INNOVATION

THEORY AND CONCEPT

Part III of Theory of Form: Role of Genetics in the Self-Organizing Form

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Abstract

The current consensus is that biological forms are not modifiable. With this assumption, the origin of deformities has been conveniently attributed to genetics, preventing clinicians and scientists from investigating the real cause for changes in the trajectory of form. However, clinical experience does not support this position, showing that form is, in fact, modifiable over time. In addition, it has never been clearly explained how genetics affects form. In this article, we dissect the role of genetics in the context of the self-organizing biological form. Genetics, by introducing new proteins, creates new constraints at each micro-state of the biological form, upon which Entropy and Emergence exert their effects to define the trajectory of the form. As the biological form evolves, different opportunities arise for the clinician to change the form trajectory, intercept and correct any developing deformities.

Genes and form

As we discussed in Part II of Theory of Form, the result of gene function is the production of proteins, which due to physical and chemical forces, change from primary to secondary, tertiary, and quaternary forms. The limited shape of proteins alone cannot explain the diverse forms of biological entities. This emphasizes the role of the organization of units, rather than their structure, as the significant factor influencing the final form. As an analogy, the final form of a building is not determine by the shape of the bricks, but by their arrangement. In addition, proteins are not the only units of biological material, and the interaction with other molecules can further change the trajectory of the form. Since genes only contribute to protein synthesis, who or what oversees assembling and organizing of the blocks of biological form to produce a certain shape? The answer to this question lies in the cells and the self-organizing process.

Cells at the center of the self-organizing form

There is an important question at the core of the discussion of the form. Do proteins, produced automatically and sequentially, push the form in a specific direction? If that was the case, the DNA would be considered the mastermind behind form creation. However, DNA does not automatically or sequentially produce proteins. Instead, the cells based on their surroundings (constraints) turn DNA transcription on or off, as needed (Figure 1). The cells activate DNA to create new proteins at different times which help them adapt to a constantly changing environment.

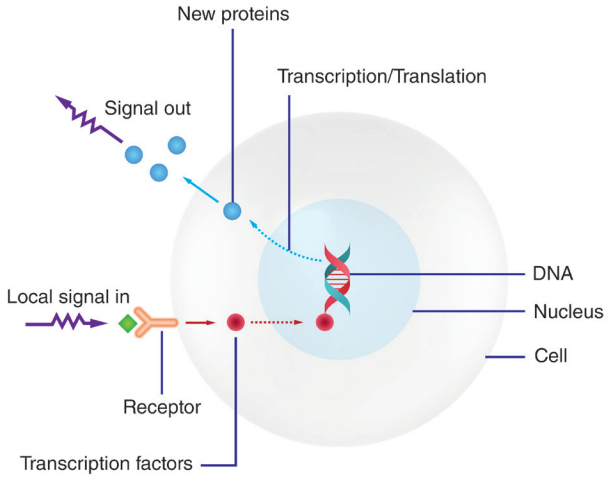

Figure 1. Cells adapt to their surrounding environment. *Cells respond to environmental changes by continuously receiving signals through various cell surface receptors. These signals activate specific proteins inside the cells, called transcription factors. Activated transcription factors move to the nucleus, attach to the DNA, and unravel only a tiny segment of the DNA to start the process of RNA synthesis (transcription), followed by protein synthesis (translation) allowing cells to adapt. Some of those proteins may be released into the extracellular space and can, in turn, act as signals to neighboring cells.*

From monocellular to multicellular form

In this article, we do not try to address the constraints that cause the emergence of macro-molecules such as DNA, RNA, or proteins and how life emerged from their interactions in the format of a cell. Neither do we try to explain what causes the monocellular organisms to proliferate or combine their efforts with existing cells to create a multicellular form. Instead, we want to understand biological form much later, at the multi-cellular stage.

The form, at the level of one cell, is primarily the result of that cell's internal (macro-molecules and their interaction) and external (all the physical and chemical forces applied to a cell) constraints. When the multicellular level starts to evolve through proliferation, two new factors can affect the form. First, an increase in the number of cells by Entropy automatically creates a primitive spherical form (Figure 2). Second, as the number of the cells increases, it creates new constraints for the existing cells.

