sensor (MP3V5050V, Freescale Semiconductor). This is a vacuum sensor with a range of 50kPa (from -375 to 0 mmHg), suitable for IP range as estimated before.

The catheter was inserted into the teat through an incision at its base. The tube was then threaded into the inside of the teat and out through one of the three manufactured feeding holes at the top. To be able to measure the intraoral sucking pressure, the tube was positioned so that it protruded about 2 mm through the end of the teat (the validation of this method will be later detailed when presenting the module developed for IP/EP monitoring, see Section II.3.1).

The method here proposed to estimate the volume of milk delivered to the newborn is based on a measurement of pressure. During a single suck, the infant closes her/his lips around the bottle teat and, as the jaw and tongue drop down, produces a negative pressure inside the oral cavity that causes the milk flow towards the mouth. In this phase, as long as a good seal around the teat is maintained, no air can flow inside the bottle. The flow of milk toward the mouth causes the generation of a gradual negative air pressure inside the bottle which persists until the newborn releases her/his lips allowing air to flow inside the bottle. Therefore, by measuring the pressure of a gas (the air inside the bottle), an estimation of the milk volume delivered to the infant during each suck may be obtained.

In general, the relationship between volume (V) and pressure (P) of a gas may be expressed as a function of number of moles (n), gas volume and temperature (T).

Taking into account all the different variables, the pressure drop (dP) within the bottle can be expressed as:

$$dP = \frac{\partial P}{\partial n} \cdot dn + \frac{\partial P}{\partial V} \cdot dV + \frac{\partial P}{\partial T} \cdot dT \quad (1)$$

During each suck, the number of moles of the gas inside the bottle may be considered constant because there is not air exchange between the bottle and the environment (dn=0). Moreover, variation of air temperature may be hypothesized as negligible during a suck. Taking into account these assumptions, and considering the air inside the bottle as an ideal gas ($PV=nRT$), equation (1) may be rewritten to estimate the variation of air volume (dV) inside the bottle as:

$$dV \cong -\frac{V^2}{nRT} \cdot dP \quad (2)$$

V in this equation represents the volume of air inside the bottle before the suck. This volume may be updated using a recursive algorithm that increments its value by the estimate dV (see Fig. 17):

$$\begin{gathered} V_1 = V_0 + dV_0 \\ \dots \\ V_{i+1} = V_i + dV_i \end{gathered} \quad (3)$$

where V0 is the initial volume of air inside the bottle. The change in volume of air for each suck will be equal (disregarding the sign) to the volume of milk delivered to the child.

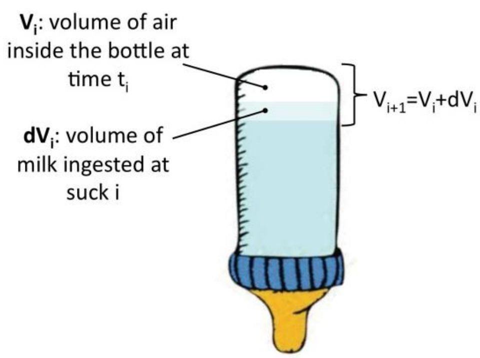


Fig. 17 Recursive algorithm for SEF volume estimation: at time t_i there is an inner air volume equal to V_i; after one suck, a volume variation equal to dV_i will be obtained.

The term nRT in absence of air flow may be considered constant and equal to the product between P and V (according to the Boyle-Mariotte's law), for this reason (2) may be expressed as:

$$dV = \frac{V}{P} \cdot dP \quad (4)$$

V_0 may be estimated producing a perturbation of known volume (ΔV) and measuring the air pressure before (P_1) and after (P_2) the volume variation. It will be:

$$V_0 = \frac{P_2 \Delta V}{P_1 - P_2} \quad (5)$$

In this way a semiautomatic initialization of the device will be possible enabling its use ecologically in non-structured environments. In order to estimate the volume of milk delivered to the infant during the sucking acts, using the method described above, the sensing core has been equipped with a second pressure sensor, MPX7025 (Freescale Semiconductor) having a range of ±25 kPa.

II.2.4. Integration

The sensing core has been integrated on a commercially available infant feeding bottle. For solving the contamination and electrical safety problems, described in II.2.2, a commercial bottle was used (First Bottle, MAM Babyartikel GesmbH, Vienna, Austria): it has a vented base with eight air holes, and an embedded silicone membrane that blocks liquid but not air, allowing an actual separation of the electronic part from the milk reservoir. The vented base was experimentally modified to prevent air entering into the bottle as milk flowed out, to satisfy the method described above. Hence, all the holes except one (the one that is used for the intra-bottle pressure measurement) were sealed with a non-toxic smooth consistency moldable silicone rubber (RTV-530, Prochima S.r.l.). Due to this modification, if the newborn does not release his/her lips around the teat, a decreasing pressure inside the bottle will generate. If such pressure reaches the equilibrium with the opposing suction pressure exerted by the infant, milk flow may be hampered [65].

Since such conditions would alter the infant's sucking behavior, an additional mechanical safety device has been included at the bottle base, with the aim of preserving the newborn from excessive fatigue rather than estimating the volume of milk taken in under such altered conditions. The device is a polypropylene check valve (Check Valve PP695-2B2BF, Coast Pneumatics Inc.) with a 60 mmHg cracking pressure; it allows the air to flow inside the bottle when the negative pressure inside it exceeds the value of -60 mmHg. A series of tests have been carried out on the valve, showing that 1 s after its opening the mean intra-bottle pressure increase is 10.7 ± 0.4 mmHg, preventing in this way the negative pressure inside the bottle to rise above values that can cause excessive fatigue to the infant, in case she/he does not release the teat. To allow for bottle sterilization in between uses, an external support for the electronics has been designed. This support consists of two parts connected through a bayonet closure: one part is attached to the bottle base, whereas the other one, including the electronics, can be easily removed (see Fig. 18) allowing for easy washing and sterilization of the bottle.

II.2.5. Experimental Validation

Experimental validation of the proposed method for volume estimation has been carried out as described below. The experimental setup used is shown in Fig. 19. A graduated reservoir was filled with water at room temperature. The reservoir was connected to the atmosphere by means of a manual on/off valve. The pressure sensor MPXV7025 is used to measure the air pressure. The base of the reservoir is connected by means of three-way valve to a syringe (Vmax =1 mL, resolution 0.01 mL). The manual on/off valve simulates the child's lips: when the lips are closed around the teat the valve is closed, when the lips are released, allowing air flow inside the bottle, the valve is opened. The syringe is used to simulate suck and burst allowing intake from 0.1 mL to 1 mL of liquid.

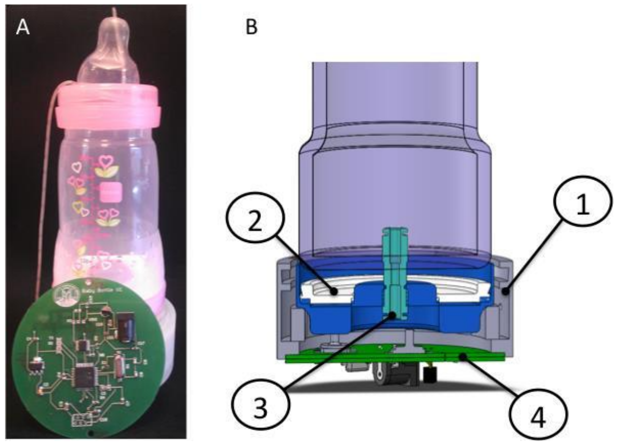


Fig. 18 Instrumented feeding bottle: A) prototype; B) 3D-CAD of the prototype. In B it is possible to observe: 1 external electronic support, 2 silicon membrane; 3 MSD; 4 electronics

According to (4) and for a fixed ΔV, the measured pressure variation is inversely proportional to the inner air volume. For this reason, the maximal inner air volume compatible with pressure sensor resolution (about 1 mmHg) needed to be estimated. A fixed volume of water equal to 1 suck (0.2 mL) was subtracted for ten times to the reservoir and the corresponding pressure drop measured. After each subtraction, the water was reinserted into the reservoir and the on/off valve opened to allow atmospheric pressure in the chamber.

Trials have been repeated at different initial air volumes: 25, 35, 45, 55, 65 mL, to simulate the reduction of liquid inside the bottle due to nutrition. Results of these trials are reported in Fig. 20: as reported in (4), the pressure drop was inversely proportional to the inner air volume and may be fitted with a power law ($f(x)=ax^b$, a=167.3, b=-1.034, R^2 =0.99). According to this fit, the maximal inner volume compatible with pressure sensor resolution was equal to 140 mL, corresponding to a volume of ingested milk equal to 115 mL (almost two times higher than volume of milk ingested by healthy newborns).

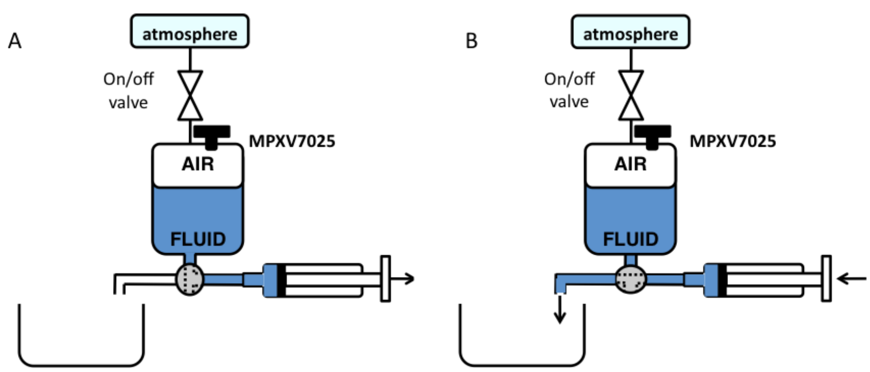


Fig. 19 Experimental setup used for empirical validation.

In order to assess the performances of the proposed method, a set of measurements at the same inner air volumes reported above was carried out, for a total variation of liquid equal to 40 mL. Ten preliminary measurements with 25 mL of air were performed to estimate the initial V0 according to (5). The estimated volume was 25.59 ± 0.07 mL (percent error = 2.4%). For each inner air volume, 0.2 mL of liquid (equal to 1 suck) was subtracted by the reservoir (see Fig. 19.A), then the reservoir was closed using the three way valve and the syringe emptied in an external tub (see Fig. 19.B). After 15 sucks the on/off valve was opened simulating the releasing of the lips around the teat and the consequent air flow allowed inside the bottle. For each suck, the volume of subtracted liquid was estimated according to (4) and compared with the actual subtracted volume. Trials were repeated at different inner air volumes to verify if the reduction of sensitivity may affect the estimation of volume in the considered range (see Fig. 21.A).

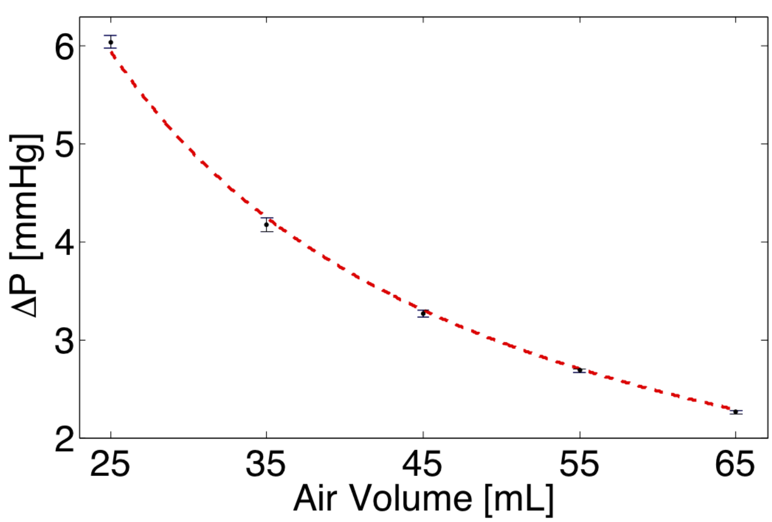


Fig. 20 Pressure variation for different air volumes inside the bottle. The subtracted liquid volume is equal to 0.2 mL. The dotted red line represents the power regression model.

In Fig. 21.B volume estimation results (blue points) are compared with the actual volume subtracted (red dotted line). Despite decrease of sensitivity with increasing inner air volume, the error remains small and does not exceed the 2% of the actual volume subtracted.

A

Inner Air Volume [mL]	Estimated ΔV [mL]
25	0.204± 0.003
35	0.197 ± 0.002
45	0.198 ± 0.002
55	0.200 ± 0.002
65	0.204 ± 0.004

B

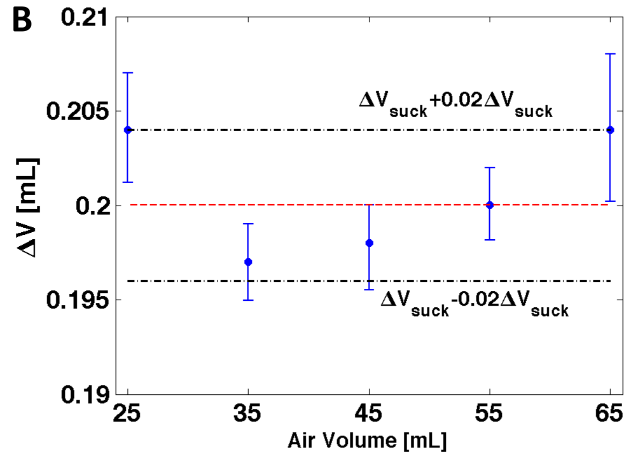


Fig. 21 A) *ΔV* estimation at different inner air volumes; **B**) Volume variation estimation for different air volume inside the bottle. The dotted red line represents the actual liquid volume variation, equal to 0.2 mL. The dash-dotted black lines represent the actual value ±2%

II.3. Suction/Expression Monitoring Device

Intraoral suction pressure is a fundamental quantity to measure for the evaluation of oral-motor behavior while feeding, as discussed before (see I.3.3). However, its alternation with the expression component and their rhythmicity play an essential role in NS, which make expression pressure another fundamental quantity to monitor, especially in order to identify immature sucking behavior in preterm or neuro-disabled infants, as reported in several studies [14,28,35]. Then, for a technology-assisted assessment of neonatal oral-motor behavior, the simultaneous measurement of suction and expression components is essential.

In this section, the design and development of a low-cost portable device for S/E monitoring will be described. The design has been driven by the principal intent of providing a module that was easily usable on every typical feeding bottle, thanks to its easiness of use, as well as its low cost which would also foster an easy implementation in different settings. In fact, the current lack of a widely and commonly used technological solution for sucking monitoring is principally due to the complexity and the cost of the systems proposed so far, and so to the fact that their design has not been focused on the implementation problem. Hence, during this work a low cost portable hardware module has been designed and developed to this intent. It exploits two pressure measurement methods that emerged from the SoA analysis as the most appropriate for the goal of this work (see Fig. 10). Both IP (suction) and EP (expression) are measured by using two PTs: for intraoral pressure a PT is connected to the end of an open uncompressible catheter whose tip ends in the oral cavity (see II.3.1); while for expression, a PT is connected to a closed compressible catheter properly placed inside the teat (see II.3.2).

However, in literature some limitations of these methods have been reported. The monitoring system presented in this work has been designed to circumvent some of these limitations, and the experimental validation has been carried out in order to verify or deny the presence of limits, that had been also suggested by past studies, for the specific range of application.

This monitoring device has been also tested during the clinical practice collecting data from 9 newborns in a hospital neonatal care unit: details and results will be reported later in this work (IV.3.2).

II.3.1. IP Measurement Method

The most common method for suction component monitoring is measuring IP using a PT connected to a catheter ending at the tip of the nipple, while the nutrient flows from the lumen of nipple to the infant's mouth through the orifice normally present on the nipple tip. Thus, in the design of this module, this configuration has been used as it allows the use of a common nipple without any alteration of the normal bottle feeding conditions.

However, literature is not clear about some aspects of this method: some studies [16,50,51] using this configuration specify that the catheter is filled with fluid for a more robust pressure measurement, while some others, using the same configuration, do not specify. McGowan et al. [51] affirm that filling transducer and lines with water is essential if the system is to respond rapidly to pressure changes, and that air-filled lines may underestimate sucking peak pressures. Nevertheless, some common shortfalls of fluid-filled catheters for pressure measurement include: motion artifacts due to catheter distortions, gravitational effects on the offset, influence of air bubbles inside the catheter. Further, a PT compatible with fluid is required, which implies a higher cost.

In this work, a PT connected to an air-filled catheter has been chosen as measuring system after a proper validation procedure that eliminated the concerns stated before about the inadequacy of this solution for suction pressure monitoring during NS.

II.3.1.1. Experimental Validation

In order to verify the system response at oscillating negative pressures, experiments have been performed by simulating different suction patterns. IP waveforms have been simulated as sine curves of different frequencies. We accounted for the conditions supposed to be the worst in terms of performance for an air-filled catheter measurement, i.e. high frequency oscillating patterns. We simulated three IP waveforms characterized by very short inter-suck periods (high frequency), starting from the values reported in McGowan work (where the shortest mean inter-suck period was 0.6 s [51]). The results show how the signal, recorded by means of an air-filled catheter, actually coincides with the signal of a PT directly placed in the measurement point, for the simulated patterns.

Experimental Setup

A cylinder-piston (2KS444P Airport Corporation) has been connected to the piston of a syringe, and moved back-forward by a closed-loop DC brushless actuator (M-235.2DD Physik Instrumente), in order to generate a sinusoidal negative pressure in the lumen of the syringe (see Fig. 22).

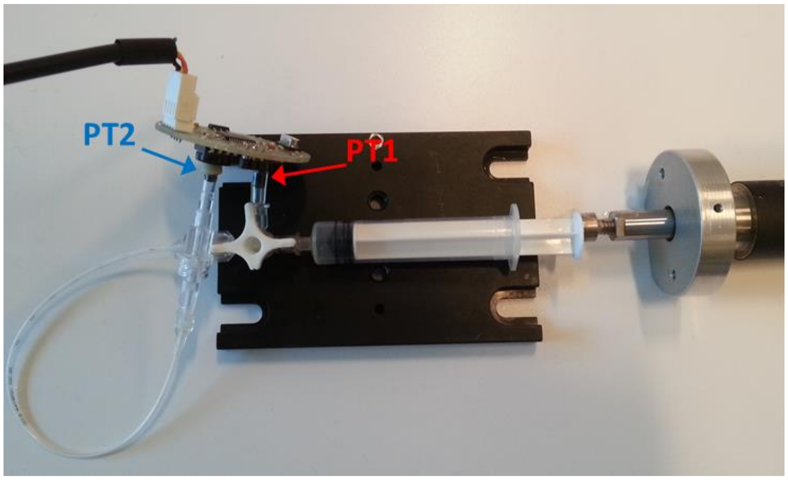


Fig. 22 Experimental setup for IP simulation and measurement. A cylinder-piston is connected to the piston of a syringe. A three-way valve connects the syringe outlet, the port of a PT (PT1), and the end of a PVC catheter connected to another PT on the opposite end (PT2).

Two low cost integrated silicon pressure sensors (MP3V5050V, Freescale Semiconductor) have been used to measure: 1) the negative pressure generated by the simulating system (PT1), and 2) the negative pressure recorded through an air-filled catheter ending in the point where the vacuum was created (PT2). The catheter was an uncompressible PVC feeding tube with an internal diameter of 1mm, external diameter of 1.7mm, and a length of 20 cm. The length of the catheter was chosen as the one that could allow connecting the teat tip of a feeding bottle to a PT placed on the bottom of the bottle (see Fig. 30.b). A three-way valve connected the syringe outlet, the PT1 port and the end of the catheter connected to PT2 (Fig. 22).

Validation Procedure and Results

First of all, a typical IP pattern has been simulated: the syringe piston has been moved back-forward in a sinusoidal way at the typical NS frequency (1Hz), and with a maximum displacement that corresponded with the generation of a negative pressure of 210 mmHg (in [51] this is the value reported as mean peak height for newborns at 1 month of age). The piston was controlled in order to generate three bursts of 10 cycles (bursts of sucks), separated by a pause of 5 s where the piston stayed still in the starting position (pause period between bursts).

Then, three increasingly extreme conditions have been simulated in order to test the validity of the measurement method. Three increasing frequencies were generated: 1.6 Hz, 2.5Hz and 3.3Hz, corresponding to inter-suck periods (T) of 0.6 s, 0.4 s and 0.3 s.

The signal recorded through the catheter (S_{cath}) was compared to the reference signal (S_{ref}) directly recorded by the PT whose port was placed in the measurement point. A set of features of correlation/similarity between signals has been used to compare S_{cath} and S_{ref}:

i) the root mean square error (*RMSE*). It is a good measure of accuracy, that can be used to measure the average difference between two time series *x* and *y* (of length *n*), as follows:

$$RMSE = \sqrt{\frac{\sum_{t=1}^{n}(x_t - y_t)^2}{n}}$$

ii) the Pearson's linear correlation coefficient r^2. It is widely used as a measure of the strength of linear dependence between two variables, defined as the covariance of the variables divided by the product of their standard deviations.

iii) the mean spectral coherence (C_m). Spectral coherence (C) is a frequency domain measure of the similarity of two signals. It identifies frequency-domain correlation between signals x and y, and it is defined as,

$$C(f) = \frac{|S_{xy}(f)|^2}{S_{xx}(f) \cdot S_{yy}(f)}$$

where x and y are the two simultaneous recordings, S_{xy}, is the cross-power spectrum, and S_{xx} and S_{yy} are the individual power spectra. C_m is then calculated as the average coherence across the frequency band of interest (in this case it has been considered [0,10] Hz). Two linearly related signals (in the absence of noise) will have a C equal to one at all frequencies, while two random, uncorrelated signals will have a C equal to zero.

Hence, $RMSE$, r^2 and C_m have been calculated between S_{cath} and S_{ref} for each simulated pattern of suction. Results are reported in Table 8, and they show how the signal recorded through the air-filled catheter S_{cath} is very accurate ($RMSE$ is always lower than 1 mmHg, that is even lower than the sensor accuracy), and significantly linearly related to S_{ref} both in time (r^2=1) and frequency domain (C_m=1). Fig. 23 shows the simulated suction pattern at the highest value of frequency simulated and the linear relation with the signal S_{cath} recorded through the catheter.

	T =1 s (1Hz)	**T =0.6 s (1.3Hz)**	**T =0.4 s (2.5Hz)**	**T =0.3 s (3.3Hz)**
***RMSE* [mmHg]**	0.2	0.4	0.7	0.8
r^2	1	1	0.99	0.99
C_m	1	1	1	1

Table 8 Results from the analysis of correlation and similarity between S_{cath} and S_{ref}

Moreover, some fundamental features characterizing the sucking signal have been extracted and compared, using paired *t*-test, between S_{cath} and S_{ref}. Fig. 24 shows the extracted features from a simulated suction cycle with a period of 0.3 s.

The negative peak values were calculated from S_{cath} and compared to the one of reference in order to verify the presence and the extent of an underestimation effect. The results deny the presence of a valuable underestimation: a difference of 0.2 mmHg resulted even at the highest frequency simulated.

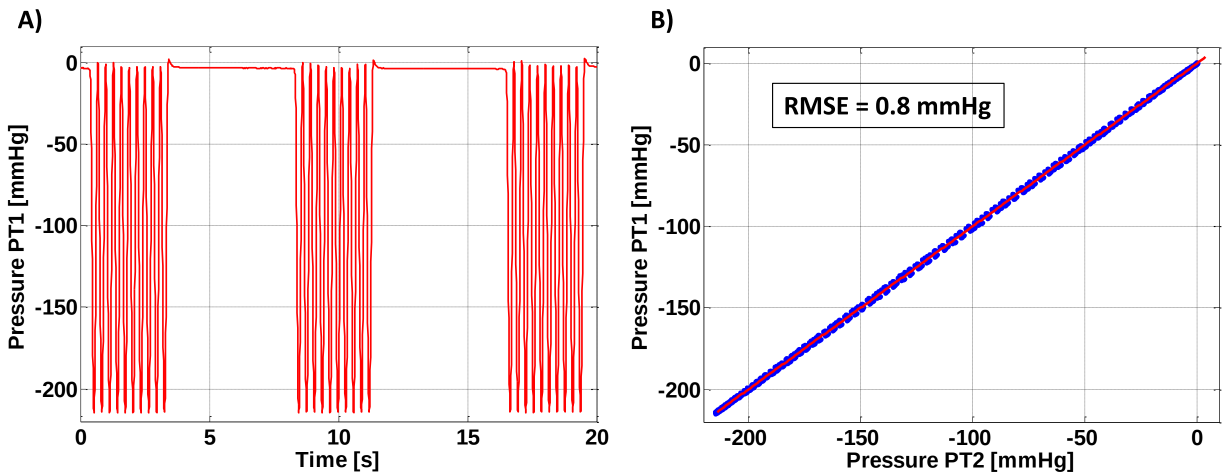


Fig. 23 A) Pressure signal recorded by PT1: a 3.3 Hz pattern of suction is simulated with a peak amplitude of 210 mmHg. **B**) PT2 signal is plotted vs. PT1 signal showing the coincidence of the values recorded: a linear correlation with unitary slope is shown, also proven by a very low RMSE. The line of equality is plotted in red.

Several features characterizing the temporal pattern of the rhythmic pressure signal have been extracted as well, and compared to the ones from the reference signal, in order to verify if the measurement method may affect or not the fundamental temporal pattern of the recorded signal.

For each cycle (identified by each negative peak), we calculated the time of occurrence of the peak, the start and ending, and then: the total width of a cycle (*W*: distance between start and ending), the width of the decreasing and increasing phase (*DSW* and *ISW*: distance between peak and start/ending), the cycle period (*T*: inter-peak distance). The results of the paired *t*-test deny the presence of any difference in the temporal pattern of the recorded signal compared to the reference at each frequency investigated (no significant differences resulted for any temporal feature).

Finally, the signal smoothness has been calculated for each cycle, in order to verify any difference between the two signals even in terms of regularity of the speed profile. This measure has been used because it may represent an important feature to evaluate sucking skills, as we will see later (Section IV.3). Thus, the smoothness has been calculated using the spectral arc length metric, as proposed in [93] (further details about this measure will be given in IV.2.1). *T*-test at each frequency did not show any difference in terms of smoothness, denying the presence of a signal distortion in terms of smoothness too.

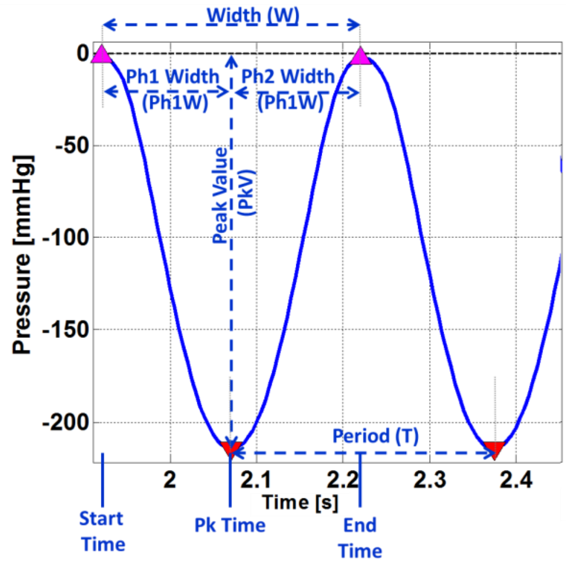


Fig. 24 Some of the features extracted to characterize the oscillatory pressure pattern.

II.3.2. EP Measurement Method

The method here proposed for EP measurement is based on the same principle of the method described in past works (see I.3.2), where a closed compressible tube was placed on the bottle teat (as shown in Fig. 6.a) so that the pressure changes inside the tube were measured, as reflecting the compression pressure over the teat where the tube lies. Though this measuring system was reported as presenting a limitation due to the rapid reaching of a plateau when the catheter's is fully compressed between the palate and the teat [28]. Further, no experimental validation to evaluate reliability and/or limitations of the method in the range of application has been ever actually reported in literature.

The method proposed in this work basically differs from the one just mentioned for the configuration of the compressible catheter: a PT is used to measure the pressure change occurring inside a compressible catheter that is placed inside the teat forming a U-shape, as shown in Fig. 25.a. The catheter enters the teat from two diametrically opposite holes at the base of the teat (*p1* and *p2* in the figure), until about 1 cm from the teat tip. This method implies, as also the one reported in literature, to take care so that the two sides of the U tube are positioned in the middle of the infant's lips to optimize the positive pressure to be recorded, as well as to standardize the position of the tube from one infant to another. However, later in II.3.2.1 the influence of a small position change of the teat with respect to the infant's lips will be investigated in order to verify the method reliability in a situation that is actually likely to occur.

Fig. 25 A) The compressible rubber catheter is placed inside the teat forming a U-shape; the tube enters the teat through two diametrically opposite points (*p1* and *p2*), that are required to be placed in the middle of the infant's lips while measuring. B) Full catheter compression is achieved when the teat is totally compressed.

This configuration of the catheter presents some enhancements with respect to the configuration reported in literature: it is more sensitive to compression movements as the compressible catheter is anchored to two diametrically opposite points of the teat, where both the hard palate and the tongue press; moreover the catheter full compression is not achieved unless the teat is completely compressed (see Fig. 25.b).

An experimental validation has been carried out in order to assess the applicability of the measuring method to the monitoring of the temporal pattern of the expression movements typical of NS. Experiments have been carried out to investigate the response of the measuring system to different oscillating patterns of compression movements and relative positions between the teat and the infant's mouth during bottle-feeding.

II.3.2.1. Experimental Validation

In order to verify the system response at oscillating expression pressures, different compression patterns have been simulated by means of a dedicated setup. EP waveforms have been simulated as sine curves with typical sucking frequencies (1 and 1.5 Hz). The amplitude of the EP waveforms has been chosen in order to be in the range reported as characterizing a "weak pattern", i.e. 25 mmHg of intra-teat pressure peak as reported in [14]. This study has been taken as reference as it classified the expression pattern from a *weak* to a *mature* pattern, and reported the pressure values characterizing the different maturational levels. The signal recorded through the measuring system proposed has been compared to a reference signal, i.e. the one recorded by means of a catheter connected to the lumen of a fluid-filled teat. The results show the agreement between the two methods in the characterization of the expression temporal pattern in all the simulated experimental conditions that accounted also for likely "bad" measurement conditions.

