General and Craniofacial Development are Complex Adaptive Processes influenced by Diversity

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Abstract

Complex systems are present in such diverse areas as social systems, economies, ecosystems and biology and, therefore, are highly relevant to dental research, education and practice. A Complex Adaptive System in biological development is a dynamic process in which, from interacting components at a lower level, higher level phenomena and structures emerge. Diversity makes substantial contributions to the performance of Complex Adaptive Systems. It enhances the robustness of the process, allowing multiple responses to external stimuli as well as internal changes. From Diversity comes variation in outcome and the possibility of major change; outliers in the distribution enhance the tipping points.

The development of the dentition is a valuable, accessible model with extensive and reliable databases for investigating the role of Complex Adaptive Systems in craniofacial and general development. The general characteristics of such systems are seen during tooth development: self-organisation; bottom-up emergence; multitasking; self-adaptation; variation; tipping points; critical phases; and robustness. Dental findings are compatible with the Random Network Model, the Threshold Model and also with the Scale Free Network Model which has a Power Law distribution. In addition, dental development shows the characteristics of Modularity and Clustering to form Hierarchical Networks. The interactions between the genes (nodes) demonstrate Small World phenomena, Subgraph Motifs and Gene Regulatory Networks.

Genetic mechanisms are involved in the creation and evolution of variation during development. The genetic factors interact with epigenetic and environmental factors at the molecular level and form complex networks within the cells. From these interactions emerge the higher level tissues, tooth germs and mineralised teeth. Approaching development in this way allows investigation of why there can be variations in phenotypes from identical genotypes; the phenotype is the outcome of perturbations in the cellular systems and networks, as well as of the genotype.

Understanding and applying complexity theory will bring about substantial advances not only in dental research and education but also in the organisation and delivery of oral health care.

Introduction

Dental development displays the characteristics of a Complex Adaptive System, being Self Adaptive and Self Organising.[1] The multiple interacting components at a lower level give rise to higher level emergent phenomena. The mature dentition also behaves dynamically, retaining the capacity for its individual units and the whole to adapt to environmental demands.[2] In contrast, in a system that is complicated rather than complex, the various elements maintain a degree of independence and do not develop a new structure. In this paper we use the dentition, for which there is extensive, hard data for many aspects of development, as a paradigm for craniofacial and general development. The genetic code is identical in 99% of the cells of the body and it is the epigenetic mechanisms which control the switching on and off of particular genes in specific tissues.[3]

Complex systems are present in such diverse areas as social systems, economies, ecosystems and biology. Complex biological systems and cellular networks may underlie most genotype to phenotype relationships.[4] There are many aspects of dentistry where understanding complex systems has a major role in advancing understanding, treatment and the organisation of care. Examples have already been provided in identifying molecular biotypes for periodontal disease[5] and in dental education.[6]

The main aim of this paper is to provide additional evidence that the dentition is a Complex Adaptive System, as an example of how this approach can be more widely exploited in dentistry. This will be done by outlining the characteristics of complex systems and of networks, emphasising the preferential attachment model of network growth in such systems. Diversity makes substantial contributions to the performance of a Complex Adaptive System. It enhances the robustness of the process, allowing multiple responses to external stimuli as well as internal changes. From Diversity comes variation in outcome and the possibility of major change as outliers in the distribution enhance the probability of exceeding thresholds or tipping points. The major components and phases of the development of the dentition into a mature functioning system will then be examined and considered against the general characteristics of Complex Adaptive Systems. Specific examples and further evidence will be considered, including several statistical models that have been linked to aspects of Complex Adaptive Systems.

Characteristics of a developmental Complex Adaptive System

A Complex Adaptive System in biological development is a dynamic process in which higher level phenomena and structures emerge from interacting components at a lower level. Complexity science aims at the quantitative modelling of emergent phenomena at a macroscopic level caused by the many interactions taking place at a microscopic level. Everything changes with time and in complex systems the dynamic interactions of the microscopic mechanisms may include spasmodic release of an internal strain with major changes. Interactions among the constituents give rise to emergent hierarchical network structures.

Self-organisation and emergence

Bottom-up self-organisation in a biological system arises from the interaction at a molecular level of genetic, epigenetic and environmental factors. From these interactions within cells and with the surrounding matrix, development and organisation within the tissues occur and higher level organs emerge. These organs bear no physical resemblance to the precursor entities.[7,8] The emergence and stability of these biological patterns can be influenced by stochastic, random perturbations of highly non-linear systems; noise in a system may contribute to a temporal pattern of gene expression during development.