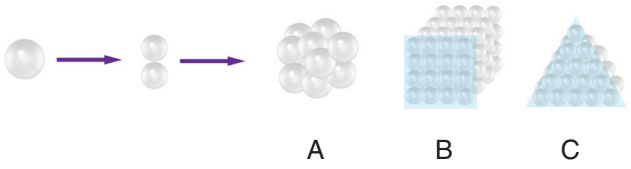

Figure 2: Laws of physics determine the early stages of form development. *As cells proliferate and their number increase, the form assumes a sphere or ball shape (A), not a cube (B) nor a pyramid shape (C). A sphere has a minimal surface area for a given body and requires less energy.*

This primitive form automatically changes the environment of the cells in the different areas of that spherical mass. Cells in the center of the mass are exposed to different constraints compared to the cells on the surface. For example, access to nutrients and energy through exchange with its surroundings is more difficult for cells located in the center of the mass than those at the surface, which could push those cells towards differentiation or death. In a multicellular organization, different cells assume different functions leading to differentiation. Differentiation has two immediate effects. First, it increases the survival of the cells in some areas of the mass, and second, it simultaneously prevents redundancy of all cells carrying the same function, preserving energy. Differentiation has a larger impact on the form leaving its undeniable signature in many aspects of the biological forms. The shape of the cells and the proteins they release differ based on their assigned function. This creates new surroundings in different areas and give different regions of the mass distinct characteristics and shapes. Therefore, one can say that differentiation adds to the diversification of the form. As diversification continues, compartmentalization occurs, where cells with similar functions join to become part of a larger compartment (hierarchy).

Proteins as dynamic constraints of form

As we discussed above, different constraints change the entropy of the form. That is why each micro-state has its own Entropy. The presence of the new constraint changes the organization of the units and therefore, represents the new functional form. Based on the concept of encapsulation (discussed in Part I of Theory of Form), the functional form of one micro-state becomes the mass unit for the next micro-state and its new functional form. Hence, we can have multiple mass and functional forms, as the biological form evolve.

Cell-dependent effects of proteins on the form

Proteins as tools for cell sorting

Differentiation and diversification results in cells with similar functionality staying close to each other, which produces different patterns in a multicellular organism, especially at an early stage of the creation of form. Proteins on the cells' surface help arrange the cells based on physical and chemical interactions between them, which contribute to the sorting of the cells. Sorting is not specific to biological forms and can also be seen in non-biological forms (Figure 3). For example, a heterogeneous mixture of liquids, such as oil and water, sort themselves into specific shapes that coalesce into a larger island of one homogenous fluid, enveloped by the other fluid. The least cohesive droplets (lower surface tension) envelop the most cohesive droplets (higher surface tension).

The number of adhesion molecules or the type of adhesion molecules on the surface of the cells, can play a vital role in sorting the cells and creating specific shapes. The exchange of weaker for stronger adhesion guides the cell rearrangements. This drives the system towards a configuration in which total cell-cell bonding energy is maximized and a thermodynamically favorable structure is created. In this form, energy is distributed to produce an equilibrium. By introducing new proteins at the surface of the cells a new thermodynamically favorable structure can be created. Cell sorting could also explain the migration of the cells observed during embryonic life (Figure 4). Cellular migration decreases as the density of the cells increases, and matrix formation by cells prevents further movements.

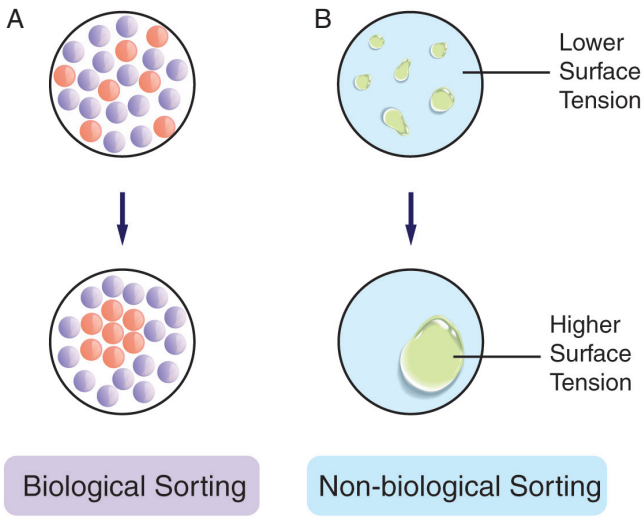

Figure 3: Similarity in the sorting behaviors of biological materials (cells) and non-biological materials (liquids). *A mixture of two different cells (orange and purple spheres) with different affinities (different number or types of adhesion molecules) spontaneously sorts itself into two distinct cell populations (A), just like a mixture of droplets of two liquids (yellow and blue) with different surface tension (B) sorts itself into a liquid surrounded by another.*

