The Spatial Constraint Requiring Organogenetic Termination: Supplemental to Haeckel and von Baer for Development and Evolution

Zi-Jian Cai
CaiFortune TriL Consulting, No. 129, Building 6, Room 404, North Dongwu Road
Suzhou City, Jiangsu Province, 215128 PR China

Abstract:

In this article, it is pointed out that the requirement for organogenetic termination is the new spatial constraint for animal development and heredity, based on that: (a) organogenesis manifests limitation in time and possession of termination, while infinite cell proliferation known as cancer is lethal; (b) the notable indeterminate growth in some fishes and a few outgrowing skin derivatives reversely demonstrates that termination is required for organogenesis inside the animal. In further, it is supplemented this new spatial constraint to Haeckel and von Baer for development and evolution. While not influencing the temporal and spatial reorganization of morphogenesis during evolution, it places restrictions on alteration of organogenetic mechanisms themselves, as that: (a) addition of new induction mechanism or elimination of termination mechanism would usually cause endless organogenesis, liable to become lethal; (b) addition of new termination mechanism or elimination of induction mechanism in evolution not be affected by this spatial constraint. Finally, it is identified this spatial constraint as partial convergence and partial difference with Haeckel’s recapitulation, and as restriction onto Baer’s tree. It is perspectives to use the method of mathematical probability and statistics to study the spatial constraint of development onto evolution in future.

Keywords: Organogenesis, Termination, Contact Inhibition, Spatial Constraint, Outward Growth, Evolution.

Introduction

In 1800s, as represented by Haeckel and von Baer, the study of development and evolution led to the formulation of principle as recapitulation or biogenetic law. Ernst Haeckel was a pioneer in studying developmental sequences in an evolutionary context, and introduced the idea of sequence heterochrony (evolutionary changes in the sequence of developmental events) (Bininda-Emonds, et al., 2002). von Baer argued that changes in development were responsible for changes in phenotype with a branching tree from species-specific embryogenesis (Brauckmann, 2012), making it convenient to consider the evolutionary relationship among various species. Nowadays, with some exceptions having accumulated (Bininda-Emonds, et al., 2002, Raff, 1992), the hypothesis of recapitulation is no longer universal. Whereas, how developmental processes are correlated with evolution is still one of the most important subjects in present life sciences, and has attracted the attention of many scientists (Bininda-
In 2015, Zi-Jian Cai published a theoretical paper, proposing a new spatial constraint requiring organogenetic termination to stop infinite cell proliferation in development and growth, and applying such new constraint to evolution (Cai, 2015). The core thought expressed in this theory was initially formed in the mind of Cai in 1987 when Cai was a graduate student at University of Notre Dame in USA. Now almost 10 years having passed, there have been appearing many new progressions in contact inhibition, indeterminate growth, aging and so on related to this issue. In accordance, herein in this article, it is attempted to update the related progressions into this new constraint and its effects on evolution.

Spatial Constraint Requiring Organogenetic Termination for Animal Development

Four Cellular Constituents for Morphology of Tissues and Organs

The morphology of individual organs is determined by the morphological constituents at cellular level, namely the cell number, position, shape and sometimes the secretes, manifesting as four cellular characteristics (Cai, 2015). For intuitive demonstration, the neuron number in cortex determines the cortical modality number in mammals (Borrell, 2019, Kalebic, & Huttner, 2020), the neuron position in cortex arranges neurons into various laminates (Borrell, 2019, Pearce, & Marotte, 2003), and the neuron shape contributes to the formation of synapses and neuronal interactions (Pearce, & Marotte, 2003). In some other tissues and organs, such as the bone, cell secretes also constitute the morphological components of the organs (Bolean, et al., 2017).

