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Review article

The oral organ: A new vision of the mouth as a whole for a gerophysiological approach to healthy aging

Chiara Cecchin-Albertoni [a,b,1], Olivier Deny [a,b,1], Valérie Planat-Bénard [b,1], Christophe Guissard [a,b], Jenny Paupert [b], Frédéric Vaysse [a], Mathieu Marty [a,c], Louis Casteilla [b,1], Paul Monsarrat [a,b,d,1], Philippe Kémoun [a,b,1,*]

[a] Oral Medicine Department and CHU de Toulouse, Toulouse Institute of Oral Medicine and Science, Toulouse, France
[b] RESTORE Research Center, Université de Toulouse, INSERM, CNRS, EFS, ENVT, Université P. Sabatier, Toulouse, France
[c] LIRDEF, Faculty of Educational Sciences, Paul Valery University, Montpellier CEDEX 5 34199, France
[d] Artificial and Natural Intelligence Toulouse Institute ANITI, Toulouse, France

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ABSTRACT

This article brings a new perspective on oral physiology by presenting the oral organ as an integrated entity within the entire organism and its surrounding environment. Rather than considering the mouth solely as a collection of discrete functions, this novel approach emphasizes its role as a dynamic interphase, supporting interactions between the body and external factors. As a resilient ecosystem, the equilibrium of mouth ecological niches is the result of a large number of interconnected factors including the heterogeneity of different oral structures, diversity of resources, external and internal pressures and biological actors. The manuscript seeks to deepen the understanding of age-related changes within the oral cavity and throughout the organism, aligning with the evolving field of gerophysiology. The strategic position and fundamental function of the mouth make it an invaluable target for early prevention, diagnosis, treatment, and even reversal of aging effects throughout the entire organism. Recognizing the oral cavity capacity for sensory perception, element capture and information processing underscores its vital role in continuous health monitoring. Overall, this integrated understanding of the oral physiology aims at advancing comprehensive approaches to the oral healthcare and promoting broader awareness of its implications on the overall well-being.

1. Introduction

The mouth is commonly perceived as a juxtaposition of diverse structures, each playing its own unique role, immersed in a microbial ecosystem. Such a reductionist approach, that blunts the intricate interactions among oral structures, limits the comprehension of the oral biological system and of its relations with the whole body. A holistic perspective of oral cavity physiology is therefore lacking. Achieving this necessitates an integrated approach, considering physiology as was theorized by Claude Bernard, who defined the organism as a whole, with feedback loops ensuring the stability of the internal environment (Noble, 2008). In this article, a novel perspective on oral physiology concept is proposed by redefining and thoroughly examining the mouth and its multifaceted functions. The aim is to gain a comprehensive understanding of the oral ecosystem and its interactions with both the external environment and the entire organism. Through the integration of gerophysiological concepts, new insights into age-related changes are then offered, elucidating alterations occurring within the oral cavity as well as across the entire organism. By exploring these connections, the authors aspire to contribute to the advancement of holistic approaches to oral health care and to promote a deeper understanding of the broader implications of the oral physiology on the overall well-being.

2. The conventional vision of oral activities

The oral cavity is anatomically described as the space extending from the lips anteriorly to the oro-pharynx posteriorly. It is bounded laterally by the cheeks, superiorly by the palate and inferiorly by its floor. The oral cavity encompasses diverse structures such as teeth, tooth-supporting tissues (i.e., periodontium, including the gingiva) and

* Correspondence to: RESTORE Research Center, 4bis Av. Hubert Curien, Toulouse 31100, France.
E-mail address: philippe.kemoun@inserm.fr (P. Kémoun).
[1] These authors contributed equally to this work

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specialized mucosa of tongue, cheeks, lips and hard/soft palate. The oral cavity exhibits a humid environment, immersed in saliva and gingival sulcular fluid that flows from the dento-gingival junction. Each of these structures fulfills a specific role in the overall functioning of the mouth, with its central role of being the starting point of the digestive system. As an integral component of craniofacial structures, the oral cavity is closely interlaced with the anatomical elements of the temporomandibular joint, facial expression and mastication muscles, as well as their corresponding vascularization. Moreover, a specific innervation network acts as the coordinator for all the information the individual perceives from the environment and the influx of energy flows, as well as for the ability to respond to the surrounding stimuli. From a classical perspective, oral activities are considered to encompass motor, secretory, sensory and immune undertakings (Bhateja et al., 2019; Bogaerts et al., 2012; van der Bilt et al., 2006).

Motor activity. Fine neuromuscular control enables mastication, swallowing, ventilation and phonation. Mastication and swallowing involve the coordinated activity of teeth, muscles, jaws and temporomandibular joint to support biting, catching, capturing, and extracting elements from the external environment. Motor activity significantly relies on saliva, which plays a pivotal role in both the formation and transportation of the bolus (Taylor and Preshaw, 2016).

Oral secretory activity of saliva. Humans swallow saliva between 500 and 700 times a day, around three times an hour during sleep, once per minute while awake and even more during meals (Shaw and Martino, 2013). Saliva is a dilute aqueous solution that contains both inorganic and organic constituents. It is of great importance in digestion (salivary amylase and lipase, food bolus formation), in oral tissues lubrication and in the oral cavity metabolism regulation (Iorgulescu, 2009). Saliva plays a significant role in regulating the oral cavity metabolism through various mechanisms, such as pH regulation, calcium and phosphate homeostasis and temperature control. Saliva also has a pivotal immunomodulating role (immunoglobulins, mucins, histatins, defensins, cystatins and lysozyme production (Bhateja et al., 2019; Pedersen et al., 2018). Finally, salivary components, particularly antimicrobial factors, exert significant selective pressures on the microbiota (almost 700 species of microorganisms coexisting in the oral cavity), helping the shaping and control of resident communities (Marsh et al., 2016).