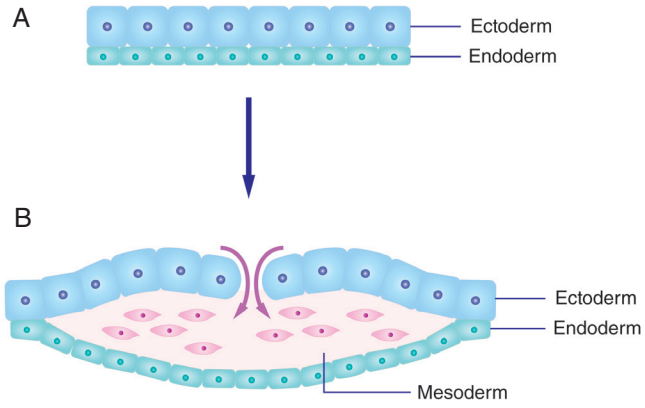

Figure 4: Migration of cells plays a significant role in creating the body's general form during development. *Early during development, the embryo adopts the form of a disk with two cell lawyers, ectoderm and endoderm. The migration of a group of cells from the ectoderm toward the space between the endoderm and ectoderm gives rise to the mesoderm layer. This migration changes the embryo form from a 2-layer (A) to a 3-layer (B) structure. Each of these lawyers later give rise to different body structures with different shapes and functions.*

Proteins as networking tools

Physical and chemical interaction between free proteins and proteins attached to the surface of the cells can initiate a chain reaction in the cells, which may change the characteristics of the cells and their activity. Since these proteins are produced by different cells, one can claim that in a multicellular mass, proteins carry another function: cell communication (Figure 5).

Signaling between released proteins and cell membrane receptor proteins allows cells to communicate and harmonize their activity and differentiation. When soluble proteins diffuse from their cell source following thermodynamic laws, they can produce a gradient. Cells exposed to different protein concentrations along that gradient will have distinct responses, resulting in DNA transcription and translation that produce new proteins, which in turn can change the behavior of adjacent cells. The overlap between gradients of different proteins is another important factor in changing cell behavior and, therefore, the final form (Figure 6).

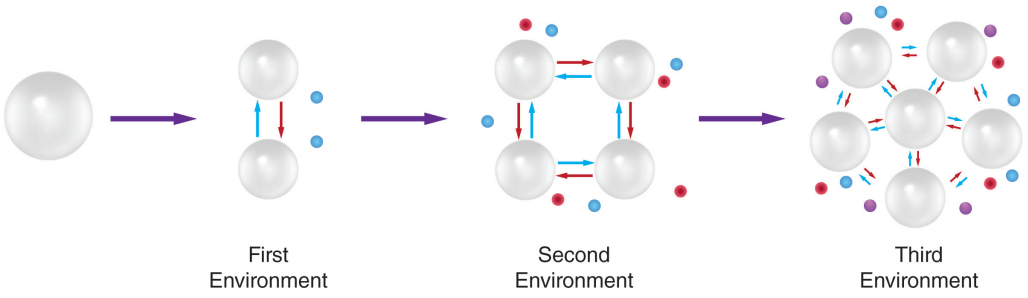

Figure 5: Cells communicated through cell-to-cell interactions and protein signaling. *Interaction between the cells evolves as the number of cells increases. In addition to the cell-to-cell direct interactions, protein production increases. Released proteins signal through cell membrane receptors, to activate transcription factors and produce new proteins. This cascade of events produces a self-evolving environment with increased complexity and structural organization.*

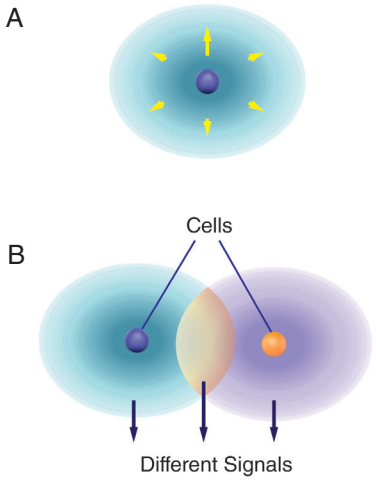

Figure 6: Gradients created by diffusion of proteins modulate cell activity. *As soon as soluble proteins are released into the extracellular space, they diffuse. This diffusion produces areas with different concentrations of proteins or gradients (A). The response of cells to different concentrations of the same proteins is distinct, which causes their differentiation and activity to change affecting the final macro-state. At the same time, many proteins are produced at different locations creating overlapping gradients that interact with each other (B). These proteins may have synergistic or antagonistic effects on signaling, further modulating the activity of the cells and their differentiation.*

Signaling contributes to the creation of form not only by stimulating cells into different fates, but also by causing apoptosis or programmed cell death. For example, during limb development, apoptosis helps guide the formation and shape of the digits, by eliminating the cells in the web between the fingers (Figure 7).