Experimental Setup

Fig. 22 shows the setup used for the experiments. Two cylinder-pistons (2KS444P Airport Corporation), moved by two closed-loop DC brushless actuators (M-235.2DD Physik Instrumente), were used to compress the teat of a bottle placed between them. The pistons moved generating synchronous sinusoidal forward-back movements, starting from a position where both were in touch with the teat. The bottle was fixed on an angle regulator to allow changes of the teat tilt with respect to the axis of the compression movement. Two rectangular plastic plates (1 cm wide, 2 cm long) were placed on the tip of the two pistons in order to simulate the infant's lips surface compressing the teat.

Two identical low cost integrated silicon pressure sensors (MP3V5004GP, Freescale Semiconductor) have been used to measure: i) the pressure inside the compressible catheter placed in the teat as shown in Fig. 25.a; and ii) the pressure inside the teat. The compressible catheter was a siliconized latex rubber catheter with an external diameter of 3.3 mm: one end of the catheter was connected to the PT, while the other one was closed. The bottle and the teat were full of water, and the in-teat pressure was measured by means of a PVC catheter ending in the lumen of the teat through a tip hole (method used in several studies and in the one taken as reference [14]).

Validation Procedure and Results

First, the EP pattern during NS has been simulated generating 5 compression cycles at two different frequencies (1 Hz and 1.5 Hz) and with an amplitude characterizing a weak expression pattern, according to the values reported in [14]. Data have been acquired simulating the condition in which the two extremities of the U shaped catheter on the teat are in the midpoint of the infant's lips (θ=0°, i.e. the axis of the U coincides with the axis of the pistons generating the compression movements).

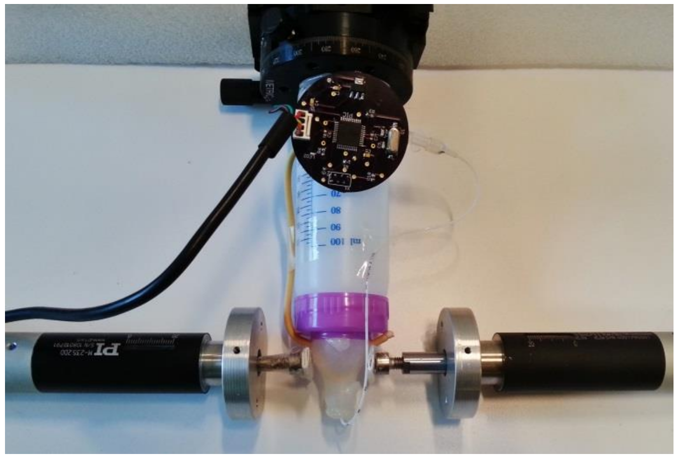


Fig. 26 Experimental setup for compression movements simulation: two cylinder-pistons are used and controlled to compress the bottle teat. The bottle is fixed on an angle regulator to allow changes of the teat tilt with respect to the axis of the compression movement.

The temporal pattern of the signal recorded through the rubber catheter (S_{cath}) was compared to the reference signal (S_{ref}) recorded in the teat lumen. The temporal features characterizing the sucking pattern, described before in Section II.3.1.1, and shown in Fig. 24, have been used to compare S_{cath} and S_{ref}, using statistical paired tests. Hence, for each compression cycle, peak time, start and stop time, width, phase1 and 2 width, period and smoothness have been calculated. No differences between the signals resulted: the temporal features characterizing the expression signal recorded through the method here proposed coincide with the reference ones in the simulated conditions. Also *RMSE*, r^2 and C_m have been calculated between S_{cath} and S_{ref} to evaluate the correlation/similarity of the two signals, as previously described (II.3.1.1). Given the amplitude difference between the two signals, the *RMSE* has been calculated using the signals normalized between -1 and 1. Results showed that S_{cath} is significantly linearly related to S_{ref} both in time (r^2=1) and frequency domain (C_m=1). Further, the *RMSE*, calculated as percentage of the normalized signal range, was very low (3%): the pressure waveform recorded through the compressible catheter does not significantly differ from the reference pressure signal.

Then, more simulations have been carried out in order to investigate the system response and reliability in case of teat tilt θ different from zero at both frequencies (see Fig. 27), and then in the extreme case of a very low amplitude of compression movements (intra-teat pressure peak=10 mmHg, see Fig. 28).

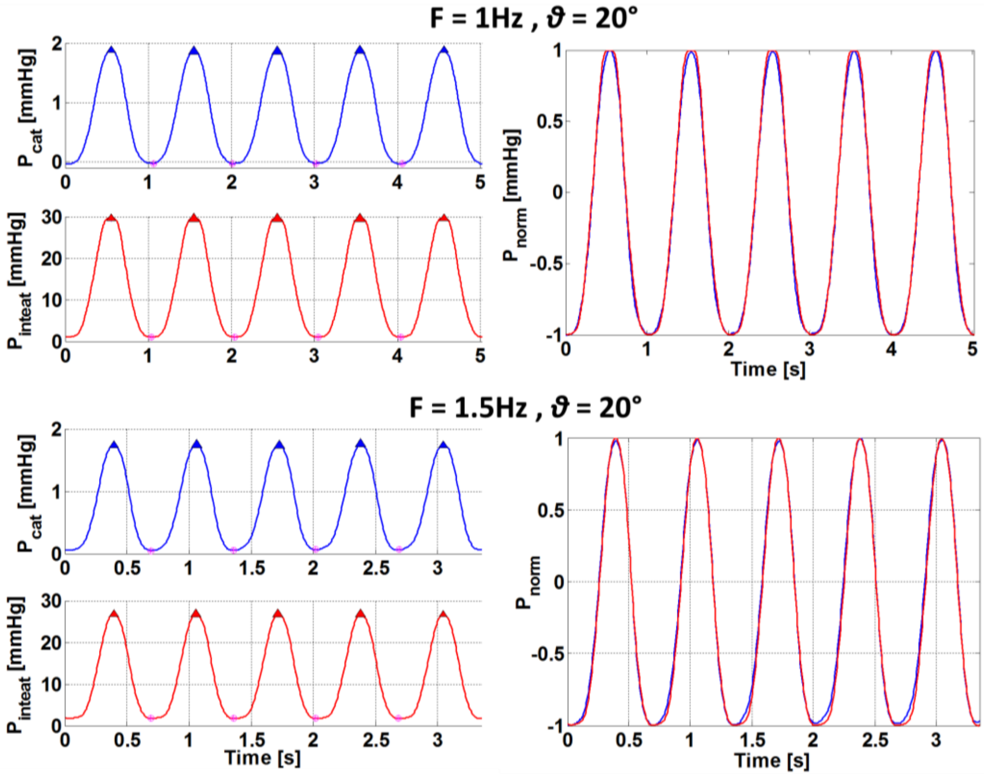


Fig. 27 Validation of EP measurement. A sinusoidal compression movements of 1Hz (top) and 1.5 Hz (bottom) frequency generates a pressure in the teat (red line) and a pressure in the latex catheter (blue line). Normalized pressure waveforms (between -1 and 1) are reported on the right.

The analysis of temporal and smoothness features shows a promising behavior also in these worse conditions: no differences were observed between the EP temporal pattern resulting from the measurement method proposed and the reference signal, for any of the simulated worse condition. The results of *RMSE* and correlation analysis are reported in Table 9. A 20° tilt of the teat does not compromise the signal correlation neither in time nor in frequency, as well as its accuracy, being the *RMSE* percentage still low (a 4% corresponds to 1.1 mmHg of error in the intra-teat pressure). The low amplitude condition though makes the *RMSE* rise, while the correlation measures still resulted being very close to the unit.

In conclusion, the method here proposed, based on the use of a PT connected to a U shaped compressible catheter placed inside a common bottle teat, resulted to be suitable to the monitoring the temporal pattern and rhythmicity of the expression sucking movements during bottle feeding.

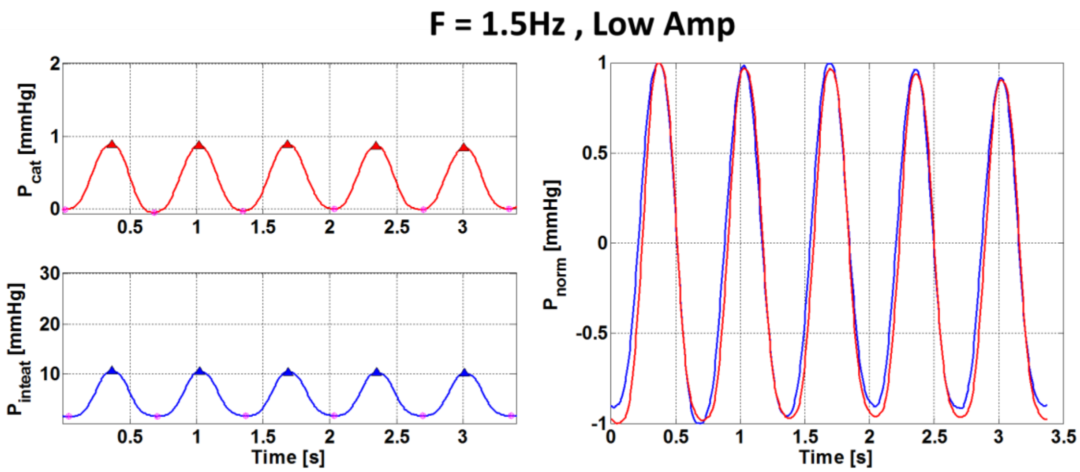


Fig. 28 Validation of EP measurement. A sinusoidal compression movements of 1.5 Hz frequency and very low amplitude generates a pressure in the teat (blue line) and a pressure in the rubber catheter (red line). Normalized pressure waveforms (between -1 and 1) are reported on the right.

	θ =20° 1 Hz	θ =20° 1.5 Hz	Low Amp
***RMSE* [%]**	4%	4%	13%
r^2	1	1	0.99
C_m	1	1	0.97

Table 9 Results from the analysis of correlation and similarity between S_{cath} and S_{ref}

II.3.3. Development of the IP/EP Monitoring Device

As introduced before, the design of this sensor-based module for sucking monitoring has been focused on the implementation problem. This means that the principal functional requirements were portability, adaptability, ease of use and low cost, in order to facilitate an easy and wide implementation in different settings. The monitoring device we developed is composed by a sensor-based unit that can be integrated on the base of a commercially available feeding bottle through a properly developed mechanical support.

II.3.3.1. Electronic Core

The electronic core has been developed in order to acquire data from the two PTs needed for the measurement of suction (IP) and expression (EP) as described before:

- IP is measured via a non-compliant catheter connected to a low cost integrated silicon PT (PT_{ip}) for vacuum measurement (MP3V5050V, whose details have been given in 0).

- EP is measured via a rubber compressible catheter connected to a low cost integrated silicon PT (PT_{ep}, MP3V5004GP). The sensor range goes from 0 to 3.92 kPa, i.e. 0 to 29.5 mmHg.

The two PT output signals are digitally converted (12 bits) by a microprocessor PIC18F46J13 and sent to a laptop for real time visualization, storing, saving and following analysis of the signals. A serial RS232 wired connection (TTL-232R cable, FTDI Chip), is used for data transfer and module control (to launch and stop the acquisition). The unit is also equipped with a LED (OSRAM Opto Semiconductor), controlled by the microcontroller, which signals the data acquisition start and scans 10 s intervals of the acquisition via intermittent lighting. The battery of the laptop is used to power the device, preventing from any electrical safety problem. Fig. 29 shows the block diagram of the hardware module and the integration on a feeding bottle, that is described in the next section.

II.3.3.2. Integration

The integration of the electronics has been designed at first in order to fit the 100 ml single-use bottle (Flormed Commerciale Srl) commonly used in the neonatal unit care where the device has been tested (Santa Maria Goretti Hospital in Latina).

A circular double-layer PCB (printed circuit board) has been designed and developed with a diameter size of 5 cm, i.e. comparable to the bottle diameter, in order to do not make it bulky or awkward. A mechanical support has been designed and built using a rapid prototyping printer (Project 3000 by 3D Printer Inc.). Fig. 30 shows the PCB and the support developed for the integration.

The PT_{ip} port is connected to a non-compliant catheter whose opposite extremity is threaded into the bottle teat through a hole made at the teat base (see Fig. 30.b) and then out of it through a hole made close to the feeding one. The catheter tip is positioned so that it protruded about 2 mm out of the teat, which ensures that IP is reliably measured without interfering with the natural sucking process. The catheter used for IP measurement is the PVC feeding tube described in II.3.1.1.

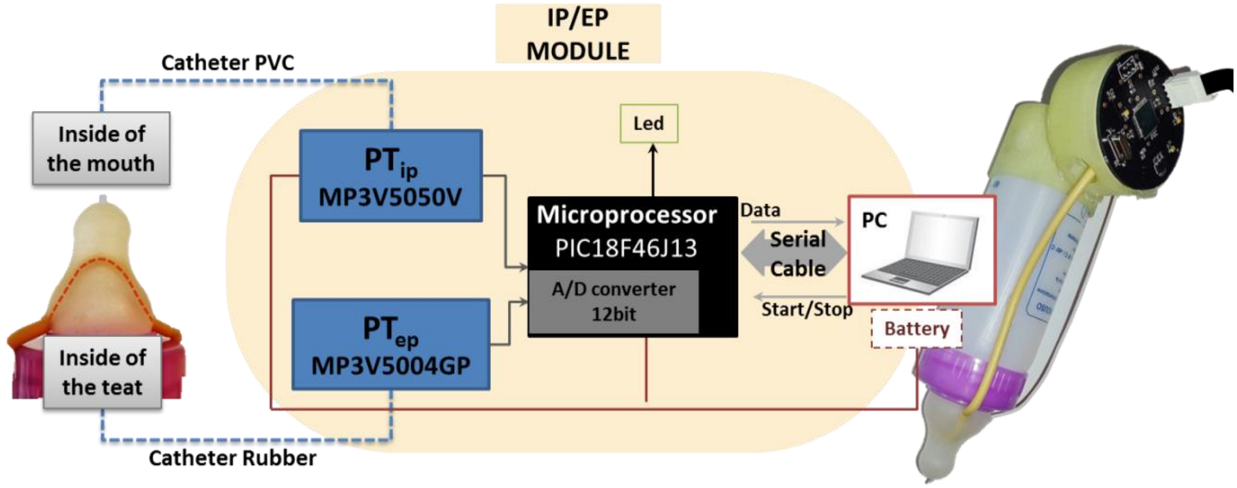


Fig. 29 Block diagram of the IP/EP Module and its integration on a common feeding bottle.

The PT_{ep} port is connected to a compressible catheter whose opposite extremity is closed and made pass through the teat according to the configuration described in II.3.2.1. The compressible catheter used for EP measurement is a rubber latex siliconized catheter as described in II.3.1.1.

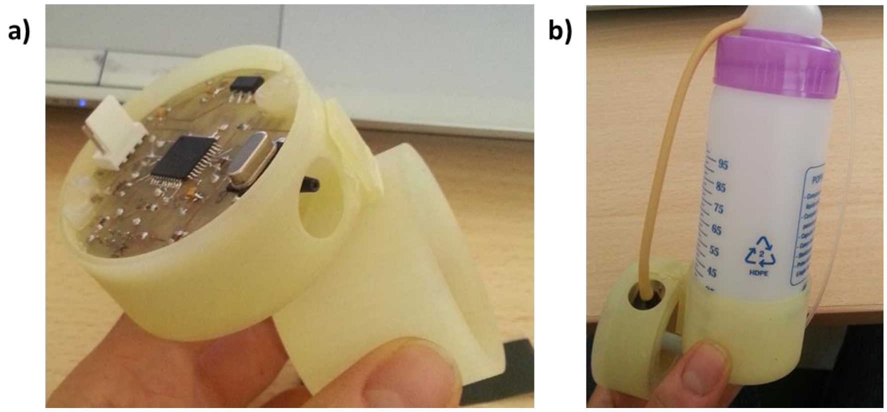


Fig. 30 a) Double-layer PCB inserted into the support designed for the integration on a feeding bottle; b) integration of the IP/EP Module on the bottle commonly used in a neonatal unit care

Milk and infant are in contact just with the two catheters used for pressure measurement. This avoids any sterilization issue and electrical safety risk. The two catheters indeed are sterile and single-use (their choice has been made also because of their low cost). No other parts of the device get in contact with the milk, then implying the possibility of using the same module for multiple measures. Fig. 29 shows and outlines the integration of the sensor-based module on the feeding bottle.

III. MONITORING RESPIRATORY EVENTS DURING BOTTLE FEEDING

Understanding how preterm infants breathe during feeding represents an important step for the assessment of the overall infant's motor development during the first day of life. Indeed, breathing and feeding share common anatomical structures and their efficient accomplishment require the development of a good coordination level by the infant.

Breathing events during neonatal feeding have been investigated using several non-invasive [62] and invasive techniques [88]: there is not a standard approach to the problem, but the particular needs of the group under exam impose constraints that limit the choice of appropriate transducers. A common rule is to avoid the use of invasive approaches when possible, especially in the case of preterm infants, in order to avoid additional stress [29]. It is also crucial that the transducer(s) chosen are acceptable to the newborn without imposing stress, neither to him/her nor to the caregiver. Given that, more research effort is needed to design sensing solutions that can be easily embeddable on a common bottle for feeding, and that can be used to assess the temporal breathing pattern (as discussed in 0)

In this work, we propose a novel non-invasive device for recording newborns' respiratory events, designed to be embedded on a common feeding bottle. The proposed device working principle is based on the convective heat exchanged between two hot bodies and the infants' breathing. The sensing elements are inserted into a duct and the gas exchanged by infants is conveyed into this duct thanks to a system properly designed to be mounted on a commercial feeding bottle. The device discrimination threshold and response at oscillating flows has been investigated, as well as the effect of distance and tilt between nostrils and device, simulating nostrils and neonatal respiratory pattern. The results foster the successful application of this device to the assessment of the breathing temporal pattern of newborns during bottle feeding with a non-invasive approach. However, after the laboratory validation, further work is needed to test and validate the system on newborns during bottle feeding.

III.1. Sensor Design

The main novelty of the sensor is related to the choice of the hot elements, which consists of two commercially available NPN bipolar junction transistors. This choice has been driven basically by two essential requirements: low-cost and small size. Low cost is an essential requirement for the final goal of this work (as previously detailed in section I.1), and further it allows a disposable use. Besides, the small size of transistors enables the development of miniaturized solutions, that are particularly required for preterm infants' breathing monitoring.

The ability to discriminate flow direction, together with the small dimension, is the novelty of the proposed transducer with respect to similar previous approaches [89]. The bidirectionality is obtained thanks to the mechanical solution that will be described below.

III.1.1. Working principle

The sensor working principle is based on the convective heat transfer between the surface of the transistors, heated by Joule effect, and the colder hitting fluid. In steady-state conditions, a hot element, placed in a fluid stream at temperature T*f*, reaches an equilibrium superficial temperature, which depends on the heat flow exchanged with the fluid. If this element is a transistor, the base-emitter junction temperature ($\boldsymbol{T_{be}^{S}}$) can be obtained by the following equation:

$$I_C^2 R_{CE} = hS(T_{be}^S - T_f) = Q \tag{1}$$

where I_C is the collector current, R_{CE} is the equivalent collector emitter resistance, *h* is the heat transfer coefficient, *Q* is the heat exchanged between the transistor and the fluid at equilibrium, and *S* is the heat exchange surface.

The heat transfer coefficient *h* depends on the system geometry, the physical properties of the fluid, and the fluid velocity. It can be expressed by the King's Law:

$$h = A + B\sqrt{\rho v} \tag{2}$$

where *A* and *B* are two calibration constants, □ is the fluid density, and v is the mean fluid speed.

The relationship between the base-emitter voltage (V_{be}) and the base-emitter temperature (T_{be}^{S}) can be considered as linear in a wide range of temperature:

$$V_{be}(T_{be}^{S}) \cong a + bT_{be}^{S}\,. \tag{3}$$

The coefficients a and b are constant, and in particular b represents the thermal sensitivity of V_{be} (equal to -2mV/K^{-1}). Introducing (1) and (2) in (3), and solving for V_{be}, the relationship between the base-emitter voltage and flow speed can be expressed as:

$$V_{be}(v) = a + b\left(\frac{Q}{S\left(A + B\sqrt{\rho v}\right)} + T_f\right) \tag{4}$$

Equation (4) relates V_{be} with v, in function of other parameters depending on the transistors and on the characteristics of the fluid.

In order to discriminate flow direction, the sensor is made of two identical transistors, placed in the center of the pipe cross-section, and designed as shown in Fig.1: the front transistor is directly hit by the fluid, while the rear one is shielded by the PCB where it is soldered on.

Since the two transistors are nominally identical, the two constants a and b can be considered equal. In steady state conditions, the two transistors reach different T_{be}^{S}, hence different V_{be}, because the fluid hits them with different speeds.

In fact, the heat exchanged by the transistor directly hit by the flow (front transistor in Fig. 31) is bigger than the heat exchanged by the shielded transistor (rear transistor in Fig. 31).

As a consequence, the equilibrium temperature of the front transistor is lower than the one of the rear transistor. This entails that the two V_{be} are not equal, and their difference ΔV_{be} can be expressed as follows:

$$\Delta V_{be}(v_1, v_2) = b\left[\frac{Q_1}{S\left(A + B\sqrt{\rho v_1}\right)} - \frac{Q_2}{S\left(A + B\sqrt{\rho v_2}\right)}\right] \tag{5}$$

where Q_1 and Q_2 are the heats exchanged between the transistors and the fluid, and v_1 and v_2 are the speeds of the gas hitting the two transistors Tr_1 and Tr_2, respectively.

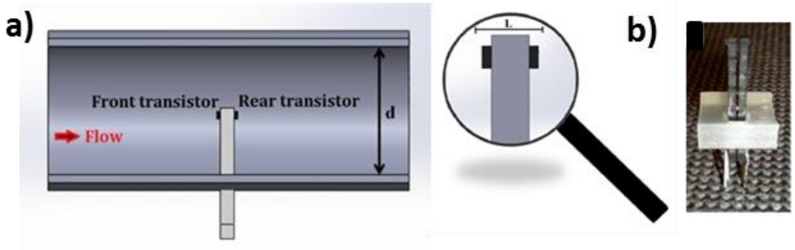


Fig. 31 a) Geometrical configuration of the sensing element. The transistors are mounted on a PCB board placed at the center of the pipe cross-section. b) Transistors soldered on two PCBs.

Equation (5) can be simplified considering the following hypotheses:

- the heats exchanged Q1 and Q2 are considered to be the same, assuming that the transistors are nominally identical and that they are supplied by the same constant Ic (hereafter Q1 = Q2 = Q);
- the speed of the gas hitting the rear transistor is considered negligible because this transistor is shielded by its own PCB;
- the flow regime is considered laminar. Under this hypothesis, the speed of the gas hitting the front transistor corresponds to the maximum speed of the gas flowing within the pipe. This speed is equal to 2v where v is the gas speed averaged on the whole pipe cross-section. This hypothesis is verified in the whole range of flowrate: in the worst case (d=10mm and F=9 L·min-1) Re≈1000.

Considering these hypotheses, ΔV_{be} can be expressed as a function of the volumetric flowrate, $F = v \cdot \Omega$, as follows:

$$\Delta V_{be}(F) = \pm b\left[\frac{Q}{S\left(A + B\sqrt{\rho\frac{2F}{\Omega}}\right)} - \frac{Q}{SA}\right] \qquad (6)$$

where Ω is the cross-sectional area of the pipe. The sign of ΔV_{be} is determined by the direction of the gas flow: for example, if the transistor Tr_1 is the front transistor, ΔV_{be} as defined in (5) will assume a negative value.

By defining the following two additional constants:

$$\mathrm{k} = \frac{\mathrm{bQ}}{\mathrm{SA}}, \qquad \mathrm{c} = B\sqrt{\frac{2\rho}{\Omega}} \qquad (7)$$

we obtain the calibration function of the transducer as:

$$\Delta V_{be}(F) = \pm kc \frac{\sqrt{F}}{A + c\sqrt{F}} \tag{8}$$

III.2. Design and manufacturing

Among several available transistors, we have chosen two nominally identical NPN bipolar junction transistors (PBSS2515M by Philips), each one soldered on a PCB. The two PCBs have been positioned 1 mm apart in order to avoid the effects of heat conduction on the base-emitter junctions of the two transistors. The PCBs are inserted into a duct with a diameter equal to 10 mm, designed to be mounted on the ring of a commercial feeding bottle (Angled Well-Being Chicco, Artsana S.p.A) and to avoid direct contact with the infant.

One end of the duct is inserted into a pneumatic connector (Fig. 32a.A), designed to get a profile matching with the teat (Fig. 32a.B) and to channel most of the air expired/inspired by the infant into the duct. A mechanical support (Fig. 32a.D) has been designed in order to guarantee the PCBs placement at the chosen distance, in line with the duct axis and with the surface perpendicular to the flow direction.

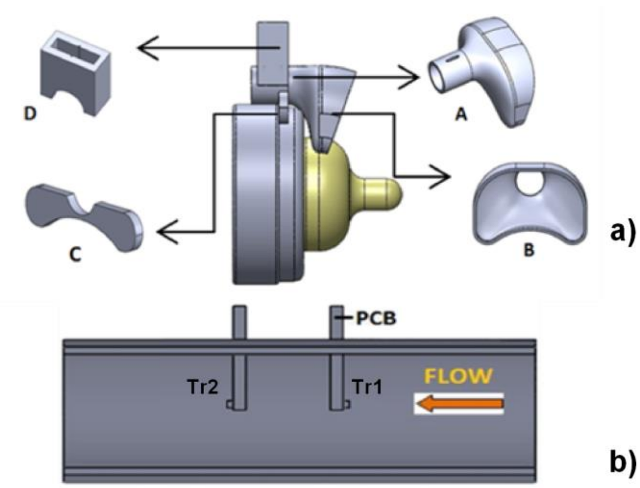


Fig. 32 a) Assembly of mechanical components: (A) duct inserted into a pneumatic connector, (B) pneumatic connector, (C) duct support, (D) PCBs support. b) Transistors inserted into the duct and mounted.

These mechanical components have been designed in SolidWorks and built using a rapid prototyping printer (Project 3000 by 3D Printer Inc.). The base and emitter voltages have been processed by an analog circuit providing an output, V_{out}, proportional to their difference.

III.2.1. Discrimination threshold

In order to investigate the discrimination threshold of the device in different configurations, an experimental set-up simulating the infant's nostrils has been set (Fig. 33).

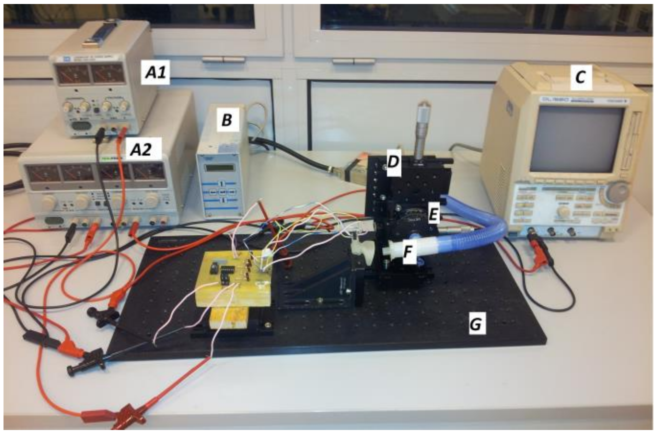


Fig. 33 Experimental setup: (A1) DC power supply for transistor, (A2) DC power supply for amplifiers, (B) Air flow controller, (C) Oscilloscope, (D) Micropositioners, (E) Tilt angle regulator, (F) Nostrils, (G) Optical table.

The infant's nostrils have been simulated through two pipes of 5 mm diameter; the distance between their centers was 8.5 mm [90]. The pipes have been inserted on a plastic base, which has been fixed to the end of a breathing circuit. This circuit is connected to a mass flow controller, which delivers constant flow rates (from 0.1 L/min to 0.5 L/min with step of 0.1 L/min; from 0.5 L/min to 2.5 L/min with step of 0.5 L/min; 3.5 L/min, 5 L/min, 6 L/min and 7 L/min). micropositioners have been used in order to allow horizontal and vertical movements of the nostrils. An angle regulator, connected to the micropositioners, has been used to allow the changes of the nostril tilt with respect to the axis of the duct.

III.2.2. Response to oscillating flows

We used an Active Lung Simulator (ALS) to deliver flows similar to a neonatal respiratory pattern. It is composed of four cylinder-pistons (2KS444P Airport Corporation, 15.5 cm2 cross-section each) perpendicularly connected to a central spherical chamber. Pistons are moved by four closed-loop DC brushless actuators (M-235.2DD Physik Instrumente). When the ALS delivers gas, it simulates the expiratory phase. In this case, the fluid passes through a fast mono-directional flow meter (4121 TSI, accuracy of 2% of measured value, range of measurement up to 20 L/min, and response time of 4 ms), and then hits the transistors (Fig. 30b). During the simulation of inspiratory phase, the gas hits the device and then passes through the flowmeter. Flows and volumes generated by the ALS are measured by the flowmeter and used as reference.

III.2.3. Validation Procedures

Discrimination threshold has been assessed setting three different distances between the nostrils and the connector (10 mm, 15 mm and 20 mm) and three different tilt angles of the nostrils relative to the duct axis (10°, 20° and 30°). Angles bigger than 30° have not been investigated since the considered feeding bottle already has its own 30° tilt. The 10 mm minimum distance corresponds to the average distance between the nose and upper lip of the infant [91]; the 20 mm maximum distance is suggested by the geometry of the considered teat. Therefore, this range allows covering all the angles and distances which can occur during bottle feeding. In order to characterize the device response at oscillating flows, experiments have been performed by simulating two different respiratory patterns: i) the first one was characterized by a respiratory rate of 30 bpm (0.5 Hz) and, ii) the second one by 60 bpm (1 Hz), in order to cover all the respiratory rates typical of neonatal ventilation during bottle feeding [34] (Fig. 34).