Corresponding Four Cellular Processes for Morphogenesis of Organs

Development is complex and comprises morphogenesis and differentiation. With regard to the above mentioned cell number, position, shape and secretes as four cellular constituents of morphology, the corresponding morphogenesis of an organ also involves four cellular processes respectively as cell proliferation/elimination for number, migration for position, shaping for shape, and secretion for secretes (Cai, 2015). For intuitive demonstration, in the development of mammalian cortex (Borrell, 2019, Kalebic, & Huttner, 2020), neuronal cells are generated at the germinal zones from precursor cells through cell proliferation (Borrell, 2019, Kalebic, & Huttner, 2020). Later, the generated cells migrate to their corresponding cortical laminate (Borrell, 2019, Pearce, & Marotte, 2003). Finally, axons project out from the cortical neurons until they reach their targets (Pearce, & Marotte, 2003). In some other tissues or organs, such as the bone, cell secretion also participates in the morphogenesis of the tissues or organs (Bolean, et al., 2017). In some special organs, such as vertebrate limbs (Hernández-Martínez, & Covarrubias, 2011, Zuzarte-Luís, & Hurlé, 2002) and remodeling face bone (Xiao, et al., 2016), programmed cell death finally modifies the shape of organ into appropriate for usage (Hernández-Martínez, & Covarrubias, 2011, Xiao, et al., 2016, Zuzarte-Luís, & Hurlé, 2002). Cell proliferation/elimination, migration, shaping, and secretion make up the morphogenesis of organs.

Induction and Termination for Organogenesis

Morphogenesis of an organ is initiated by inductive events. There are many types of inductive events. Some inductive processes occur very early in the gastrula stage (Jia, & Meng, 2021). Organogenesis proceeds on the subsequent inductive events, initiating the cellular processes of organogenesis, such as cell proliferation, migration, shaping and secretion, for the generation of various organs, such as neural system (Pera, et al., 2014), liver (Yang, et al., 2019), lens (Gunhaga, 2011) and so on.

The cellular process of organogenesis manifests limitation in time and possession of termination. Appropriate size of organ requires appropriate quantity of cell number or cell secretes without
infinite increase (Cai, 2015). Thus, termination is required for the organogenesis of cell proliferation and secretion (Cai, 2015). For intuitive demonstration, the hippo signaling pathway has been shown to control organogenesis of liver and the size of liver (Avruch, et al., 2011, Patel, et al., 2017). Likewise, Fgf signalling has been discovered to control the proliferation/differentiation timing and duration of patterning for limb outgrowth (Perez, et al., 2023). Furthermore, contact inhibition is well known to control cell proliferation to form epithelial tissues (Mendonsa, et al., 2018). More fascinating recently, YAP and TAZ have been shown to mediate mechanoregulation onto cell proliferation within organs (Cai et al., 2021).

In addition, as mentioned above, programmed cell death sometimes helps modify the final shape of some organs into appropriate for use, such as the digit separation in limbs (Hernández-Martínez, & Covarrubias, 2011, Zuzarte-Luís, & Hurlé, 2002) and remodeling face bone (Xiao, et al., 2016). Hence, it is appropriate to term the termination directly against organogenesis as organogenetic termination or simply as termination, while the additional processes modifying the final shape of some organs as terminal degenerative modification (Cai, 2015).

Termination as Spatial Constraint for Animal Organogenesis

More importantly, at the organizational level in animals, termination of organogenesis in further plays a key role in controlling organogenesis more than induction. Without termination, morphogenesis of an organ would proceed infinitely, disorganize the overall morphology of animal and cause lethality, especially with excessive cell proliferation and secretion. Infinite cell proliferation due to loss of contact inhibition is called as cancer (Avruch, et al., 2011, Mendonsa, et al., 2018, Patel, et al., 2017), and is one of the top causes of lethality in global epidemiology even with updated medication (Mattiuzzi, & Lippi, 2019, Sedeta, et al., 2023), demonstrating the importance requiring organogenetic termination.

Organogenetic Constraint Requiring Termination in Contrast to Indeterminate Outward Growth

Development continues as the postnatal growth. After birth, the growth hormone secreted from hypothalamus stimulates the elongation of cartilage of long bones (Nilsson, et al., 2005). After puberty, the hypothalamus stimulates the secretion of sex hormones. The estrogen can counteract against the growth hormone and control the growth of longitudinal bone in both females and males (Chagin, et al., 2004, Karimian, & Sävendahl, 2011). Accordingly, the hypothalamus terminates the growth while controls the height of humans and size of mammals within limitation after mature.

