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## A network approach to orthodontic diagnosis

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### Structured Abstract

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**Background** – Network analysis, a recent advancement in complexity science, enables understanding of the properties of complex biological processes characterized by the interaction, adaptive regulation, and coordination of a large number of participating components.

**Objective** – We applied network analysis to orthodontics to detect and visualize the most interconnected clinical, radiographic, and functional data pertaining to the orofacial system.

**Materials and Methods** – The sample consisted of 104 individuals from 7 to 13 years of age in the mixed dentition phase without previous orthodontic intervention. The subjects were divided according to skeletal class; their clinical, radiographic, and functional features were represented as vertices (nodes) and links (edges) connecting them.

**Results** – Class II subjects exhibited few highly connected orthodontic features (hubs), while Class III patients showed a more compact network structure characterized by strong co-occurrence of normal and abnormal clinical, functional, and radiological features. Restricting our analysis to the highest correlations, we identified critical peculiarities of Class II and Class III malocclusions.

**Conclusions** – The topology of the dentofacial system obtained by network analysis could allow orthodontists to visually evaluate and anticipate the co-occurrence of auxological anomalies during individual craniofacial growth and possibly localize reactive sites for a therapeutic approach to malocclusion.

**Key words:** class II and class III malocclusions; craniofacial topology; network analysis

## Introduction

A major challenge in contemporary orthodontics is to map, understand, and model the architectural and dynamic properties of the various networks that control the behavior of the craniofacial system. The knowledge basis of orthodontic diagnosis and treatment planning involves an understanding of the huge amount of (possibly interrelated) data obtained from clinical examination and functional and radiographic analyses (1, 2). Given the environmental, lifestyle, and/or genetic factors

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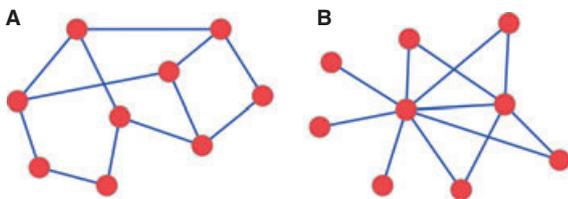
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 A network approach to orthodontic diagnosis  
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that together contribute to the co-occurrence of malocclusion features, it is not clear whether these orthodontic network-based interdependencies manifest themselves at the individual or at the population level. Discovering the systematic correlations between orthodontic networks and malocclusion patterns could potentially open new routes to uncovering possible, hitherto unknown, malocclusion pathogeneses. In diagnosing malocclusion, the measurements obtained with clinical and radiological methods are likely to be less important than the underlying (and possibly undervalued) correlations among the measurements themselves. The orthodontist is thus exposed to the risk of sub-optimal decisions owing to the complexity of the parameter space. As pointed out by McDonald and Ireland, ‘The interrelationship between the different aetiological agents involved in the development of a malocclusion can be complex. In any case it is essential to understand the action of the principal agent and how its effect can be modified by any others’ (3).

Complex systems – ranging from a biological system to our society of billions of cooperating individuals – display endless features of interaction, order, collaboration, and self-organization. Unpredictable behaviors emerge from the non-linear interactions of a few critical components that regulate the entire network (4). A system of elements that interact or regulate each other can be represented by a mathematical object called a network (Fig. 1) (5). The emerging science of complex networks, a recent advancement of complexity science based on graph theory, is of increasing interest to scientists across disciplines. Networks provide tools and methodologies to understand systems

in which each component can influence the behavior of many others. In such complex systems, the relationship(s) among the elements may have more importance than the elements themselves in representing the collective properties of the system. At a highly abstract level, the components can be reduced to a series of nodes that are connected to each other by links, with each link representing the interaction between two components. The nodes and links together form a network, or, in more formal mathematical language, a graph. The set of nodes must include all distinct entities that are capable of participating in the relationship under study. Graph theory provides a powerful representation of these functional interactions and highlights their global interdependence (6). Network structure, and the particular pattern of interactions, can have a major effect on the behavior of the system; it is the pattern that matters, the architecture of relationships, not the precise identities of the elements themselves.