Ventilation is an essential reflex involved in the oxygen supply to the organism; it is the first event of respiration, the result of inhalation and exhalation, and allows transport of gases from the atmospheric air through nose and oral cavity to lungs, and vice versa (Petersson and Glenny, 2014). Ventilation also plays a crucial role in energy metabolism by ensuring oxygen supply for the optimal functioning of the whole body.

Phonation enables the individual to interact with the external environment and serves a basic social function (Fawcus, 1991). It results from the coordinated activity of glottis, vocal folds, laryngeal, facial muscles, muscles of mastication, nose, oral cavity - including teeth - and paranasal sinus (Zhang, 2016). The production of a single phoneme could involve up to one hundred muscular contractions and adjustments (Lenneberg, 1967). In fluent speech this would represent over five hundred muscular adjustments per second within the speech tract.

Oral sensory activities mainly include taste, proprioception and temperature control (Nishi et al., 2022). Taste perception involves the transmission of sensory information from taste buds. In the brain, sensory information is integrated with other sensory inputs, such as smell and texture, to create the overall perception of flavor (Bogaerts et al., 2012). Oral proprioception refers to the sensory information and awareness related to the position, movement, and orientation of oral structures in relation to each other and to the surrounding environment (Rathee et al., 2014). Temperature control in the oral cavity involves several mechanisms, including temperature-sensitive receptors in the oral mucosa, saliva production, blood flow regulation and respiratory function. The mouth temperature control mechanisms work in concert with the body overall thermoregulatory system to maintain a stable internal temperature for optimal comfort and functions (Lemon et al., 2016).

Immune activity. Capturing information from the environment is not the only responsibility of the sensory activity, since the oral cavity is a site of first encounters for the whole immune system (Moutsopoulos and Konkel, 2018). Commensal microorganisms, ongoing damage from mastication, airborne antigens and food are all initially encountered in oral cavity before entering the gastrointestinal and respiratory tracts (Wu et al., 2014). For that reason, the mouth is characterized by an intense immune activity (immune cells populations in oral mucosa, saliva, Waldeyer's ring and numerous draining lymph nodes) to maintain oral tissues integrity. The oral immune system displays a rare ability to maintain a delicate balance by performing effective immune surveillance without exuberant inflammatory responses, while tolerating commensals and innocuous antigens (Belkaid and Harrison, 2017).

Oral activities are often examined separately within the realm of oral physiology. Nevertheless, there is a pressing requirement for a comprehensive and integrated comprehension of oral physiology, which is crucial not only for gaining insights into the individual role and significance of the mouth but also to grasp how it plays a part in the overall functioning of the entire body, with permanent interactions with the environment. Therefore, although numerous authors have previously and deeply described the various oral activities (Bhateja et al., 2019; Bogaerts et al., 2012; van der Bilt et al., 2006), an integrated vision of oral physiology remains to be updated.

3. The oral organ: an interphase and resilient ecosystem in the body

The oral cavity is a complex structure that performs specific and interconnected structural, immune and metabolic activities (Neumann, 2017), and not only a sum of different, fragmented undertakings. The dynamics of oral motor activities are intrinsically swayed by sensory and immune activities. Reciprocally, these activities are impacted as well. Such an intricate interplay suggests that any alteration within a single facet of oral physiology invariably reverberates across the entirety of the oral system. For instance, a reduction in saliva production can lead to immune and metabolic alterations in the oral cavity, as well as modifications in mastication, swallowing, taste, and speech (Iorgulescu, 2009). Changes in the oral immune system may cause dysbiosis, mainly resulting in tooth decay and tooth-supporting tissues disease, which can, in turn, lead to occlusal changes, alterations in phonation, and impaired mastication (Ptasiewicz et al., 2022). Furthermore, since the proper articulation of sounds requires precise coordination between tongue, lips, palate, cheek and teeth, patients displaying occlusal or swallowing disorders often experience changes in voice quality and phonation (Murugappan et al., 2010). Interactions of structural, immune and metabolic activities allow the mouth to fulfill a specific function: it senses and communicates with the environment, capturing and processing its elements to ensure their safe accessibility to the organism.

All together, these observations allow a new definition of the oral cavity as an organ, since an organ refers to a group of different tissues that work together to perform a specific physiological function in a multicellular organism (Vander's human physiology, 2016)

4. The oral cavity: from an interface with external environment to an interphase organ between external and internal environments

The oral cavity acts as a pivotal zone of connection between the external environment and the entire body. The term "interface" has already been used to describe the oral cavity (Moutsopoulos and Konkel, 2018; Sato et al., 2008), and is defined as a strict boundary between two spaces or two parts of matter (Geckeler et al., 1997), while "interphase", in material sciences, refers to a distinct gradual zone of transition with specific properties, between two distinct phases or materials (Swain et al., 1990). The oral cavity therefore fits the "interphase" definition: it is not only a simple barrier or boundary, but also a zone of exchange and transformation between the external and the internal environment (Fig. 1). By virtue of its position, it serves as a pivotal zone for these communications and interactions.