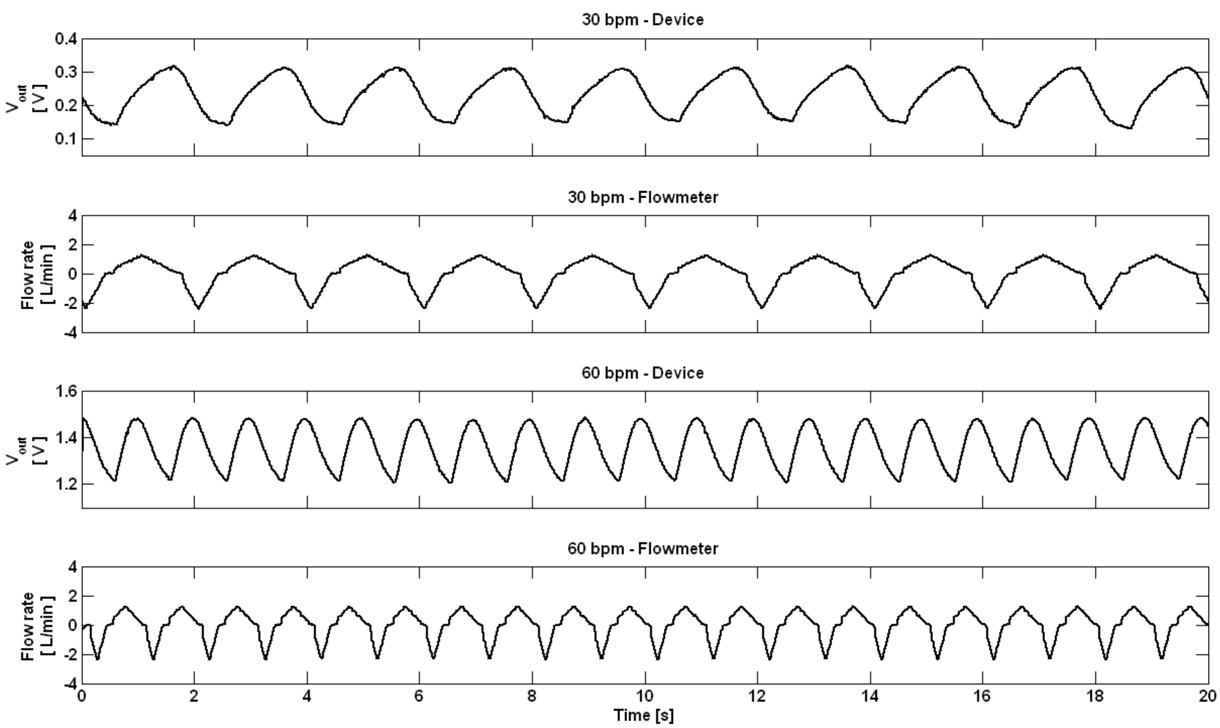


Fig. 34 Device and flowmeter outputs at 30 and 60 bpm.

For both the experiments a typical minute volume encountered in neonatal ventilation (i.e., 1.0 L/min) has been delivered [92]. The outputs of both flowmeter and device (Vout) have been sampled at 1 kHz and processed applying a 10-sample moving average filter (Fig. 34).

III.2.4. Discrimination threshold

Nine measures have been performed at each air flow rate and compared with those recorded in no flow conditions: the minimum flow rate with a resulting p-value < 0.05 (one sample t-test) has been considered as the discrimination threshold. Table 10 reports the results for the different investigated configurations. Experimental results show that the proposed device represents an interesting solution for the monitoring of respiratory events during bottle feeding. In fact, at 10° and 20°, the device is able to discriminate air flow rates smaller than 0.5 L/min at all the distances, which is the half of the infant's minimum expiratory peak value (1L/min [13]). A relevant decrease of performances is experienced at 30°, as the device presents a discrimination threshold equal to 2 L/min, 6 L/min and 7 L/min for a distance of 10 mm, 15 mm and 20 mm, respectively.

Distance [mm]	**THRESHOLD [L/min]**		
	10°	**20°**	**30°**
10	0.2	0.3	2
15	0.2	0.3	6
20	0.2	0.3	7

Table 10 Discrimination threshold at different configurations

III.2.5. Response to oscillating flows

The signal from our device is delayed with respect to the one of the flowmeter. Considering 30 and 60 bpm, the delay is 80 ± 15 ms and 65 ± 16 ms, respectively. The mean duration of a single breath detected by the flow meter and our device is respectively 996 ± 19 ms and 994 ± 8 ms at 60 bpm, and 2007 ± 28 ms and 2007 ± 23 ms at 30 bpm. In both cases, the difference between the mean breath duration detected by the flowmeter and our device was not statistically significant.

Hence, the proposed system allows detecting the starting and the ending of all single breaths during oscillating flows having trends similar to typical neonatal respiratory acts.

III.2.6. Conclusion

A non-invasive device for monitoring newborns' breathing pattern has been designed and developed in order to be easily integrated on a common feeding bottle. The experimental validation has demonstrated that such sensing device has a discrimination threshold lower than 0.5 L/min in most of the investigated configurations, and that it is able to discriminate the respiratory acts.

Further work is required to implement a dedicated algorithm for identifying the onset of the inspiratory phase, and to extend the number of trials and the measurement range.

Summing up, the proposed device exhibits promising results, which foster its successful application to the assessment of the temporal breathing pattern of newborns during bottle feeding with a non-invasive approach.

IV. AN AUTOMATED SYSTEM FOR THE ORAL-MOTOR BEHAVIOR ANALYSIS

The development of a technology-assisted tool for oral-motor behavior assessment implies the fundamental development of an automated analysis system capable to systematically treat and analyze the data recorded with the device. This is an essential step in the development of an objective tool that may assist clinicians or researchers in the assessment of the infant.

With the increasing need for an objective assessment tool, it has become extremely important to establish a set of standardized, quantitative and reliable measures for a proper analysis of oral-motor function. However, the progress on this direction has been limited: as shown in Section I.3, literature is scattered and there is no straightforward indication of the most sensitive and reliable measures to evaluate. Further efforts are needed in this direction; hence, another objective of this work, as previously introduced, is the development of an automated software system for signal analysis that allows, from one hand, extracting the most significant parameters for the infant's assessment, and from the other hand, minimizing the cost and maximize the easiness of use, thus reducing the need for specialized training in test delivery and interpretation.

This chapter will be focused on the development of the ad-hoc software system designed for the quantitative analysis of infants' oral-motor behavior and coordination. The main feature and functionalities of the software will be discussed in details, and in particular: Section IV.1 will present algorithms for signal Segmentation; Section IV.2 will describe the algorithms to calculate quantitative measures of oral-motor behavior and coordination; and finally Section IV.3 will address the issue of the Assessment, describing the strategies explored for data analysis in order to evaluate developmental trends and/or distinguish normal versus immature behavior.

The algorithms have been conceived in order to be applicable to any input signal presenting the characteristics of sucking pattern: as reported in section IV.3, different datasets, collected from different classes of newborns and also with different devices, have been processed and analyzed, providing promising preliminary results, i.e.:

- The capacity to track sucking behavior development in healthy infants: in section IV.3.1, longitudinal IP data from 4 healthy term infants have been analyzed, suggesting a set of features useful to characterize and monitor the developmental trend.

- The capacity to discriminate immature versus typical healthy behavior (section IV.3.2): sucking pressure data (IP and EP) have been collected from 9 newborns (four at-Risk and five healthy newborns) by means of the IP/EP monitoring module presented in Section II.3 and shown in Fig. 29. The software has been used to analyze infants' oral-motor behavior and results have highlighted a set of sensitive measures that may help in discriminating immature versus typical healthy behavior.

MATLAB (The MathWorks, Inc., Natick, MA) has been used as programming language and environment for software development.

IV.1. Signal Segmentation

The software has been designed to read sucking pressures (IP and EP) and automatically identify the different components of the sucking pattern, i.e. sucks and bursts. Suction and expression represent two components of newborns' NS activity characterized by a pattern of bursts of sucking cycles that are alternated with pause periods. A burst is made of a series of events occurring at the typical frequency of about 1 Hz (see Fig. 35). In the IP signal an event (*Ev*) is a negative pressure deflection: negative IP increases (Increasing Suction, *IS*) until it reaches a negative peak value, which is then followed by a decreasing suction (*DS*) phase, until it reaches a trough value. In the suction component, a peak is intended as a negative peak (local minimum) while a trough as a local maximum.

As Fig. 35 shows, in the EP a sucking event is similarly identified by a peak between two troughs, where the peak, contrary to the suction signal, is a local maximum (positive value) while a trough is a local minimum. Similarly to the suction event, the trough-to-peak portion of the signal represents the Increasing Expression (IE), while the peak-to-trough represents the Decreasing Expression phase (DE).

A set of algorithms have been coded to automatically segment events and bursts after a proper filtering process. In literature there is no detailed description of the algorithms used [13, 29], or the ones that have been reported were not generalizable [51] and/or not validated [37] as well. The lack of a defined method for signal segmentation has prevented so far from having coherent measures across different studies, and then from inferring general results despite the large literature. Therefore, a detailed definition of an algorithm for automated event detection represents a novel fundamental contribution in the development of a standardized analysis tool. Moreover, the preliminary results obtained (see IV.3) are promising and suggest the suitability of the method for quantitative assessment of sucking behavior.

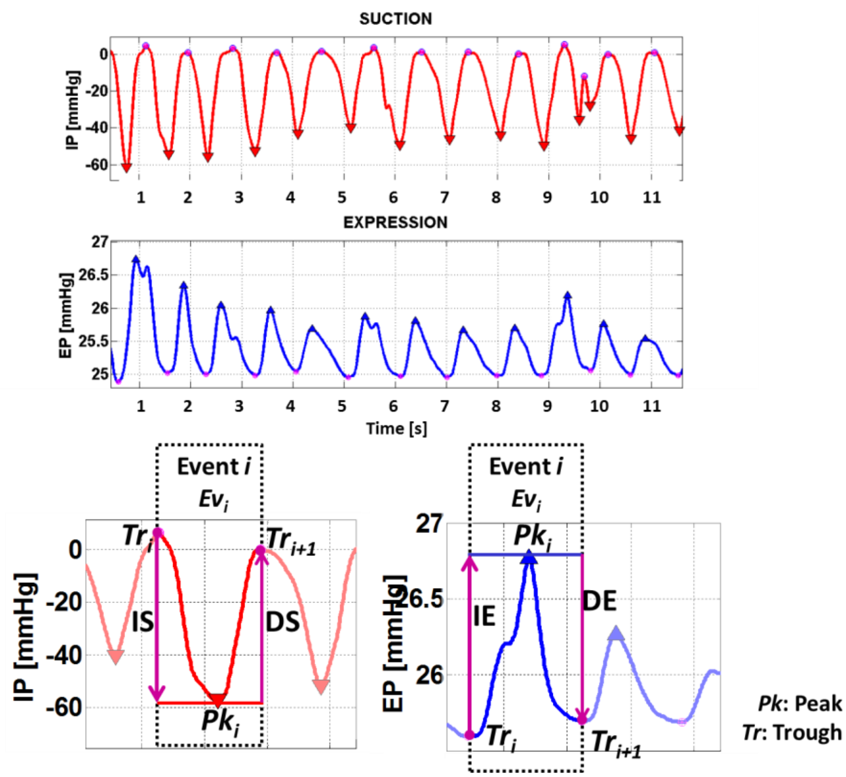


Fig. 35 Example of a burst of sucks in Suction (IP) and Expression (EP) component (top), recorded by means of the S/E monitoring device described in II.3. A sucking event (bottom) is marked by a negative or positive peak (Pk_i), respectively in IP and EP, between two troughs (Tr_i, Tr_{i+1}): the trough-to-peak portion of the signal represents the Increasing phase (IS or IE), while the peak-to-trough represents the Decreasing phase (DS or DE).

Filtering

Pressure signals are filtered using a first-order low-pass digital Butterworth filter, with a cut-off frequency of 10 Hz. The bandwidth of the pressure signals can be considered well below 20 Hz according to the results obtained from the analysis of the power spectral density reported before in section II.2.1. A 10 Hz cut-off frequency has been chosen in order to remove the noise given by frequency components higher than the ones of interest: the dominant frequency in the signals is given by the sucking rhythm around 1-2 Hz, and besides an additional frequency may be observed in the case of jaw tremor around 7 Hz (as observed in [49]). Thus, we removed any frequency over 10 Hz in order to consider just the bandwidth of interest, and remove any false peaks due to the presence of higher-frequency noise in experimental signals. After filtering, the signals are given as input to the algorithms designed for the signal segmentation.

Noise Analysis

The level of noise is estimated from the analysis of a portion of the signal corresponding to the sensor output in absence of sucking activity. The system automatically selects the initial flat portion of the signal, but also allows selecting a random portion, in order to be generalizable to any signal. Then the maximum trough-to-peak value in the noise is estimated, and it is use to define the minimum amplitude threshold in the peak detection algorithm that is described in the following section.

Besides, the mean value of this portion of signal is calculated in order to estimate and remove the initial offset from the signal.

IV.1.1. Event Detection

The first requirement in processing sucking signals is to detect peaks and troughs in order to identify sucking events. However, the presence of random noise in real experimental signal may cause false peaks. To avoid this problem, an algorithm has been properly designed and implemented to detect events and excluding artefacts (low peaks), as well as to be robust to changes in amplitude range between different recordings or subjects. The event detection algorithm consists of two parts: i) a threshold peak detection and ii) a peak-to-peak correction. Fig. 36 outlines the algorithm steps that are described in the following.

First of all, the event detection algorithm picks only those peaks exceeding a certain amplitude threshold (ΔA: trough-to-peak amplitude) that is initially set as equal to 1.5 times the maximum noise level (calculated as described above).

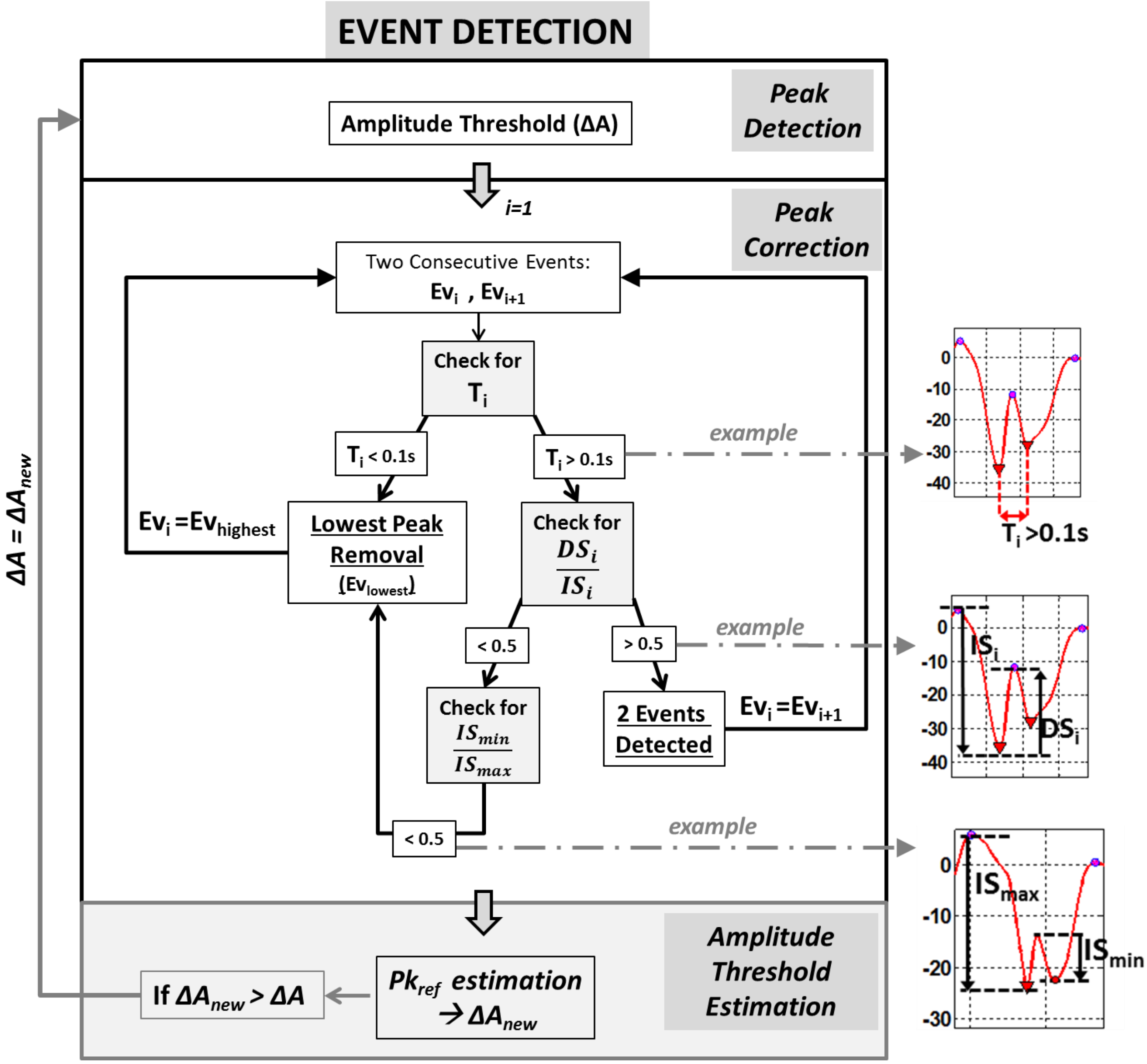


Fig. 36 Outline of the Event Detection Algorithm

Then, in order to exclude pressure fluctuations that should not be considered as separate events, a peak-to-peak correction algorithm has been coded. The correction looks at each couple of consecutive peaks in order to check if they can be considered as two separate events or as being part of a single one. Two consecutive peaks are counted as separate sucks if:

i) they are not "*too close*": the time interval between them exceeds the inter-peak time threshold set to the minimum value of 0.1 s (coherently with the maximum frequency component considered). Let t_k be the time vector of the sampled signal, the algorithm checks for:

$$T_i = t_{pki+1} - t_{pki} > 0.1 \text{ s}$$

ii) the pressure returns to a baseline between two peaks: the ratio between decreasing and increasing phase amplitude (DS/IS or DE/IE) is at least 0.5 (i.e. the signal returns to at least the 50% of its initial value):

$$\frac{DS_i}{IS_i} = \frac{y_{pk_i} - y_{t_{i+1}}}{y_{pk_i} - y_{t_i}} > 0.5$$

If the first condition is not verified, the two deflections are considered parts of a single sucking event, ignoring the lowest peak. If the second one is not verified, the amplitudes of the increasing phase of the two peaks are checked: if the smallest one reaches at least the half of value of the main one (the highest), the two peaks are considered as part of two events. Otherwise, the two deflections are considered parts of a single sucking event, with the peak value corresponding to the highest of the two.

After the peak-to-peak correction is complete, a new value for ΔA is calculated: an iterative threshold estimation technique has been implemented, as described below, in order to define a proper ΔA for each signal. This allows the algorithm to be applied equally to IP and EP, that are characterized by different pressure ranges.

Automated Threshold Estimation

To be considered as a peak, a sample value must be at least a given value ΔA greater than a trough. Thus the operation of peak detection depends upon the value chosen for the threshold ΔA. Visual inspection of the data might allow for threshold selection; however, this requires supplemental training of the person acquiring the data and anyway lacks of standardization across different users and different acquisitions. Thus, an automated threshold estimation greatly improves the peak picking algorithm and standardizes the procedure. Even so, using an auto-threshold algorithm may imply the risk of being sensitive to outliers in the data; hence the proposed technique has been designed in order to be robust to small outliers, which are the ones characterizing the signals of interest.

At each iteration, a reference peak value (Pk_{ref}) is calculated and the 10% of its value is taken as the new minimum threshold (ΔA_{new}) for peak detection at the next iteration. The iteration ends when the ΔA does not increase respect to the previous value.

At the end of each iteration, of the peak detection algorithm, Pk_{ref} is calculated as the 75th percentile of the peak amplitude values, which is can be taken as a measure robust to the presence of possible small outliers. Sucking pattern in fact is affected by a fatigue component which makes the sucking amplitude decrease across the feeding session. This is why, in order to estimate a peak reference value, not affected by the fatigue, the 75th percentile has been taken instead of a typical central tendency measure: it is more robust to the presence of small outliers and to the influence of all the low peaks characterizing the last part of the feeding. Fig. 37 shows the peaks, sorted by amplitude, detected across the iterations of the algorithm.

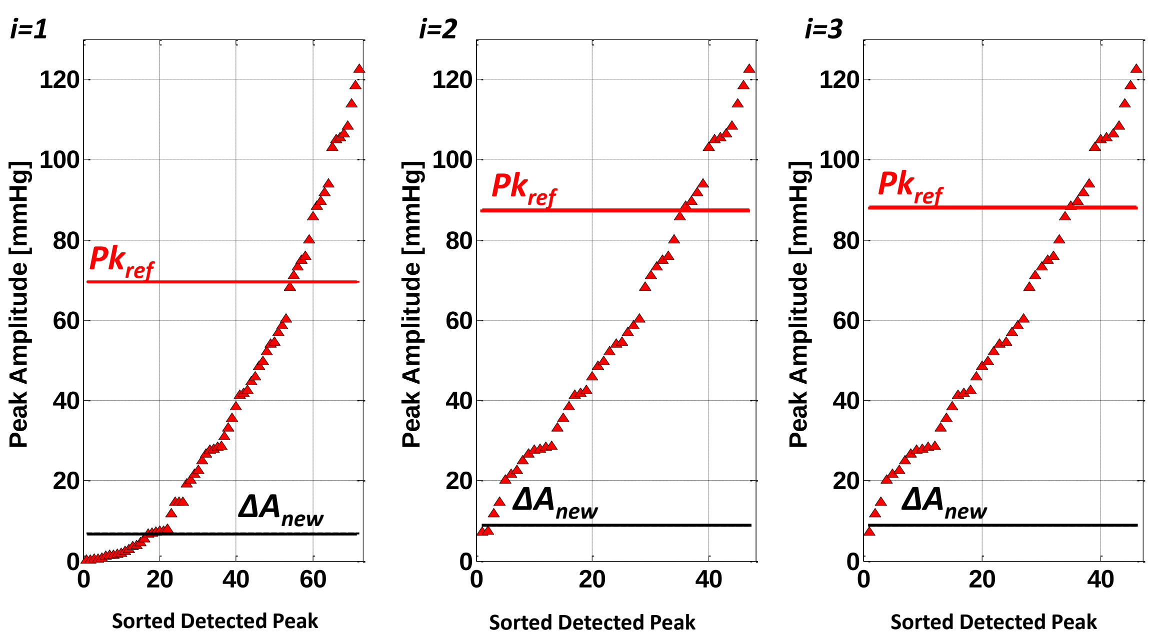


Fig. 37 Three iterations (i) of the automated threshold estimation algorithm. After last iteration ($i=3$), the 30% of the peaks initially detected (at $i=1$) have been excluded.

IV.1.2. Burst/Pause Segmentation

A burst is defined as a series of at least 3 consecutive events whose peak-to-peak period (T) is lower than 2 s. Any event not being part of a burst is considered as a sporadic event, and is not considered in the following analysis, being possible source of outliers. Thus, a pause is detected as any inter-peak period larger than 2 s. The onset and end points of a pause are identified through an algorithm properly designed to detect the flat portions of the signal. The algorithm identifies those samples, within a pause period, with a first derivative lower than a minimum value. This reference value is the minimum slope of all the detected events: both increasing and decreasing slope are considered for each event and calculated as the absolute event amplitude divided by the duration), and then taking the minimum value.

Fig. 38 shows the output of the segmentation process of a portion of experimental IP and EP signals, collected from a healthy newborn by means of the IP/EP Monitoring Device developed during this work.

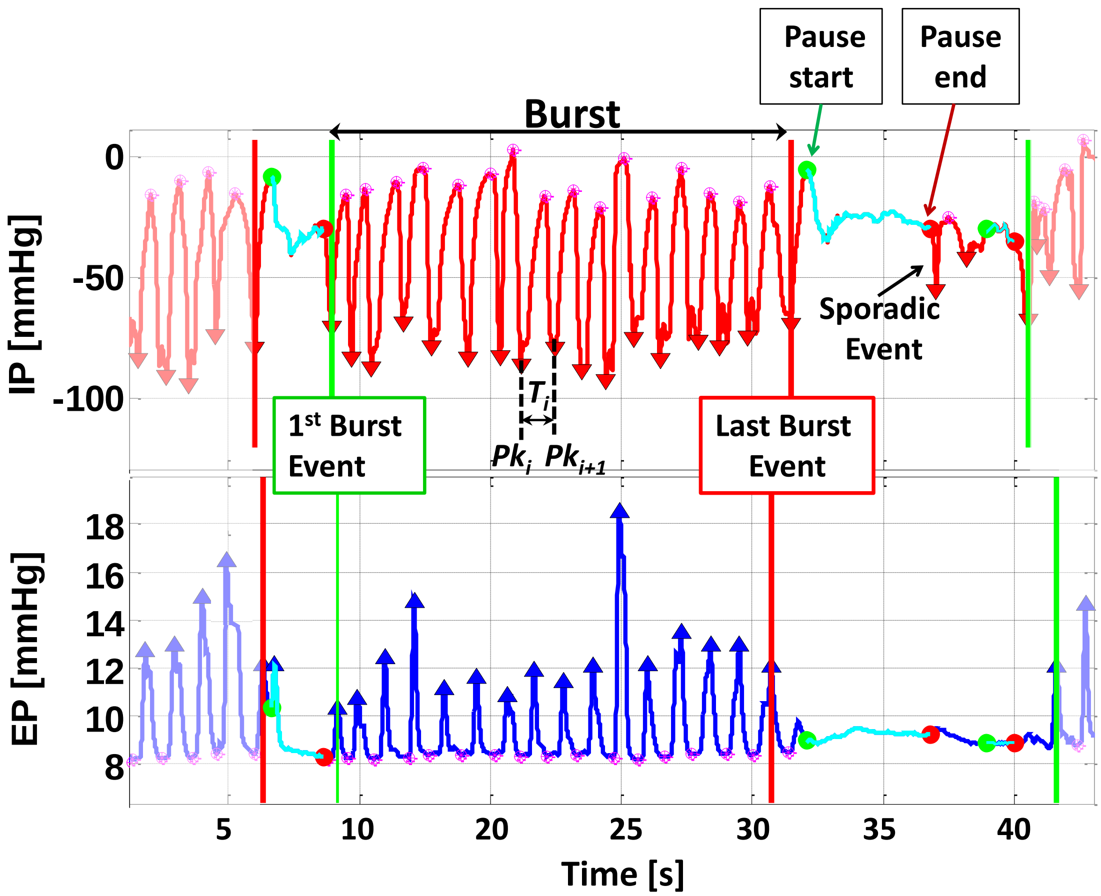


Fig. 38 Output of the segmentation process on a portion of simultaneous IP and EP signals, collected by the IP/EP Monitoring Device developed during this work.

IV.2. Methods: Feature Extraction

Once sucks and bursts are detected, the software proceeds with the estimation of a set of features characterizing the oral-motor pattern.

First, NS pattern is characterized by means of a set of features extracted from the segmented IP signal (section IV.2.1). As largely reported in literature, IP is the main component of NS behavior and the analysis of its pattern through quantitative features may provide valuable developmental information. Then, a more complete characterization of the NS pattern is carried out extracting a set of features from both IP and EP signals: oral-motor behavior is analyzed as a dynamic pattern using quantitative methods for investigating coordination and its variability.

IV.2.1. IP Pattern

The following indices are estimated for each suck:

i. Peak Value (*PkV*), defined as the absolute value of the negative peak corresponding to a sucking event;

i. Period (*T*), defined as the interval between the peaks of each couple of consecutive events in a burst;

ii. Frequency (*F*), defined as the inverse of the period (1/T);

iii. Width (*W*), defined as the sucking event duration, i.e., the inter-trough interval;

iv. Effect (*E*), defined as the area below the sucking event waveform (see Fig. 39.a).

v. Number of Peaks (N_{pk}) besides the main sucking peak; we introduced this measure as indicative of the waveform regularity.

Then, the two different phases of each event, i.e., IS and DS, are considered, and separate features are extracted from each one (see Fig. 39.a):

vi. IS Width (*ISW*), defined as the time interval between the onset and the peak of the event;

vii. DS Width (*DSW*), defined as the time interval between the peak and the end of the event;

viii. IS Slope (*ISS*), calculated as the *PkV* divided by the *ISW*;

ix. DS Slope (*DSS*), calculated as the *PkV* divided by the *DSW*.

The *ISW* and *DSW* can be considered as indirect measures of the duration of musculature activation and relaxation; whereas the *ISS* and *DSS* as measures of activation and relaxation intensity.

By controlling the motor coordination of different oral structures (see Fig. 39.b), the infant modulates IP to optimize the flow of milk into the mouth first, and then to accumulate the expressed milk into the back of the mouth prior to swallowing [11]. For this reason, we also employed some indices typically used for the assessment of motor coordination and control, in order to enable improved sensitivity of developmental advance in analysis of the IP signal. If successful, these measures may improve sensitivity to neurological complication or neurodevelopmental health.