In a few special situations, when the constant cell proliferation or secretion occurs on the surface of body, mostly as skin derivatives, or the whole body grows outward from the surface of body, they no longer disrupt the internal organization and overall morphology of animal (Cai, 2015). Thus, there is no requirement for organogenetic termination as spatial constraint (Cai, 2015). There are a few notable models related to this special issue, as the followings:

(a) The human nail can grow for decades due to cell proliferation without termination, as manifested in many Guinness World Records on length of it (Suggitt, 2021). Similar situation occurs to human hair (Guinness World Records, 2019).

(b) The epidermal scales in some reptilian species are continually thickened due to continual proliferation of epidermal cells, with the outer layer of the epidermal scales shed in lizards and snakes (Alibardi, 2009, Chang, et al., 2009).

(c) In a few fishes, such as short-lived killifish Nothobranchius furzeri(Cellerino, et al., 2016), indeterminate growth occurs in an extensive post-maturity period(Žák, & Reichard, 2021), ending with short life and aging(Cellerino, et al., 2016). Besides, in such fishes as pacu (Perez, et
al., 2023) and giant danio (Biga, & Meyer, 2009), it occurs indeterminate muscle growth. However, it is noted that, in Zebrafish (Danio rerio), the common age-related phenotype as spinal curvature might result from muscle abnormalities (Gerhard, et al., 2002), compatible with the spatial constraint requiring organogenetic termination.

It is necessary to point out that, from the common manifestation of indeterminate growth as expanding outward without spatial restriction by the body of animal, the requirement for organogenetic termination is the spatial constraint within the body of animal (Cai, 2015).

Two Forms of Changes in Animal Morphogenesis during Evolution

Temporal or Spatial Reorganization of Existing Morphogenetic Processes

Genetic changes resulting only in the temporal and spatial reorganization of existing morphogenetic processes occurred often in animal evolution. For temporal reorganization, there have been efforts to create some temporal models to demonstrate the heterochrony with changes in time of developmental events in animals (Bininda-Emonds, et al., 2002), with many examples fitting into the models.

Spatial reorganization of existing animal morphogenesis can be best represented as example by the generation of different spiral patterns in pond snail Lymnaea stagnalis. In this case, the generated dextral and sinistral forms in adult Lymnaea stagnalis is determined by the earliest spiral cleavage patterns different in expression of Lsdial gene (Kuroda, et al., 2016), making the two forms of Lymnaea stagnalis interchangeable through hybridization.

Alteration of Organogenetic Mechanisms Themselves

Genetic alteration in the nature of organogenetic mechanisms themselves may also cause changes in morphology of animal. To further distinguish this concept from the temporal and spatial reorganization of existing morphogenetic processes, it is herein to inspect the development of mammary glands. On the one hand, there are different numbers of mammary glands in various mammals which may even be located at different positions on the abdominal surface of body. Changes in location of mammary glands in evolution just represent spatial reorganization of mammogenesis. On the other hand, during mammary development, the vigorous proliferation of ducts and alveoli in pregnancy and lactation may be induced by several hormones, notably by growth hormone, prolactin, placental lactogen and so on (Forsyth, 1986, Neville, et al., 2002). Whereas, the primitive mammary glands are present in monotremes which are not viviparous (Oftedal, & Dhouailly, 2013), so that the precursor mammary glands should not have possessed this pregnancy-related mammogenesis. Therefore, this hormonal-controlled cellular proliferation in mammary glands in pregnancy is a new morphogenetic mechanism acquired recently in evolution, representing a genetic change in the nature of organogenetic mechanism itself (Cai, 2015).