Multitasking

Cells multitask by carrying out multiple functions. Multitasking also occurs as separate genetic pathways run in parallel and certain functional genes and signalling pathways act reiteratively controlling different stages of development. Further multitasking also occurs as an individual cell type controls different functions simultaneously.

Self-adaptation

Marked variation arises during development, not from a different number or type of genes in a specific tissue but rather from the epigenetic switches that are used to turn genes on and off and control their expression, together with the influences of environment.

During a complex biological development process there are critical phases or tipping points. These are temporo-spatial events that must be completed to allow further progress, acting as

thresholds. Failure to complete such a critical phase is likely to result in regression, apoptosis, or, if the overall development of the organ continues, a developmental defect.

The robustness of the biological system, on the other hand, is its ability to proceed with development in the face of challenges such as a genetic mutation or a major environmental insult and so maintain functionality. This robustness is increased by excess provision or 'redundancy'. This occurs when different genes can produce similar products, so that when there is insufficiency due to a mutation, another gene can be switched on to cover the deficiency. Moreover, the outcome of the developmental process, e.g. the dentition, may be robust enough and sufficiently well-formed to function satisfactorily in spite of containing some marked variation or developmental defects.

Diversity

The performance of Complex Adaptive Systems is enhanced by diversity with variation increasing the robustness of the system. The possibility of multiple responses to external events, as well as internal changes, increases the robustness of the process. Variation also increases the possibility of major changes in outcome as the probability of passing a threshold is greater.

Networks

Networks in biological systems follow a series of organising principles in their structure. Therefore, Network Theory aims to understand the origins and characteristics of the network components in Complex Systems. Such networks are regulated by fundamental laws that determine their behaviour.[9] Seeking to understand cell function must include exploring the intricate networks through which the proteins and metabolites interact.

Extensive databases contain details of the human genome. However, these databases do not explain how the multiple components required for development interact and function as a system. Rather the multiple functions within and between cells occur by networks with a discrete modular organisation. The network contains groups of diverse molecules, referred to as nodes, each having a different cellular function. Nodes are connected via links with other nodes, and those with more connections to other nodes become the hubs of the network. Modularity is a defining feature of most Complex Systems. Most networks show a high degree of clustering with modules that represent highly interlinked local regions in the network.

Network models and Complex Adaptive Systems

Several network models have been linked with different aspects of Complex Adaptive Systems. The behaviour of most Complex Systems emerges from the orchestrated interactions of many

components. Cellular function exhibits quantifiable patterns.[10] Network models are essential for understanding complex networks and such network models can be explored to help in interpreting observed characteristics.

Random network model

In random networks, most nodes have approximately the same number of links. Nodes that are highly connected and significantly deviate from the average are infrequent. A continuous normal distribution is found in studies of a number of parameters of development, such as adult height and the mesio-distal and bucco-lingual linear crown dimensions of teeth.

Threshold model

In this model there is a normal distribution of an underlying, continuously varying parameter upon which a threshold is superimposed. Beyond this threshold a different character is expressed, which is seemingly discontinuous with that of the underlying distribution (Fig. 1). For this reason it has sometimes been termed a quasi-continuous distribution.

INSERT FIG 1 HERE

Scale-free network model

The concept of scale-free networks and a proposed mechanism for their emergence has been outlined.[11] When all the different examples of a parameter under consideration are counted, e.g. the individual words in a scientific paper, most will have occurred infrequently but a small number will have been present more frequently and a few very frequently. When plotted graphically such findings give rise to a Power Law distribution (Fig. 2) which in linguistic studies has often been termed a Zif Distribution.[12] Thus the network's properties are often determined by a small number of highly connected nodes, the hubs.[11]

INSERT FIG 2 HERE

Many real networks, including human protein-protein interaction and metabolic networks are scale-free.[13] In complex networks with scale-free topology, two mechanisms are at work, growth and preferential attachment. Growth occurs as new nodes are added. Preferential

attachments occur when new nodes link preferentially to nodes that already have more attachments.[11]