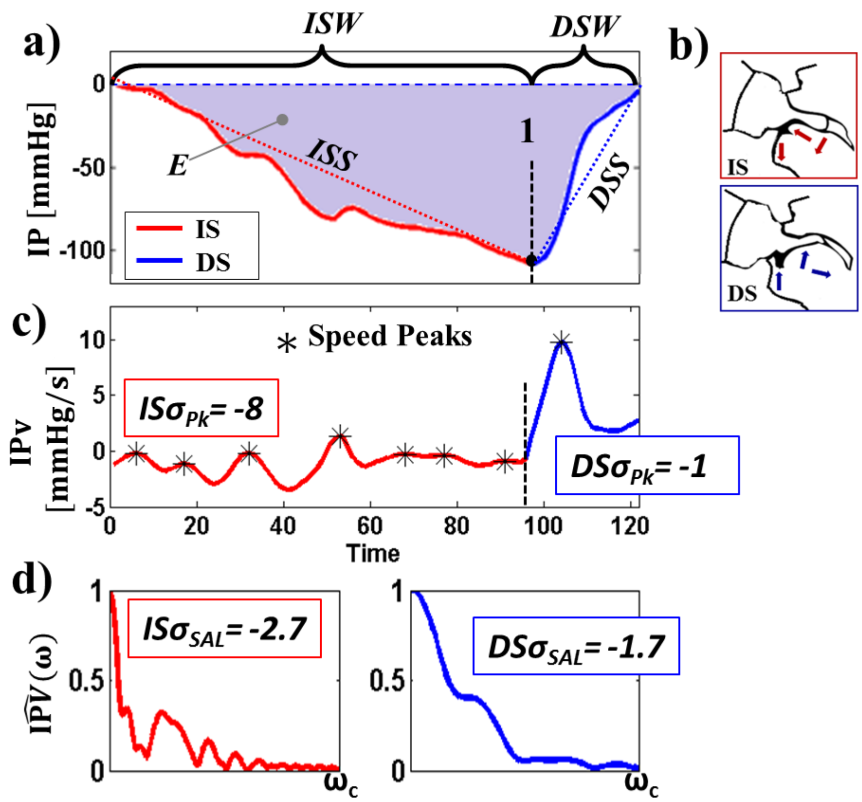


Fig. 39 Features of IS and DS phases. a) A sucking event is charaterized by the following features: Effect (*E*, grey area); IS Width (*ISW*) between the onset and peak (1); DS Width (*DSW*), between the peak (1) and the end of the event; IS and a DS Slope (*ISS* and *DSS*, red and blue dotted line). b) Movements during IS and DS phase: during IS, the tongue moves forward and down as the jaw is lowered; during DS, the tongue moves upwards and backwards as the jaw is raised. c) IP velocity profile (IPv) of IS (red) and DS (blue): DS is smoother than IS ($IS\sigma_{Pk}$=-8 vs. $DS\sigma_{Pk}$=-1). d) IP speed normalized spectrum ($\widehat{IPV}$) of IS and DS, and the respective values of spectral arc length (σ_{SAL}).

The velocity profile of the IP (*IPv*) during each suck is calculated, in order to extract some *smoothness* measures. Movement smoothness in fact is a measure of motor performance, often based on the speed profile, that reflects also the neonate's motor development [11]. Hence, considering the IP changes as results of the movement of oral structures (Fig. 39.b), the IP smoothness (σ) is calculated separately for IS and DS phase. There is not a standard quantitative measure for movement smoothness [93], so two different metrics have been implemented:

x. Peaks metric (σ_{Pk}): the number of local maxima in the speed profile (Fig. 39.c) [94], fewer peaks in speed represent fewer periods of acceleration and deceleration, making a smoother movement. In this study, the peaks metric is taken to be the negative of the number of peaks to relate decrease in the peaks metric to decrease in smoothness.

xi. Spectral arc length metric (σ_{SAL}): the arc length of the amplitude- and frequency-normalized Fourier magnitude spectrum of the speed profile (Fig. 39.d), as defined in [93]. It is taken negative as well, so that the higher its value, the higher the smoothness;

The σ_{Pk} is one of the most commonly used smoothness measures for motor control [94], while σ_{SAL} has recently been proposed as a valid and consistent measure sensitive to modifications in motor behavior and robust to measurement noise [93].

Burst Features and Sucking Instability

The features described above are calculated for each sucking event; these values are then averaged across each burst, in order to provide overall *burst features* representing a more global indicators characterizing each signal. In addition, the estimation of features of sucking *instability* has been implemented: for each burst, different measures of sucking *variability* and *inconsistency* are calculated providing different measures of instability in terms of amplitude, rhythmicity or smoothness.

The Coefficient Of Variation (COV, the standard deviation divided by the mean) of different features is calculated across each burst in order to measure sucking variability in terms of:

- amplitude: $COV_{PkV} = \frac{SD(PkV)}{mean(PkV)}$;
- duration: $COV_W = \frac{SD(W)}{mean(W)}$;

- frequency: $COV_F = \frac{SD(F)}{mean(F)}$;

- smoothness: $COV_\sigma = \frac{SD(\sigma)}{mean(\sigma)}$.

A sucking burst with relatively small measures of variability can be referred to as exhibiting a stable pattern. Besides, we also defined sucking *inconsistency* (*I*) as a measure of the suck-to-suck fluctuation in amplitude (strength inconsistency) and duration (rhythmic inconsistency) within a burst, that is calculated respectively as:

$$I_{Amp} = SD(\left|1 - \frac{PkV_{i+1}}{PkV_i}\right|),$$

$$I_W = SD(\left|1 - \frac{W_{i+1}}{W_i}\right|),$$

where *i*=[1,2,…,n-1], with *n* being the number of events within a burst. These measures can be also referred to as indices of *chaos* throughout a burst.

Considering the two phases of each suck, measures of inconsistency in terms of the activation/relaxation pattern, have been also introduced and implemented. We have defined these measures as the SD of the ratios between the IS and DS duration of each suck, as well as between the IS and DS slope, i.e.:

$$I_{PhDurat} = SD(\frac{DSW_i}{ISW_i}),$$

$$I_{PhSlope} = SD(\frac{DSS_i}{ISS_i}),$$

where *i*=[1,2,…,n].

IV.2.2. Measures of Coordination and Variability in Coordination

Over the past decades a dynamical systems approach to infant development has suggested new mathematical tools to analyze the emergency of coordination patterns during infancy. Oral-motor behavior during feeding can be considered as a complex dynamical system, and the NS cycle as the result of the coupling between oscillators involved in expression and oscillators involved in suction. Here, such approach is proposed, and quantitative measures derived from dynamical systems approach are employed to analyze the coordination of jaw oscillation (expression) and suction.

Since no single ideal technique exists for measuring coordination and variability in coordination, different methods have been implemented, so that the system is able to provide different coordination and variability features from simultaneous rhythmic signals.

Different techniques have been implemented to quantify the coordination between sucking components, including: Discrete Relative Phase (*DRP*), frequency coupling (*FC*), Continuous Relative Phase (*CRP*) and a vector coding technique (*VC*). Furthermore, given the central importance of the stability of coordination states in coordination dynamics, algorithms to measure variability in coordination (i.e., instability) have been implemented. Finally, a technique for detecting rhythmic co-occurrence in the frequency domain has been implemented, providing a quantitative measure of the strength of coordination across the frequency band of interest.

Discrete Relative Phase (DRP) and Variability (V_{DRP})

DRP is a measure of the latency of an expression event (E) with respect to suction (S). It is calculated between each discrete E and its coupled S (S_{coup}), which is defined as the S where E occurs. The algorithm takes the IP and EP signals, segmented as previously described, and identifies the occurrence of each E and S by taking the timing of the peak of each expression and suction cycle respectively.

For each E, its S_{coup} is identified as that S in which the peak of E falls and the DRP is calculated as follows:

$$\mathrm{DRP(E)} = \frac{\mathrm{t_{E/S}(E)}}{\mathrm{T_{Ph}}\left(S_{coup}\right)} \cdot 180°,$$

where $t_{E/S}$ is the time lag from the peak of S_{coup} to E, and T_{ph} is the duration of the phase (IS or DS) of the S_{coup} where E occurs. DRP so calculated can range from -180° to 180°, where:

- DRP=-180° implies that E occurs at the beginning of the IS of S_{coup},
- DRP=0° implies that E is in phase with S_{coup} (no phase shift or time lag),
- DRP=180° implies that E occurs at the end of the DS of S_{coup}

To illustrate this calculation of DRP, an experimental suction signal and discrete expression events resulting from segmentation are plotted in Fig. 40.

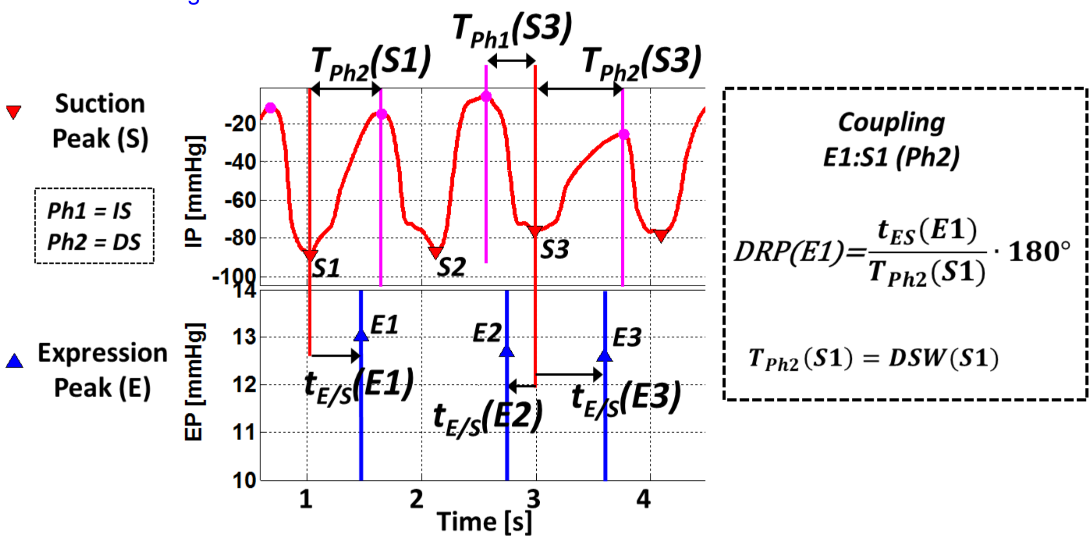


Fig. 40 Calculation of Discrete Relative Phase. An experimental segmented suction signal, with peaks (red triangles) and troughs (purple circles), is plotted on top; discrete expression events (E, blue triangles) are plotted below. T_{ph} is the duration of the phase (IS or DS) of the S where E occurs, and $t_{E/S}$ is the time lag (with sign) from the peak of S to E

The sign of the DRP is given by the phase of the S_{coup} where E occurs: if E occurs within the increasing phase (IS or Phase 1), $t_{E/S}$ is negative, while if it occurs within the decreasing phase (DS or Phase 2), $t_{E/S}$ is positive. We proposed this definition of DRP in order to have a measure of phase shift between E and S that is: i) indicative of the phase of the suction in which the E occurs, and ii) suitable for rhythmic events that are not pure sinusoids: the two phases of the suction cycle in fact can have different duration, and this definition has been formulated to take care of this aspect.

The variability of E/S coordination within a burst is so calculated as the angular deviation (AD, i.e., SD in circular statistics) of DRP:

$$V_{DRP}=AD(DRP).$$

Note that DRP is treated as a circular variable, since it is calculated in the range of [-180, 180°] and there is redundancy in the angles. Therefore, to avoid phase wrapping, the variability of DRP over several cycles, as well as the average, must be calculated using circular statistics.

Frequency Coupling (FC)

We defined the *FC* as the ratio of the number of E and the number of S that form a sequence of events that are coupled each other. The set of S and E that are coupled is identified as follows. Each E in the EP signal is considered coupled to a S in the IP signal (S_{coup}) identified as the one in which the peak of E falls. S_{coup} in turn can be coupled to any event in the EP signal that occurs within it, as well as to the event in the EP signal where S_{coup} occurs itself. To illustrate this calculation of FC, Fig. 40 reports three examples of FC between E and S cycles.

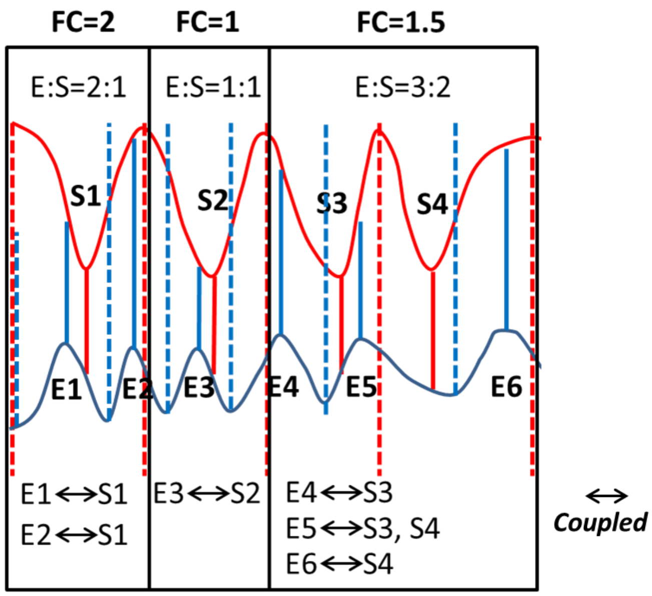


Fig. 41 Example of FC calculation between Suction (red) and Expression signal (blue). Peaks (full line), beginning and end (dotted line) of each event are marked in order to show the coupling between events. The values of the Frequency Coupling (FC) between E ans S are reported.

Hence, for each sucking burst a series of values of FC are identified. FC represents a categorical variable, as its values do not have quantitative content. However, within each burst, a dominant frequency coupling is identified and the percentage of occurrence of this dominant coupling (DC) is used as a measure of the strength of coupling.

Variability in coupling (V_{FC}) is calculated over each burst using the *coefficient of unalikeability* [132], which is a measure of categorical variability, defined as:

$$V_{FC} = 1 - \sum_i p_i^2,$$

where i stays for each value (or category) of FC, that is identified within a burst, and p_i is its percentage of occurrence. V_{FC} can range from 0 to 1: the more the value approaches the unit, the more the FC of that burst is variable.

Variability in E/S Coupling assessed by VC and CRP

CRP and VC are two of the most popular continuous techniques for quantifying variability in human multi-cyclic behaviors [96,97], as they enable the evaluation of coordination throughout the entire movement cycle. Both techniques involve the assessment of coordination by the quantification of phase plane trajectories, even though the phase planes constructed with the two techniques are fundamentally different.

The coordination between IP and EP is evaluated during each sucking cycle (defined by the IP pattern given by the previous segmentation); each cycle is interpolated to a fixed number of data points using a spline interpolation technique for both IP and EP data. The number of points for interpolation has been taken equal to the number of samples per second, as the typical duration of a suck is 1s.

Vector Coding (VC) is performed using the method described in [96] for quantification of coupling in multi-cyclic behaviors. Each sucking cycle is represented on a phase plane consisting of IP on the x-axis and EP on the y-axis. A similar approach to the analysis of sucking rhythm has been proposed in [40], where a qualitative assessment of sucking rhythm has been carried out. Here, we propose the application of quantitative measures to evaluate the stability of E/S coupling. In particular, coupling between IP and EP has been quantified by the coupling angle (θ_{VC}) between consecutive coordinates in the phase plane

$$\theta_{VC}(i) = \tan^{-1}\left[\frac{EP(i+1) - EP(i)}{IP(i+1) - IP(i)}\right], \qquad i = 1,2,\dots,99$$

where *i* indicates the sample within the interpolated time series.

Then the angular variability is calculated as defined in [96]: it is first estimated for each point-to-point interval over multiple cycles that are part of a burst, then the average of these values is calculated providing the overall variability (V_{VC}) of the S/E relationship in the burst. V_{VC} can range from 0 to 1, and it has been calculated so that the more the value approaches the zero, the more the coupling between E and S in that burst is stable.

Continuous relative phase (CRP) is performed using the method detailed in [97]. A phase plane is constructed, for each E and S cycle separately, with the pressure (IP or EP) on the x-axis and its derivative on the y-axis. Then, the phase ϕ is calculated as the angle between each coordinate in the phase plane and the phase plane origin:

$$\phi_s(i) = \tan^{-1}\left[\frac{s'(i)}{s(i)}\right], \qquad i = 1,2,\ldots,99$$

where *s* is the generic signal (which is actually either IP or EP). Hence, S/E coupling is quantified by the CRP which is the calculated as the difference between the phase angles of the two signals IP and EP :

$$CRP = |\phi_{IP} - \phi_{EP}|.$$

Before calculating CRP though, the *s* vs. *s'* phase plane are scaled to s_{norm} and s'_{norm}, according to the normalization proposed in [97]. Fig. 42 shows the steps for CRP calculation on a S/E cycle and over multiple cycles within a burst. Finally, the variability in E/S coupling is calculated for each point i over all the cycles of a burst, and then then the average of these values is calculated providing an overall measure of variability (V_{CRP}) of the S/E coordination within a burst.

Weighted Coherence (C_W)

Bidirectional weighted coherence (C_W) may be used to assess the strength of coupling between two rhythmic signals, in our case E and S. CW has been calculated over each sucking burst identified from the IP signal after segmentation, and the corresponding EP signal, according to the method defined in [98] and [74]. Since this technique provides a method for assessing rhythmic co-occurrence in the frequency domain, the cross-spectrum of IP and EP waveforms during each burst has been calculated, and then their coherence spectrum ρ_f. The coherence spectrum is a frequency domain function that quantifies the cross-spectral correlation of the two time series (IP and EP) across the range of component frequencies *f*. Let *x* and *y* be the two signals of interest, it is calculated as follows:

$$\rho_f = \frac{|S_{xy}|^2}{S_{xx} \cdot S_{yy}}$$

where S_{xx} and S_{yy} represent the power spectra of *x* and *y*, and S_{xy} their cross-spectrum.

In order to have a summary measure describing the proportional of variance shared between the two processes, a weighted average coherence [98] across the frequency band of interest is calculated for both signals, as follows

$$C_{w_x} = \frac{\sum_f {\rho_f}^2 \cdot S_{xx}}{\sum_f S_{xx}}, \qquad C_{w_y} = \frac{\sum_f {\rho_f}^2 \cdot S_{yy}}{\sum_f S_{yy}}.$$

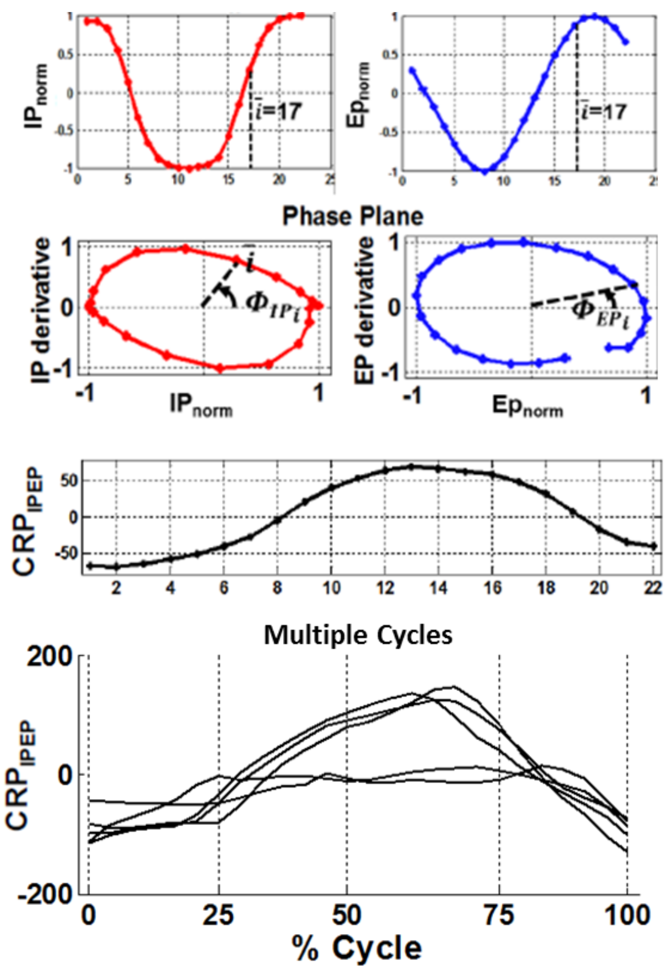


Fig. 42 Example of calculation of CRP between IP and EP during the time interval delimitated by a suction cycle. From top to bottom: i) normalized signals of IP and EP (between -1 and 1) during a S/E cycle; ii) Phase planes of IP and EP (signal derivative is normalized dividing by its absolute maximum value): phase ϕ for the i^{th} point of the cycle (i=17) if plotted; iii) CRP calculated for all the points of the S/E cycle is plotted; iv) CRP over multiple S/E cycles of a burst are plotted (all signals for this calculation have been interpolated to a fixed number of data points using a spline interpolation technique).

Fig. 43 illustrates the ρ_f and the weighted coherence between E and S during a burst of sucks, as calculated by the system on experimental data. Such weighted average is preferred to an unweighted mean coherence, as the spectral densities of the two time series (IP and EP) may not be equally distributed in their range of frequency. Then, in order to have a summary measure describing the proportional of variance shared between the two processes, a bidirectional weighted coherence is calculated as proposed in [74],

$$C_w = mean(C_{w_x}, C_{w_y}).$$

The range of frequency where the C_w is calculated has been set equal to 1-3 Hz in order to consider the range of likely dominant frequencies in NS signals.

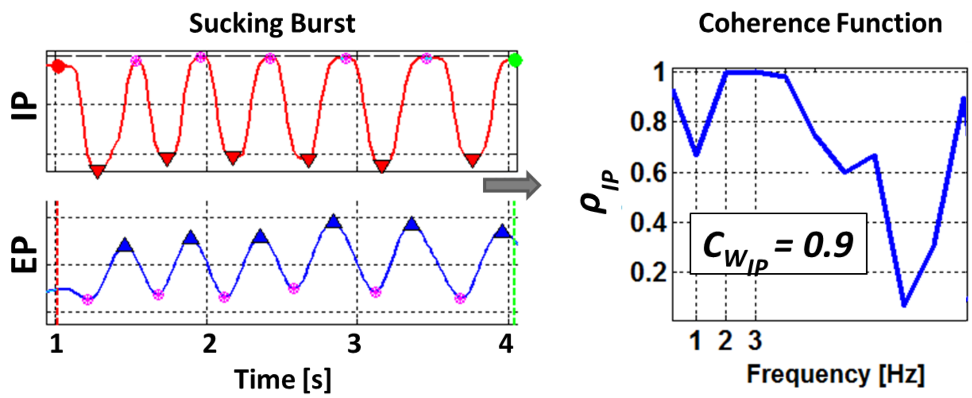


Fig. 43 Coherence Spectrum (right) between Suction (IP) and Expression (EP) during a burst of sucks (left).

IV.3. Data Analysis and Results

IV.3.1. Oral-Motor Behavior Development in Healthy Infants: IP Analysis

Part of the algorithms discussed in the previous section has been used to quantify the development of healthy term infants during the first weeks of life thanks to a collaboration with the University of Edinburgh. The aim of these preliminary trials was to identify the variables that better describe development of feeding ability in infants.

Measuring Apparatus

IP was measured using a pressure transducer (TranStar, Medex, UK/France/Italy/Germany), connected to a catheter primed with distilled water (40 cm in length, internal diameter of 1.0 mm, external diameter of 1.7 mm; Vygon, France). The catheter was inserted through the teat (Standard Teat, Cow & Gate, UK) of a feeding bottle so that it protruded about 2 mm from its tip into the middle of the infant's oral cavity. Data, sampled at 100 Hz, were captured to a laptop PC using proprietary software (Collect4, General Electric Healthcare, Finland).

Subjects

Four term-birth healthy infants (GA at birth: 37-40 weeks), labeled as *s1*, *s2*, *s3*, *s4*, have been analyzed. Infants were tested twice over time: shortly after birth, at 1-2 days postnatal age (PNA), and about 8 weeks later, at 46-48 weeks of GA.

Data Analysis

The previously described set of variables, characterizing the IP pattern of each detected sucking event, was estimated for each subject (sporadic sucks, not being part of a burst, have not been considered for the analysis). For each subject, a number of observations equal to the number of sucks in bursts of his/her feeding session was used for the analysis.

Subjects were tested twice in order to test the effect of the *Age* factor on each dependent variable. We will refer to the two age levels as *Age 1* (1-2 days PNA) and *Age 2* (8 weeks PNA). For each subject the trend across the ages has been analyzed comparing values of *Age 1* and *2* with an independent *t*-test. Moreover, a two-way random-effect ANOVA has been performed on each variable to determine whether the *Age* has an effect on the variable considering all the subjects, but taking into account the random variation of such effect from one subject to another (due to the inter-subject variability). To this aim, the *Subject* factor has been considered as a *random-effect* variable, as its levels are a small subset of the possible values that we want to generalize to. Random subject effects were used to account for the correlations between repeated measures from the same infant.

Finally, paired *t*-tests have been used to compare IS and DS within a suck at the two different levels of age, in order to investigate the differences between the two suction phases at the different ages. For all analysis, p-values <0.05 were considered significant. Mean values will be reported as mean (±standard deviation).

Results

A total number of 3304 sucks has been detected from the eight pressure traces (768 from the recordings at *Age 1*, and 2536 at *Age 2*). Each detected suck has been characterized by the previously described indices.

Results of the analysis revealed that several estimated indices significantly change as infants grow, as shown in Fig. 4. Results of random-effect ANOVA point out that PkV significantly increases (Fig. 44.a), from 79 (±42) to 115 (±53) mmHg (p=0.03), while ISW shortens from 0.9 (±0.4) to 0.7 (±0.3) s (p<0.001), with F consequently increasing (Fig. 44.b), from 1.2 (±0.3) to 1.8 (±0.6) Hz (p<0.001).

Moreover, considering the two different phases of suction (IS and DS), the IS slope significantly increases with age from 227 (±164) to 555 (±299) mmHg/s (p<0.001), contrary to DS where a significant effect was not observed in all subjects. This suggests that the musculature contraction becomes faster and more intense as the infant grows. An evolution in the contraction-relaxation pattern of suction musculature also emerged from paired t-tests comparing IS (activation) and DS (relaxation) of each suck, separately for age (see Fig. 45): at *Age 1* the contraction phase is longer and less intense (IS slope is significantly lower than DS slope, p<0.001); while at *Age 2*, the trend is inverted as the contraction becomes faster, and thus more intense (IS slope higher than DS slope, p<0.001). Since skeletal muscle undergoes profound changes in morphological, physiological, and biochemical character when subjected to prolonged periods of increased use [99], these results may be an indirect indication of these modifications and may account for the increase in the power infants are able to generate.

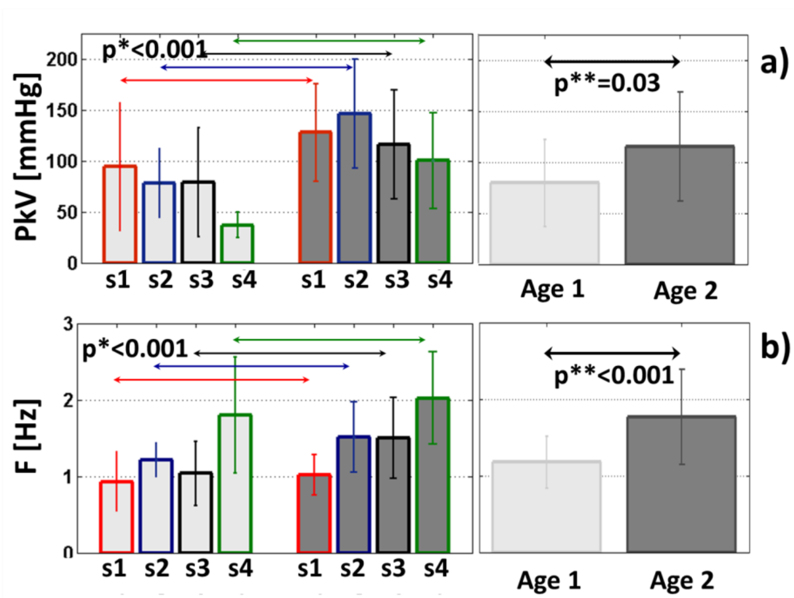


Fig. 44 Statistical results on different sucking indices (*independent t-test; ** random-effect ANOVA). As the age increases we observed: a) a significant increase in Peak value (PkV); b) a significant increase in sucking Frequency (F); c) a significant increase in the smoothness (σ_{Pk}) of the increasing suction phase; d) an inversion in the activation/ralaxation (IS/DS) pattern, with the IS slope becoming higher than DS.

The analysis of pressure speed profiles showed that the smoothness of the entire sucks does not significantly change with age, while significant changes were observed in the smoothness of the only IS phase across the age: the average σ_{Pk} of IS significantly increases from -2 to -0.7 (p=0.04), contrary to DS where no significant changes were observed (Fig. 46.top). The smoothness of IS phase resulted to increase also if measured through σ_{SAL} in all subjects separately; however, this trend did not achieve statistical significance, when considering the whole sample (p=0.08), maybe because of the inter-subject variability of the age effect on this measure (Fig. 46.bottom).

The different smoothness evolution of the two suction phases also emerged from the paired t-test of IS and DS at different ages: σ_{SAL} of IS and DS do not differ at *Age 1*, whereas, at *Age 2*, the IS phase becomes significantly smoother than DS phase (p<0.001). The increase of the IS smoothness with age suggests that the control of the oral movements needed to draw the milk into the mouth, matures during the first months of life.

All the other indices, whose results have not been reported, did not show any statistically significant change from the analysis. However, further investigation is suggested with a greater sample and/or considering other independent factors (e.g. weight).

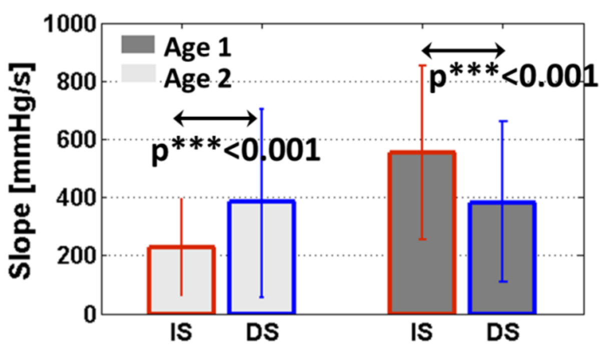


Fig. 45 Statistical results on the analysis of IS and DS phases (***paired *t*-test). As the age increases we observe an inversion in the activation/ralaxation (IS/DS) pattern, with the IS slope becoming higher than DS.

Discussion

The analysis of a set of automatically estimated indices of IP pattern pointed out some typical aspects of the evolution of feeding behavior as infants grow. These preliminary findings we obtained may represent a first step to evaluate the validity of the proposed system for a quantitative analysis of the IP pattern over the first weeks of life: values and trends of sucking amplitude and frequency, in fact, are coherent with those reported in earlier studies on the evolution of feeding behavior of term infants over the first months of life [37,40].