Genetic changes involving the nature of organogenetic mechanisms themselves may in further be classified into several forms in animals. Changes in mechanisms of organogenesis may introduce a new organogenetic mechanism, eliminate some existing mechanisms, and may also change an existing mechanism into another novel mechanism. Because the change of existing mechanism can be understood as simultaneously introducing a new mechanism while disrupting an existing mechanism, all changes in mechanisms of organogenesis in animals can ultimately be classified into the two forms as introduction of a new organogenetic mechanism and elimination of some existing organogenetic mechanisms (Cai, 2015).
Organogenetic Termination as Spatial Constraint on Development and Growth in Evolution

The Spatial Constraint on Temporal/Spatial Reorganization of Morphogenesis

With regard to the genetic changes as temporal and spatial reorganization of existing morphogenetic processes in animals, organogenesis in descendents would certainly be terminated in the same way as in progenitors. No matter in the cases fitting in the temporal models created by some scientists recently (Bininda-Emonds, et al., 2002), or in the two dextral and sinistral forms of Lymnaea stagnalis representing spatial rearrangement of existing morphogenesis (Kuroda, et al., 2016), termination mechanisms of organogenesis all preserved in the same way as in progenitors. In this regard, the spatial constraint requiring organogenetic termination would not affect the temporal and spatial reorganization of morphogenetic processes in animals (Cai, 2015).

The Spatial Constraint on Addition of Organogenetic Mechanisms

The spatial constraint requiring organogenetic termination would place some new restrictions on alteration of organogenetic mechanisms themselves in animal evolution. In this subsection, it will only be considered the constraint on addition of organogenetic mechanisms, as the followings:

(a) Addition or alteration of an induction mechanism for organogenesis: This would have to be confronted with the requirement of termination against the organogenesis initiated by the newly introduced induction in animals. Without termination, the newly acquired organogenetic process would also proceed infinitely and cause lethality. In this regard, requiring termination would exert an additional constraint on genetic addition or alteration of induction mechanisms for organogenesis. However, in a few special cases, a new induction mechanism may have been introduced in animal evolution as it just happened to be able to make use of some existing mechanisms for termination. For instance, as stated above, the cellular proliferation in mammary duct and alveolus was the consequence of genetic addition of novel organogenetic induction by pregnancy and lactation (Cai, 2015, Oftedal, & Dhouldi, 2013), especially induced by several hormones such as growth hormone, prolactin, placental lactogen and so on (Forsyth, 1986, Neville, et al., 2002). Nonetheless, these hormones decline with the termination of pregnancy and lactation so as the evolutionary addition of this hormonal induction of mammogenesis happened to make use of the existing decline in hormonal secretion as termination (Cai, 2015).

(b) Addition of new termination mechanisms to the existing organogenetic processes: The would make the descendents possess more termination mechanisms for stopping organogenesis than their progenitors, so that not be affected by the spatial constraint requiring organogenetic termination. In higher mammals, although the mammary rudiments develop in both sexes in their embryos, the morphogenesis of mammary glands in male embryo is terminated early in response to testosterone before the formation of any ductal structures (Dürnberger, & Kratochwil, 1980, Imperato-McGinley, 1986), while it still continues in female embryo due to the lack of testosterone. Since the primitive mammary glands are present in both sexes in monotremes(Oftedal, & Dhouldi, 2013), it is likely that it is the testosterone-related male termination mechanism of mammogenesis that was added more lately in evolution to the original mammogenesis. This is an example as terminal addition of developmental mechanism in animal evolution.
(c) Addition of terminal degenerative modification: This should neither be constrained by the spatial requirement for organogenetic termination either, as the descendants would likewise possess more termination mechanisms to stop organogenesis than their progenitors. Some functional larval structures of amphibians such as the tail of tadpole are absorbed as a whole during metamorphosis with programmed cell death (Nakajima, et al., 2005, Yaoita, 2019), representing the addition of terminal degeneration in animals. Likewise, in higher vertebrates, local programmed cell death in limb interdigital zones is a degenerative process accessory to the termination mechanisms against organogenetic proliferation, necessary for the separation of digits (Hernández-Martínez, & Covarrubias, 2011, Zuzarte-Luís, & Hurlé, 2002). However, the development of free digits in amphibians does not involve cell death (Nakajima, et al., 2005). Obviously, the local programmed cell death in interdigital zones to separate digits was lately acquired in higher vertebrates in evolution.