Cell-independent effect of proteins on the form

Proteins as a component of the extracellular matrix

Cells in humans differentiate into approximately 200 distinct cell types. As soon as a cell accepts one specific fate, in most conditions, it cannot return to a less differentiated

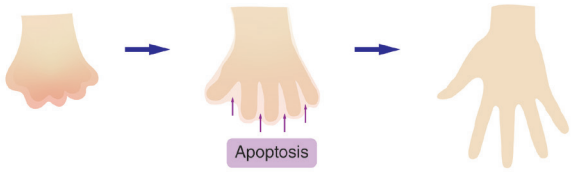

Figure 7: Apoptosis or programmed cell death helps shaping the hand. *Apoptosis plays a significant role in morphogenesis during development. For example, during limb development, apoptosis of the cells in the area between fingers allows the separation of digits into individual structures, giving rise to the characteristic hand shape.*

or specialized stage, however, some exceptions have been reported. Differentiation causes the cells to produce specific matrix proteins that are the basis of the extracellular matrix surrounding the cells of different tissues. The shape we see, is mostly comprised of different matrices, as cells alone, in general do not contribute significantly to it (Figure 8). From all different matrices, the matrix of bone, cartilage, connective tissue, and muscles are the most prominent factors in the form of animals.

Interaction of Genetics with Entropy and Emergence

Based on the above discussion, one can conclude that proteins produce new interactions between the cells or become part of their surrounding matrix, changing the trajectory of form by Emergence. Energy is required for DNA to produce proteins. The energy is not consumed for arranging the molecules but rather for creating new molecules that spontaneously attain a specific configuration and function (Figure 9). In this context, the energy does not push toward one form or another directly, it just helps introduce new players into the game, dramatically changing the Entropy of each micro-state and the Emergence of new micro-states.

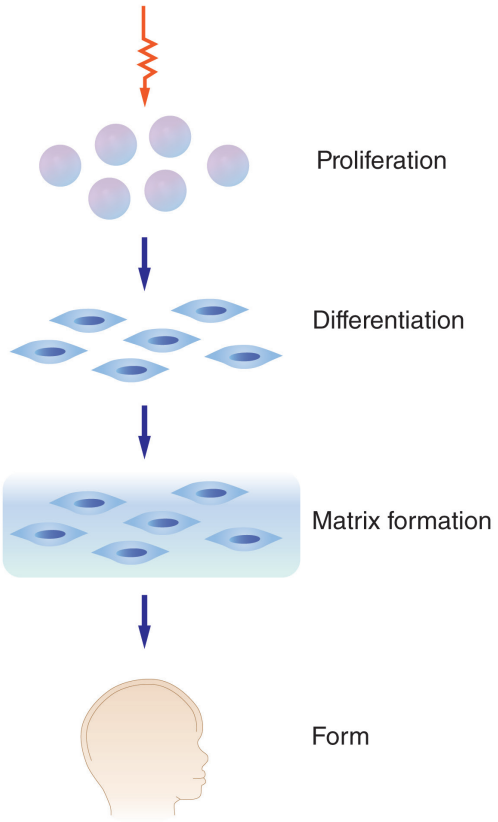

Figure 8: Extracellular matrix production plays a crucial role defining the overall form. *Proliferation increases the number of cells until local signaling instructs cells to differentiate into a particular cell type. As a group of cells differentiates, they produce a specialized extracellular matrix around themselves composed of different structural proteins that adopt a specific shape, participating in the overall form of the individual.*