Moreover, the analysis of increasing and decreasing suction phases seems to provide an important source of information about infants' motor skills. The activation of suction musculature (IS phase) seems to become shorter, smoother and more intense as infants grow, suggesting that the control of increasing negative pressure during IS is refined by infants during the first period of life. The application of smoothness measures to IP signals, as proposed in this study, showed promising results as they seem to characterize a developmental trend over time. This fosters further investigation to verify if such analysis of sucking pressures, intended as a measure of movement, may provide a novel and direct means of monitoring infants' motor control at an early stage of development.

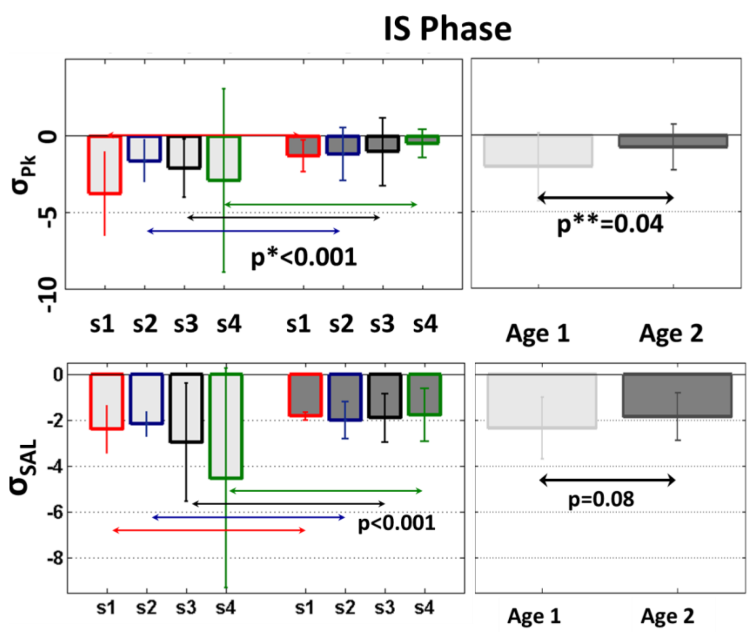


Fig. 46 Statistical results on the smoothness of IS phase (*independent t-test; ** random-effect ANOVA). As the age increases we observed a significant increase in both σ_{Pk} and σ_{SAL} of the increasing suction phase.

IV.3.2. Healthy versus At Risk Oral-Motor Behavior: S/E Analysis

All the measures described in IV.2 have been used to quantify the differences between healthy and LBW infants in the first days after birth. Data were collected in the neonatal care unit of Santa Maria Goretti Hospital in Latina, during the daily clinical routine, with the device for the measurement of IP and EP, that was developed during this work. The aim of this study was to identify the features that seem to be the most sensitive to discriminate typical versus immature behavior. Promising results might represent a first step to test the whole technology-assisted system for assessment here proposed, made by both the hardware and software component.

Data Collection

IP and EP were measured using the *IP/EP Monitoring Device* presented in II.3.3 and shown in Fig. 29. Data were sampled at 200 Hz, and acquired by a laptop PC via an application developed in MATLAB, which is also used for real-time visualization.

Data have been collected from 9 newborns (PNA: 2-6 days): four *at-Risk* subjects (*R* group) including preterm and/or LBW newborns (BW≤2500g), and five Healthy subjects (*H* group), including newborns with GA>36 weeks and birth weight>2800g (*H* group). Further, data from one *R* subject (GA at birth: 33.3; BW: 2160g) have been collected also one week after the first test.

Data Analysis

IP and EP data have been processed and segmented by means of the algorithms previously described. For each subject, only the events being part of the first burst have been considered for the analysis, in order to standardize the analysis across the two groups of subjects: the feeding of some LBW babies in fact was short, compared to the healthy group, and made of just one burst of sucking.

Sucking pattern in the first burst of the IP signal has been assessed according to the features defined in section IV.2.1 for each sucking event. In order to identify the most sensitive features in discriminating infants' maturational level, independent *t*-tests have been performed on each variable considering *group* as independent factor. The set of features that revealed as being the most sensitive to the *group* factor, has been selected and the corresponding *burst features* have been explored, in order to identify the ones still sensitive to group differences. Hence, exploratory data analysis and non-parametric tests (Wilcoxon rank sum test: robust non-parametric analogue of the two-sample *t*-test) have been carried out on these *burst features* and on the *instability features*, which include *variability* (COV) and *inconsistency* (*I*) per burst, described in IV.2.1. Finally, *burst* and *instability features* have been used to define a new metric useful to objectively classify infants with respect to their autonomous feeding readiness. In particular, a Principal Component Analysis (PCA) has been performed in order to investigate the possibility to define behavioral cluster from the analysis of the IP pattern, and to investigate the coherence of these clusters with the belonging group.

The joint analysis of IP and EP has been performed to investigate the S/E coordination. In particular, the analysis of coordination variability (V) per burst, described in IV.2.2 has been carried out and, similarly to what done for IP analysis, an exploratory data analysis and non-parametric tests have been performed on each variable to investigate when the *group* factor shows to have an effect on the dependent variable. In case of circular variable, proper test for inferential statistics with angular data have been used. Also in this case a PCA has been performed to define any cluster of behavior in terms of coordination, and to investigate the coherence of these clusters with the belonging group.

A final PCA has been performed on all the variables that have been identified as the most sensitive features to *group* effect from the analysis of IP pattern, IP stability, and S/E coordination. We looked at the Hotelling's T^2 (a measure of the multivariate distance of each observation from the center of the data set) in order to identify the most extreme points in the data. We explored in this way, the system suitability to automatically identify specific behaviors and their deviation from the norm.

All the values reported refer to the mean or median, depending on the use of parametric or non-parametric tests respectively for the analysis.

Results

IP Pattern

From the segmentation of the IP signals, a total number of 293 sucks has been detected from the *H* group and 148 for the *R* group, with a mean number of sucks per burst of 59 and 37 respectively.

For the analysis of the IP pattern, each detected event in the IP signal has been characterized by the previously described features. The results of the independent *t*-tests showed that *PkV* is significantly higher in *H* than in *R* group (80 vs. 61 mmHg, $p<0.001$), while *F* is significantly higher in *R* than in *H* infants (1.3 vs. 1.1 Hz, $p<0.01$, Fig. 47a). The increase in sucking strength, i.e. in sucking amplitude (*PkV*), from the *at-risk* to the *healthy* condition is coherent, in trend as well in values, with the results obtained from the typical development of healthy infants: as the infant matures, both in terms of PNA and in terms of transition from *R* to *H* condition, his/her sucking strength increases. On the contrary the change in sucking frequency is opposite to the developmental trend reported in healthy infants; however, higher values of sucking frequency in high-risk than in healthy infants are coherent with results from literature [73]. Further longitudinal data on high-risk infants are needed in order to investigate this trend, as our preliminary findings may suggest the occurrence of an inversion of trend as the infant passes from an immature to mature pattern.

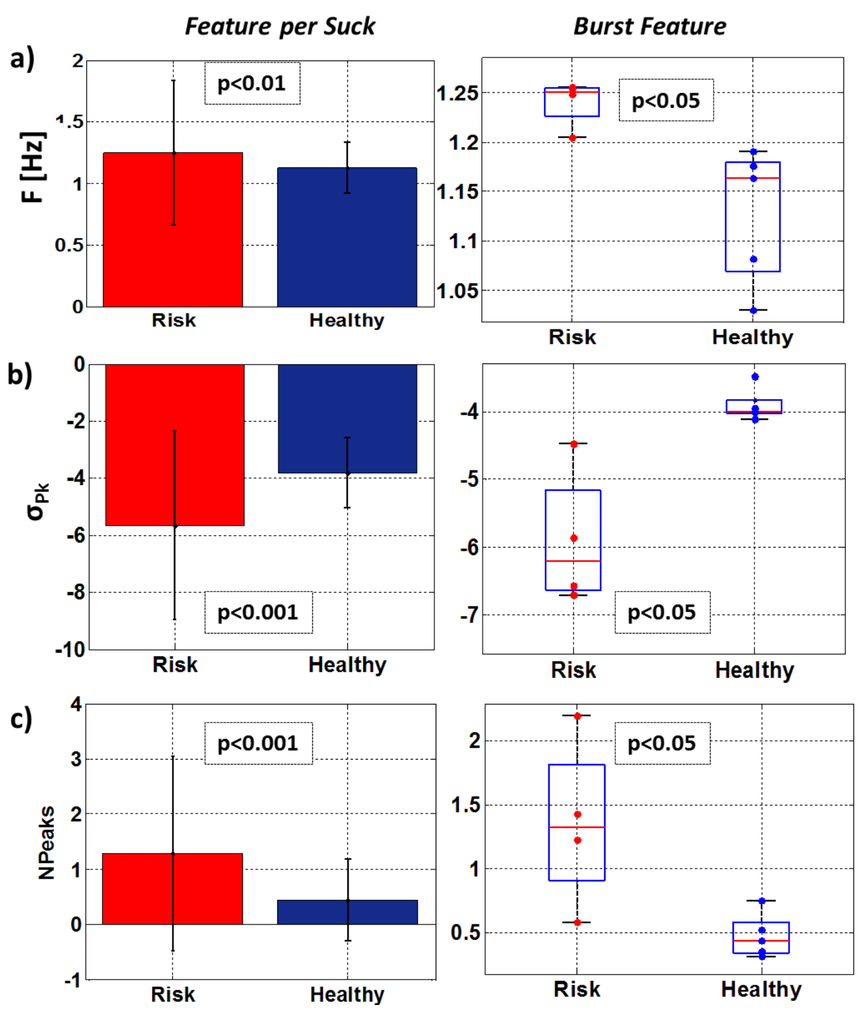


Fig. 47 Statistical results on some of the IP features. Comparaisons between at-Risk (R, red) and Healthy (H, blue) infants showed significant difference in terms of: a) sucking Frequency (F); b) smoothness (σ_{Pk}); c) number of peaks (N_{Pk}). Significant differences were observed analyzing the values of all the sucks (left column), as well as analyzing burst values (right column).

Independent *t*-test also showed that smoothness σ is higher in *H* than in *R* infants (σ_{Pk}: -3.8 vs. -5.6, Fig. 47b; σ_{SAL}: -2.4 vs. -2.8), and also that the N_{pk} is significantly lower in *H* compared to *R* infants (0.4 vs. 1.3, Fig. 47c). The higher number of the multiple peaks during a sucking events indicates a less regular profile of the pressure waveform in the *R* infants. This is even more confirmed by the analysis of the velocity profile: the lower σ, characterizing the sucking events of the at-risk subjects if compared to the healthy ones, suggests that sucking control of these infants needs to develop to reach typical levels. These results are also coherent with the ones obtained from the typical development of healthy infants: they both suggest the suitability of this measure of motor performance to discriminate different maturational pattern of sucking behavior.

Moreover, the results obtained from the features of the two different phases of the suction cycle (IS and DS) suggest the importance of the analysis of the IS for the evaluation of the sucking pattern development, since:

- IS showed significant differences between *H* and *R* both in terms of duration (*Width*, Fig. 48a) and smoothness (σ_{SAL}, Fig. 48b), contrary to DS;
- Sucking events in *H* infants are characterized by an IS significantly faster than DS, while in *R* infants the IS phase is as long as the DS (Fig. 48a).
- *H* infants generate an IS as smooth as DS, contrary to *R* infants who show an IS which is significantly less smooth than DS (Fig. 48b).

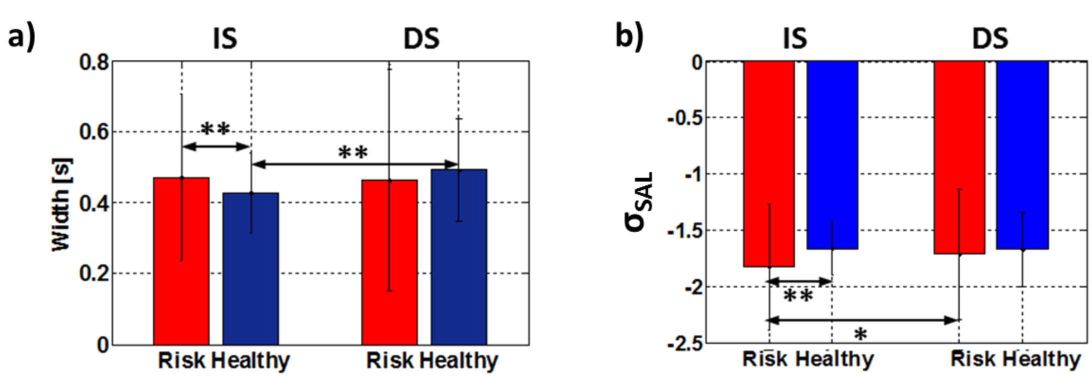


Fig. 48 Statistical results from the analysis of IS and DS phase in terms of: a) duration (Width) and b) smoothness σ_{SAL} (**p<0.001, *p<0.05; independent *t*-test).

These results suggest a maturational trend of the sucking pattern characterized by the development of a better control of the IS phase, i.e. faster and smoother contraction.

Non-parametric tests on the *burst features* indicated those features that still show significant differences between groups (Wilcoxon rank-sum test, $p<0.05$): *burst* values of frequency (F), smoothness (σ_{Pk}), and number of peaks (N_{pk}) show significant differences between the two groups (see Fig. 47). Furthermore, the analysis of sucking *instability* shows significant differences between *H* and *R* infants. As shown in Fig. 49, amplitude and smoothness variability within a burst resulted significantly higher in *R* than in *H* subjects (COV_{Pk}: 0.47 vs. 0.22; $COV\sigma_{Pk}$: 0.46 vs. 0.32; $COV\sigma_{SAL}$: 0.3 vs. 0.16), as well as the rhythmic inconsistency (I_w: 0.11 vs. 0.37) and the inconsistency in the DS/IS ratio in terms slope ($I_{PhSlope}$: 0.27 vs. 0.49). These results suggest a less rhythmic and stable IP pattern, within a sucking burst, in infants at-risk compared to the healthy ones, both in sucking amplitude and duration. Besides, the less stable DS/IS pattern in the *R* group, confirms the importance of these two sucking phases in the assessment of the developmental trend.

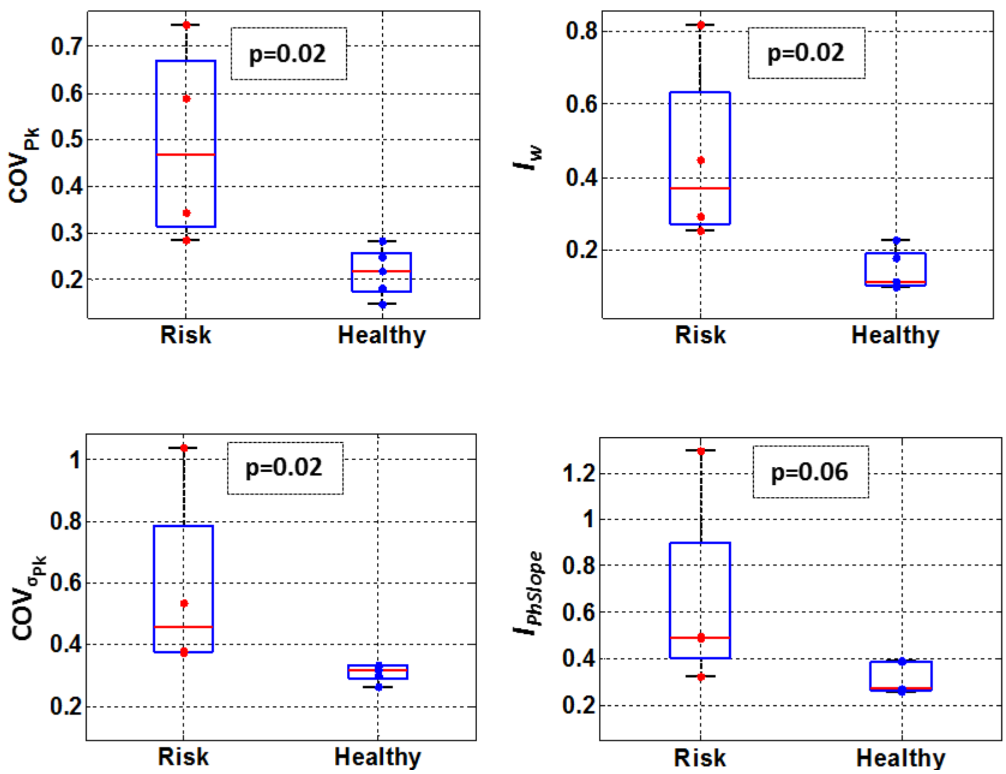


Fig. 49 Statistical results from the analysis of sucking *stability* by means of different features per burst, i.e.: amplitude and smoothness variability (COV_{Pk} and $COV\sigma_{Pk}$); rhythmic inconsistency (I_w) and inconcistency in the DS/IS ratio in terms slope ($I_{PhSlope}$)

The *burst* and *instability* features that revealed as being the most sensitive to the *group* factor have been used to perform a PCA to explore the presence of any peculiar behavior or cluster that can be identified through this set of features. According to the results obtained, we used the following set of eight IP features per each subject:

- three *burst* features: N_{pk}, σ_{Pk}, F;
- three *burst variability* features: COV_{PkV}, $COV\sigma_{Pk}$, $COV\sigma_{SAL}$;
- two *burst inconsistency* features: I_W, $I_{PhSlope}$.

Fig. 50 illustrates the results of the analysis on a biplot. Two principal components (PCs) are sufficient to explain the 90% of the data variance. Observing the distribution of the *H* and *R* subjects, we can note that the *H* subjects are grouped in the same area, that is well defined by the direction of the 1st PC and characterized by high smoothness and low number of peaks (here N_{Pk} has been considered negative, so that its increase meant higher regularity). In addition, two subjects in the *R* group (labeled as *R1* and *R2*) seem to show a peculiar behavior characterized by high values in both the 1st and 2nd PC. In particular the two subjects are shifted toward the direction of high values of the instability original variables (as we can observe from the loadings on Fig. 50), suggesting those subjects present an IP pattern clearly different from the others in the direction of high sucking instability.

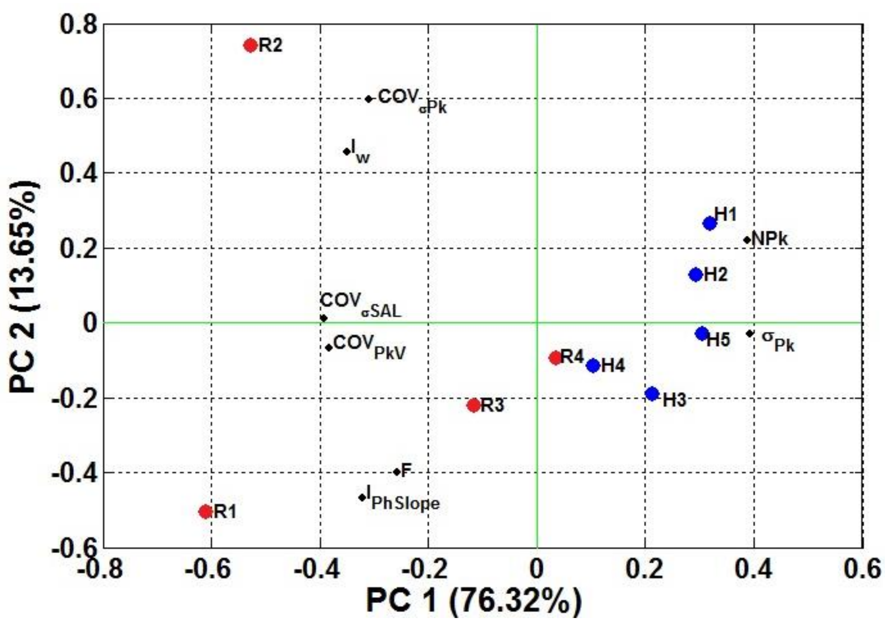


Fig. 50 Biplot from the Principal Component Analysis on *burst* and *instability* features. Blue circle markers represents the 5 healthy (*H*) subjects, while red circle markers the 4 at-Risk (*R*) subjects. Black dots indicate the direction of the original variables.

S/E Coordination

S/E coordination has been analyzed using the set of features extracted from both IP and EP signals, as described in IV.2.2. The analysis of *DRP* of each E with respect to coupled S showed that the phase shift between E and S is significantly higher in *R* than in *H* subjects, as illustrated in Fig. 51.

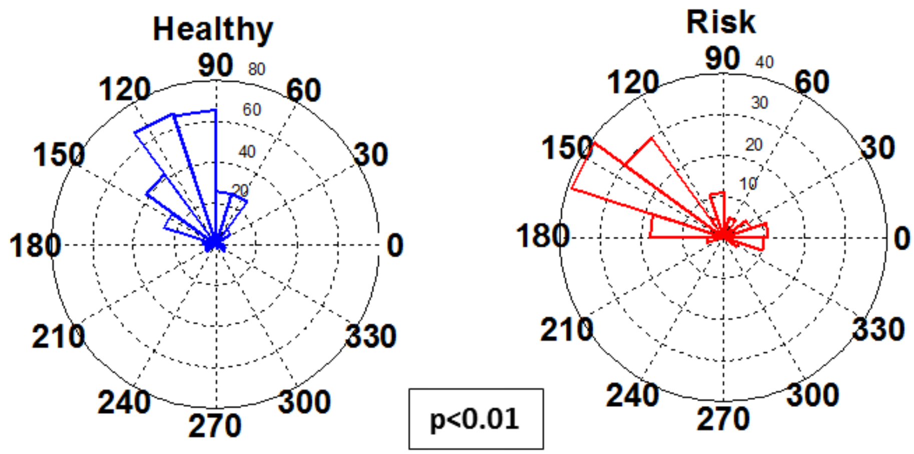


Fig. 51 Discrete Relative Phase (DRP) between Expression (E) and Suction (S) events in healthy and at-risk subjects. Values per each E are plotted on an angular histogram: R group show a significantly higher DRP than H group (p<0.01).

Among the features of c*oordination variability* (*V*) per burst (see Fig. 52), V_{VC} showed a good sensitivity in discriminating *H* vs *R* group (p=0.06). The other features seemed not to show sensitivity to the *group* factor, however given the small number of observations per group, an exploratory analysis of data has been also carried out: looking at the distribution of C_W, V_{FC}, and V_{CRP}, as shown in Fig. 52, we can observe that the range of values of H and R subjects actually overlaps in all the cases just because of one subject (label as *R3*), whereas the rest of the *H* and *R* values define two clearly distinct ranges. This suggests the possible sensitivity of these features to the *group* factor that we further explored through a PCA. Five features of S/E coordination (V_{VC}, *DRP*, C_W, V_{FC}, and V_{CRP}) have been used as set of input variables, and 2 PCs have been used for the analysis (83% of the variance deployed). Observing the distribution of the *H* and *R* subjects, shown in Fig. 53, we can note that the *H* subjects seem to define a cluster area, contrary to the *R* subjects that are pretty scattered. We can also note that the subject labeled as *R3*, that has been previously observed as showing some values of coordination variability in the same range of the healthy group, is actually close to the *H* group in terms of the 1st PC; however it is pretty far from the *H* area because of the high contribution of the 2nd PC.

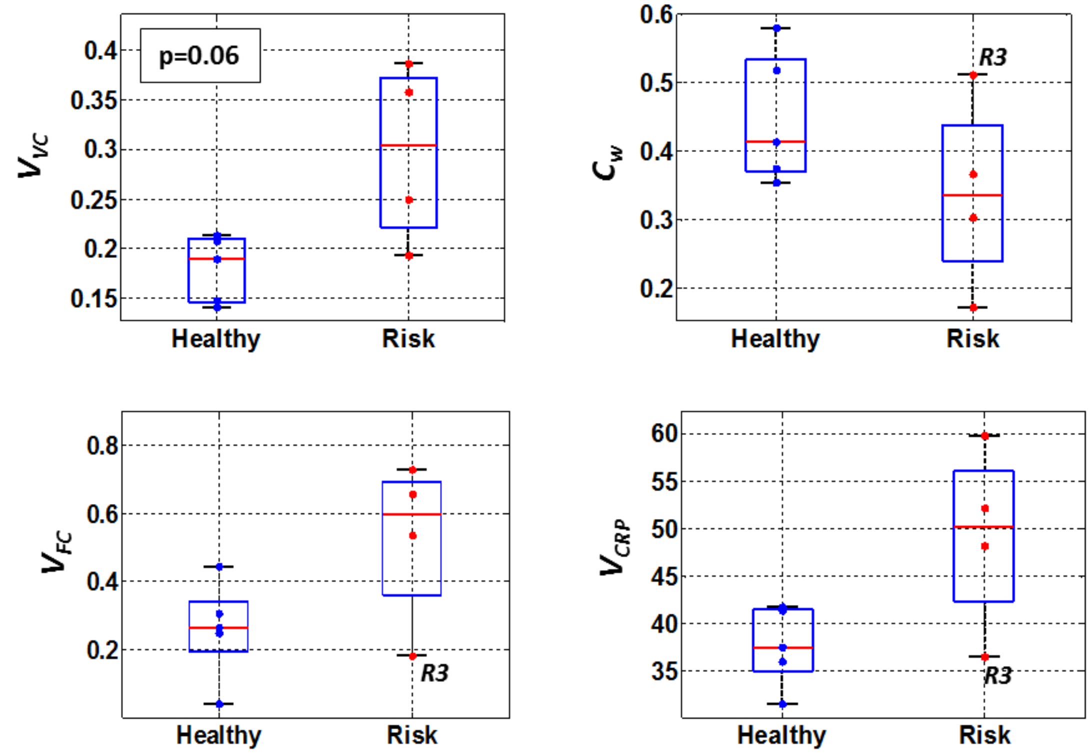


Fig. 52 Results on features of variability in the E/S coordination within a sucking burst. V_{VC} shows a good sensitivity in discriminating *H* vs *R* group (p=0.06). Further, looking at the boxplot of the other features analyzed (C_W, V_{FC}, V_{CRP}), we can observe that the range of values of H and R subjects overlaps in all the cases because of one subject label as R3.

Finally, a PCA has been performed merging the set of eight features from the IP pattern and the five measures of S/E coordination. As Fig. 54 shows, the *H* subjects define a clear cluster, contrary to the *R* subjects that are much more scattered and distant from the area identified by the *H* group. We also looked at the Hotelling's T^2 (a measure of the multivariate distance of each observation from the center of the data set) in order to quantify the distance between points or clusters of points, as well as to identify the most extreme data. As Fig. 55 shows, T^2 values of *R* subjects are all markedly higher than the ones of *H* subjects, as well as higher than the mean T^2 calculated within the *H* group ($\bar{T}_H^2$=0.6).

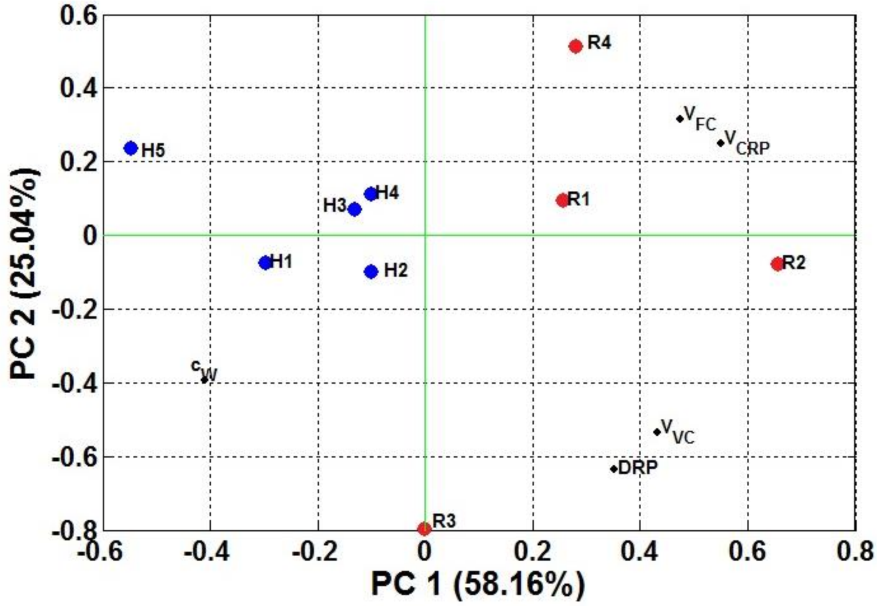


Fig. 53 Principal Component Analysis: biplot obtained from S/E coordination features. Blue circle markers represents the 5 healthy (H) subjects, while red circle markers the 4 at-Risk (R) subjects. Black dots indicate the direction of the original variables.