In clinical orthodontics, the starting point and treatment priorities are still under discussion. Some researchers suggest beginning the treatment from the most evident clinical problem in the patient (7), some focus on the simplest problem to solve (8), and others suggest that soft tissue analysis is of paramount importance in contemporary orthodontics (9). Patients also have priorities, usually esthetic in nature. Another approach involves dealing with each problem as a single entity that is independent of the others problems (10). An additional issue is the incompleteness of information; in clinical situations, only limited functional information about respiration, mandibular movements, tongue posture, and deglutition is usually available (11). Finally, other major variables may play a role in planning the treatment, such as operator skill and patient cooperation. These issues do not simply sum together, but because of their mutual interactions, they combine their effects to produce an amplified/attenuated result, and some reciprocal interactions play a facilitating and multiplicative role in the development of a malocclusion, as in the case of oral respiration, adenoidal hypertrophy, anterior open bite, and tongue thrusting (12, 13). In contrast, one clinical sign may compete with another, possibly minimizing it over time, as is the case of an open bite accompanied by hypertrophy of the masticatory muscles (11–13).



**Fig. 1.** Networks or graphs are mathematical objects formed by vertices (nodes) and the links (edges) connecting them. Networks with the same number of edges and nodes can have profoundly different structures. (A) A random network in which nodes are connected with uniform probability and therefore have approximately the same number of links. (B) A ‘scale-free’ network characterized by a few highly connected nodes (hubs). This type of network is often because of a growth process in which a new node preferentially links to the most-connected nodes. A large number of biological networks have been shown to be scale-free.

Network analysis extends the data mining approach. As an example, conventional multivariate analysis allows reduction in the number of variables needed to describe the system, but it is not oriented to reveal systemic relations among them. Indeed, network analysis reveals ‘clusters’ emerging from the correlations of the data set, allowing the identification of the strongest inter-related components in the system. While enabling the discovery of systemic components, network analysis also allows visualization of multiple relations as a whole, in contrast to single-relation analysis. Furthermore, it can highlight unexpected correlations and quantitate their strengths (14).

In this study, we show that graph representation and analysis can be used to gain biological insight through an understanding of orofacial organization and function. We introduce networks as maps summarizing orthodontic connections that promote understanding of how features are connected and how these connections can be informative about the causative mechanisms of malocclusion occurrence and progression. This approach has been proven useful in different various aspects of health research (6, 14), ranging from the spread of epidemics and the consequences of bad health habits (15–18) to the network(s) of disorder and disease genes (19–22).

## Materials and methods

### Patient population

The patient set consisted of 104 patients (52 girls, 52 boys, 7–13 years of age) of Italian ancestry selected from a population that attended our Pediatric Dentistry Department from 2009 to 2010. Patients were divided according to their skeletal class (Table 1). We randomly selected a group of 44 Angle Class II malocclusion division one subjects (ANBangle > 4°, overjet > 2 mm, Wits > 2 mm) and a group of 30 Angle Class

III patients (ANBangle < 1°, overjet < 1 mm, Wits < -2 mm). Thirty subjects with good facial balance and normal occlusion were recruited as controls. The participants were selected on the basis of normal growth, no history of orthodontic treatment, and completeness of records. The diagnoses were performed separately by three examiners on the basis of a set of clinical, functional, and radiographic criteria (23). Controversial diagnoses were excluded from this study. The subjects enrolled in this study were judged to represent a typical orthodontic patient population with Class II and III skeletal malocclusions in a conventional clinical setting. To characterize the patient population, we recorded 41 clinical, anatomic, functional, and radiographic features (Tables 2 and 3).

### Determination of landmarks and cephalometric analysis

Skeletal, dental, and soft tissue landmarks on the lateral pre-treatment cephalogram were traced and digitized by a single examiner using the Ortophos Plus Ds system (T.I.M. srl, Pordenone, Italy). Twenty-three landmarks were identified and digitized in each radiograph (Fig. 2). Means and standard deviations for all cephalometric variables were calculated for the entire patient sample (Table 3).

Twenty-two functional and clinical signs or oral habits were included in this study (Table 2). A score from -3 to +3 was attributed to each sign in relation to the deviation from the mean radiographic, functional, or clinical value (Tables 4–9). The assessment of swallowing pattern was performed using a method suggested previously (24). Three examiners determined the mode of breathing, and the consensus determination was accepted. Information on each subject’s deleteri-

**Table 1. The distribution of the sample subjects**

Class	Number (gender)	Mean age (years ± SD)
Class I (controls)	30 (16 M, 14 F)	10.4 ± 1.3
Class II (patients)	44 (21 M, 23 F)	10.9 ± 1.6
Class III (patients)	30 (15 M, 15 F)	10.5 ± 1.6