The Spatial Constraint on Elimination of Organogenetic Mechanisms

In contrast, elimination of organogenetic mechanisms has been less studied in comparison to addition. In this subsection, it will be considered this issue, as the followings:

(a) Elimination or disruption of organogenetic induction: This would lead to deletion of the whole subsequent organogenetic processes initiated by the inductive event in animals, so that it would not cause endless organogenesis, nor be restricted by the spatial constraint requiring organogenetic termination. It has been shown that the evolutionary loss of teeth in birds was the result of dysfunction in induction mechanism for tooth morphogenesis (Wang, et al., 1998).

It is necessary to point out that disruption of organogenetic induction may sometimes cause dramatic loss of functional, resulting in functional lethality, rather than restricted from the spatial constraint stopping endless organogenesis.

(b) Elimination of organogenetic termination mechanisms: This would have to run the risk of causing endless organogenesis, so that the spatial constraint requiring organogenetic termination would place restriction. However, when the resulted constant organogenetic growth happened on the body surface protruding outward without causing morphological disorganization, elimination of termination might be observed in animal evolution. It is common knowledge that the human skull hair can grow continuously in length if not cut mechanically, as manifested in many Guinness World Records on length of it (Guinness World Records, 2019). It was evolved from the short hair in apes, and was obviously acquired in human evolution as elimination of termination for hair growth (Cai, 2015). Similar story occurred to the evolutionary acquisition of constant growth of human nail with many Guinness world records on length of it (Suggitt, 2021).

(c) Elimination or disruption of terminal degenerative modification: This may not necessarily eliminate (primary) termination against organogenesis, nor cause endless organogenesis, so that nor necessarily be restricted by the spatial constraint requiring organogenetic termination. In vertebrate limb development, interdigital cell death is the terminal degenerative mechanisms helping to separate digits (Hernández-Martínez, & Covarrubias, 2011, Zuzarte-Luís, & Hurlé, 2002). Partial dysfunction of this process in web-footed birds, as characterized by smaller scale and shorter duration, has not led to endless limb growth but just annealed the toe digits (Gañan, et al., 1998).

In brief summarization, the constraint requiring organogenetic termination on organogenetic changes during evolution are summarized in the Table 1.
Table 1. Constraint Requiring Organogenetic Termination on Organogenetic Evolution

<table>
<thead>
<tr>
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<th>Temporal/spatial change</th>
<th>Addition</th>
<th>Elimination</th>
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<tbody>
<tr>
<td>Organogenetic induction</td>
<td>No spatial constraint</td>
<td>Spatial Constraint</td>
<td>No spatial constraint</td>
</tr>
<tr>
<td>Organogenegetic termination</td>
<td>No spatial constraint</td>
<td>No spatial constraint</td>
<td>Spatial Constraint</td>
</tr>
</tbody>
</table>

Discussions

The Spatial Constraint Requiring Organogenetic Termination

Corresponding to the four cellular constituents of morphology as cell number, position, shape and secrete, the morphogenesis of an organ also respectively involves four cellular processes as cell proliferation/elimination for number, migration for position, shaping for shape, and secretion for secrete (Cai, 2015). Organogenesis possesses both induction and termination (Cai, 2015), with programmed cell death sometimes as terminal degenerative modification to modify the final shape of some organs into appropriate for use (Hernández-Martínez, & Covarrubias, 2011, Xiao, et al., 2016, Zuzarte-Luís, & Hurlé, 2002).

At the organizational level in animals, without termination, the excessive cell proliferation and secretion during organogenesis would proceed infinitely, extend beyond the range of body, or disorganize the overall morphology of animal, and cause lethality (Cai, 2015). The lethal infinite cell proliferation of cancer and the counteracting mechanisms of contact inhibition such as the hippo signaling (Patel, et al., 2017), E-cadherin (Mendonsa, et al., 2018), mechanoregulation (Cai et al., 2021) and so on obviously deserve more investigations.