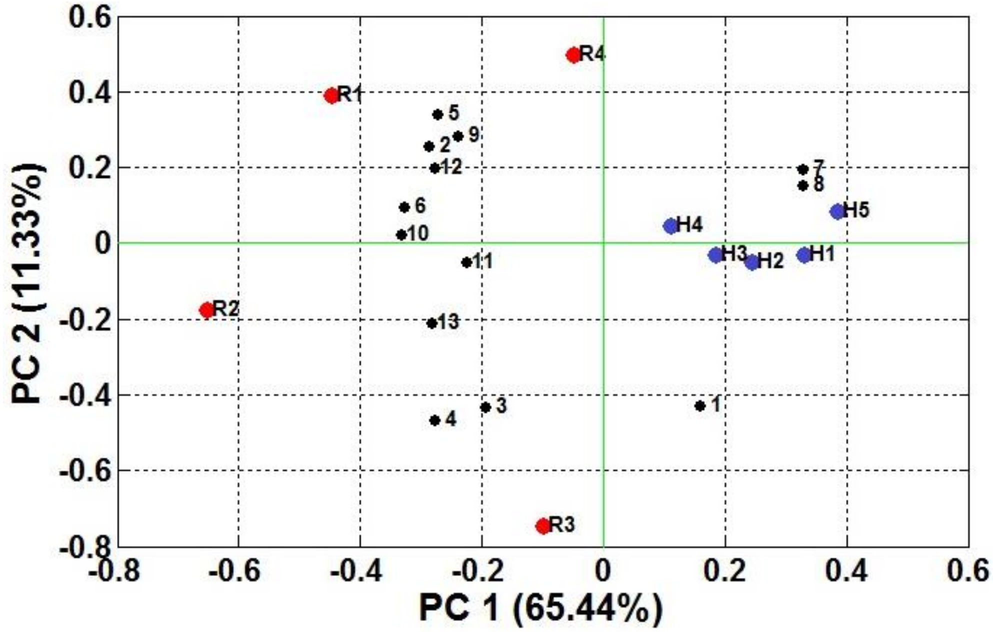


Fig. 54 Biplot from the PCA performed on IP and S/E coordination features. Blue circle markers represents healthy (H) subjects, while red circle markers at-Risk (R) subjects. Black dots indicate the direction of the original variables: 1.$C_{W;}$ 2.V_{CRP}; 3.DRP; 4.V_{VC}; 5.V_{FC}; 6.COV_{Pk}; 7.NPk; 8.σ_{Pk}; 9.$COV\sigma_{Pk}$, 10.$COV\sigma_{SAL}$; 11.F; 12.I_W; 13.$I_{PhSlope}$

These results suggest the system suitability to automatically identify atypical behaviors and their deviation from the norm, starting from a set of different features extracted from both sucking signals. It is interesting to notice how the integration of the features of both IP pattern and S/E coordination revealed to be valuable. Looking only at the IP pattern in fact, we had been able to identify a deviated behavior in two *R* subjects, i.e. *R1* and *R2*, (see Fig. 50); however analyzing S/E coordination features (Fig. 53), also *R3* and *R4* showed to differ from the healthy subjects, as also confirmed once integrated all the features together (Fig. 54), suggesting these two subjects present an abnormal pattern in the S/E coordination, although the IP pattern seemed to be close to the one of the healthy group. Further, we can observe as the peculiar behavior of the subjects *R1* and *R2* is always detectable, suggesting they present a more immature oral-motor pattern, both in terms of sucking stability and control (IP features) and motor coordination (S/E coordination features).

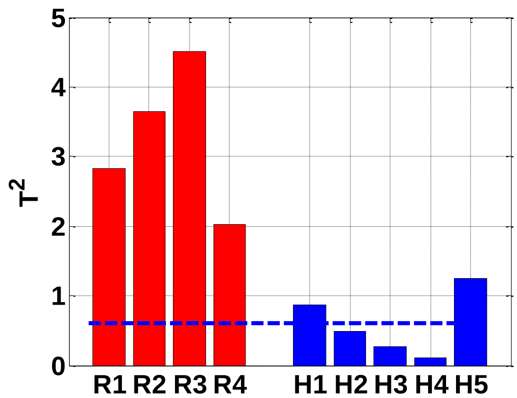


Fig. 55 Hotelling's T^2 for *H* (blue) and *R* (red) subjects, corresponding to the PCA showed in Fig. 54. The mean value of the T^2 calculated within the H group has been taken as reference value ($\overline{T}_H^2$=0.6, blued dotted line).

Furthermore, one the *R* subjects (*R1*) has been also tested one week after the first test. The results from this second test have been reported on the same space of PCs identified before. Results are shown in Fig. 56. From the analysis of IP pattern, we can observe as the subject approaches to the cluster of the *H* group on the second test. However, when including coordination features to the model, we can observe that the subject moves toward the *H* group along the 1st PC, but it is still far from the *H* cluster. This suggests that the infant, compared to his/her first test, has developed a better sucking competence, in terms of control and stability of the S component, but it has not acquired yet typical coordination competences between S and E.

Discussion

The analysis of the oral-motor pattern, by means of the features extracted from both IP and EP, pointed out some aspects that seem to characterize different maturational levels of feeding behavior. The findings here reported seem to be very promising: a subset of the most sensitive features to maturity level has been identified, and a set of preliminary tests has revealed their potential suitability to discriminate different oro-motor behavior.

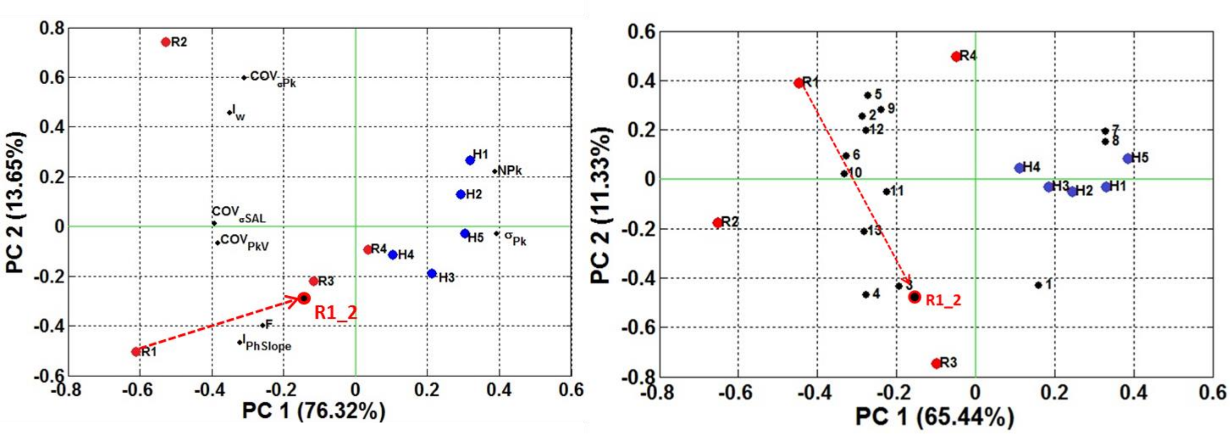


Fig. 56 Biplot from the PCA performed on IP (left) and IP plus S/E coordination features (right). The results from a subject who has been tested twice over time (R1 and R1_2), are highlited (red arrow).

In particular, PCA has been used to test the possibility of identifying peculiar behaviors, reducing the set of multiple features to a bi-dimensional space, where the behavior of each subject can be more easily represented. These results seem to suggest also that the coordination of the oral-motor components during feeding may be assessed using the general principles of coordination dynamics observed for other coupled oscillating behaviors: the promising findings, obtained also from the application of coordination features from a dynamical perspective, suggest that it may be actually useful to incorporate such measures into standardized assessment of early oral-motor function.

This study represents a first step to evaluate the suitability of the proposed system to perform an objective technology-aided assessment of the oral-motor behavior of the newborn during the first days of life: further investigation on a larger longitudinal dataset of both high-risk and typical infants is needed, in order to define normative data and support these preliminary promising results with a stronger statistical significance.

V. CONCLUSIONS AND FUTURE WORKS

The goal of this thesis work was to provide new tools and methods for a technology-aided assessment of newborns' oral-motor behavior during feeding. Indeed, with the increase of survival rate of infants at risk for neurological disorders (premature and LBW), medical and research communities are calling for new and more reliable tools for the assessment of the newborn's neuromotor status, for the objective evaluation of readiness to discharge, and for planning of subsequent care at home. The objective assessment of oral-motor activity may address these issues providing one the earliest non-invasive way to evaluate the infant's neuromotor status, and may allow the early identification of abnormal motor behaviors.

Over the last decades significant advances occurred in the technology-assisted monitoring of feeding disorders in newborns, however there are no accepted standards for their implementation in clinical practice. First of all, a careful and critical analysis of the main advantages and weaknesses of the sensing systems, reported in literature, has been produced during this work. This review work was carried out considering the application to both clinical practice and domestic use, and it allowed identifying the main functional specifications necessary for the assessment of feeding behavior. These specifications drove the design of a modular platform for NS monitoring that was suitable for a wide and regular application in an unstructured setting. The design has been driven by the principal intent of providing a system that was easily usable on every typical feeding bottle, thanks to its easiness of use and low cost, which would also foster an easy and wide implementation in different settings.

A device for monitoring sucking behavior in terms of suction and expression has been developed exploiting two pressure measurement methods that emerged from the SoA analysis as being the most appropriate for the pursued goal. A proper validation procedure of the system has been carried out, and the results confirmed the suitability of the sensing system to the measurement in the specific range of application. As far as we know from literature, this represents the first systematic laboratory validation of these methods. Further, the solution for EP measurement has been implemented in order to improve the method reported in literature and overcome some of its limitations. Finally, the suction/expression monitoring system has been tested in the clinical setting: data collection has been carried out on nine newborns just after birth in a neonatal care unit, where it has been used by the clinical staff during the routine clinical practice.

A software system to systematically treat and analyze sucking data has been developed. This software provides quantitative and reliable measures for a proper analysis of oral-motor function removing the subjectivity issue from the assessment procedure.

A literature-driven definition for the signal segmentation process has been developed and a completely automatic segmentation algorithm has been implemented: this represents a novel fundamental contribution in the development of a standardized analysis tool for the analysis of oral-motor behavior. Indeed, the systematical review of literature highlighted the use of several heterogeneous methods, not always clearly defined, which can cause incoherent or not-comparable findings. The results reported in this thesis from the use of the segmentation algorithm have been promising, and future work will be focused on its validation.

After segmentation, the software for the analysis extracts a large set of features from the segmented signals. The features extraction has been first of all driven by literature: algorithms to extract the most important sucking features emerging from the SoA have been implemented. Furthermore, this work introduced and explored the use of some quantitative measures derived from the analysis of motor control and dynamic coordination. Promising results have been obtained from the application of this new set of features on experimental data, suggesting the inclusion of such measures in the objective technology-aided assessment of early oral-motor function. Two different sets of experimental data have been used to test the algorithms: i) data collected with the sucking monitoring module, developed during this work, on four preterm and/or LBW and five healthy newborns; ii) longitudinal IP data from four healthy term infants collected by means of third party apparatus and acquired thanks to a collaboration with the University of Edinburgh. Data analysis allowed to suggest a set of the most relevant features for the patient's assessment, usable for intra-subject and inter-subject comparisons. The promising results demonstrated how the software system proposed in this thesis might allow evaluating the patient's maturational course, and the patient's displacement from normative behaviors, removing the subjective element from any assessment. Further work is now focused on collecting a larger longitudinal set of data from both healthy term and high-risk infants, in order to confirm these findings and define normative data.

Besides the development of a device for monitoring sucking behavior in terms of IP and EP, this thesis also presented two novel methods for the ecological estimation of nutrient consumption during bottle-feeding. Two low-cost sensor-based modules have been developed and experimentally validated in laboratory. Future work will aim at their integration on the IP/EP monitoring device and at testing the methodology on field.

Finally, given the importance of oral-respiratory coordination during NS, another objective of this work was to design a sensing non-invasive solution that is easily embeddable on a common bottle for feeding, and that can be used to assess the temporal breathing pattern. A novel low-cost non-invasive device for recording newborns' respiratory events has been designed and developed in order to be embedded on a common feeding bottle. The results from its laboratory experimental validation foster the successful application of this device to the assessment of the breathing temporal pattern of newborns during bottle feeding with a non-invasive approach. However, further work is needed to test and validate the system on newborns.

In conclusion this thesis presented the design and development of a technology-aided system for the assessment of newborns' oral-motor behavior, as well as the results obtained from testing it on newborns in a clinical setting. Moreover, the integration of breathing and nutrient consumption monitoring has been explored, presenting some low-cost sensor-based solutions designed for an easy integration on a feeding bottle.

References

1. March of Dimes, PMNCH, Save the Children, WHO. *Born Too Soon: The Global Action Report on Preterm Birth*; Howson, C.P., Kinney, M.V., Lawn, J.E., Eds.; World Health Organization: Geneva, Switzerland, 2012.

2. American Academy of Pediatrics. Hospital discharge of the high-risk neonate. *Pediatrics* 2008, *122*, 1119–1126.

3. Mcgrath, J.M.; Braescu, A.V.B. State of the science: Feeding readiness in the preterm infant. *J. Perinat. Neonatal Nurs.* 2004, *18*, 353–368.

4. Dodrill, P. Feeding difficulties in preterm infants. *ICAN: Infant Child Adolesc. Nutr.* 2011, *3*, 324–331.

5. Crowe, L.; Chang, A.; Wallace, K. Instruments for assessing readiness to commence suck feeds in preterm infants: Effects on time to establish full oral feeding and duration of hospitalisation. *Cochrane Database Syst. Rev.* 2012, doi:10.1002/14651858.CD005586.pub2.

6. Reilly, S.; Skuse, D.; Poblete, X. Prevalence of feeding problems and oral motor dysfunction in children with cerebral palsy: A community survey. *J. Pediatr.* 1996, *129*, 877–882.

7. McBride, M.C.; Danner, S.C. Sucking disorders in neurologically impaired infants: Assessment and facilitation of breastfeeding. *Clin. Perinatol.* 1987, *14*, 109.

8. Medoff-Cooper, B.; Weininger, S.; Zukowsky, K. Neonatal sucking as a clinical assessment tool: Preliminary findings. *Nurs. Res.* 1989, *38*, 162–165.

9. Rogers, B.; Arvedson, J. Assessment of infant oral sensorimotor and swallowing function. *Ment. Retard. Dev. Disabil. Res. Rev.* 2005, *11*, 74–82.

10. Selley, W.G.; Ellis, R.E.; Flack, F.C.; Brooks, W.A. Coordination of sucking, swallowing and breathing in the newborn: Its relationship to infant feeding and normal development. *Int. J. Lang. Commun. Disord.* 1990, *25*, 311–327.

11. Craig, C.M.; Lee, D.N. Neonatal control of nutritive sucking pressure: Evidence for an intrinsic τ-guide. *Exp. Brain Res.* 1999, *124*, 371–382.

12. Poore, M.A.; Barlow, S.M. Suck predicts neuromotor integrity and developmental outcomes. *Perspect. Speech Sci. Orofac. Disord.* 2009, *19*, 44–51.

13. Medoff-Cooper, B.; Shults, J.; Kaplan, J. Sucking behavior of preterm neonates as a predictor of developmental outcomes. *J. Dev. Behav. Pediatr.* 2009, *30*, 16–22.

14. Mizuno, K.; Ueda, A. Neonatal feeding performance as a predictor of neurodevelopmental outcome at 18 months. *Dev. Med. Child Neurol.* 2005, *47*, 299–304.

15. Slattery, J.; Morgan, A; Douglas, J. Early sucking and swallowing problems as predictors of neurodevelopmental outcome in children with neonatal brain injury: A systematic review. *Dev. Med. Child Neurol.* 2012, *54*, 796–806.

16. Craig, C.M.; Grealy, M.A.; Lee, D.N. Detecting motor abnormalities in preterm infants. *Exp. Brain Res.* 2000, *131*, 359–365.

17. Ballantyne, M.; Frisk, V.; Green, P. Language Impairment in Extremely-Low-Birth-Weight Infants. In Proceedings of the Pediatric Academic Societies Annual Meeting, San Francisco, CA, USA, 29 April–2 May 2006.

18. Morris, S.E.; Klein, M.D. *Pre-Feeding Skills*; Therapy Skill Builders: Tucson, AZ, USA, 1987.

19. Da Costa, S.P.; van Den Engel–Hoek, L.; Bos, A.F. Sucking and swallowing in infants and diagnostic tools. *J. Perinatol.* 2008, *28*, 247–257.

20. Doty, R.W.; Bosma, J.F. An electromyographic analysis of reflex deglutition. *J. Neurophysiol.* 1956, *19*, 44–60.

21. Wolff, P.H. The serial organization of sucking in the young infant. *Pediatrics* 1968, *42*, 943–956.

22. Macías, M.E.R.; Meneses, G.J.S.M. Physiology of nutritive sucking in newborns and infants. Bol *Med. Hosp. Infant. Mex.* 2011, *68*, 296–303.

23. Taffoni, F.; Tamilia, E.; Palminteri, M.R.; Schena, E.; Formica, D.; Delafiel-Butt, J.; Keller, F.; Silvestri, S.; Guglielmelli, E. Ecological Sucking monitoring of newborns. *Sens. J. IEEE* 2013, *13*, 4561–4568.

24. Pickler, R.H.; Mauck, A.G.; Geldmaker, B. Bottle-feeding histories of preterm infants. *J. Obstet. Gynecol. Neonatal Nurs.* 1997, *26*, 414–420.

25. Mizuno, K.; Ueda, A. The maturation and coordination of sucking, swallowing, and respiration in preterm infants. *J. Pediatr.* 2003, *142*, 36–40.

26. Howe, T.H.; Lin, K.C.; Fu, C.P.; Su, C.T.; Hsieh, C.L. A review of psychometric properties of feeding assessment tools used in neonates. *J. Obstet. Gynecol. Neonatal Nurs.* 2008, *37*, 338–349.

27. Medoff-Cooper, B. Changes in nutritive sucking patterns with increasing gestational age. *Nurs. Res.* 1991, *40*, 245–247.

28. Lau, C.; Alagugurusamy, R.; Schanler, R.J.; Smith, E.O.; Shulman, R.J. Characterization of the developmental stages of sucking in preterm infants during bottle feeding. *Acta Paediatr.* 2000, *89*, 846–852.

29. Amaizu, N.; Shulman, R.J.; Schanler, R.J.; Lau, C. Maturation of oral feeding skills in preterm infants. *Acta Paediatr.* 2008, *97*, 61–67.

30. Gewolb, I.H.; Vice, F.L.; Schweitzer-Kenney, E.L.; Taciak, V.L.; Bosma, J.F. Developmental patterns of rhythmic suck and swallow in preterm infants. *Dev. Med. Child Neurol.* 2001, *43*, 22–27.

31. Pickler, R.H.; Chiaranai, C.; Reyna, B.A. Relationship of the first suck burst to feeding outcomes in preterm infants. *J. Perinat. Neonatal Nurs.* 2006, *20*, 157.

32. Lau, C.; Smith, E.O.; Schanler, R.J. Coordination of suck-swallow and swallow respiration in preterm infants. *Acta Paediatr.* 2003, *92*, 721–727.

33. Gewolb, I.H.; Vice, F.L. Maturational changes in the rhythms, patterning, and coordination of respiration and swallow during feeding in preterm and term infants. *Dev. Med. Child Neurol.* 2006, *48*, 589–594.

34. Mathew, O.P. Breathing patterns of preterm infants during bottle feeding: Role of milk flow. *J. Pediatr.* 1991, *119*, 960–965.

35. Mizuno, K.; Ueda, A. Development of sucking behavior in infants with Down's syndrome. *Acta Paediatr.* 2001, *90*, 1384–1388.

36. Casaer, P.; Daniels, H.; Devlieger, H.; de Cock, P.; Eggermont, E. Feeding behaviour in preterm neonates. *Early Hum. Dev.* 1982, *7*, 331–346.

37. Lang, W.C.; Buist, N.R.; Geary, A.; Buckley, S.; Adams, E.; Jones, A.C.; Gorsek, S.; Winter, S.C.; Tran, H.; Rogers, B.R. Quantification of intraoral pressures during nutritive sucking: Methods with normal infants. *Dysphagia* 2011, *26*, 277–286.

38. Medoff-Cooper, B.; Bilker, W.; Kaplan, J.M. Sucking patterns and behavioral state in One- and Two-day old full term infants. *J. Obstet. Gynecol. Neonatal Nurs.* 2010, *39*, 519–524.

39. Kron, R.E.; Stein, M.; Goddard, K.E. A method of measuring sucking behavior of newborn infants. *Psychosom. Med.* 1963, *25*, 181–191.

40. Qureshi, M.A.; Vice, F.L.; Taciak, V.L.; Bosma, J.F.; Gewolb, I.H. Changes in rhythmic suckle feeding patterns in term infants in the first month of life. *Dev. Med. Child Neurol.*2002,*44*, 34–39.

41. Van Der Meer, A.; Holden, G.; van Der Weel, R. Coordination of sucking, swallowing, and breathing in healthy newborns. *Ped Neonatal* 2005, *2*, 69–72.

42. Taki, M.; Mizuno, K.; Murase, M.; Nishida, Y.; Itabashi, K.; Mukai, Y. Maturational changes in the feeding behaviour of infants–a comparison between breast-feeding and bottle-feeding.
Acta Paediatr. 2010, *99*, 61–67.

43. Hanlon, M.B.; Tripp, J.H.; Ellis, R.E.; Flack, F.C.; Selley, W.G.; Shoesmith, H.J. Deglutition apnoea as indicator of maturation of suckle feeding in bottle-fed preterm infants. *Dev. Med. Child Neurol.* 1997, *39*, 534–542.

44. Mizuno, K.; Aizawa, M.; Saito, S.; Kani, K.; Tanaka, S.; Kawamura, H.; Hartmann P.E.; Doherty, D. Analysis of feeding behavior with direct linear transformation. *Early Hum. Dev.* 2006, *82*, 199–204.

45. Tsai, S.W.; Chen, C.H.; Lin, M.C. Prediction for developmental delay on Neonatal Oral Motor Assessment Scale in preterm infants without brain lesion. *Pediatr. Int.* 2010, *52*, 65–68.

46. Nieuwenhuis, T.; da Costa, S.P.; Bilderbeek, E.; Geven, W.B.; van Der Schans, C.P.; Bos, A.F. Uncoordinated sucking patterns in preterm infants are associated with abnormal general movements. *J. Pediatr.* 2012, *161*, 792–798.

47. Reilly, S.; Skuse, D. Characteristics and management of feeding problems of young children with cerebral palsy. *Dev. Med. Child Neurol.* 1992, *34*, 379–388.

48. Lau, C.; Sheena, H.R.; Shulman, R.J.; Schanler, R.J. Oral feeding in low birth weight infants. *J. Pediatr.* 1997, *130*, 561–569.

49. Goldfield, E.C. A dynamical systems approach to infant oral feeding and dysphagia: From model system to therapeutic medical device. *Ecol. Psychol.* 2007, *19*, 21–48.

50. Al-Sayed, L.E.; Schrank, W.I.; Thach, B.T. Ventilatory sparing strategies and swallowing pattern during bottle feeding in human infants. *J. Appl. Physiol.* 1994, *77*, 78–83.

51. Mc Gowan, J.S.; Marsh, R.R.; Fowler, S.M.; Levy, S.E.; Stallings, V.A. Developmental patterns of normal nutritive sucking in infants. *Dev. Med. Child Neurol.* 1991, *33*, 891–897.

52. Koenig, J.S.; Davies, A.M.; Thach, B.T. Coordination of breathing, sucking, and swallowing during bottle feedings in human infants. *J. Appl. Physiol.* 1990, *69*, 1623–1629.

53. Demonterice, D.; Meier, P.P.; Engstrom, J.L.; Crichton, C.L.; Mangurten, H.H. Concurrent validity of a new instrument for measuring nutritive sucking in preterm infants. *Nurs. Res.* 1992, *41*, 342–346.

54. Jain, L.; Sivieri; E.; Abbasi, S.; Bhutani, V.K. Energetics and mechanics of nutritive sucking in the preterm and term neonate. *J. Pediatr.* 1987, *111*, 894–898.

55. Fadavi, S.; Punwani, I.C.; Jain, L.; Vidyasagar, D. Mechanics and energetics of nutritive sucking: A functional comparison of commercially available nipples. *J. Pediatr.* 1997, *130*, 740–745.

56. Tamilia, E.; Taffoni, F.; Schena, E.; Formica, D.; Ricci, L.; Guglielmelli, E. A Novel Ecological Method for the Estimation of Nutritive Sucking Efficiency in Newborns: Measurement Principle and Experimental Assessment. In Proceedings of the International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC'13), Osaka, Japan, 3–7 July 2013.

57. Waterland, R.A.; Berkowitz, R.I.; Stunkard, A.J.; Stallings, V.A. Calibrated-orifice nipples for measurement of infant nutritive sucking. *J. Pediatr.* 1998, *132*, 523–526.

58. Pickler, R.H; Reyna, B.A. Effects of nonnutritive sucking on nutritive sucking, breathing, and behavior during bottle feedings of preterm infants. *Adv. Neonatal Care*. 2004, *4*, 226–234.

59. Logan, W.J.; Kavanagh, J.F.; Wornall, A.W. Sonic correlates of human deglutition. *J. Appl. Physiol.* 1967, *23*, 279–284.

60. Da Nobrega, L.; Boiron, M.; Henrot, A.; Saliba, E. Acoustic study of swallowing behaviour in premature infants during tube-bottle feeding and bottle feeding period. *Early Hum. Dev.* 2004, *78*, 53–60.

61. Vice, F.L.; Heinz, J.M.; Giurati, G.; Hood, M.; Bosma, J.F. Cervical auscultation of suckle feeding in newborn infants, *Dev. Med. Child Neurol.* 1990, *32*, 760–768.

62. Tarrant, S.C.; Ellis, R.E.; Flack, F.C.; Selley, W.G. Comparative review of techniques for recording respiratory events at rest and during deglutition. *Dysphagia* 1997, *12*, 24–38.

63. Sameroff, A.J. The components of sucking in the human newborn. *J. Exp. Child Psychol.* 1968, *6*, 607–623.

64. Segami, Y.; Mizuno, K.; Taki, M.; Itabashi, K. Perioral movements and sucking pattern during bottle feeding with a novel, experimental teat are similar to breastfeeding. *J. Perinatol.* 2013, *33*, 319–323.

65. Lau, C.; Schanler, R.J. Oral feeding in premature infants: Advantage of a self-paced milk flow. *Acta Paediatr.* 2000, *89*, 453–459.

66. Escobar G. J., Joffe S., Gardner M. N., Armstrong M. A., Folck B. F., Carpenter D. M.; Background A., Rehospitalization in the First Two Weeks After Discharge From the Neonatal Intensive Care Unit, *Pediatrics*, 1999, *104*, 1–9.

67. Bu'Lock F., Woolridge M. W., Baum J. D., Development of co-ordination of sucking, swallowing and breathing: ultrasound study of termand preterminfants, *Developmental Medicine and Child Neurology*, 1990, 32, 669–678.

68. Medoff Cooper B, Holditch-Davis D, Verklan MT, et al. Newborn clinical outcomes of the AWHONN late preterm infant research-based practice project. *J Obstet Gynecol Neonatal Nurs*, 2012, 41(6), 774–85.

69. Goldfield, E.C. (1995). Emergent forms: Origins and early development of human action and perception. New York: Oxford University Press.

70. Thelen, E., & Smith, L. (1994). A dynamic systems approach to the development of cognition and action. Cambridge, MA: MIT Press.

71. Teune MJ, Bakhuizen S, Gyamfi Bannerman C, et al. A systematic review of severe morbidity in infants born late preterm. *Am J Obstet Gynecol*, 2011, 205(4), 374.e1–9.

72. Balasubramaniam, R.,&Turvey,M. T. (2004). Coordination modes in the multisegmental dynamics of hula hooping. Biological Cybernetics.

73. E. C. Goldfield, P. H. Wolff, and R. C. Schmidt, Dynamics of oral ± respiratory coordination in full-term and preterm infants : II . Continuing effects at 3 months post term, *Developmental Science*, 1999, 3, 374–384.

74. E. C. Goldfield, P. H. Wolff, and R. C. Schmidt, "Dynamics of oral ± respiratory coordination in full-term and preterm infants : I . Comparisons at 38 ± 40 weeks postconceptional age, 1999, 3, 363–373.

75. A. L. Delaney and J. C. Arvedson, Development of Swallowing and Feeding: Prenatal Through First Year of Life, *Developmental disabilities research reviews*, 2008, 14, 105–17.

76. J. Hamill, J. M. Haddad, W. J. Mcdermott, Issues in Quantifying Variability From a Dynamical Systems Perspective, 2000, 407–418.

77. Kelso, J. A. S. (1995). Dynamic patterns. Cambridge, MA: MIT Press.

78. Davids, K., Glazier, P., Araújo, D., Bartlett, R.M., 2003. Movement systems as dynamical systems. Sports Med. 33, 245–260.

79. Glazier, P.S., Davids, K., 2009. Constraints on the complete optimization of humanmotion. Sports Med. 39, 15–28.

80. Shannon, C.E., 1948. A mathematical theory of communication. The Bell System Journal 27 379–423 and 623–656.

81. Fitts, P.M., 1954. The information capacity of the human motor system in controlling the amplitude of movement. Journal of Experimental Psychology 47, 381–391.

82. Schmidt, R.A., Zelaznik, H.N., Hawkins, B., Frank, J.S., Quinn, J.T., 1979. Motor output variability: a theory for the accuracy of rapid motor acts. Psychological Review 86, 415–451.

83. Haken, H., Kelso, J.A.S., Bunz, H., 1985. A theoretical model of phase transitions in human hand movements. Biological Cybernetics 51, 347–356.

84. J. S. Wheat and P. S. Glazier, Measuring Coordination and Variability in Coordination, 167–182.

85. Breton S, Steinwender S. Timing introduction and transition to oral feeding in preterm infants: current trends and practice. Newborn and Infant Nursing Reviews 2008; 8(3):153-9.

86. A. G. Allievi, T. Arichi, A. L. Gordon, and E. Burdet, Technology-aided assessment of sensorimotor function in early infancy, *Frontiers in Neurology*, vol. 5, no. October, pp. 1–10, 2014.

87. Y. Tamura, Y. Horikawa, and S. Yoshida, Co-ordination of tongue movements and peri-oral muscle activities during nutritive sucking, *Developmental medicine and child neurology*, vol. 38, no. 6, pp. 503–10, Jun. 1996.

88. L. Sabrina Lopes , R. Adriana Duarte, C. Anniele Medeiros, R. Jose Roberto de Moraes, L. Jose Maria de Andrade, M. Maria Elisabeth Lopes, "A non-invasive technique for evaluation of respiratory efforts in preterm infants during feeding", Journal of Neonatal Nursing, 2013.

89. E. Schena and S.Silvestri. A transistor based air flow transducer for thermohygrometric control of neonatal ventilatory applications. Review of Scientific Instruments 79, 104301, 2008.

90. T. Yamada, Y.Mori, K. Minami, K. Mishima, Y. Tsukamoto, "Three-Dimensional Analysis of Facial Morphology in Normal JapaneseChildren as Control Data for Cleft Surgery", Cleft Palate-Cran J, 39 (5), pp. 517–526, 2008.

91. G Agnihotri, D Singh, "Craniofacial anthropometry in newborns and infants", Iran J Pediatr, vol. 17 (4), pp. 332–338, 2007.