**Table 2. List of the 22 functional and clinical signs used for the characterization of patient population**

Age	Sex	Face
Midline	Profile	Dental class
Skeletal class	Crowding	Lip competence
Overjet	Overbite	Speech
Anterior crossbite	Lateral crossbite	Respiration
Muscular orofacial tone	Skeletal muscular tone	Posture
Tongue thrusting	Non-nutritive suckling	Caries
Speech disorders of <i>r, s, n, t</i>		

**Table 3. Cephalometric variables calculated for the entire patient sample (mean and standard deviation)**

	Mean	±SD
<b>Skeletal ap</b>		
SNA	82	2
SNB	80	2
ANB	2	2
WITS	0	2
<b>Skeletal – vertical</b>		
Mandible unit length GoMe (mm)	71 (11 years)	3
SN length (mm)	71 (11 years)	5
Mandible plane angle (SN to GoMe)	33.5	3
Intermaxillary angle (ANS-PNS to GoMe)	26	3
Articular angle (Sar to arGo)	144	6
Gonial angle tot	126	4
Gonial angle sup	53	1.5
Gonial angle inf	73	2.5
Sella angle (NS to Sar)	122	5
<b>Dental</b>		
Interincisal angle	131	4
Overjet	2.5	1.5
Overbite	2.5	1.5
Lower 1 to APog	1	2
<b>Soft tissue</b>		
Lower lip to E (mm)	-3	2

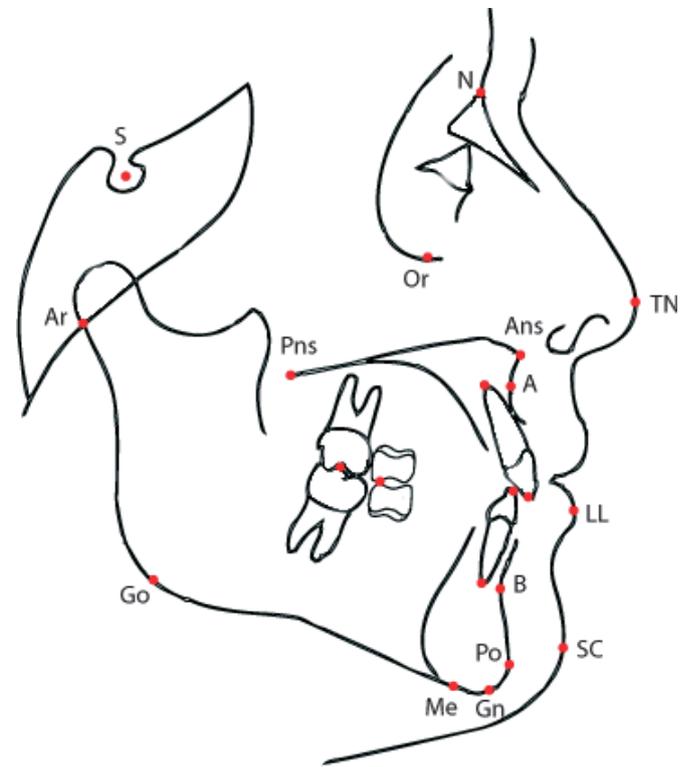


Fig. 2. Cephalometric landmarks.

**Table 4. The scoring table for SN–GoMe divergence angle (mean ± SD: 33.5° ± 3°)**

SN–GoMe value	Distance from the mean	Scoring value
> 42.5°	≥3 SDs	+3 severe hyperdivergence
39.5°–42.5°	Between 2 and 3 SDs	+2 moderate hyperdivergence
36.5°–39.5°	Between 1 and 2 SDs	+1 mild hyperdivergence
30.5°–36.5°	Between -1 and 1 SD	0 normodivergence
27.5°–30.5°	Between -1 and -2 SDs	-1 mild hypodivergence
24.5°–27.5°	Between -2 and -3 SDs	-2 moderate hypodivergence
<24.5°	≤ -3SDs	-3 severe hypodivergence

ous habits was recorded through parental interview (25).

**Reliability**

To minimize the measurement error, 20 cephalograms were randomly selected and traced and digitized again on separate days 1 month after the initial tracing. The error in the estimation of the angles ranged from 0.04° to 0.18° and that of the linear measurements ranged from 0.00 to 0.14 mm (26).