Hierarchical network model

Modularity appears to be a characteristic of interactions within cells, as considered above. To account for the co-existence of modularity, scale-free networks and local clustering in biological systems, it is postulated that clusters combine to form a hierarchical network.[14]

A theoretical example of this model can be generated by starting with a single node which, when connected to each of three other nodes, becomes a hub. This process is then repeated a number of times. The resultant structure will have a very small number of 'super-hubs', a few hubs and many nodes (Fig. 3). When plotted graphically this modular network will conform with a scale-free, power law distribution. This hierarchical clustering is a generic property of a large number of real networks including those in the cell[9] and metabolism.[15]

INSERT FIG 3 here

Small World phenomena

Most complex networks, including random networks, have the Small-World property, so that there are relatively short paths between any pair of nodes. Therefore, perturbing the state of a given node can affect the activity of other nodes in the vicinity and of the network itself. [13] Figure 4 shows a theoretical example of the preferential attachment model of network growth in which the most highly connected nodes attract more new connections.

INSERT FIGURE 4 here

Subgraphs, motifs and motif clusters

The scale-free and hierarchical features of complex networks illustrate the principles of a network's large scale structure. Another way of characterising a network is to consider what patterns of interactions are present. A subset of nodes connected to each other in a specific pattern can be

represented as a connected subgraph. Networks with a more intricate structure may have various different subgraphs.[16] Within this more intricate structure, or complex network, all subgraphs may be present but they do not occur with equal frequency.

Subgraphs which occur significantly more frequently in a real network are designated to be motifs. Network motifs can be considered as the building blocks of a complex network.[17] The subgraphs and motifs that are found in a network are not independent of each other. Clustering of motifs into 'motif clusters' may be a general property of real networks.[10]

Gene regulation networks

Gene expression models address the mechanisms of gene regulation. The stochastic nature of biological processes can have important functional roles in a cell, such as physiological regulation and adaptation. Gelenke[18] introduced a probability model for gene regulatory networks that represents the concentration levels of each agent in the network.

The components of dental development

In this section, the major characteristics and phases of dental development will be outlined and analysed. (For more detailed consideration of genetic aspects see the paper of Thesleff [19] in this Issue). Dental development displays spatiotemporal, multidimensional, multilevel and multifactorial properties. It occurs by multiple interactions between various factors and is influenced by a series of developmental fields. As each tooth progresses through its different developmental stages, it is affected by its timing and position in relation to other teeth. These components are set out in Table 1.

INSERT TABLE 1 HERE

Dental development is multidimensional. The molecular and cellular interactions, the soft tissue tooth germ and the calcified tooth all operate and are formed in three spatial dimensions. These spatial dimensions also relate to the position of the unit in the tooth type series, in the same dental arch and the opposing arch. The dimension of time has great influence as there are thresholds to be passed at specific developmental stages and the total time of tooth development extends from 6 weeks in utero to some 20 years of age.

Multiple levels are present. From molecular and cellular interactions, within and between tissues, the soft tissue tooth germ emerges, grows and organises. From this germ, the macroscopic calcified tooth emerges.

The process is multifactorial, with genetic, epigenetic and environmental influences. Key components are signalling pathways mediating communication between cells and complex gene regulatory networks. What is also important to note here is that 99% of genes are present in all somatic cells and it is the epigenetic factors which activate and deactivate different genes in different cells and tissues at specific stages in development. The linear DNA structure is modified by DNA methylation, and the DNA structural complexes are modified by histone acetylation. Environmental factors that affect development can either be systemic, such as nutrition and generalised infection, or local, such as trauma or localised infection.[20]

The interactions which drive forward and balance development are multiple. The signalling pathways between the genes in epithelial and mesenchymal cells function reciprocally, reiteratively and progressively. Gene action is switched on and off by epigenetic factors. Cells interact with other cells and the surrounding matrix. Tooth germs compete for space within the growing dental arches and are affected by blood supply and innervation.