92. K.L. Carlsen, P. Magnus, K. H. Carlsen, "Lung function by tidalbreathing in awake healthy newborn infants", Eur Respir J, vol. 7 (9), pp. 1660–1668, 2004.

93. S. Balasubramanian, A. Melendez-Calderon, and E. Burdet, A Robust and Sensitive Metric for Quantifying Movement Smoothness, *IEEE Transactions On Biomedical Engineering*, 2012, 59, 8, 2126–2136.

94. B. Rohrer, S. Fasoli, et al. Movement smoothness changes during stroke recovery, *The Journal of Neuroscience*, 22, 2002, 8297–8304.

95. Journal of Statistics Education Volume 15, Number 2 (2007), http://www.amstat.org/publications/jse/v15n2/kader.html

96. Tepavac, Dejan, and Edelle Carmen Field-Fote. "Vector coding: a technique for quantification of intersegmental coupling in multicyclic behaviors." *Journal of Applied Biomechanics* 17.3 (2001): 259-270.

97. Miller, Ross H., et al. "Variability in kinematic coupling assessed by vector coding and continuous relative phase." *Journal of biomechanics* 43.13 (2010): 2554-2560.

98. Porges, S.W., Bohrer, R.E., Cheung, M.N., Drasgow, F., McCabe, P.M., Keren, G. New time-series statistic for detecting rhythmic co-occurrence in the frequency domain: the weighted coherence and its application to psychophysiological research. *Psychological Bulletin*, 1980, 88, 580±587.

99. Salmons, S., and J. Henriksson. The adaptive response of skeletal muscle to increased use. Muscle & nerve 4.2 (1981): 94-105.

List of Publications

Peer-reviewed journals

1. **E. Tamilia***, F. Taffoni*, F. Focaroli, D. Formica, L. Ricci, G. Di Pino, G. Baldassarre, M. Mirolli, E. Guglielmelli, F. Keller. Development of goal-directed action selection guided by intrinsic motivations: an experiment with children, *Experimental Brain Research*, 2014, 232(7), 2167-2177. (*equally contributing authors).
2. **E. Tamilia**, F. Taffoni, D. Formica, L. Ricci, E. Schena, F. Keller, E. Guglielmelli, Technological Solutions and Main Indices for the Assessment of Newborns' Nutritive Sucking: A Review. *Sensors* 2014, 14(1), 634-658.
3. M. Giorgino, G. Morbidoni, **E. Tamilia**, F. Taffoni, D. Formica, E. Schena, Design and characterization of a bidirectional, low cost flowmeter for neonatal ventilation, *IEEE Sensors*, 2014, 14(12), 4354-4360.
4. L. Ricci, D. Formica, L. Sparaci, F.R. Lasorsa, F. Taffoni, **E. Tamilia**, E. Guglielmelli, A New Calibration Methodology for Thorax and Upper Limbs Motion Capture in Children Using Magneto and Inertial Sensors. *Sensors* 2014, 14(1), 1057-1072.
5. Taffoni, F., **Tamilia, E.**, Palminteri, M., Schena, E., Formica, D., Delafield-Butt, J. & Guglielmelli, E. Ecological Sucking Monitoring of Newborns, *IEEE Sensors Journal*, 2013, 13(11), 4561-4568.
6. **E. Tamilia**, D. Formica, A. Scaini, F. Taffoni, An Automated System for the Analysis of Newborns' Oral-Motor Behavior. *IEEE Transactions on Neural Systems and Rehabilitation Engineering* (submitted)

International Peer-Reviewed conferences

1. **E. Tamilia**, J. Delafield-Butt, S. Fiore, F. Taffoni, "An Automatized System for the Assessment of Nutritive Sucking Behavior in Infants: A Preliminary Analysis on Term Neonates", In *Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE* (pp. 5752-5755). IEEE.

2. C. Cavaiola, **E. Tamilia**, C. Massaroni, G. Morbidoni, E. Schena, D. Formica, F. Taffoni, "Design, Development and Experimental Validation of a Non-Invasive Device for Recording Respiratory Events During Bottle Feeding", In *Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE* (pp. 2123-2126). IEEE.

3. M. Giorgino, G. Morbidoni, **E. Tamilia**, F. Taffoni, D. Formica, E. Schena, "A Transistors-Based, Bidirectional Flowmeter for Neonatal Ventilation: Design and Experimental Characterization", In *Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE* (pp. 2131-2134). IEEE.

4. F. Taffoni, V. Focaroli, **E. Tamilia**, F. Keller, J. M. Iverson, "A Technological Approach to Studying Motor Planning Ability in Children at High Risk for ASD", In *Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE* (pp. 3638-3641). IEEE.

5. **E. Tamilia**, F. Taffoni, E. Schena, D. Formica, L. Ricci, E. Guglielmelli. "A new ecological method for the estimation of Nutritive Sucking Efficiency in newborns: Measurement principle and experimental assessment", In *Engineering in Medicine and Biology Society (EMBC), 2013 35th Annual International Conference of the IEEE* (pp. 6720-6723). IEEE.

6. L. Ricci, D. Formica, **E. Tamilia**, F. Taffoni, L. Sparaci, O. Capirci, E. Guglielmelli, "An experimental protocol for the definition of upper limb anatomical frames on children using magneto-inertial sensors", In *Engineering in Medicine and Biology Society (EMBC), 2013 35th Annual International Conference of the* IEEE (pp. 4903-4906). IEEE.

7. **E. Tamilia**, D. Formica, A. M. Visco, A. Scaini, F. Taffoni, An Automated System for Quantitative Analysis of Newborns' Oral-Motor Behavior and Coordination during Bottle Feeding, In *Engineering in Medicine and Biology Society (EMBC), 2013 35th Annual International Conference of the* IEEE (submitted).

National and International Conference

1. **E. Tamilia**, F. Taffoni, J. Delafield-Butt and E. Guglielmelli, "An Automatic Approach for the Assessment of Sucking Behavior during Bottle-Feeding in Term Infants: Preliminary Analysis and Findings", IV Congresso del Gruppo Nazionale di Bioingegneria (GNB), June 25-27, 2014, Roma, Italy

Appendix

Neuro-Developmental Engineering

This PhD thesis has been developed in theoretical framework of the Neuro-Developmental Engineering (NDE). NDE is an emerging interdisciplinary research area at the intersection of developmental neuroscience and bioengineering, whose objective is providing new methods and tools for:

1. understanding neuro-biological mechanisms of human brain development;
2. quantitatively analyzing and modeling of human behavior during neurodevelopment;
3. assessment of neuro-developmental milestones achieved from birth onwards.

The main application fields of NDE are:

I. New clinical protocols and standards for early diagnosis, functional evaluation and therapeutic treatments of neuro-developmental disorders;

II. New generations of educational, interactive toys based on a rigorous scientific approach, which can provide adequate stimuli and guidance for supporting the physiological neuro-development process.

The work described in this thesis so far is in line with the philosophy of NDE as it aimed at providing new tools in order to quantitative analyzing an infants' motor behavior during the first months of life, modelling it to infer information about neuro-motor development, and define metrics to objectively assess development and assist clinicians in their therapeutic choices. .

A further work in line with the NDE, that has been carried during this PhD and that is philosophy, is reported below. This work aimed at providing methods and tools for understanding neuro-biological mechanisms of human brain development (objective 1), in the main application field of new educational and interactive toys. The published paper describing this work is attached below.

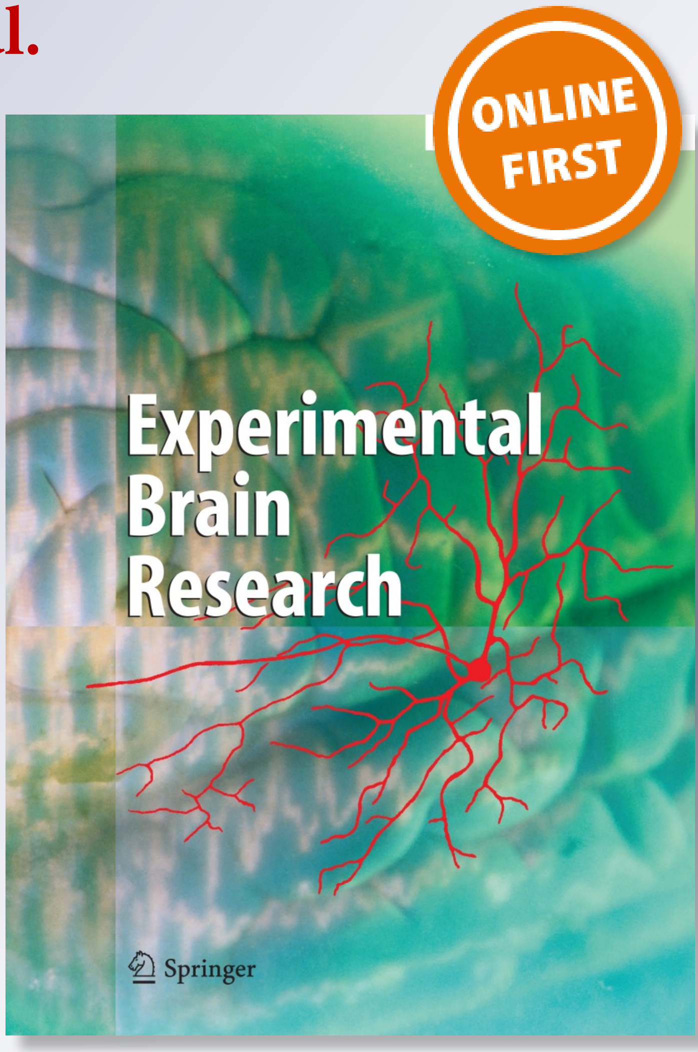
Development of goal-directed action selection guided by intrinsic motivations: an experiment with children

Fabrizio Taffoni, Eleonora Tamilia, Valentina Focaroli, Domenico Formica, Luca Ricci, Giovanni Di Pino, Gianluca Baldassarre, et al.

Experimental Brain Research

ISSN 0014-4819

Exp Brain Res
DOI 10.1007/s00221-014-3907-z



Springer

Exp Brain Res
DOI 10.1007/s00221-014-3907-z

RESEARCH ARTICLE

Development of goal-directed action selection guided by intrinsic motivations: an experiment with children

Fabrizio Taffoni · Eleonora Tamilia · Valentina Focaroli · Domenico Formica · Luca Ricci · Giovanni Di Pino · Gianluca Baldassarre · Marco Mirolli · Eugenio Guglielmelli · Flavio Keller

Received: 31 October 2013 / Accepted: 5 March 2014

Abstract Action selection is extremely important, particularly when the accomplishment of competitive tasks may require access to limited motor resources. The spontaneous exploration of the world plays a fundamental role in the development of this capacity, providing subjects with an increasingly diverse set of opportunities to acquire, practice and refine the understanding of action–outcome connection. The computational modeling literature proposed a number of specific mechanisms for autonomous agents to discover and target interesting outcomes: intrinsic motivations hold a central importance among those mechanisms. Unfortunately, the study of the acquisition of action–outcome relation was mostly carried out with experiments involving extrinsic tasks, either based on rewards or on predefined task goals. This work presents a new experimental paradigm to study the effect of intrinsic motivation on action–outcome relation learning and action selection during free exploration of the world. Three- and four-year-old children were observed during the free exploration of a new toy: half of them were allowed to develop the knowledge concerning its functioning; the other half were not allowed to learn anything. The knowledge acquired during the free exploration of the toy was subsequently assessed and compared.

Keywords Intrinsic motivation · Action selection · Curiosity · Action–outcome contingency · Novelty detection

Fabrizio Taffoni and Eleonora Tamilia have equally contributed to this work.

F. Taffoni (✉) · E. Tamilia · D. Formica · L. Ricci · E. Guglielmelli
Laboratory of Biomedical Robotics and Biomicrosystems, Università Campus Bio-Medico di Roma, Via A. del Portillo 21, 00128 Rome, Italy
e-mail: f.taffoni@unicampus.it

V. Focaroli · F. Keller
Laboratory of Developmental Neuroscience and Neural Plasticity, Università Campus Bio-Medico di Roma, Via A. del Portillo 21, 00128 Rome, Italy

G. Di Pino
Laboratory of Biomedical Robotics and Biomicrosystems, Institute of Neurology, Fondazione Alberto Sordi - Research Institute for Ageing, Università Campus Bio-Medico di Roma, Via A. del Portillo 21, 00128 Rome, Italy

G. Baldassarre · M. Mirolli
Laboratory of Computational Embodied Neuroscience, Institute of Cognitive Sciences and Technologies, CNR, Via S. M. della Battaglia 44, 00185 Rome, Italy

Introduction

The fast acquisition of the capacity to interact with the world, solve problems and pursue own personal goals is one of the most astonishing manifestations of human intelligence (Piaget and Cook 1952; von Hofsten 2004; Keen 2011). The mechanisms underlying this process are only partially known (see Gottlieb et al. 2013 for a review). The observation of infants makes it quite clear that the ability to perform goal-directed actions develops with a continuous open-ended process. This process leads them to understand how actions can accomplish different goals (von Hofsten 2004; Smith and Gasser 2005). In particular, thanks to a free exploration of the world, infants discover the potential changes (or *outcomes*) that their actions can cause in the environment, and register the dependencies between such changes and the performance of specific actions, i.e. *action–outcome contingencies* (Kenward et al. 2009).

Published online: 02 April 2014

Indeed, learning of action–outcome contingencies allows children to select the most appropriate motor program to reach a desired outcome, i.e. a goal (Kenward et al. 2009).

The computational modeling literature has proposed a number of specific mechanisms for autonomous agents to discover and target interesting outcomes (see Botvinick et al. 2009, for a brief review). Among these, intrinsic motivations (Baldassarre and Mirolli 2013) hold a central importance in the independent identification of potentially useful outcomes and self generation of goals. According to Ryan and Deci (2000), intrinsic motivations are defined as the motivations driving an activity for its inherent satisfaction rather than because it is instrumental for the attainment of outcomes having a direct biological value (e.g., the achievement of food or the avoidance of pain). In this view, intrinsic motivations drive children to learn for the sake of experience itself, rather than because of any reward given by an adult or the environment. This perspective is very close to the constructivist approach suggested by Piaget and Cook (1952). As in constructivism, learning has a central role, but while constructivism is mainly concerned with the learning process, intrinsic motivations are related to the particular forces that drive children to learn. Intrinsic motivations may be divided into two main classes: competence-based and knowledge-based intrinsic motivations (Oudeyer and Kaplan 2007; Mirolli and Baldassarre 2013). Competence-based intrinsic motivations are linked to an agent's behavior, and in particular to the ability (competence) of the agent to modify the world in certain ways (White 1959). In the computational models of competence-based intrinsic motivations, the agent is typically rewarded when its ability to accomplish a goal improves, independently from the origin of the goal (Chentanez et al. 2004; Schembri et al. 2007; Baranes and Oudeyer 2013; Santucci et al. 2013). In contrast, knowledge-based intrinsic motivations are linked to the stimuli the agent perceives and to their relation with the agent's previous knowledge (Berlyne 1960). Recent studies have suggested to divide knowledge-based intrinsic motivations into two subclasses: novelty-based and prediction-based (Baldassarre and Mirolli 2013; Barto et al. 2013). Prediction-based intrinsic motivations come forward when the agent's expectations are not met; they are typically modeled through prediction errors or improvements in prediction errors of an agent's model of the world (e.g. Schmidhuber 1991; Oudeyer and Kaplan 2007; Mirolli et al. 2013). Novelty-based intrinsic motivations are elicited by objects, or object combinations, that have not been experienced before and hence are not in the agent's memory. Computational models of this sort are typically based on the detection of anomalous/unfamiliar items (see Nehmzow et al. 2013 for a review).

Recent neuroscientific research has started to uncover the neural bases of intrinsic motivation mechanisms. Redgrave and Gurney (2006) have argued that sensory prediction errors related to surprising events cause bursts of dopamine, which lead the basal-ganglia to repeat and refine the action that produced the interesting event (Redgrave et al. 2011). Unfamiliar items or a novel combination of sequences of them seems to be detected by the hippocampus system (see Ranganath and Rainer 2003; Kumaran and Maguire 2007 for two reviews). Notwithstanding the heterogeneity of the different neural mechanisms promoting intrinsic motivations, they seem to have the same adaptive function: to drive the agent to acquire knowledge and competences without any extrinsic feedbacks. Such knowledge and skills can be exploited later, e.g. in adulthood, to attain biologically useful outcomes (Singh et al. 2010; Baldassarre 2011).

Unfortunately, the study of the acquisition of new skills and knowledge was mostly carried out with experiments involving tasks either based on rewards (involving mainly animals, see Balleine and Dickinson 1998), or on predefined task goals (involving mainly humans, see Elsner and Hommel 2004). This has contributed to generate a large psychological and neuroscientific literature on decision making and on goal-directed behavior (see Balleine et al. 2008, for a review). However, to the best of our knowledge, very little research has been carried out on the acquisition of new knowledge and skills based on intrinsic motivations. This work proposes a new experimental paradigm to study the effect of intrinsic motivations on action–outcome relation learning and action selection in absence of a reward or of a predefined task goal. The experiment, carried out on 3- and 4-year old children, uses an experimental apparatus specifically designed to study intrinsic motivations and other processes with children (Taffoni et al. 2012a), monkeys (Taffoni et al. 2012b), and humanoid robots (Taffoni et al. 2013). The goal of this study is to verify if: (1) intrinsic motivations toward the board may be triggered by the novelty and by the surprising features of the produced stimuli; (2) motivations may be kept alive in absence of an external reward or goal, by experiencing of action–outcome contingency alone; (3) action–outcome contingency may promote the acquisition of action–outcome relations; (4) learning may be split into sub-components related to some features of the action (i.e. where the action should be performed; what should be done).

Methods

Participants

Since children seem to develop the capacity to link their actions with environmental changes (causal mapping) with age (Hickling and Wellman 2001), two groups with different mean age were enrolled: 12 3-year-old children

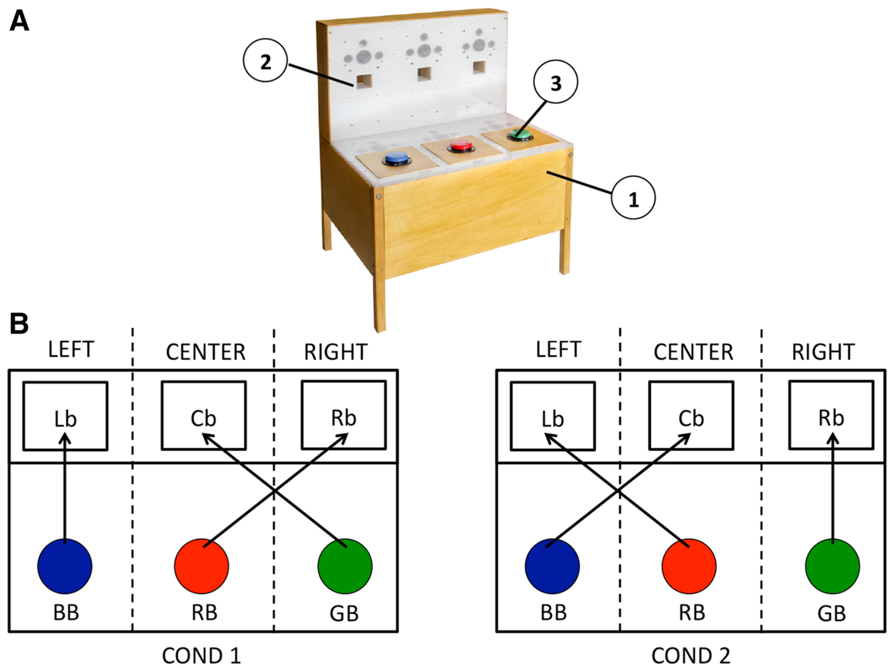


Fig. 1 **a** The mechatronic board. *1* The planar base, *2* the frontal unit, *3* mechatronic modules, in figure simple pushbuttons. **b** Relations between *buttons* and *boxes*: *Cond 1* crossed relations on the *right side* of the board, *Cond 2* crossed relation on the *left side* of the board. *Lb* left box, *Cb* central box, *Rb* right box, *BB* blue button, *RB* red button, *GB* green button

(36.7 ±0.8 months, mean ± SD) and 12 4-year-old children (48.7 ± 0.8). Subjects were recruited from a day-care center and were individually tested in a quiet and familiar room of the center. Parents of the children signed a written informed consent[1] describing the purpose of the experiment. The study involved tasks requiring free exploration of an experimental apparatus, which will be presented in the following section. Such kind of task requires a good level of attention span. A pilot experiment (Taffoni et al. 2012a) was carried out on 12 subjects aged between 24 and 68 months to test the equipment. We did not consider younger ages to avoid limitations stemming from lack of understanding of the task, or insufficient attention span, or insufficient motor coordination. Preliminary results of the pilot study led us to focus our investigation on 3 and 4 year old children. Indeed, children younger than 3 years of age were not able to keep their attention focused on the board for the necessary length time without the intervention of the experimenter, while children older than five found the task boring, so much that they did not perform it.

Stimuli and apparatus

A programmable apparatus was developed to investigate free exploration of the world, which is known to be a primary activity in children's motor knowledge and skill development. This apparatus, called mechatronic board, allows to control two key elements that facilitate free exploration: (1) the use of complex, unexpected, and surprising stimuli triggered by actions; (2) the introduction of unknown causality links between those stimuli and the children's action (i.e. action–outcome relations to be discovered). It is composed of a planar base ($W \times H \times D$: 650 × 500 × 450 mm) and a frontal unit ($W \times H \times D$: 650 × 400 × 120 mm) (see Fig. 1a). The planar base is provided with three slots (180 × 180 mm) where different smart-objects (i.e. objects instrumented with sensors to measure the interaction with the user) can be plugged in. For this study, three simple round pushbuttons (diameter 60 mm) were used: a blue button (BB) on the left, a red button (RB) in the center, and a green button (GB) on the right. A unit for delivering both visual and acoustical stimuli was mounted above each button. The frontal unit contains three boxes, closed by sliding doors and controlled to open/close in a reprogrammable way by the actions performed on the buttons. A unit for delivering both visual and acoustical stimuli was mounted above each box also in the frontal unit.

Procedure

Each child was tested in a single session. Before any experimental session child and experimenters played together to familiarize. Subsequently, the experimenters showed the board to the child, saying that it was a *magic toy* for

[1] Approved by the local Institute Ethical Committee of the Università Campus Bio-Medico di Roma, Prot. 10.CI_REV(05).12. ComEt-CBM 07/2012.

her/him. The experimental session started when the child sat on a chair in front of the board and was ready to begin the exploration. It was composed of three phases: Baseline, Learning, and Test, always presented in the same order. Subjects were randomly assigned to two different groups: EXPerimental (EXP) group and ConTRoL (CTRL) group. Each subject of the CTRL group was yoked with one subject of the EXP group, matched for age. The protocols administered to the two groups solely differed in the Learning phase.

The Baseline phase

This phase was the first to be administered. The goal of this phase was to estimate the initial skills of children and their interest in exploring the board. It lasted 5 min. During this phase, the audio–visual stimuli solely came from the planar base: whenever a button was pressed, the lights above it switched on and a xylophone sound was produced (three different tones corresponded to the three different buttons).

The Learning phase

During this phase, children were allowed to play with the board and to freely explore it. For the EXP subjects, the board was programmed to respond to any pressing of the buttons with contingent visual and auditory stimuli and to open a single box when its specific button was kept pressed for more than one second. A simple push (SP), i.e a button pressed for <1 s, switched on the lights above the button (on the planar base) and produced a xylophone sound as in the Baseline. An extended push (EP), i.e. when the button was pressed for more than 1 s, produced the same stimuli as a SP from the planar base, but it also produced the opening of a box (always empty in this phase) and the corresponding visual and audio stimuli from the frontal unit: the interior of the box lit up, the lights above the box switched on, and the speaker near the box produced an animal sound (a different one for each box: a rooster's, a frog's or a cat's call). The relations between buttons and boxes was programmed to be direct (the button opens the box in front of it) or crossed (the button opens the box on its left or right side) (see Fig. 1b). Half of the subjects for each age group were tested with crossed relation on the right side of the board (Condition 1, COND 1) and the other half with crossed relation on the left side (Condition 2, COND 2). The CTRL children were yoked to the EXP ones: the mechatronic board recorded how the CTRL subjects interacted with it, but it was programmed to deliver the outcomes of the actions performed by their paired EXP subjects. In this way, CTRL subjects received the same number and kind of stimuli as their paired EXP subjects, but independently from their actions. This artifice prevented CTRL subjects from learning any action–outcome relationship. Moreover, it allowed to identify the different effects of action–outcome contingency and of unexpected events on children's behaviour. In particular, it allowed to verify how and how much these two aspects of the stimuli may promote or undermine the intrinsic motivation to interact with the board and if these mechanisms depend on age.

The Test phase

In this phase, a sticker was used as a reward, introducing an external goal to promote the child's actions. The outcomes depended on the subject's actions for both EXP and CTRL groups, so both of them could experience the action–outcome contingency. Relations between actions and outcomes were set to be the same as the ones proposed in the Learning phase to the EXP group, for both the CTRL and the EXP subjects. Each CTRL subject was tested using the same relations between buttons and boxes as his/her paired EXP subject. The Test phase consisted of nine trials. During each trial, the subject was asked to retrieve a sticker placed in one of the three closed boxes (the sticker was always visible as the box door was transparent). Three different sequences of the sticker position were used[2] in order to avoid a bias effect due to the presentation order of the reward. The sequences were randomly assigned and counterbalanced among EXP subjects. Paired CTRL subjects received the same sequence order (Table 1). To open the box and retrieve the sticker children had to keep the correct button pressed for at least one second. Children were encouraged to retrieve the sticker without any suggestion on the action to perform. Each trial began with the reward inside a box and finished within 2 min, or earlier if the child took a shorter time to retrieve the reward. When the subject succeeded in opening the door and getting the reward, a new reward was placed inside the next box of the sequence. When the subject did not get the reward within 2 min, the same reward was moved inside the following box. The testing session ended when the nine trials were concluded, regardless of success in getting the rewards. The goal of this phase was to verify if children were able to exploit the skills acquired during the previous phase, in which only EXP subjects were allowed to understand the action–outcome relations.

Measures

The explorative behavior of each EXP and CTRL subject, during the Baseline and Learning phase, was assessed in terms of:

[2] **Seq A**: Lb Cb Rb Lb Cb Rb Lb Cb Rb; **seq B**: Cb Rb Lb Cb Rb Lb Cb Rb Lb; **seq C**: Rb Lb Cb Rb Lb Cb Rb Lb Cb.

Table 1 Experimental sample: for each subject the experimental setting used to program the board is reported as well as the reward sequences followed in the Test phase

Age	EXP			CTRL		
	Code	Cond	Seq	Code	Cond	Seq
3 years old	001	I	A	004	I	A
	002	I	B	005	I	B
	003	I	C	006	I	C
	007	II	A	010	II	A
	008	II	B	011	II	B
	009	II	C	012	II	C
4 years old	013	I	B	017	I	B
	014	I	C	018	I	C
	015	I	A	016	I	A
	019	II	A	022	II	A
	020	II	B	023	II	B
	021	II	C	024	II	C

- Number of pushes (NP): the total number of pushes, both SP and EP;
- Frequency of pushes (FP): NP divided by the phase duration expressed in minutes (NP/min);
- Push percentage (PP) of each button: NP of each specific button divided by the total NP;
- Number of extended pushes (NEP);
- Extended push frequency (EPF);
- Extended push percentage (EPP): the ratio between NEP and NP;
- Mean holding time (MHT): the mean value of the holding time (HT) of all the pushes, where the HT is the time (s) the child keeps the button pressed;
- Holding time standard deviation (HTSD): the standard deviation of the HT of all the pushes.

During the Test phase, the exploration behavior and the performance of each EXP and CTRL subject were assessed separately for each trial, adding the following indices to the ones described above:

- Spatial correctness index (SC): the difference between the number of correct button pushes (CP) and the number of wrong button pushes (WP), divided by the NP; its values belong to the range [−1, 1], where −1 indicates the complete absence of spatial correctness in the subject's pushes (he/she never presses the right button), 0 indicates the subject performing an equal number of wrong and right pushes, and 1 indicates the subject understanding the button–box relation (she/he only presses the correct button);
- Time to reward (TtR): the time (s) used by the subject to retrieve the reward (the value is considered as 'NaN', i.e. not a number, if the reward was not retrieved);
- Trials to criterion (TtC): the number of WP before the first right push (RP).
- In addition, the number of rewards (NR) retrieved by each subject during the whole Test phase was measured and used as a subject's performance index. To select the most appropriate statistical test to be performed, the assumptions of normality and variance homogeneity of the relevant variables were verified each time. When worthwhile, appropriate data transformation (logarithmic, square root, or arcsin transformation) was used. In the case of assumption failure, despite transformation, non-parametric tests were performed, as reported in the next section.

Results

The initial skills of EXP and CTRL groups were assessed using the data collected during the Baseline phase. No significant differences were observed between the two groups. The modality of exploration seems to be affected by age: a repeated-measures ANOVA reveals a slight statistically significant difference in the PP of the three different buttons in 3-year-old children [$F(2,22) = 3.48$, $p = 0.05$]. The post-hoc tests (Bonferroni correction) showed a preference for the central button versus the left one. No statistically significant differences, on the contrary, resulted in 4-year-old children. No additional differences were observed in the present phase. This finding may be explained by a poorer motor coordination (not fully developed) of younger children, who tend to prefer exploring buttons which are simpler to reach.