**Complex networks**

Networks or graphs are mathematical objects formed by vertices (nodes) and the links (edges) connecting them (Fig. 1). They are often used as simple models to extract useful structural information from a variety of mechanical and biological systems. Structural aspects are typically important in problems involving multiple

interacting agents. We used the above-defined orthodontic clinical, functional, and radiographic features as vertices (nodes) of the network. The degree corresponds to the number of nodes adjacent (directly connected) to a given node and is a measure of the centrality of a node. In biological terms, the degree

**Table 5. The scoring table for maxillary overjet (mean ± SD: 2.5 mm ± 1.5)**

Value (mm)	Clinical grade	Scoring value
1–4	Normal	0
4–5.5	Mild overjet	1
5.5–7	Moderate overjet	2
> 7	Severe overjet	3

**Table 6. The scoring table for overbite (mean ± SD: 2.5 mm ± 1.5)**

Value (mm)	Clinical grade	Scoring value
1–4	Normal	0
4–5.5	Mild overbite	1
5.5–7	Moderate overbite	2
> 7	Severe overbite	3

**Table 7. The scoring value for midline deviation value (mm) clinical grade scoring value**

Value (mm)	Clinical grade	Scoring value
0–1	Normal	0
2–3	Mild	1
3–4	Moderate	2
> 4	Severe	3

**Table 8. The scoring value for crowding value (mm) clinical grade scoring value**

Value (mm)	Clinical grade	Scoring value
0–1	Normal	0
1–3	Mild	1
3–6	Moderate	2
> 6	Severe	3

allows an immediate evaluation of the regulatory relevance of the node. For instance, in cellular signaling networks, proteins with very high degree interact with several other signaling proteins, suggesting a central regulatory node. They are likely to be regulatory hubs (Fig. 1B). The clustering coefficient measures whether nodes adjacent to a given node are also mutually adjacent; it is a good measure of the local structure around a feature indicating how much the network is locally compact around a given node. The shortest path

**Table 9. Criteria adopted to define functional characteristics (24)**

Scoring value 0	Normal
Scoring value 1	Minor deviation from normal, little cosmetic and/or functional significance
Scoring value 2	Moderate deviation from normal, moderate cosmetic and/or functional disturbance pattern
Scoring value 3	Severe deviation from normal, severe cosmetically and/or functionally disturbing

between two nodes measures how far apart (dissimilar) they are in the structure, while the mean shortest path of a biological network, for instance a protein-signaling network, can be interpreted as the overall facility with which the proteins exert their reciprocal functions (14).

**Correlations**

We constructed our networks from the Pearson product-moment correlation coefficients between pairs of orthodontic features (correlation matrix). Each node corresponds to a feature, and each link represents the correlation between two features. The networks were built by fixing a (generally positive) threshold value *T*: two vertices (features) were connected (linked) if the correlation between them was closer than the fixed threshold value *T*. A link was discarded if two features co-occurred in fewer than five patients. To prevent false positives, the significance of each correlation was also assessed by calculating the *p*-value for the null hypothesis that the co-occurrence for two features *a, b* is binomially distributed with probability  $f_a f_b$ , where  $f_a$  is the frequency of occurrence of feature *a* and  $f_b$  is the frequency of occurrence of feature *b*; we rejected links with  $p < 0.05$ . Our networks therefore represent the significant correlations among features by discarding false positives and cases of poor statistics.

Selecting a positive threshold makes it possible to cluster similar features that are likely to be associated during orofacial development. For each skeletal class, we built the network of features for *T* = 0.3 corresponding to a selection of medium and high correlations. We detected the dominant features among all interrelated features by computing key network

**Table 10. Global graph metrics of clinical, functional, and radiographic data. Global graph metrics provide information about the general properties of the orofacial system owing to the structure of the entire graph. Network data are obtained by linking orthodontic features that have medium or high positive Pearson correlation coefficient. All the reported metrics are pure numbers: average degree is the mean of the number of neighbors of a node; clustering coefficient is the average fraction of mutually connected neighbors respect to the maximum possible number of connections; mean shortest path is the average minimum number of links connecting two nodes**

Skeletal class	Average degree	Clustering coefficient	Mean shortest path
I (controls)	4.04	0.28	3.43
II (patients)	6.45	0.36	3.13
III (patients)	7.09	0.31	2.39

quantities (Table 10) and by simple visual inspection (Fig. 3) of the resulting network.