Various developmental fields influence the dentition. A clinically relevant update of the concept of morphogenetic fields,[21] originally postulated for the mammalian dentition[22] and then applied to human dentition,[23] incorporates a synthesis with the clone theory[24] and the odontogenic homeobox theory.[25] During the development of the dentition there is synchronised development of the innervation of each tooth and the vascular supply. Some workers have proposed that these fields are important in determining the position of tooth germ development.[26] Each tooth emerges through a continuous process that has a series of identifiable stages. It is initiated from a thickening of the oral epithelium at specific sites to form dental placodes. The genes, Msx1 and Osr2, act antagonistically in the patterning of the tooth morphogenetic field by controlling the expression and spatial distribution of mesenchymal odontogenic signals along the bucco-lingual axis.[27] During early tooth morphogenesis the Dlx genes are involved in the epithelial-mesenchymal reciprocal signalling events.[28] The transition from the bud to the cap stage relates to the induction of the enamel knot. Having undergone apoptosis at the late cap stage, the primary enamel knot is no longer detected at the bell stage. Secondary enamel knots develop at the sites of the future cusps in multi-cusped teeth. Signalling molecules from the secondary enamel knots stimulate proliferation of nearby cells, leading to folding of the inner enamel epithelium and subsequent cusp formation. Next, at the bell stage, after the underlying pattern for the cusps has been established, the dentine and enamel

forming cells differentiate. Dentinogenesis and amelogenesis proceed with mineralisation in the respective secreted matrices. Histodifferentiation for root development follows and dentine and cementum are formed.

Progression over time is an important component of this complex developmental process. Each tooth progresses from initiation to eruption into the oral cavity, although the length of this development process varies from tooth to tooth, particularly between those in the primary and those in the permanent dentition. Time is also a factor within each morphogenetic field, with later developing teeth of each tooth type in humans being smaller, less complex in shape and having greater variability. In the mouse, the mandibular first molar tooth can inhibit second molar development and an inhibitory cascade model in which initiation of posterior molars depends on the balance between intermolar inhibition and mesenchymal activation to determine sequential molar formation has been proposed.[27] Another example is in mouse Evc mutants where the morphogenesis of the first molar is strongly affected while the second molar both develops precociously and is larger than controls. [29]

Consideration of dental development against the general characteristics of a Complex Adaptive System

Self-organisation and emergence

Initiation and morphogenesis stages

Bottom up self-organisation is present in the interactions of genetic and epigenetic factors that control cellular development and produce the emergence of soft tissue tooth germs which develop at specific sites, with varying sizes and shapes, around the dental arch.

At the molecular level there are interactions between genes in which the functional genes are switched on by the action of signature sequences that have been activated by the release of regulatory proteins from regulatory 'master' genes. The action of functional genes is also influenced by specific and general epigenetic factors, as in the regulation of dental stem cell differentiation by histone demethylase. In addition, general and local environmental factors affect these interactions. Reciprocal and sequential interactions between the ectodermal and mesenchymal cells and transcription factors are controlled by multigene signalling pathways, such as Fgf,Bmp,Shh,Wnt and Tnf. In addition to these intracellular links, extracellular effects occur, as in the modulation of the extracellular integration of cell signalling pathways by Lrp4.

An example of a motif within the larger network structure from a Sonic Hedgehog pathway is illustrated in Figure 5. Disruption of the Shh pathway results in a variety of dental anomalies.[29]

INSERT FIGURE 5 HERE

During dental morphogenesis both sex chromosomes and intrauterine male hormones influence tooth size, possibly influencing different dimensions. A proposed mechanism for testosterone action is that is binds to androgen receptors in the cytoplasm and that this complex enters the nucleus where it bonds to DNA and affects transcription.[30]

This series of interactions that regulate the initiation and morphogenesis of tooth germs, determine their number, the region of the dental arch (the morphogenetic field) in which they develop, and the type, size and complex shape of each tooth.[20,31]

Differentiation stage

As odontogenesis progresses to differentiation and mineralisation the characteristics of self-organisation and emergence are still evident. With the underlying pattern and dimensions of the cusps determined, the dentine-forming cells (the odontoblasts) and the enamel-forming cells (the ameloblasts) differentiate, controlled by additional genes not active during the previous stages. Dspp expression in maturing odontoblasts is affected by Tgf-B signalling:[29] through an epigenetic mechanism, the histone demethylase Jmjd3 influences the expression of extracellular dentine matrix. The ameloblasts secrete the enamel protein matrix to which the amelogenin gene (Amelx) contributes the greatest percentage of protein but the enamelin gene (Enam) provides the protein which controls the initiation of enamel mineralisation. As mineral deposition advances the proteases, Enamelysin (Mmp20) and Kallikrein (Klk4), act to remove matrix proteins and allow increased mineralisation. Amelogenesis determines the final outline size and shape of the tooth with different thicknesses of enamel on different aspects of the tooth.