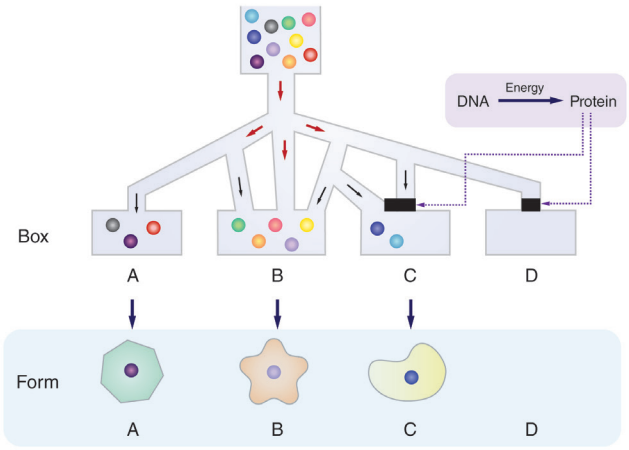

Figure 9: Interaction of Genetics, Entropy, and Emergence. *At each stage of development, proteins can change the probability of the formation of one micro-state over the others. In this schematic, balls (units) collected in the basket randomly take one path leading to creation of a form (forms A through D). Protein synthesis changed the probability of form C occurring, and blocked the formation of form D. These changes in micro-state probability constantly evolve depending on where and how many proteins are produced. Under these conditions, complex forms are reproducible without a "DNA map" of a pre-determined form.*

Adaptability

Adaptability is one of the main characteristics of biological forms. It demonstrates the interaction between Entropy and constraining factors that can change the trajectory of the form and stimulate the emergence of a new form. Adaptability can be studied at different time intervals. Suppose adaptability is studied during different generations of biological forms. In that case, it exposes the evolution of form between generations. Depending on how many generations we study, we can see the evolution of form between species (more extended time period) or sub-groups of the same species (shorter time period). Since this adaptability is transferred from one generation to another, it expresses the constraints applied to the form due to gene mutations, which introduce changes in protein structure or level. These mutations reflect the changes in the environment that select specific mutations to continue into the next generation and others to disappear by natural selection. Some changes in shorter intervals of time between different generations may be related not to mutations but modifications in DNA structure or epigenetic factors.

However, the adaptability of form that an organism can demonstrate during its life is not due to mutations. This adaptability is mediated through the machinery that reads the DNA. The interaction of the cells with each other and their surroundings, constantly modulates gene expression through the activity of transcription factors, and the production of distinct proteins at different times. This is how DNA puts its fingerprint in the biological form, by changing the trajectory of form. Cells can change their organization as needed by controlling the production of proteins. Only multi-cellular organisms with the optimized machinery to read DNA as needed, can evolve. This machinery is transferred to the next generation, mainly through the cytoplasm of the zygote. Transferring DNA to the next generation would be useless without transferring the machinery to read it. That is why the zygote plays a fundamental role in starting the biological form. It should be emphasized that during an individual's life, DNA modification (not mutation) has also been used by cells as a tool to regulate DNA transcription and therefore, protein production.

Sequential creation of form

Even in the absence of adaptability that leads to changes in the trajectory of the form, the form of a multicellular organism is constantly changing based on its self-organization process, which reflects the magnitude of proliferation, differentiation, migration, apoptosis, and matrix formation of the cells at that particular stage. These cellular changes produce a dynamic self-organizing form (Figure 10).

During the sequential creation of the form, the constraining factors gradually change. In this process, proteins create the most important constraints. During morphogenesis and patterning, the form created is not functioning yet, however, it is prepared for its future survival. How is that possible?

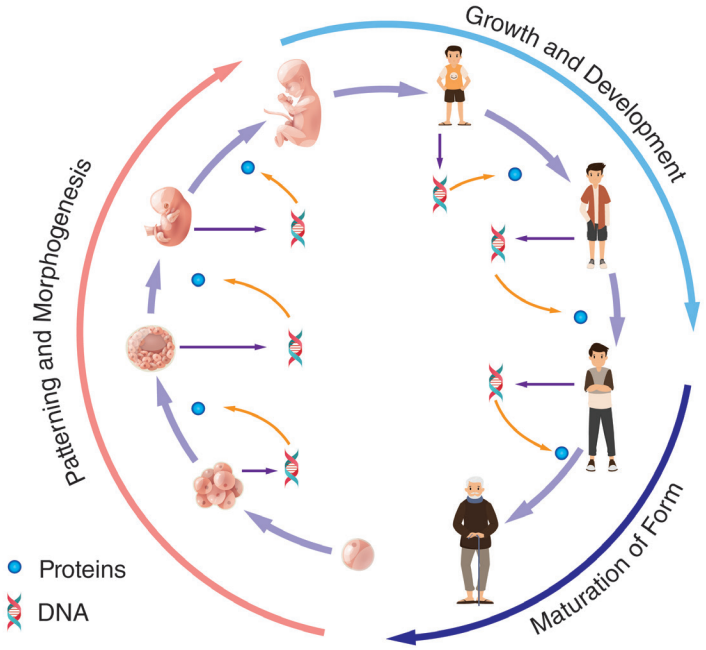

Figure 10: Sequential creation of a dynamic form. *The first stage of shape formation is patterning and morphogenesis. In this stage, the general form of the body is defined in the protected environment of the womb. The second stage is a coordinated increase in the size of the form after birth, also considered growth and development. The third stage that continues throughout the life of the organism is the maturation of form.*