## Results

We analyzed the network obtained by considering the average degree, clustering coefficient, and mean shortest path of the orofacial data (Fig. 3). The average degree was lower in the Class I (normal) network and highest in the Class III network, indicating that malocclusions are characterized by more highly connected clinical, radiographic, and functional features (Table 10). This observation is reinforced by the larger clustering coefficients of Classes II and III compared

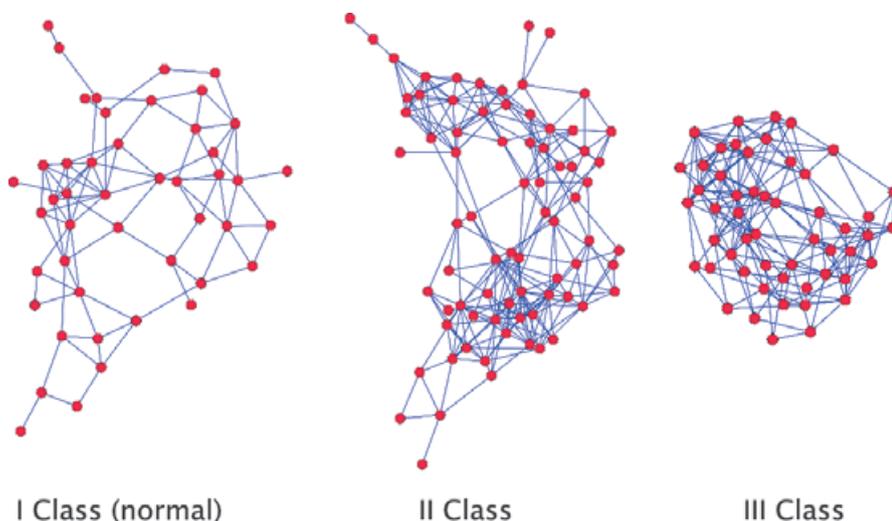
with control subjects (Table 10). Class II and III networks also have very distinct structures (Fig. 3); this characteristic is captured by the lower value of the mean shortest path for Class III patients (Table 10), indicating that the network is globally more compact – all features are likely to influence each other reciprocally.

Networks allow the immediate visualization of complex system properties. Indeed, visual inspection of Fig. 3 provides a clear understanding of all the characteristics discussed previously. The Class III network is characterized by a compact and uniform structure without critical hubs and is compact on both the local and the global scales. The global compactness of this network indicates that all the nodes (features) are equally relevant to the coherence of the system.

Conversely, the Class II network contains a few highly connected nodes (hubs), a typical characteristic of scale-free, small-world structures (14). These central features are represented mainly by orofacial musculature hypotonicity, speech problems, tongue thrusting, and posterior unilateral crossbite. The network obtained from control subjects does not display any particular local or global structures (Fig. 3).

## Discussion

It is increasingly recognized that to better understand the dynamics and function of a mechanical or biological system, we need to elucidate the components that constitute it, the relationships and interactions among



**Fig. 3.** The network of orofacial data reveals the connections among the features. From left to right: networks obtained by integration of orofacial clinical, functional, and cephalographic features (nodes) exhibit distinct patterns in normal patients (Class I) and in Class II and III malocclusions. The Class II network contains sparse, less-connected nodes that surround a few nodes with high degrees of linkage (hubs); on the orofacial systemic level, these hubs correspond to central (key) features that dominate the response of the system to treatment. The Class III network shows a more uniform and compact topology, revealing an organizational structure in which most features are strictly interrelated and suggesting that single feature-focused treatments are likely to influence many inter-related features.

these components, and the dynamic behavior of the system (21). The integration of these topics represents the core paradigm of systems biology. We adopted a novel approach to clinical orthodontics based on the biology of complex systems to better understand the interrelationships of complex data. Several factors determine whether two features co-occur in a patient, some of which are genetic, oral habits related, or treatment induced. Although our model captures only a portion of these interactions, it nevertheless allows us to formulate predictive hypotheses about therapeutic effects, robustness, and the stability in the system.

We determined that Class II and III malocclusions are characterized by clearly distinctive network properties (Fig. 3). The Class III network architecture contains higher overall connection and closeness (short distances among nodes) than the Class II network; this inclusive topology facilitates the transmission of information, bite forces, and neuromuscular inputs. As Class III malocclusion is highly connected but has no distinguishing hubs, we predict that a simultaneous multiple-therapeutic approach aimed at several features would possibly have a wide and profound influence on orofacial morphology, structure, and function.