4.1. The oral cavity: an organ of first encounters crucial for organism education

As one of the main site of first encounters (Moutsopoulos and Konkel, 2018), the oral cavity receives stimuli from external environment, processes them, and sends the processed information to the entire organism, contributing to its education. Through the mouth, the entire system learns to recognize, coexist, and defend itself against a wide range of external stimuli. For example, the mouth is constantly exposed to microorganisms through air, food and inter-individual interactions. These exposures allow the immune oral system to interact with and respond to the diversity of microorganisms (Wu et al., 2014). Moreover, the interphase mouth also plays an essential role in the education and development of the sense of taste (with ventilation and contact with food and beverages). Taste acts as a gatekeeper, influencing the selection of appropriate food for one's existence, maintenance, and optimal functioning (Barlow, 2022; Rabinerson et al., 2006). It also serves a purpose as a defense against ingesting harmful substances (Schier and Spector, 2019). Taste exploration in childhood helps shape food preferences throughout life and nutrition in early life is increasingly considered to be an important factor influencing later health (De Cosmi et al., 2017). Furthermore, gustation activity contributes to the feeling of satiety, helps prevent overeating (Li et al., 2020) and has a profound psychological impact on individuals, affecting emotions, memories, identity, social connections, and overall well-being.

Overall, the oral cavity plays a crucial role in analyzing signals from the surrounding world and in distributing them throughout a variety of communication pathways into relevant parts of the body, to educate and help the whole organism "grow up" (Georgiades, 1998). To cope with daily life stressors, the oral cavity has a remarkable capacity to absorb physical and chemical stresses (e.g., antigens, microorganisms, chewing, hygiene regimens, etc.), to recover from disturbances, and to adapt to changing conditions while maintaining its core function and structure. The oral function is sustained by continuous oral structure remodeling, constant immune vigilance and metabolic flexibility, to promptly respond to the system's variations. The ability to react to constant stimuli and return to a state of equilibrium makes the mouth a resilient system, "resilience" being the ability of a system or individual to withstand, adapt to, and recover from challenges or stressors (Chhetri et al., 2021).

4.2. The oral cavity as an interphase is a biological and resilient ecosystem

Considering the mouth as an interphase involves acknowledging spatial heterogeneity, which is not only influenced by external pressures but also by the intrinsic activities within the mouth. A further step is therefore to consolidate these concepts by regarding the mouth as an interphase ecosystem. Usually, the term ecosystem is limited to a microbiological aspect but, when referring to the oral cavity, it should be understood within a more expansive and comprehensive context. Like an ecosystem, the oral cavity could appear as a biological community of interacting cells and their chemo/physical environment, functioning together as a unit to maintain temporal stability in response to perturbations (Cortina et al., 2006). The oral prokaryote and eukaryote cell populations use their reserves (e.g., differentiation and multiplication capacities, cell selection, immune defense, energy metabolism) to cope with daily stresses originating from both external and internal environments. Diverse factors shape the temporal stability and robustness of an ecosystem, including the extent of available reserves, species richness and diversity (biodiversity being essential for ecosystem stabilization). Additionally, the characteristics of perturbations contribute to define the ecosystem recovery capacity. The more the oral ecosystem loses its flexibility and exhibits a decrease in reserves or biodiversity, the less it is capable of effectively responding to stresses and of maintaining its balance (Dong and Fisher, 2019). When the oral ecosystem fails to cope with increasing changes, it suddenly shifts from one state to another (tipping point) (Dakos et al., 2018). The new state usually has less biodiversity and is less productive than the ecosystem it replaces. The crossing of tipping points may come about as a result of a series of small changes or as a large abrupt change to system properties (Dakos et al., 2018).

The equilibrium of the different ecological niches of the mouth is therefore the result of a large number of interconnected factors including the heterogeneity of the different oral structures, the diversity of resources (e.g. oxygen, nutrients), external and internal pressures (mechanical, immune, metabolic), and biological actors (e.g. immune, mesenchymal cells, microorganisms). Moreover, to maintain a global and dynamic equilibrium, mouth ecological niches are interconnected by both chemical and mechanical signals (Dong and Fisher, 2019). According to such a definition, the whole body can be considered as a meta-ecosystem. Meta-ecosystem refers to a set of ecosystems

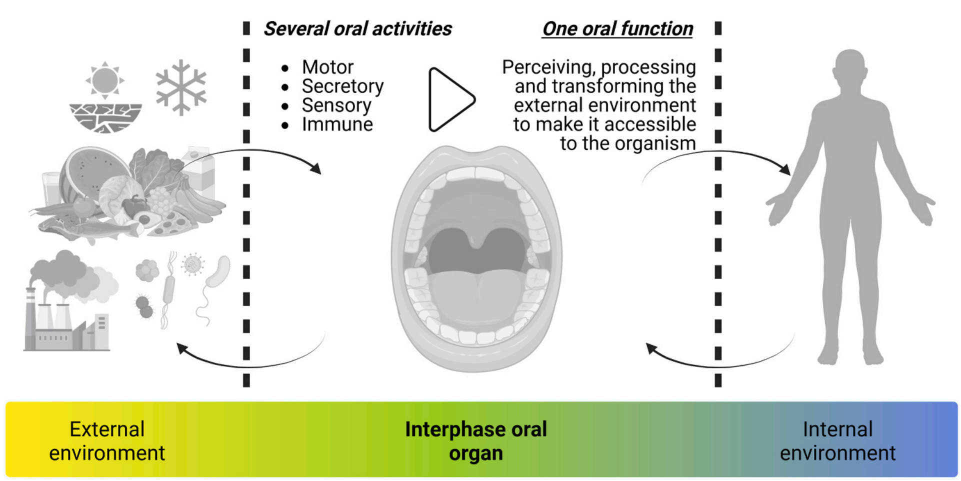

Fig. 1. The mouth, along with its components and activities, plays a unique and crucial role in sensing the environment, capturing its elements, and processing them for an easy accessibility to the organism. It is more than just a simple barrier or boundary as it functions as a transition zone of exchange and transformation between the external and internal environment.