Non-sydromic abnormalities of enamel formation have been associated with mutations in an number of genes with different functions: secretion and later removal of enamel matrix proteins (AMELX, ENAM, C4orf26, MMP20, KLK4); intracellular (FAM83H, WDR72); transmembrane (SLC24A4, COL17A1) and basement membrane (LAMA3, LAMB3).[32] Thus , amelogenesis exhibits the features of a motif cluster in a complex network.

Multitasking

Multitasking occurs during dental development as different genetic pathways act simultaneously and in parallel. Further, certain functional genes and signalling pathways act reiteratively controlling different stages of development, e.g. p21, Msx2, Lef1, in ectoderm, Msx1, Barx1, Dlx1-2, Pax9, as in mesenchyme, and Bmp, Fgf, Shh, Wnt as signalling pathways between these two tissues from the initiation stage to the end of morphogenesis.[20] Multitasking is also seen later during the differentiation phase in enamel as simultaneously mineralisation increases and enamel proteins undergo breakdown and removal, allowing mineralisation to advance. The onset of enamel formation involves fenestration of the basement membrane, extension of the ameloblast process into irregularities on the pre-dentine surface and expression of enamel proteins. Coordinated replacement of the hemidesmosome / basement membrane complexes with the mineralisation front apparatus is critical for normal function.[32]

Summary of evidence for self-organisation, bottom-up emergence and multitasking

From interactions at the lower level, i.e. molecular, cellular and developmental soft tissue interactions, the macroscopic mineralised teeth emerge at the higher level. The individual teeth are organised under the influence of morphogenetic fields into spatially distributed groups to form an integrated, effective, functioning system. The mature individual teeth and the dentition bear no resemblance to the earlier components from which they have emerged by self-organisation. Enamel formation during dental formation shows evidence of self-organisation, emergence and multitasking with different genes and types of cell products essential to the process orchestrated by the ameloblasts. The multitasking seen during odontogenesis is characteristic of a complex adaptive system.

Self-adaptation

Three further characteristics of complex systems are diversity, critical phases and robustness.

Diversity

Self-adaptation is seen in the diversity of the dentitions which are present in different species. This diversity arises not so much from different numbers or types of genes, as these are similar in the different species, but rather from the epigenetic switches that are used to turn genes on and off. Diversity also occurs within species, as seen in the variation in human tooth number, size, shape and mineralisation. This range of variation allow adaptation to different masticatory demands and to

changes of the skeletal base in which the dentition develops and functions. Substantial differences have been shown between four human ethnic groups in mesiodistal crown dimensions and also in the relative sizes of different tooth types.[33]

Interaction between the soft tissue tooth germs as they are developing adds to the diversity of the forming teeth. Within the morphogenetic fields, the later forming teeth are more variable, with some evidence from the murine dentition that the dimensions of the earlier forming teeth influence the size of later forming teeth, and even whether a supernumerary tooth will develop.[34]

Critical phases

There are a series of critical phases during dental development which determine whether a mature tooth will be formed, and, if it is formed, whether it will have a developmental defect or not. Transcription factors in the Msx, Dlx and Lhx families are necessary for both initiation of the tooth germ and for progression from the initiation stage into morphogenesis.[20] If progression does not occur at a critical phase, the tooth germ may undergo apoptosis. During the differentiation stage, partial or complete failure in the secretion of enamel matrix proteins leads to hypoplastic enamel defects in the mature tooth of varying types and severity. Later, in amelogenesis, failure to remove the secreted matrix proteins leads to hypomineralisation defects of varying degrees.

Robustness

Although it incorporates many detailed interactions with critical phases, another aspect of dental development is the robustness of the process and the relative efficiency of the outcome, even with variations and mild or moderate anomalies. During development, when a gene has a mutation which decreases or prevents its function, compensation may sometimes occur between different members of the same gene family, e.g. other members of the MSX family may be activated when a mutation has decreased the function of one of them.[31] In the mature dentition, adequate mastication is possible with some variation in tooth number, size and shape and in the presence of mild or moderate mineralisation defects.

Summary of evidence for self-adaptation

Diversity is seen in the markedly different dentitions present in different species of animals. Within species, dental variations also allow adaptation to different environmental challenges. Dental development has multiple critical phases, interference with which can lead to a range of dental variations. Even so, the process and outcome have a considerable degree of robustness.