The functional world, selects the most adaptable multicellular organisms with a particular protein structure. In other words, those trajectories of the form that better fit and adapt to its surroundings continue to produce successive generations, while the others are gradually eliminated. Since proteins define the trajectory of the forms in biological forms, one can say that the most fit self-organizing form had access to adequate proteins. Natural selection defines the material that cells can utilize to create the form. This makes the result of self-organizing form very predictable. Proteins did not create the form, but the presence of adequate proteins push the self-organization process to a successful form that can better fit its surroundings.

At the beginning of the creation of the form, it may seem strange that the initial form can predict its future functionality. In reality, this process has already been "tested" by nature, and those self-organizing forms have been selected for having the proper trajectory, through the necessary proteins. Information about these proteins is stored in DNA. Therefore, while DNA does not dictate the form, it plays a fundamental role in the creation of form.

A protected environment was required before birth to allow the self-organization of the cells to emerge into a predictable form. However, after birth, exposure of multicellular organisms to other constraints further modifies the form. In addition, the form never reaches its final shape since internal and external constraints are constantly changing. This constant adaptation of the form during life is considered the maturation of form.

Role of CNS in Form Creation

Centralization and feedback-based network

As the number of cells increases, the number of signaling proteins increases, allowing a network between the cells to emerge. In contrast to some of the signals connecting the neighboring cells (paracrine factors), some secreted proteins connect cells in remote locations and organize far apart areas of the mass of cells (endocrine factors).

While endocrine factors are one mechanism of signaling between separated areas of the mass of cells, some cells adopt further specialized communication roles, giving rise to the nervous system. As we discussed in Part I of Theory of Form, centralization is necessary as the mass size and diversity increase. The Central Nervous System (CNS) coordinates not only the functions of different parts of the multicellular organism but also keeps their size (growth) harmonized for the tasks they have to perform. While at the beginning, the form did not have any center coordinating its different parts, the CNS gradually takes this role and, through the endocrine system and the peripheral nervous system, ensures that far apart areas of the form remains coordinated and functional. One can argue that the self-organizing form through upward feedback, gradually produces a center that, through downward feedback affects the self-organizing form. This is similar to the organization of people in a society, when a government is gradually created that then controls and coordinates the function of the members of that society.

Centralization through feedback loops plays a significant role in creating the form, especially after birth. Any changes in the feedback that CNS receives from different body parts cause CNS to react by changing the coordination between the different parts of the form through changes in neuromuscular activity in that area. If neuromuscular changes become chronic, they will be associated with matrix adaptation, such as bone and cartilage adaptation. Extreme form adaptation could create a deformity or a significant deviation from the original form. For example, when a person adopts a mouth breathing habit, the general coordination of different parts of the oral and nasal cavity will be affected and can produce a deformity of the jaws.

More importantly, the same way that changes in feedback received from local areas of the form can affect the CNS reaction, and in the long term cause a deformity, so can normalizing this feedback lead to correction of these deformities with vast clinical applications.

Autonomy of different parts of the form

While the CNS can control the coordination between different body parts, each part has a certain degree of autonomy in adapting to local factors. Exposure of one hand to higher stress can change the form of that hand without affecting other parts of the body. Paralysis of one leg can affect the form of that leg without directly affecting the form of the other leg. This autonomy plays a purpose: first, it allows adaptation to local factors right where it is needed, and second, it prevents the progression of the deformity to different areas of the form.

It should be emphasized that while different parts of the form, to some extent, have autonomy in the progression of the localized form, since they are in network with other parts of the form, they can, directly or indirectly, affect the progress of the form in other areas with significant clinical importance. A simple example of these networking effects is the fact that deformities in the oral cavity can affect the nasal cavity form, and vice-versa.