To understand the functional organization of the orofacial system, insight is needed into the interplay between the structure of the network and its robustness. The structure of the Angle Class II malocclusion network that emerges from our data (a few peculiar hubs that regulate the entire network) may have important therapeutic consequences. This network is characterized by a few hubs (hypotonicity of the orofacial musculature, lateral crossbite, speech problems, tongue thrusting) that represent critical starting points for a selective approach to orthodontic therapy. By connecting the interacting network to the dynamic behavior of the system, these hubs are likely to play an important role in orofacial regulation and development. As the scale-free network in biological systems is characterized by extreme robustness against random removal of nodes, the random removal of more than 80% of nodes is necessary for the complete breakdown of this type of network; however, the selective removal of even a few hubs (only 20%) may easily destroy the entire scale-free network (20). These hubs, which constitute the skeleton of the Class II network, do not necessarily correspond to the most evident clinical signs collected during the orthodontic diagnostic

procedure. By removing a few of these hubs (by treating the corresponding orthodontic features), the entire structure of the system can be changed.

When a novel diagnostic approach is proposed, to minimize the difference between theory and actual findings, the investigator must distinguish between what is real and what is artifact, biological paradox, geometric invariance, or measurements error (27). During craniofacial morphogenesis, positional effects can influence the process that controls the development of the dental and alveolar arches to secure occlusion of the teeth and adaptation to the basal part of the jaws (28). As all cephalometric landmarks are established relative to each other, the correlations between cephalometric measurements may be due at least partly to geometric factors (29). When two variables share a reference point and cover the same anatomical region, a variation of this point will be common to both variables and will likely drive a correlation between them. For example, a low sella produces decreased numerical values in angles that intersect the anterior portion of the NS line; 63% of the variation of the ANB angle can be explained by the variation of the SNA and NS/ML angles, and so on (30). These positional effects in cephalometric analysis call for knowledge of the individual nature of orthodontic features (31). Network analysis reveals that further topological non-geometric correlations between cephalometric, functional, and morphologic features occur in the development of Class II and III malocclusions in the growing child. In the interpretation of anthropological associations, it is generally assumed that the presence of a significant non-geometric correlation indicates a biological coordination (29).

The pattern of co-occurrences observed in Classes II and III presumably reflects the auto-organizational properties of growing complex biological systems, as well as the preferential attachment of the new nodes to the most-connected hubs, a well-known phenomenon (4, 6, 32). The orofacial system exhibits a tendency to maintain normal occlusal relationships, despite variation in intermaxillary relations, through dentoalveolar compensatory mechanisms that can influence the vertical and horizontal balance of disharmony in skeletal, dental, and soft tissue forms and position (33, 34). In the process of formalizing the treatment plan, these unexpected emergent morphological properties are likely to affect subsequent therapeutic options. Finally,

the potential effects on treatment planning and on actual treatment emerging from our analysis were derived from the mathematical network model. Further experimental research is needed to clarify whether the clinical scenario will respond to change as the mathematical model would suggest.

## Conclusions

Orthodontic networks are able to represent the orofacial system in a visually intuitive way, making it possible to focus on the most closely connected features. These networks are presumably able to influence the treatment plan, perhaps even shortening it. Here, we present evidence that Class II and III malocclusions have different network structures. In the treatment of a new case, the value of every sign (feature) could be considered in the context of the network specific to that malocclusion. An important issue raised by calls for orthodontic network information is the potential integration of clinical data with radiographic and functional data to better elucidate the etiology, occurrence, and progression of malocclusion. The structures of the correlation networks provide indications of the

strength of interactions among orthodontic variables; the correction of interacting additive orthodontic problems could help shorten the treatment and perhaps increase its effectiveness. There are, however, other potential applications of a network-based approach to orthodontics, including the study of the morphogenesis of dentofacial deformities such as cleft palate.

## Clinical relevance

In the last decade, the science of complexity has undergone a revolution resulting in new tools and techniques for characterizing and visualizing biological systems through networks. These techniques have, for example, been applied to medical research ranging from epidemics to drug discovery. Here, we apply complex networks to orthodontics, representing clinical co-occurrence visually and analyzing and filtering information from patient data. We demonstrate that various types of malocclusion are characterized by different networks, suggesting the possibility of novel orthodontic diagnostic and treatment approaches.

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