interconnected by flow of energy, matter and organisms (Loreau et al., 2003). Any modification of an ecosystem will therefore lead to a modification of the ecosystem as a whole, given the interrelationships involved. It becomes obvious that any alteration in the oral ecosystem can impact other extra-oral ecosystems, triggering the activation of mechanisms to restore their respective equilibria. Similarly, any perturbation occurring in an extra-oral ecosystem will unavoidably have consequences for the oral environment. The mouth can thus be considered as an accessible mirror of the organism's dynamic equilibrium. The oral-to-extra oral bidirectional interactions are often documented through oral microbiota dysbiosis role on different infectious/inflammatory disease. Indeed, the oral microbiome plays a pivotal role in pathophysiology, with a commensal, symbiotic bacterial flora transitioning to a pathogenic state and a risk of systemic bacterial or bacterial by-products dissemination. This dissemination can trigger a chronic, low-grade local and systemic inflammatory response that may increase the risk of chronic inflammatory diseases including myocardial infarction and coronary disease (Baniulyte et al., 2021; Giles et al., 2021; Lee et al., 2019; Mougeot et al., 2017), metabolic diseases such as type 2 diabetes mellitus (Barutta et al., 2022; Borgnakke et al., 2018; Wu et al., 2020), adverse pregnancy outcome (Bui et al., 2019; Ide and Papapanou, 2013), atherosclerosis, pneumonia, inflammatory bowel diseases, rheumatoid arthritis (Byrd and Gulati, 2021; Jia et al., 2018; Krishnan et al., 2017) and gastrointestinal cancers (Krishnan et al., 2017; Singh et al., 2019). However, the systemic impact of oral organ dysfunctions is not limited to infectious/immune mechanisms. Dental occlusion may affect body posture (Fiorillo and Musumeci, 2020) by influencing the muscle tone of both masticatory and postural muscles (Julià-Sánchez et al., 2019): musculoskeletal systems are interconnected by fascial network, to support a functional continuity in order to maintain tissue integrity (i.e. biotensegrity). In addition, many systemic alterations such as immune deficiency disorders and nutritional deficiencies may be visible in the mouth. Inaugural oral diseases can also affect general health - e.g., pustular eruptions of the oral mucosa, defined as pyostomatitis vegetans, may be a specific marker of a silent form of inflammatory bowel disease; gingival swelling and mucosal ulcerations can be first signs of acute myeloid leukemia; the mucous membrane pemphigoid can first appear as a diffuse series of vesicles, ulcers, and erythematous areas that can involve palatal, buccal, or labial mucosa (Mays et al., 2012; Odell, 2017; Sachdeva et al., 2021; Yap, 2017). Ultimately, the significance of oral aesthetics cannot be overstated, as the appearance of the mouth profoundly influences an individual's self-esteem and overall well-being (Grecu et al., 2019; Huff et al., 2006; Locker, 2009). A wealth of literature underscores the critical link between oral health and quality of life (Durham et al., 2013; Grecu et al., 2019; Haag et al., 2017; Su et al., 2021). Missing or decayed teeth can detrimentally impact one's appearance, leading to feelings of self-consciousness and diminished confidence (Gerritsen et al., 2010; Özhayat, 2013; Saintrain and de Souza, 2012). Moreover, the associated pain and discomfort can exacerbate these emotional effects, further compromising the individual's quality of life. Beyond its psychological implications, poor oral health can also have practical ramifications, extending to professional opportunities. Individuals with visible dental issues may encounter challenges in securing employment where aesthetics plays an important role in the decision-making processes (Hall et al., 2013; Hyde et al., 2006). Several measuring instruments are available such as the Oral Health Impact Profile (OHIP) (Slade and Spencer, 1994; Su et al., 2021), providing valuable insights into the multifaceted impact of oral health on individuals' physical, emotional, and social well-being, proposing comprehensive approaches to oral care and policy interventions aimed at improving public health outcomes (Rousseau et al., 2014).

Due to a consistent and systematic exposure of the oral ecosystem to a multitude of stressors, changes in the oral ecosystem may serve as indicators or even precursors of changes that occur throughout the entire organism. Evidence suggests that oral tissues can act as a biological model for how tissues in any part of the body behave. As a corollary, targeted intervention in the oral ecosystem could allow rectification or prevention of imbalances or dysfunctions within an extra-oral ecosystem. However, existing studies that investigate the link between oral health and general health usually focus on specific aspects (e.g., microbiota, occlusion, immune system), without considering the oral organ relation to the entire organism (Byrd and Gulati, 2021; Fiorillo and Musumeci, 2020; Jia et al., 2018; Mays et al., 2012; Odell, 2017).

The holistic perspective of considering the oral cavity as an integral part of the entire organism, intimately linked to its surrounding environment, aligns with the gerophysiological paradigm (Kemoun et al., 2022). This approach facilitates an integrated understanding of the interconnections between the aging process in the oral cavity and the broader biological and physiological factors influencing aging throughout the body.