Adaptation, Variation and Malformation

Different degrees of adaptability

While all tissues in biological forms have a certain degree of adaptability, tissues more affected by the surrounding environment, such as muscles and intra-membranous skeleton, express a higher degree of adaptability throughout life. On the other hand, some tissues, such as the endochondral skeleton, demonstrate less adaptability since they play a more fundamental role in preserving the basic form. Therefore, some parts of the form are more modifiable than others. The different degrees of adaptability cause the form to progress in different directions at the early stages of life, called growth and development. For example, endochondral bone formation allows an increase in the length of the long bones until puberty, after which the increase in length is limited or nonexistent. However, during maturation of the form the thickness of the bone can change constantly based on the mechanical stress applied to it. The adaptability of the intra-membranous skeleton, such as facial bones, can continue throughout life which can explain why facial changes are so prominent during life.

Based on the above discussion clinicians should select the proper biological targets for their treatment at different stages of life to stimulate adaptation and modify the form as needed. While during growth and development the majority of the tissues demonstrate significant adaptability, during the later stages of life, malformations should be corrected by targeting the intra-membranous skeleton, secondary cartilages, and muscles.

Generalized versus localized malformations

Variability in biological forms and therefore, malformations, can be DNA-dependent or self-organization-dependent. DNA-dependent deformities demonstrate themselves primarily as a generalized malformation. A mutation affecting a protein structure, can simultaneously affect many tissues where that protein is normally active. While the majority of these mutations are lethal, individuals with milder versions of these mutations can survive and contribute to the population generalized malformations. However, they never become the mainstream biological form in the population

On the other hand, localized deformities are mostly self-organization-dependent. These occur when a factor or factors locally affect the self-organizing process and cause an adaptation of the form, interrupting the coordination between the affected part and the rest of the biological form. This lack of coordination is considered a malformation. Localized deformities in an area or compartment of the form may not affect other areas of the form. This interruption and adaptation can occur at the level of cell proliferation, cell differentiation, or matrix formation. The earlier the interrupting factors appear in the process of creation of form, the larger can be the affected area of the form.

As we discussed earlier, centralization occurs later in the process of form creation, which can play a very important role in controlling the form after birth. Therefore, later in life, an interrupting factor with a local effect on the form, can change the feedback to the organizing center of the form, such as the CNS in humans. The CNS may then change the coordination between different parts of the form to accommodate the local deformity. For example, if local factors prevent the traverse growth of the upper jaw, the CNS may need to change the position of lower jaw to accommodate this deformity of the upper jaw, changing the trajectory of the form that now starts to express some deformities in other areas, including in the mandible

Deformity is not normal variability

While major mutations in protein structures could contribute to the variability between species, minor mutations in the

regulatory area of the DNA could define the variability between individuals of the same species, without causing malformations, since protein functionality has not been affected. In other words, species mainly demonstrate changes in protein structure, while differences between individuals mostly demonstrate variation in the levels of protein production rather than differences in protein structure.

In addition, variation in self-organizing form through Entropy and adaptation allows individuals with similar DNA to gradually diversify the trajectory of their biological forms.

These variations can indirectly change the threshold of cellular response to different factors and, therefore, by hyper-sensitizing or hypo-sensitizing the tissues to how different constraints affect the form. Interestingly, in the absence of those constraints form may not be affected. Usually, the self-organizing process can also automatically compensate for any change in sensibility and prevent a malformation. For example, by changing the inclination of the teeth, nature tries to prevent the development of crossbite. Similarly, in instances when nature was not able to prevent the development of malformation, the clinician by stimulating compensatory mechanisms, can prevent the development of such deformities.

In conclusion, the changes in the regulatory sequences of DNA can indirectly contribute to malformities by changing the susceptibility of the individual to interrupting factors, however, this malformity is not directly caused by the DNA changes and therefore is not a normal variability. For example, a patient susceptible to allergies can show adaptation of facial form to changes in breathing function due to chronic nasal obstruction. However, if allergies are kept under control and breathing function normalized the deformity may not occur.

Clinical importance of self-organizing form

Genetics as the book of forms

Genetic defines the rules for the creation of form. However, based on constrains available at each stage of the creation of form, each person has a catalog of forms available. The job of the clinician is to help the patient obtain the most functional and harmonious form.

Genetics defines the spectrum of variability between species, variability in a population of the same species, variability in the creation of form at each stage of development, and variation of form during an individual's life. Self-organizing form, on the other hand, defines for each stage of development, which "page" of this "book of forms" will be selected. Self-organizing form, therefore, is not a good expression of the variability between species, but it reflects the variability in the same species, and most importantly the variability in the same individual over time.