Statistical models and the dentition

In this section evidence is presented that the findings from studies of the dentition are compatible with the statistical models characteristic of complex adaptive systems.

Random network model

From many measurement studies of different populations, the mesiodistal and buccolingual crown dimensions of teeth have been found to have a normal distribution with the range of values described by a mean value and standard deviation.[35]

Threshold model

Brook [35] proposed such a model based on the normal distribution of tooth size with thresholds at the lower end describing microdontia and hypodontia and at the upper end describing megadontia and supernumerary teeth. Females tend to have smaller teeth and a higher frequency of hypodontia and microdontia; males tend to have larger teeth and a higher frequency of megadontia and supernumeraries. The subsequent genetic and histogenetic findings of some of the mechanisms by which these anomalies arise at critical phases during development have provided the developmental rationale for this model which was based on statistical analysis of clinical and epidemiological findings. Here the model is developed to include more recent evidence that changes in shape are associated with changes in size (Fig. 6).

INSERT FIGURE 6 HERE

Scale Free network model

In a study of upper incisor teeth, multiple dimensions were measured on dental study models using 2D image analysis and customised software. When the frequencies of the factors in these measurements were plotted a Power Law Distribution, as shown in Figures 2 and 4b, was found.[36]

Hierarchical network model

Each individual entity, e.g. gene, is a node and interacts with one or more other nodes. A few nodes, such as the signalling molecules, have multiple connections to other nodes and act as hubs. The hub and the nodes connected to it form a module. Such modules can be joined together by 'super hubs' to form a hierarchical model.[9] The repeated actions of a few genes during dental development suggest that this type of model may be valuable in further studying odontogenesis (Fig. 7).

INSERT FIGURE 7 HERE

Gene regulation model

Salazar-Cuidad and Jernvall[37] developed a gene network model to account for the development of mammalian teeth. The model depicts tooth development from the cap stage to the early bell stage and successfully reproduces the crown morphologies, the intermediate stages including the correct temporal spacing between the stages, and the patterns of expression of known genes.

Conclusions and future work

The dentition, both in development and its mature form, has the general characteristics of a Self-Organising and Self-Adaptive Complex System. This exploration provides the foundation for future investigations of this model. As a basis for these computational studies there are published genetic databases, extensive histogenetic investigations, and accurate macroscopic phenotyping data from 2D and 3D measurement studies. Thus, the dentition is a valuable model for investigating the control of general development and the causes of developmental abnormalities. The stages of development are accessible though animal models and the macroscopic outcomes can be phenotyped accurately and in detail in both modern and ancient populations. Moreover, the same genes, the same epigenetic and environmental influences and similar mechanisms are present during development, whether of the dentition or other body systems.

Disclosure

The authors have no conflicts of interest to declare.

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Legends to figures

Figure 1. A Normal distribution with a threshold beyond which a different character is expressed.

Figure 2. A typical Power Law distribution. The vertical axis is the frequency with which the individual frequencies on the horizontal axis occur.

Figure 3. A typical hierarchical network based on Barabasi [9] (a) node (b) nodes joined to a hub to form a module (c) hubs joined to super-hubs to form a hierarchical network.

Figure 4. Small World & Scale Free networks. (a) preferential attachment model of network growth where most connected nodes attract new connections. (b) Power-law distribution of node degree (connectedness).

Figure 5. A subgraph constructed from a Sonic Hedgehog (Shh) pathway. In signal receiving cells, secreted Shh protein binds to the receptor Patched 1, (Ptch1), and activate Smoothed, (Smo), a transmembrane protein. Smoothed prevents proteolytic processing of the transcription factor Gli3 into its repressor form. Gli activators now regulate the transcription of Shh pathway downstream genes that include Ptch 1 and Gli1.[38] This pathway requires cells to have intact primary cilia projecting from their surfaces. Cilia formation and maintenance require mobilisation of proteins at the tip and base of the cilia by intra-flagellar transport (IFT) complexes. IFT acts downstream of Ptch1 and Smo, with one of its components restricting the Shh pathway.[39]

Figure 6. Continuous distribution of tooth size, shape and number.

Figure 7. Overview of dental development. Upper part of figure derived from http://bite-it.helsinki.fi/ (accessed 7 Jan 2014).