During the Learning phase of the EXP subjects, the lights above the button remain turned on while children keep the button pressed. This feedback can facilitate the

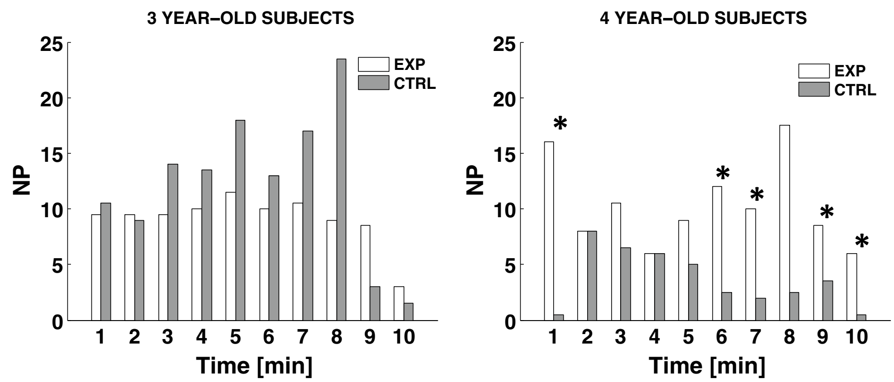


Fig. 2 The level of interaction with the board (expressed as NP) during the Learning phase: EXP (*white bars*) and CTRL (*grey bars*) subjects are compared, 3 year olds on the left and 4 year olds on the right. Four-year-old CTRL subjects show a significantly lower level of interaction than the EXP ones in the first minute (Wilcoxon rank-sum test, $p = 0.04$), as well as in the final part of the Learning phase (Wilcoxon rank-sum test: at minute 6, $p = 0.02$; at minute 7, $p = 0.02$; at minute 9, $p = 0.05$; at minute 10, $p = 0.02$). On the contrary, 3 year-old CTRL subjects maintain their level of engagement with the task consistent with the one of the EXP group

discovery of the effect of an EP and, subsequently, it may sustain the motivation to press the button. CTRL subjects cannot experience action–outcome contingency: they see the board turn on and off without any apparent reason. Such condition allows to clearly identify the different effects of action–outcome contingency and of unexpected events on children's behavior. We split the Learning phase into 10 time bins, each one lasting 1 min. Subsequently, we measured the NP in each time bin to assess if children were involved in the task. The data of CTRL subjects were then compared to the EXP ones, considering 3- and 4-year-olds separately (see Fig. 2). While 3-year-old CTRL subjects show a high level of interaction from the first minute, 4-year-old CTRL subjects seem reluctant to explore the board in this first time interval. The involvement in the task of 3-year-old CTRL subjects increases until the eighth minute when it reaches the highest value measured in all the experiment. After the eighth minute, the level of interaction drops. After the first minute, 4-year-old CTRL subjects show a pattern of involvement consistent with the one observed in age matched EXP subjects until the fifth minute; then, differently from the 3 year-old CTRL subjects, their level of interaction decreases substantially, showing significant differences with the matched EXP subjects (at minutes 6, 7, 9 and 10, as Fig. 2 shows). This behavior is different from the one observed in 3 year-old subjects, where no statistically significant differences result in the level of interaction between EXP and CTRL subjects. The observed opposite pattern of interaction in the two CTRL groups, with younger and older children respectively increasing and decreasing their board exploration, may be due to an age dependent effect of action contingency and surprise/novelty in motivating them. Younger CTRL participants are strongly motivated to explore the board by the unexpected and novel events caused by the yoked condition: experiencing these events drives their exploration and keeps their interest for the board high (their level of interaction is similar, and even higher, to the one of EXP participants). On the contrary, 4-year-old CTRL children seem to be motivated to explore the board by the possibility of learning a relation between actions and outcomes. During the first minute, 4-year-old CTRL participants experience a high prediction error, as they see the board being activated without apparent reasons. This promotes their exploration from minute 2 to minute 5. However, the impossibility of experiencing a causal relation between action and outcomes soon undermines the motivation to further explore the board (see De Charms 1968). On the contrary, their coupled EXP participants maintain a high level of exploration as they have the possibility of experiencing a feedback coherent with their action. Such possibility promotes their exploration and keeps their engagement with the task high. This finding seems to suggest that the purely novel and surprising aspects of the stimuli may be strongly motivating in 3-year-old subjects, even in the absence of action contingency. On the contrary, in 4 year-old subjects, the action–outcome contingency seems to be the strongest motivating aspect, whose absence clearly dissuades from keeping the interaction (Fig. 2).

The new experience of the box opening may promote a focusing behavior in EXP subjects: they might focus their actions on a specific button (spatial focusing) or they might repeat that particular interaction which caused the unexpected outcome, i.e. the EP, regardless of the button (action focusing). To investigate spatial focusing, the subject's actions after each BO were analyzed. No spatial focusing was observed, except for one EXP subject (Subject 002, 3 years old, COND 1) shown in Fig. 3.

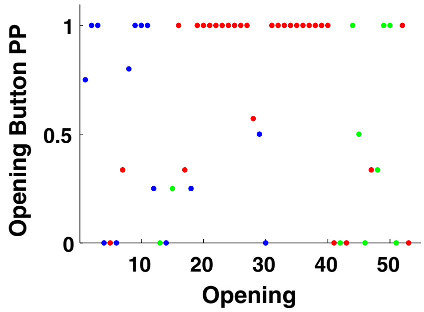


Fig. 3 Example of spatial focusing behavior during the Learning phase in a single child (Subject 2). Each *circular marker* represents a box opening (BO): the color of each marker (*blue*, *red*, *green*) corresponds to the color of the *button* used to open the *box* (opening button). The *y*-axis shows the PP of the opening button, measured after the last BO and before the following one. A PP = 1 means a focalization on the *button*, which had caused the last BO (color figure online)

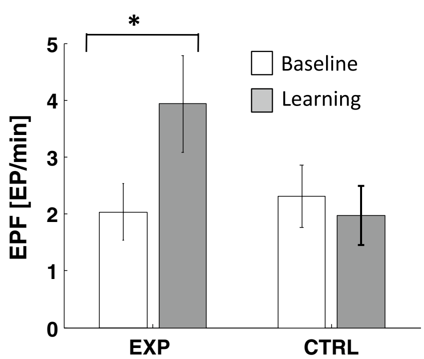


Fig. 4 Effect of novel unexpected stimuli experienced in the Learning phase: both 3- and 4-year-old EXP subjects, who had the possibility to experience these effects contingent with their actions, increased significantly their tendency to perform the action (EP) causing the unexpected effect (BO) with respect to the Baseline

This subject explored each of the three buttons for a prolonged time and seemed to change the explored button after she/he experienced the opening of a different box. Subjects experiencing the outcomes after an EP should prefer this pushing modality to SP: we named this behavior action focusing. In order to investigate the action focusing, the EPF measured in the Baseline phase was compared with the EPF measured in the Learning phase. EXP children significantly increased the EPF in the Learning phase compared with the Baseline [two-way mixed ANOVA, within-subjects effect, $F(1,10) = 18.7$, $p < 0.01$], without any dependence on the age [two-way mixed ANOVA, between-subjects effect, $F(1,10) = 0.3$, $p > 0.05$], as shown in Fig. 4. This suggests that the experience of new and unexpected visual and acoustical stimuli (BO) contingent with the action (the EP) promoted its execution regardless of the button. No differences were observed for CTRL subjects, neither in 3- nor in 4-year-old subgroups.

During the Test phase, the effect of the different Learning phases of the two groups was assessed. According to the experimental design, during the Learning phase only EXP subjects could acquire knowledge about the functioning of the board, thanks to their free exploration of the device. In detail, two aspects of action selection were assessed: action learning, i.e. the understanding that an EP causes the BO; and spatial learning, i.e. the understanding of the right relation between the button and the box which is controlled by it. These aspects may be assessed using two metrics, respectively the EPP and the SC. If the subject has learnt that an EP opens the boxes, she/he is expected to perform it more frequently when asked to retrieve a sticker put inside one of the boxes. Similarly, if she/he previously understood the spatial relation between buttons and boxes, the correct button should be pressed more frequently than the others. A preliminary exploratory data analysis was carried out. The nine trials of the Test phase were grouped into three triplets, each one including one direct trial and two crossed ones. To assess what EXP and CTRL subjects learned in the Learning phase, and to verify whether they continued to learn during the Test phase or not, the evolution of mean SC versus mean EPP was observed in the three triplets of the Test phase. In Fig. 5, the red filled markers represent CTRL subjects and the blue empty markers EXP subjects. Markers of coupled subjects have the same shape. The plot area is split into four rectangles by a vertical axis placed at 0 SC and a horizontal axis placed at 0.5 EPP, both indices measured in the Test phase. These two levels were chosen since they represent two thresholds over which there is a focalization on the correct spatial relation and on the correct action, respectively. For this reason, the four rectangles represent four different levels of learning: no learning at all (left bottom rectangle); only action learning (upper left rectangle); only spatial learning (bottom right rectangle); both spatial and action learning (upper right rectangle). In the first triplet, six EXP subjects acquired both spatial and action knowledge versus only one CTRL subject, as expected. Only EXP subjects, in fact, had the possibility to learn action and spatial relations during the Learning phase. During the Test phase, EXP subjects seem to refine their SC: the number of subjects with an SC higher than zero increased from seven in the first triplet to nine in the last one. On the contrary, CTRL subjects seem to understand the action controlling the box opening: the number of subjects with EPP higher than 0.5 increased from three in the first triplet to seven in the last one. The three EXP subjects, being in the no learning region in the first triplet, remained in this region in the last one. The reason for this finding may be that these subjects (003, 019 and 020) performed a

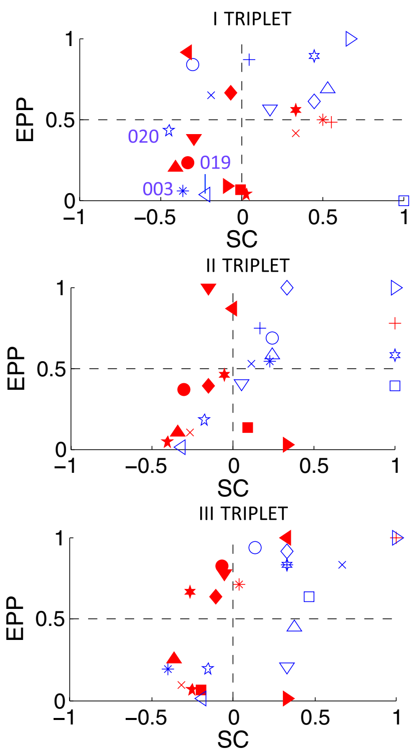


Fig. 5 Extended push percentage (EPP) versus spatial correctness index (SC) in the three triplets of the Test phase. The *red filled markers* are the CTRL subjects; the *blue empty markers* the EXP ones. When EPP is higher than 0.5, the subject prefers extended to simple pushes. When SC is higher than zero, the number of correct pushes is higher than the number of wrong pushes

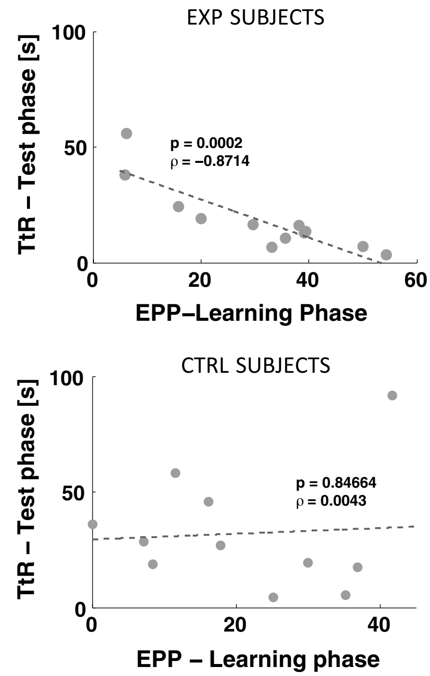


Fig. 6 Effect of action contingency on action learning: (*top*) EXP subjects who experienced the EP during the Learning phase more frequently, took less time to retrieve the reward during the Test phase. This relation is not present in CTRL subjects (*bottom*)

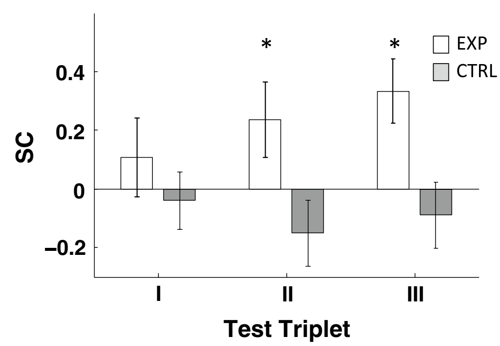


Fig. 7 Spatial learning during the Test phase: the SC is learnt by EXP subjects during the Test phase. The *asterisk* marks triplets where SC is significantly different from zero

lower NEP during the Learning phase and so they were not able to experience the correct action enough times.

The preliminary exploratory data analysis discussed, seems to suggest that action learning is acquired by EXP subjects during the Learning Phase. In particular, we hypothesized that the EXP subjects, who more frequently experienced the effect of EP during the Learning phase, were able to more efficiently retrieve the rewards in the Test phase. This hypothesis is confirmed by the correlation, proper of the EXP group, between TtR, measured in the Test phase, and EPP, measured in the Learning phase, as shown in Fig. 6. The higher the EPP in the Learning phase, the shorter the time needed by subjects to retrieve the reward in the Test phase. The correlation is also significant when 3- and 4-year-old EXP subjects are considered separately (3-year-old subjects: $p = 0.01$, $R = 0.81$; 4-year-old subjects: $p < 0.01$, $R = 0.93$), whereas it is not present at all in CTRL subjects, who were not allowed to learn any action–outcome relation during the Learning phase. Regarding spatial learning, EXP subjects presented a significantly higher level of SC than CTRL subjects (Wilcoxon rank-sum test, $Z = 2.8$, $p < 0.01$), as expected. To assess whether this knowledge had been already acquired during the Learning phase or it developed during the Test phase, the evolution of SC was analyzed in the three triplets of the Test phase. If a subject had already acquired spatial relations, this index is higher than zero. SC of the two groups is reported in Fig. 7 for each triplet. At the beginning of the Test phase, EXP subjects had not understood the spatial relations between boxes and buttons yet: in the first triplet, the difference between SC and zero only showed a small positive trend that was not statistically significant, meaning that the number of correct and wrong pushes was statistically the same. This index positively differed from zero starting from the second triplet in the EXP group, confirming that EXP subjects refined the spatial relation between buttons and boxes during the Test trials, and not during the Learning phase. However, the Learning phase is mandatory to prompt such learning process, which is indeed not observable in CTRL subjects. In this group the index was always statistically equal to zero, demonstrating that CTRL subjects, who were not allowed to learn anything during the Learning phase, did not have enough time to acquire the spatial relation during the nine trials of the Test phase.

Remarkably, when looking at the total amount of pushes, CTRL subjects revealed, in the Test phase, an explosion of interest for the board [paired t test on FP, $t(22) = -2.3$, $p = 0.03$], which was not observable in the EXP subjects [$t(22) = -0.9$, $p > 0.05$]. Since CTRL and EXP subjects, along this phase, were equally exposed to the reward, the observed difference is not attributable to this mechanism. On the contrary, in the Test phase CTRL subjects began to experience BO, thus FP burst can be justified by the novel achievement of permanent action–outcome contingency.

Finally, the performance of EXP subjects in the Test phase resulted to be overall better than CRTL ones. Although EXP and CTRL subjects retrieved the same number of rewards (Wilcoxon rank-sum test, $Z = 1.7$, $p > 0.05$), EXP subjects performed fewer pushes (Wilcoxon rank-sum test on NP, $Mdn_{CTRL} = 10$, $Mdn_{EXP} = 3$, $Z = -3.75$, $p < 0.01$), needed less time (Wilcoxon rank-sum test on TtR, $Mdn_{CTRL} = 11.2$, $Mdn_{EXP} = 7.2$, $Z = 2.2$, $p = 0.03$), and executed higher EPP (Wilcoxon rank-sum test on EPP, $Mdn_{CTRL} = 33$ %, $Mdn_{EXP} = 50$ %, $Z = 2.5$, $p = 0.01$).

Discussion

The present experiment consisted of allowing children to discover the relevant feedback stimuli of the mechatronic board, and to learn the action–outcome relations to recall a specific action when, at a later stage, the related outcome becomes desirable (i.e., it becomes an actively pursued goal).

The experiment presented in this work, even if on a small number of subjects, shows that free exploration of the world is sustained by the discovery of a hidden causal relation. Age has an effect, in this process. Children are able to develop an understanding of causal relations from external events at very early age, as shown by the fact that 2-year-old children can express causal prediction (Hickling and Wellman 2001). Even young infants seem to be able to infer some very basic laws related to the physics of the environment, as shown by the seminal work of Spelke et al. (1992), or more recently by Moll and Tomasello (2010), Téglás et al. (2011), Mascalzoni et al. (2013). To refine this knowledge, children act like scientists who verify hypotheses (Gopnik et al. 1999). This enables them to gain a deeper knowledge of causal principles of everyday physics, biology and psychology by the age of five (Gopnik et al. 2004), clearly showing that this ability rapidly evolves with age. In our experiment, the EXP participants remained engaged in the task during the whole Learning phase, while the CTRL participants seemed to show an age related effect. In detail, 4-year-old CTRL participants were discouraged to explore the board by the apparent randomness of the stimuli, while 3-year-old ones were promoted in their exploration. This finding seems to suggest that the purely novel and surprising aspects of the stimuli may be more motivating for 3-year-old children than for 4-year-olds. However, the absence of any kind of relation and the loss of the initial novelty and surprise cause a reduction in the interaction with the board also in these children. In fact, their level of engagement is comparable to that of 4 year-old CTRL children in the last part of the Learning phase, after the eighth minute.

The literature also proposes that actions are composed of different aspects, e.g. related to where the action is performed and what movements it involves (Redgrave and Gurney 2006). The experiment described in this paper tried a preliminary investigation on the possibility that intrinsic motivations drive the learning of different aspects of actions in different ways. The possibility to experience action–outcome contingencies during the Learning phase guided EXP children's exploration: our findings suggest that children adopt an exploration strategy that allows them to learn the effects of specific actions (action knowledge) and the spatial relations (spatial knowledge) separately. Even if a focusing behavior similar to the one described in Baldassarre et al. (2013) was not found during the exploration, action focusing related to the unexpected novel event was observed in those subjects who could experience the action–outcome contingency. A possible explanation of the absence of spatial focusing could reside in the effect of curiosity. Once the children experience a given button-evoked outcome, curiosity probably drives them towards the unknown effects of a different button. This indicates that novelty and contingency play a fundamental role in the action selection process.

Importantly, the experiment also showed that the knowledge acquired during free exploration, could improve the performance of subjects when they were subsequently asked to select the actions needed to accomplish useful, extrinsically-rewarding goals (gathering the stickers). In this respect, the experiment clearly showed that performance in these goal-directed tasks (e.g., the TtR) was significantly correlated with having experienced the effects of their own actions (e.g. EPP) during free exploration. Our findings also suggest that action–outcomes contingency is not sufficient to acquire spatial relations when an external goal is missing: only by forcing a spatial focusing with the use of a reward (in our experiment a sticker), this knowledge has been acquired.

Finally, the experiment reported in this work allows investigation of different motivational effects of transient outcomes versus permanent outcomes: lights and sounds may be considered as transient outcomes because they last for a short time contingent with the action; the box opening may be considered as a permanent outcome because it represents an environmental change lasting for a time sufficient to support further explorations and actions. To the best of our knowledge, this distinction is introduced here for the first time. Our findings seem to suggest that permanent outcomes have a higher motivational potential, as they more likely own a biological relevance, and also open up the possibility to perform further actions and explorations: both during free exploration, and with goal directed tasks, the perception of the impact of one's own actions on the environment proved to strongly enhance the interest towards the environment itself, in agreement with the proposals linking intrinsic motivations to competence (White 1959) and mastery (Ryan and Deci 2000).

Conclusions

Curiosity may be considered one of the driving forces that shape the process of acquisition of new skills and knowledge. The spontaneous exploration of the world plays a fundamental role in this process, providing subjects with an increasingly diverse set of opportunities for acquiring, practicing and refining new abilities. This activity is strongly promoted by the possibility to develop a causal mapping of the world. Children are motivated to explore the environment by novel events, which trigger their curiosity. Subsequently, their motivation to explore is kept high by the possibility to infer causal relations, thus increasing their knowledge and skills. This work studied how children develop the criteria for effective action selection. Three- and four-year-old children were observed during the free exploration of a new toy: half of them were allowed to develop the knowledge concerning its functioning, the other half were not allowed to learn anything. This study particularly focused on the way children acquire new knowledge during free exploration of the toy and how they reuse it for goal-directed tasks. The main results of this study can be summarized into four points: (1) the novelty and the surprising features of the mechatronic board, in particular the transient effects that actions can cause on it (e.g., lights and sounds), triggered exploratory behaviors toward the board; (2) the purely novel and surprising aspect of the stimuli is far more exciting than the fact that the contingencies may allow a causal mapping for younger children; (3) action contingencies, and in particular outcomes lasting long enough to allow the performance of new actions and explorations (e.g., box opening), produced an additional motivating effect allowing subjects to acquire new knowledge on the possible outcomes that their actions caused on the board and enhancing their capabilities to accomplish more effective, efficient, and desirable (extrinsic) goals; (4) actions are actually formed by sub-components (e.g., what, where, when, how) possibly relying on different cognitive/brain processes. Intrinsic motivations might lead to the acquisition of specific action components, at different times, within the overall learning process.

The afore mentioned points suggest that unexpected and surprising stimuli trigger children's exploration, even without a specific goal. This curiosity-triggered exploration is kept alive by the contingency between children's actions and the platform's outputs in 4-year-old children, and by the joint effect of action contingency and novelty in 3-year-old ones. In particular, action–outcome contingency allows the acquisition of new knowledge. By engaging the child for longer, it increases the likelihood of experiencing the effects of the action. When asked to perform a goal-directed task, children are able to apply the acquired know-how and to refine it. Future directions of this study may involve the electroencephalographic coregistration of the child's brain activity: monitoring the two subcomponents of the P300 wave (namely the P3a, related to the engagement of attention and the processing of novelty; and the P3b, related to unlikely action-related events (Polich 2007)) may provide the neural correlate to understand if and when the action–outcome relations become known and predictable. Moreover, EEG recording, time locked to button pushes, may be used to investigate which brain areas are recruited to perform the task, how the hand controlling cortices of the two hemispheres interacts (Di Pino et al. 2012), and how learning processes may modulate sensorimotor integration (Ferreri et al. 2014).

Acknowledgments This work was funded by FP7-ICT program (Project No. ICT-2007.3.2-231722-IM-CLeVeR). The authors would like to thank Dr. Roberta Aronica for proof-reading the document, and the anonymous reviewers for their valuable comments and suggestions to improve the work.

References

Baldassarre G (2011) What are intrinsic motivations? A biological perspective. In: IEEE international conference on development and learning (ICDL), vol 2, pp 1–8

Baldassarre G, Mirolli M (2013) Intrinsically motivated learning in natural and artificial systems. Springer, Berlin

Baldassarre G, Mannella F, Fiore VG, Redgrave P, Gurney K, Mirolli M (2013) Intrinsically motivated action–outcome learning and goal-based action recall: a system-level bio-constrained computational model. Neural Netw 41:168–187

Balleine BW, Dickinson A (1998) Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. Neuropharmacology 37(4):407–419

Balleine BW, Daw ND, O'Doherty JP (2008) Multiple forms of value learning and the function of dopamine. In: Glimcher PW, Camerer CF, Poldrack RA, Fehr E (eds) Neuroeconomics: decision making and the Brain. Academic Press, New York, pp 367–385

Baranes A, Oudeyer PY (2013) Active learning of inverse models with intrinsically motivated goal exploration in robots. Robot Auton Syst 61(1):49–73

Barto A, Mirolli M, Baldassarre G (2013) Novelty or surprise? Front Psychol 4:907. doi:1.10.3389/fpsyg.2013.00907

Berlyne DE (1960) Conflict, arousal, and curiosity. McGraw-Hill Book, New York

Botvinick MM, Niv Y, Barto AC (2009) Hierarchically organized behavior and its neural foundations: a reinforcement learning perspective. Cognition 113(3):262–280

Chentanez N, Barto AG, Singh SP (2004) Intrinsically motivated reinforcement learning. In: Saul LK, Weiss Y, Bottou L (eds) Advances in neural information processing systems 17. MIT Press, Cambridge, pp 1281–1288

De Charms R (1968) Personal causation: the internal affective determinants of behavior. Academic Press, New York

Di Pino G, Porcaro C, Tombini M, Assenza G, Pellegrino G, Tecchio F, Rossini P (2012) A neurally-interfaced hand prosthesis tuned interhemispheric communication. Restor Neurol Neurosci 30(5):407–418

Elsner B, Hommel B (2004) Contiguity and contingency in action-effect learning. Psychol Res 68(2–3):138–154

Ferreri F, Ponzo D, Vollero L, Guerra A, Di Pino G, Petrichella S, Benvenuto A, Tombini M, Rossini L, Denaro L et al (2014) Does an intraneural interface short-term implant for robotic hand control modulate sensorimotorcortical integration? An EEG-TMS co-registration study on a human amputee. Restor Neurol Neurosci 32(2):281–292

Gopnik A, Meltzoff A, Kuhl P (1999) The scientist in the crib: what early learning tells us about the mind. Harper-Collins, New York, p 1

Gopnik A, Glymour C, Sobel DM, Schulz LE, Kushnir T, Danks D (2004) A theory of causal learning in children: causal maps and bayes nets. Psychol Rev 111(1):3

Gottlieb J, Oudeyer PY, Lopes M, Baranes A (2013) Information-seeking, curiosity, and attention: computational and neural mechanisms. Trends Cogn Sci 17(11):585–593

Hickling AK, Wellman HM (2001) The emergence of children's causal explanations and theories: evidence from everyday conversation. Dev Psychol 37(5):668

Oudeyer PY, Kaplan F (2007) What is intrinsic motivation? a typology of computational approaches. Front Neurosci 1:6

Keen R (2011) The development of problem solving in young children: a critical cognitive skill. Annu Rev Psychol 62:1–21

Kenward B, Folke S, Holmberg J, Johansson A, Gredebäck G (2009) Goal directedness and decision making in infants. Dev Psychol 45(3):809

Kumaran D, Maguire EA (2007) Which computational mechanisms operate in the hippocampus during novelty detection? Hippocampus 17(9):735–748

Mascalzoni E, Regolin L, Vallortigara G, Simion F (2013) The cradle of causal reasoning: newborns preference for physical causality. Dev Sci 16(3):327–335

Mirolli M, Baldassarre G (2013) Functions and mechanisms of intrinsic motivations: the knowledge versus competence distinction. In: Baldassarre G, Mirolli M (eds) Intrinsically motivated learning in natural and artificial systems. Springer, Berlin, pp 49-72

Mirolli M, Santucci V, Baldassarre G (2013) Phasic dopamine as a prediction error signal of intrinsic and extrinsic reinforcements: a computational model. Neural Netw 39:40–51

Moll H, Tomasello M (2010) Infant cognition. Curr Biol 20(20):R872–R875

Nehmzow U, Gatsoulis Y, Kerr E, Condell J, Siddique N, McGinnity TM (2013) Novelty detection as an intrinsic motivation for cumulative learning robots. In: Baldassarre G, Mirolli M (eds) Intrinsically motivated learning in natural and artificial systems. Springer, New York, pp 185–207

Piaget J, Cook MT (1952) The origins of intelligence in children. W.W. Norton, New York

Polich J (2007) Updating p300: an integrative theory of p3a and p3b. Clin Neurophysiol 118(10):2128–2148

Ranganath C, Rainer G (2003) Neural mechanisms for detecting and remembering novel events. Nat Rev Neurosci 4(3):193–202

Redgrave P, Gurney K (2006) The short-latency dopamine signal: a role in discovering novel actions? Nat Rev Neurosci 7(12):967–975

Redgrave P, Vautrelle N, Reynolds J (2011) Functional properties of the basal ganglia's re-entrant loop architecture: selection and reinforcement. Neuroscience 198:138–151

Ryan RM, Deci EL (2000) Intrinsic and extrinsic motivations: classic definitions and new directions. Contemp Educ Psychol 25(1):54–67

Santucci VG, Baldassarre G, Mirolli M (2013) Which is the best intrinsic motivation signal for learning multiple skills? Front Neurorobot 7:22. doi:10.3389/fnbot.2013.00022

Schembri M, Mirolli M, Baldassarre G (2007) Evolving internal reinforcers for an intrinsically motivated reinforcement-learning robot. In: IEEE 6th international conference on development and learning (ICDL 2007), pp 282–287

Schmidhuber J (1991) Curious model-building control systems. In: IEEE international joint conference on neural networks, pp 1458–1463

Singh S, Lewis RL, Barto AG, Sorg J (2010) Intrinsically motivated reinforcement learning: an evolutionary perspective. IEEE Trans Auton Ment Dev 2(2):70–82

Smith L, Gasser M (2005) The development of embodied cognition: six lessons from babies. Artif Life 11(1–2):13–29

Spelke ES, Breinlinger K, Macomber J, Jacobson K (1992) Origins of knowledge. Psychol Rev 99(4):605

Taffoni F, Formica D, Zompanti A, Mirolli M, Balsassarre G, Keller F, Guglielmelli E (2012a) A mechatronic platform for behavioral studies on infants. In: 4th IEEE RAS and EMBS international conference on biomedical robotics and biomechatronics (BioRob), pp 1874–1878

Taffoni F, Vespignani M, Formica D, Cavallo G, Di Sorrentino EP, Sabbatini G, Truppa V, Mirolli M, Baldassarre G, Visalberghi E et al (2012b) A mechatronic platform for behavioral analysis on nonhuman primates. J Integr Neurosci 11(01):87–101

Taffoni F, Formica D, Schiavone G, Scorcia M, Tomassetti A, di Sorrentino EP, Sabbatini G, Truppa V, Mannella F, Fiore V et al (2013) The "mechatronic board": a tool to study intrinsic motivations in humans, monkeys, and humanoid robots. In: Baldassarre G, Mirolli M (eds) Intrinsically motivated learning in natural and artificial systems. Springer, New York, pp 411–432

Téglás E, Vul E, Girotto V, Gonzalez M, Tenenbaum JB, Bonatti LL (2011) Pure reasoning in 12-month-old infants as probabilistic inference. Science 332(6033):1054–1059

von Hofsten C (2004) An action perspective on motor development. Trends Cogn Sci 8(6):266–272

White RW (1959) Motivation reconsidered: the concept of competence. Psychol Rev 66(5):297