The Indeterminate Outward Growth

In a few special situations, the constant cell proliferation or secretion, or the growth of whole body, extends outward from body surface, and no longer requires for organogenetic termination as spatial constraint (Cai, 2015). A few notable models obviously deserve more special attention, such the hair (Guinness World Records, 2019) and nail (Suggitt, 2021) in humans, the continually thickened epidermal scales shed in lizards and snakes (Alibardi, 2009, Chang, et al., 2009), the indeterminate growth in a few fishes, such as short-lived killifish Nothobranchius furzeri (Cellerino, et al., 2016), pacu (Perez, et al., 2023) and giant danio (Biga, & Meyer, 2009).

The Spatial Constraint Requiring Organogenetic Termination on Animal Evolution

In the above section, the spatial constraint requiring organogenetic termination on animal evolution has been well demonstrated. Herein, it is compared this spatial organogenetic constraint on animal evolution with Haeckel’s recapitulation and Baer’s tree.

(a) Haeckel’s recapitulation

Ernst Haeckel hypothesized the idea of sequence heterochrony and recapitulation, with embryogenesis of an animal paralleling its own phylogenetic history, sequentially developing from more ancestral features to more derived ones (Bininda-Emonds, et al., 2002, Clune, 2012), while recent rectifications confined it more to the later organogenetic stages (Uesaka, et al., 2022). Changes to early developmental stages were suggested as selected against because they tended to disrupt later developmental program (Bininda-Emonds, et al., 2002, Clune, 2012).

Many exceptions have accumulated to recapitulation to make it not universal. As mentioned above, the change in early spatial organization of existing animal morphogenesis, such as Lymnaea stagnalis(Kuroda, et al., 2016), is not compatible with recapitulation of Haeckel (Bininda-Emonds, et al., 2002), but compatible with the branching tree of von Baer (Brauckmann, 2012). Similar situation occurred to relocation of mammary glands in mammals. Besides, duplication of morphogenetic program might also occur at earlier stages, such as duplication of segments (Minelli, 2005). All these spatial change or duplication of early
developmental stage can make use of existing program and termination.

It is interesting to compare Haeckel’s recapitulation and the spatial constraint requiring organogenetic termination in this paper. Haeckel’s recapitulation results from restriction on the change of early developmental program (Bininda-Emonds, et al., 2002, Clune, 2012), no matter addition or elimination of induction, compatible with the spatial constraint requiring organogenetic termination to restrict the addition of early induction (Cai, 2015), but different from elimination of induction which is unaffected by the spatial constraint requiring organogenetic termination herein. Besides, Haeckel’s recapitulation differs from the spatial constraint requiring organogenetic termination on change of termination, with Haeckel’s recapitulation permitting both addition and elimination of termination, while the spatial constraint herein restricting elimination of termination but not addition of termination.

(b) von Baer’s tree

Von Baer depicted the changes in development to changes in phenotype with a branching tree from species-specific embryogenesis (Brauckmann, 2012), possibly at all stages of development if survived, convenient to read out the evolutionary relationship among species. There are no exceptions for the tree, unlike Haeckel’s recapitulation.

However, restriction and constraint should be considered. Both restriction on the developmental program from Haeckel’s recapitulation and the spatial constraint requiring organogenetic termination here can supplement the considerations to von Baer’s tree.

(c) The spatial constraint requiring organogenetic termination

As mentioned above, the spatial constraint requiring organogenetic termination would not affect the genetic changes only involving the temporal and spatial reorganization of morphogenesis in animal evolution (Cai, 2015). Nonetheless, the new spatial constraint would place some restrictions on alteration of organogenetic mechanisms themselves in evolution, including addition of new induction mechanism or elimination of termination mechanism in animals which would usually cause endless organogenesis and be lethal (Cai, 2015), while addition of new termination mechanism or elimination of induction mechanism would not encounter such endless organogenesis and not be restricted by such spatial constraint (Cai, 2015).

Exceptions to such spatial constraint arise from the indeterminate outward growth from body surface (Cai, 2015), such as the hair and nail in humans, the continually thickened epidermal scales shed in lizards and snakes, the indeterminate growth in a few fishes, including the short-lived killifish Nothobranchius furzeri (Cellerino, et al., 2016), pacu (Perez, et al., 2023) and giant danio (Biga, & Meyer, 2009).