5. Evolutive changes and aging

Aging can be described as the cumulative effect of time on the organism, a process resulting from interactions between internal and external factors occurring throughout life (Kemoun et al., 2022). Aging is characterized by a progressive loss of physiological integrity, leading to impaired functions and increased vulnerability to diseases and death. This deterioration is the primary risk factor for major human pathologies (Lopez-Neyman et al., 2022). The oral function, as a part of the body's functions, is impacted by aging, as a consequence of tissue and structure modifications. As individuals age, their sensory perception diminishes, thus impacting taste sensitivity and chewing efficiency (Epstein, 1989; Lamster et al., 2016). Older adults may require higher sugar concentrations to perceive sweetness, thereby increasing the risk of dental caries (Chan et al., 2023; Khoury et al., 2022). Additionally, age-related declines in mastication and swallowing abilities, coupled with a weakened immune response, heighten susceptibility to aspiration pneumonia, particularly when food particles and dental plaque enter the airways inadvertently (Sakashita et al., 2015; Suma et al., 2018). Challenges with dexterity and muscle coordination often alter proper oral hygiene maintenance among older individuals, increasing the risk to develop or worsen oral diseases (Barouch et al., 2019; Shaw et al., 1989; Shin and Choi, 2019). The oral health challenges commonly experienced with aging may be exacerbated by the broad panel of drugs prescribed for various health conditions (Ito et al., 2023; Shetty et al., 2012; Tan et al., 2018). For instance, xerostomia or dry mouth, a prevalent side effect of many medical drugs, can significantly impair speech and mastication (Barbe, 2018; Millsop et al., 2017). Additionally, reduced saliva production negatively affects the functionality of removable prostheses, leading to oral discomfort and complications (Ouanounou, 2016). These findings underscore the need for tailored oral care interventions for aging populations. The following section will elaborate on current concepts regarding biomarkers of aging and how gerophysiology notions can be applied to the mouth. This involves considering the aging of an ecosystem with three fundamental pillars: structure/supportive compartment, immunity, and metabolism (Kemoun et al., 2022).

5.1. Current concepts on aging investigations and therapy: hallmarks of geroscience or intrinsic capacities?

In recent years, several molecular hallmarks have been identified as key drivers of aging, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, global reduction of gene expression and altered intercellular communication (Dodig et al., 2019; Farr and Almeida, 2018; Kanasi et al., 2016; Kemoun et al., 2022; López-Otín et al., 2013; Sebastiani et al., 2017). Each hallmark should ideally fulfil three criteria: (i) it should manifest during normal aging; (ii) its experimental aggravation should accelerate aging; and (iii) its reversion should retard aging consequences on tissue and, hence, increase healthy lifespan (López-Otín et al., 2013).

Aging oral hallmarks have been reported and linked to different oral conditions, such as periodontal disease, oral cancer and xerostomia (An et al., 2018; Aquino-Martinez et al., 2020; Baima et al., 2022; Barrera et al., 2021; Bayarsaihan, 2011; Bhattacharya et al., 2011; Boscolo-Rizzo et al., 2016; Jia et al., 2018; Kurosawa et al., 2021; Lee and Schmitt, 2019; Sanders et al., 2015; Sasahira and Kirita, 2018; Sumida and Hamakawa, 2001). Most biomarkers that are currently being examined are associated with age-related illnesses rather than with the process of healthy aging (Dodig et al., 2019). Moreover, aging hallmarks mainly concern molecular and cellular levels, and not an integrated and holistic physiological vision at the whole organism level. Consequently, they can only partially describe aging processes, notably physiological aging. In addition, fundamental concepts of gerosciences explain aging as the primary driver of susceptibility to chronic diseases, thus maintaining a pathologically focused perspective of aging.

In the 2015 World Report on Aging, WHO introduced the concept of intrinsic capacity (IC), thus focalizing on the functioning of people as they age, with a "non-disease centered" point of view. IC can be defined as the composite of all the physical and mental capacities that an individual can draw on at any point in their life (Jain et al., 2023). Aging can thus be considered as the result of repeated interactions between an individual and the environment in which the person lives, leading to adaptive IC changes. Five key subdomains have been identified as part of IC, each one reflecting multiple physiological functions ("WHO Clinical consortium on healthy ageing, 2022 meeting," n.d.): locomotion, cognition, sensory, psychological and the transverse domain of "vitality". As a constitutive element of the organism, the oral physiology perfectly fits with the concept of IC and oral aging changes can affect each IC subdomain. For instance, impaired oral health has an impact on self-esteem, social interaction and depression (Hakeem et al., 2019; Torre et al., 2015) (*psychological* subdomain); aging variations on proprioception and taste directly impact *sensory* aspect; chronic oral age-related inflammatory diseases (such as periodontitis) can be associated to cerebral degenerative diseases, such as Alzheimer's disease (Scannapieco and Cantos, 2016; Singhrao et al., 2015; Teixeira et al., 2017) (*cognition*) and neuromuscular and salivary changes are responsible for less efficient and longer masticatory cycles (*locomotion*). Moreover, impaired oral health affects dietary habits, nutrition, sleep, mental status, and social relationships (Hakeem et al., 2019; Helgeson et al., 2002; Kim et al., 2019).

In such a context, the authors introduce a groundbreaking gerophysiological perspective, focusing on the aging process of the oral organ and advocating for a more holistic understanding of the aging phenomena.

5.2. Oral gerophysiology

Considering the oral organ as an ecosystem within the entire body meta-ecosystem, interacting with the environment, highlights the role of the mouth as both an actor and a reflection of overall health. Variations at the organism level inevitably impact the balance of the oral ecosystem, and conversely, changes in the oral ecosystem have consequences on the whole body. Since aging is the result of a dynamic interplay between the organism and its surroundings, the privileged relation of the oral organ with the environment makes it a critical element of investigation in order to identify early indicators of biological aging in the oral ecosystem.