Clinical Applications of Theory of Form

Understanding the role of Entropy, Emergence and Genetics in the creation of a self-organizing form allows us to explain and understand form variability or the occurrence of malformations. Genetics does not directly dictate the biological form, but rather preserves the units, over time and across species, upon which Entropy and Emergence exert their effects. In self-organizing biological forms, and humans in particular, the ability to adapt to different factors may, indeed, interfere with normal development. However, a self-organizing form that responds to clues from its surrounding environment, offers numerous opportunities for therapeutic intervention to change the trajectory of form.

There are important distinctions when considering Mass form and Functional form as treatment targets. Attention should be paid to form modification overtime as Mass and Functional form, by their very nature may not respond equally to clinical intervention. In addition, modification of the Functional form should be performed very carefully to ensure the purpose behind its existence is not compromised. On the other hand, the modifications of Mass form may not affect health significantly. For example, since the skeleton has functional value, one would expect that any change in the skeleton that is not supported by functional changes would not be stable. Therefore, surgical intervention to change the form of hard tissue for cosmetic reasons, without consideration of the functional importance of that form, should not be stable, In contrast, surgical intervention in the form of soft tissue that changes the mass but not the function of that soft tissue would be more stable, for example fat reduction.

Final notes on understanding self-organizing form

Self-organizing form theory has revolutionized the basic and clinical sciences. For the first time, through this theory we can build a bridge between different disciplines of science such as physics, biology, anthropology, population genetics, genetics and many more. This understanding changes the research of craniofacial form, from focusing on genes to focusing on the interaction of proteins among themselves and with the environment around them. In this regard, genes are not the only factor that predicts the form, but one of the components that establishes the rules of the game. However, the game can unfold in many paths or directions. This understanding, diverts our effort from searching for the genetic cause to human variability, and opens the door to all other factors that can change the trajectory of form independent of DNA mutation.

The impact of this Theory of Form on clinic practice is even more significant. Craniofacial deformities in absence of genetic mutation are one path, from millions of possible ones, that a person can take during development of the form, undermining the dominant view in clinical sciences that form is fixed and therefore, cannot be changed. Self-organizing form theory explains the importance of early treatment in preventing or changing the trajectory of form that leads to deformities. Based on this theory, the form is modifiable, and does not have a fixed or predetermined destiny, especially when it relates to craniofacial structures. The fact that the trajectory of the

form can be changed, opens the possibility of non-surgical interventions to correct deformities. This theory also argues that the change in the form of craniofacial structures is not limited to children and occur throughout life, although at different speeds. In addition, the autonomy of development of form in different parts of the body allows us to focus on correcting the affected area without interfering with the form trajectory of the other parts of the body.

And finally, understanding the role of CNS in the self-organizing form, opens yet another avenue of treatment for clinicians. Form can be modified not only by application of forces or cutting the tissue, but also by modifying or normalizing signaling to the brain. This approach can increase the efficiency and stability of treatment.

Summary

The Theory of Form proposed in the series of articles that we now conclude, advances the notion that biological forms are not pre-determined by genetics but modifiable throughout the life of an organism. The primary role of genetics in self-organizing biological forms is the constant creation of new proteins. However, this does not happen automatically, but it is rather controlled by the cells in response to their surrounding environment. These proteins, in turn work as signaling molecules modulating the cell's many functions, from proliferation to differentiation and death. In addition, proteins are part of the extracellular matrix where they can significantly impact form. The ability of cells to respond to the many constraints at each stage of the trajectory of form allow the self-organizing form and its tissues to adapt. While each part of the form has a certain degree of autonomy in adapting to local factors, since they are in a network with other parts of the form, they can affect the trajectory of the form in different areas. Very soon, centralization becomes necessary to create a form that maintains coordination between its various parts for a better chance of survival of the organism. We introduced the concept of the CNS coordinating not only the functions of different parts of the multi-cellular organism, but also their size according to the tasks they perform.

Understanding self-organizing form has a significant impact in clinical sciences and patient care. This theory explains variability between species, among individuals of the same species, and changes in the form during the lifetime of each organism. In addition, according to this theory, the majority of malformities are developmental and the result of the self-organizing form adaptation, and therefore, they can be intercepted and corrected at any stage of the trajectory of the form. Finally, based on our argument, the CNS should be an important target of treatment when addressing a malformity.

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