New hypotheses are emerging on the notion of aging based on the capacity of the physiological mechanisms responsible for tissue health to adapt to the accumulation of solicitations (or stressors) over time (Kemoun et al., 2022). The whole organism is early and continuously challenged (external and internal perturbations) and physiological learning mechanisms are set up in the quest for constant stability to maintain functions (Fried et al., 2021). The individuals response to stressors throughout their life depends on their basal characteristics and reserves: as long as the reserves can face a challenge, the person is defined as robust (and its physiological functions are normal). Once the reserves start to decrease, an alteration in physiological functions occurs and the person can be defined as pre-frail or, when reserves are totally exhausted, frail, with frailty resulting in increased vulnerability to adverse outcomes when exposed to stressors (Fried et al., 2021; Kemoun et al., 2022). Healthy aging is, thus, ensured as long as the tissue is able to maintain a state of local equilibrium to sustain a specific function. One way of explaining why an individual, at some point in his/her life, will develop an age-related pathology is thus to consider that he/her has exhausted his/her reserves, e.g., the capacity to adequately respond to repeated requests with adequate timing. Such a vision, which leads to abandon the classical pathology organ-centered perception to embrace a new holistic gerophysiology perspective, can easily be applied to the mouth: the oral cavity is early and continuously challenged and physiological learning mechanisms are established since the eruption of the teeth to maintain oral functions. The depletion of reserves, the reduction in biodiversity and the gradual specialization within the oral ecosystem over time lead to a significant reduction in its ability to cope with daily challenges. This sets the stage for tipping points (Dakos et al., 2018), creating a vicious circle that propels the oral ecosystem farther from its original state and diminishes its capacity to withstand aggressions. Consequently, daily life stressors, wear and tear result initially in subclinical oral functions changes (e.g., gingival alterations), and subsequently to clearly visible modifications (e.g., periodontitis). Such a new holistic perspective is characterized by the presence of some transverse and shared components that could drive and explain aging trajectories.

5.3. The multiscale SIM paradigm to investigate aging

Healthy functions are achieved and maintained thanks to an optimized relationship between three transverse body elements: Structure/supportive compartment (S), Immune/inflammatory system (I) and Metabolism (M), hence the acronym SIM (Kemoun et al., 2022). The Supportive/structure compartment appears to be the source and the driver of tissue architecture and repair; Immune/inflammatory system is an actor of repair signaling, that apprehends and defends the organism integrity against injuries; Metabolism provides energy for organism healthy functioning. As SIM elements are strongly interrelated, they must be considered as a key "entity" to monitor healthy functions. The oral ecosystem, like all the organism's ecosystems, can therefore be considered from the perspective of the SIM triad, in which these three components coexist and synergize at all levels, whether at the organism level, the oral organ, a sub-ecosystem/tissue (e.g. saliva, periodontium) or even at oral cellular level (Kemoun et al., 2022) (Fig. 2).

Saliva contributes to the maintenance of oral structures (S) by providing lubrication to the oral cavity, promoting tissue health, and ensuring proper functioning (Pedersen et al., 2018). Additionally, saliva mineral composition plays a crucial role in teeth surface remineralization (Dipalma et al., 2023). Moreover, saliva contains various components - such as lysozyme, lactoferrin, and defensins, as well as immunoglobulins - that contribute to the function of the oral immune system (I), helping to protect the mouth from harmful microorganisms and to maintain oral health (Iorgulescu, 2009). Furthermore, saliva contains the complement system that belongs to the innate immune system. Besides its immune-related functions, saliva also serves a vital metabolic role (M), participating in the maintenance of the pH balance in the oral cavity through its buffering action (Buczko et al., 2015). Moreover, saliva contributes to the regulation of calcium and phosphate levels, the oral thermoregulation, and the facilitation of metabolic exchanges between the body and the oral microbiota (Pedersen et al., 2018).

Periodontium and periodontal alterations are key examples to illustrate the oral SIM. Periodontium includes the gingiva and the deep

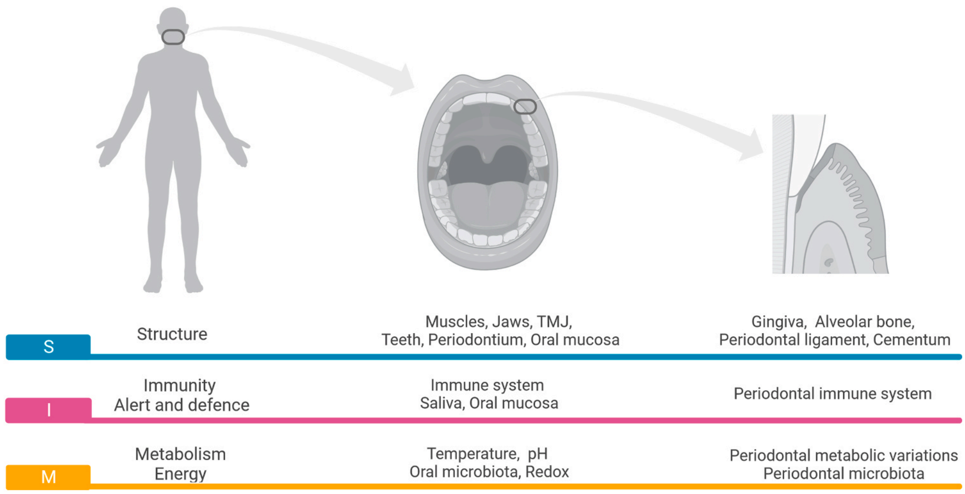

Fig. 2. The SIM paradigm can be applied to all levels and scales of the organism, in a sort of 'multiscale pattern' of nested SIM ecosystems. As the SIM triptych is transverse to the whole body, identifying a SIM signature in mouth or in periodontium as well as its age and/or disease-related variation could provide key elements to understand aging, to prevent or early intercept pre-frailty or frailty and to implement preventive or curative strategies for age-related pathologies.

periodontium, composed of the cementum (covering the root of the tooth), the surrounding bone and the periodontal ligament that anchors them together. It performs multiple functions such as sustaining the structure integrity of the orofacial complex and enabling oral activities like chewing or swallowing. Through the periodontal ligament anchorage, deep periodontium tissues maintain the tooth in the jaws, thus constituting a specific synarthrotic joint: the gomphosis (Torabi and Soni, 2022). In a healthy periodontium, gingiva-to-tooth interface crevice (or gingival sulcus) is colonized by microorganisms that synthesize products and co-aggregate to form the ecological plaque or periodontal microbiome (Belkaid and Harrison, 2017). Thus, gingiva is one of the oral sites participating in first antigenic encounters (Bartold, 2018), is in constant interaction with the whole microbial ecosystem through the oral cavity, and also with extra-oral tissues and organs mainly thanks to periodontal strong vascular network. The interdependence of the periodontal tissues underlines that deep periodontium acts as a "septic fibrous joint Structure" (Lin et al., 2017) (S), that is critical for oral mastication biomechanics sustain all along the life course, in a unique Immune environment (I). Moreover, Metabolic variations (pH, temperature, redox potential, etc.), mainly driven by gingival micro-vascularization, challenge the periodontium to adapt its structure to changes in the oral ecosystem (M) (Andras et al., 2022). Furthermore, the periodontium is susceptible to a chronic inflammatory age-related disease, called periodontitis, affecting nearly 50% of adults older than 50 (Nocini et al., 2020). Besides, periodontitis appears to be a good example of the concept of "inflammaging" (Franceschi et al., 2018; Fülöp et al., 2019), which characterizes the low-grade inflammation that progressively sets in with age, and can explain the progressive emergence of tissue damage and systemic dysfunction over time (Baima et al., 2022; Clark et al., 2022; Cutler and Diamond, 2022; Teissier and Boulanger, 2019).

Alterations in the periodontium are often associated with changes in the expression of periodontal cytokine biomarkers and gingival tissue oxidative stress increase (Isola et al., 2023; Matarese et al., 2013), highlighting the intricate relationship between oral health, systemic inflammation and metabolism, and overall well-being with rising extra-oral diseases incidence. Severe periodontitis can result in tooth mobility and loss, leading to various negative consequences. These include difficulties in mastication, often accompanied by pain. Such a discomfort often prompts individuals to prefer softer foods, which are typically high in salt, sugar and fats, thus hindering the consumption of a balanced, nutritious diet (Saksono et al., 2019; Zelig et al., 2022). Additionally, pain and halitosis arising from abscesses and periodontal pockets may occur along with impaired speech and pronunciation, which can appear following tooth loss (Bommangoudar et al., 2020; De Geest et al., 2016; Izidoro et al., 2021; Musić et al., 2021). Furthermore, the impact of periodontitis extends beyond physical discomfort to encompass psychological concerns related to appearance and self-esteem (Durham et al., 2013; Gerritsen et al., 2010; Goh et al., 2022).

From a pathophysiological standpoint, the periodontal health is preserved through interactions between its structures, immune defenses and metabolism. When the periodontal SIM is no longer able to cope with daily stresses - either due to a gradual depletion of its reserves or to an increase in stresses surpassing periodontium capacity to react effectively - an imbalance among its three different components (S, I and M) ensues. This results in the appearance of initially infra-clinical signs of pathology, that can evolve into clinical signs. It is hypothesized that an imbalance of at least one of SIM pillars may result in the development and worsening of periodontal disease. Periodontal alterations displays a broad spectrum of manifestations (Caton et al., 2018) that could be dependent on which of the SIM components has been altered and to what extent. Therefore, the periodontal disease could be not solely the consequence of a lack of hygiene, a dysbiosis or a sudden local inflammatory reaction, but rather the result of the system's inability to effectively respond to lifelong stresses, resulting from an alteration of the balance between Structure, Immunity, and Metabolism (Dahlen et al., 2020). Consequently, periodontium and periodontitis appear as an ideal model to investigate SIM and its age-related variations for better understanding, prevention or reversion of age-related oral and extra-oral diseases.

The SIM paradigm is thus a new prism for exploring the numerous players in the ecosystem and can be applied to all levels and scales of the organism, in a sort of "multiscale pattern" of nested SIM ecosystems. The mouth ecosystem and oral gerophysiological drift can be explored by analyzing oral SIM components. Since the SIM triptych is valid across the whole body, identifying a SIM signature in the mouth as well as its age and/or disease-related variation could provide key elements to understand aging, to prevent or to intercept pre-frailty or frailty in their early beginning, and to implement preventive or curative strategies for age-related pathologies (Fig. 3). Specifically, enhancing the comprehension of the evolution of oral health with aging, along with its pathophysiological variations, holds the potential to mitigate or even reverse the processes linked to resource depletion and specialization. The final objective is to protect or restore the oral and global organism's richness and biodiversity, enabling it to adeptly respond to everyday life stresses.

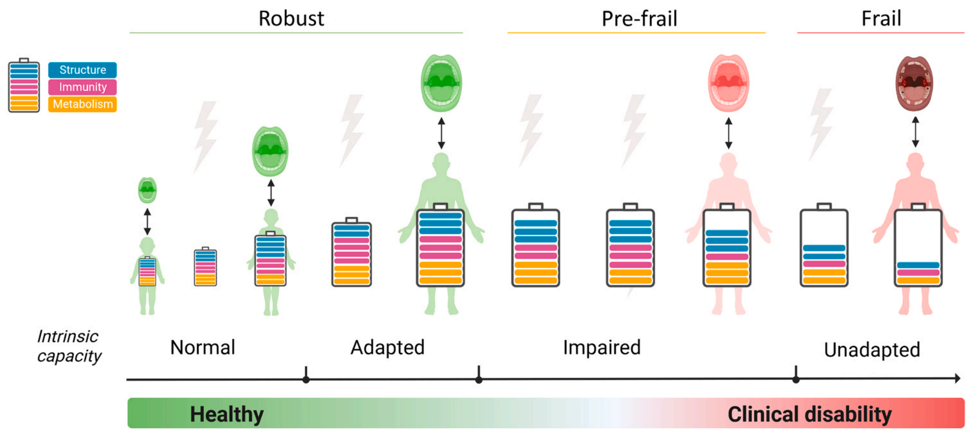

Fig. 3. The individual response to the long-life stressors depends on their basal characteristics and reserves: as long as the reserves can face a challenge, the person is defined robust (and its physiological functions are normal). Once the reserves start to decrease, an alteration in physiological functions takes place and the person can be defined as pre-frail or, when reserves are totally exhausted, frail, with frailty resulting in increased vulnerability to adverse outcomes when exposed to stressors. Since aging is the result of a constant balance and exchange between the environment and the organism, the privileged relationship of the oral cavity with the environment appears to be a key element to investigate and identify early signs of biological aging while analyzing the oral cavity. Due to its function and location, the mouth is highly susceptible to early environmental influences, and alterations in the oral cavity may precede changes in the overall body. Consequently, the oral cavity can be deemed an excellent model for studying aging and implementing preventive strategies.

The ultimate goal is to forestall the emergence of tipping points or, at least, to postpone their occurrence.

Therefore, in order to identify predictive signatures of aging trajectories through the oral organ, it is needed to measure over time variables that integrate both the multi-scale characteristic and the three components of the SIM, while following and understanding their counterbalancing process dynamics. Tailored computational approaches, incorporating interactions among all measured SIM factors, would then enable the measurement of physiological age through the mouth as a novel integrated risk factor for the development of chronic pathologies. In a therapeutic perspective of reversing age-related chronic oral conditions, addressing the interlaced components of the SIM would imply the need to act on various fronts. In the treatment of periodontitis, for instance, focusing solely on the immune aspect or structural aspect is insufficient to achieve lasting tissue regeneration. In this context, the mesenchymal stromal cell therapy, with its aspects of extracellular matrix management, immunomodulation, and metabolic switches, emerges as a promising therapeutic approach (Dubuc et al., 2022; Planat-Benard et al., 2021).

6. Conclusion

This paper introduces a novel approach of oral physiology with the aim to highlight the complex interplay between the oral ecosystem, the surrounding environment and the entire organism. By integrating gerophysiological concepts, it offers new insights into age-related changes, thus improving the understanding of the role played by the oral health in the overall well-being. The oral cavity is commonly perceived merely as a collection of specific activities and a comprehensive analysis of its entirety is usually missing. Additionally, the intricate interactions with the surrounding environment are frequently overlooked and inadequately examined. The reappraisal of the oral cavity as an organ and an interphase ecosystem largely interdependent with the environment highlights its crucial role in the overall health and well-being of the organism. The intricated interactions of the mouth with its surrounding environment, often underestimated, draw attention to the need for a comprehensive analysis that transcends its isolated activities. Acknowledging the oral cavity as a dynamic interphase capable of sensing environmental stresses, capturing elements, and processing information emphasizes its pivotal role as a key player in monitoring health over time.

Moreover, such a newfound perspective aligns with the emerging paradigm of gerophysiology, wherein the oral cavity, sharing multiscale elements with the entire body, emerges as a central hub for SIM analysis and regulation. The strategic position and fundamental function of the mouth make it an invaluable target for early prevention, diagnosis, treatment, and even reversal of aging effects throughout the entire organism. Furthermore, the easy accessibility of oral tissues and secretions paves the way for innovative investigation methods that can revolutionize conventional approaches to health interventions, including infraclinical age-related tissue lesions detection. The implications of intervening in the oral ecosystem extend far beyond oral health, reaching into the broader realm of systemic well-being. As the interconnected elements within this holistic system are explored, opportunities to enhance overall health by addressing the oral cavity clearly emerge.

In essence, the oral cavity transcends its conventional perception, evolving into a dynamic ecosystem that not only mirrors the general health of the organism but also offers a gateway for transformative interventions. Embracing this holistic perspective paves the way for a new era in healthcare in a biopsychosocial approach, where the oral cavity could become a focal point for advancing the comprehension of aging and age-related disease prevention as well as for promoting the whole organism wellbeing and quality of life. For the foreseeable future, an oral check-up could evolve into one of the essential components for analyzing the overall health and for preventing or treating age-related diseases at an early stage.

CRediT authorship contribution statement

C. Cecchin-Albertoni: Conceptualization, Writing – original draft, **O. Deny**: Conceptualization, Writing – original draft, **V. Planat-Bénard**: Conceptualization, Writing – original draft, **C. Guissard**: Writing – original draft, **J. Paupert**: Writing – original draft, **F. Vaysse**: Writing – review & editing, **M. Marty**: Writing – review & editing, **P. Monsarrat**: Conceptualization, Writing – original draft, **L. Casteilla**: Conceptualization, Writing – original draft, Supervision, **Ph. Kémoun**: Conceptualization, Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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