Both the spatial constraint from requiring organogenetic termination and Haeckel’s recapitulation restrict addition of early induction (Bininda-Emonds, et al., 2002, Clune, 2012), while Haeckel’s recapitulation further restricts elimination of induction (Bininda-Emonds, et al., 2002, Clune, 2012) but the spatial constraint does not (Cai, 2015). Besides, the spatial constraint from requiring organogenetic termination restricts elimination of later termination (Cai, 2015), but Haeckel’s recapitulation does not. Besides, the spatial constraint requiring organogenetic termination supplements restrictions to the evolution in Baer’s tree.

In all, Table 2 outlines the three hypothesis from Haeckel, von Baer and Cai.
Table 2. Comparison of Three Theories from Haeckel, von Baer and Cai

<table>
<thead>
<tr>
<th></th>
<th>Haeckel</th>
<th>von Baer</th>
<th>Cai</th>
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<tbody>
<tr>
<td>Theory</td>
<td>Recapitulation with embryogenesis paralleling phylogenetic history</td>
<td>Changes in both development and phenotype with a branching tree</td>
<td>The spatial constraint requiring organogenetic termination, evolutionary allowing spatial/temporal reorganization of organogenesis, addition of termination and elimination of induction, but restricting addition of induction and elimination of termination</td>
</tr>
<tr>
<td>Causes</td>
<td>Changes to early stages unfavorable as tending to disrupt later developmental program</td>
<td>The phenotype from gradual changes in embryogenesis</td>
<td>Without termination, infinite cell proliferation or secretes from organogenesis resulting in lethality</td>
</tr>
<tr>
<td>Exceptions</td>
<td>Early change in spatial organization of morphogenesis and early duplication of morphogenesis such as segmentation</td>
<td>Not applicable</td>
<td>A few cases of indeterminate outward growth from body surface</td>
</tr>
<tr>
<td>Defects</td>
<td>Lack of considering the constraint from later developmental stages to control infinite cell proliferation or secretes</td>
<td>Lack of insight into developmental restrictions</td>
<td>Indeterminate outward growth from body surface</td>
</tr>
</tbody>
</table>

(d) Perspectives of quantitative studies in future

The correlation of developmental processes with evolution is still one of the most important subjects attracting the attention of many scientists in present life sciences (Bininda-Emonds, et al., 2002, Cai, 2015, Minelli, 2005, Torday, & Miller, Jr., 2018, Uesaka, et al., 2022). Among them, Haeckel’s recapitulation has been studied in most detail. Especially, it is necessary to note that recent studies with digit technology revealed the trend that ontogeny recapitulated the phylogeny (Clune, 2012). Obviously, it is perspectives in future to use the method of mathematical probability and statistics to study the tendency of recapitulation, even including the occurrence of exceptions. Similar method would apply as well to the studies of the spatial constraint requiring organogenetic termination onto animal evolution.

Conclusions

In this article, it is pointed out the four cellular processes of organogenesis as cell proliferation/elimination for number, migration for position, shaping for shape, and secretion for secretes. Without organogenetic termination, infinite cell proliferation or secretion in organogenesis would usually result in lethality, such as cancer. Thus, requirement for organogenetic termination is a new spatial constraint on animal development and heredity. However, a few notable exceptions exist as the indeterminate outward growth from body surface, such as the hair and nail in humans, the continually thickened epidermal scales shed in lizards and snakes, and the indeterminate growth in a few fishes.

This spatial constraint requiring organogenetic termination would allow spatial/temporal reorganization of organogenesis, addition of termination and elimination of induction, but restrict addition of induction and elimination of termination in evolution. Whereas, Haeckel’s recapitulation results from restriction on the early change of developmental program, no matter addition or elimination of induction. Both of the spatial constraint requiring organogenetic termination and Haeckel’s recapitulation supplement the intrinsic restrictions to von Baer’s tree. It is perspectives to use the method of mathematical probability and statistics to study the spatial constraint of development onto evolution in future.
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Authors' Contributions
The sole author responsible for all of the article.

Authors' Information
Zi-Jian Cai (Orcid: 0000-0003-2378-5034) as the author of this paper is now the supervisor of CaiFortune TriL Consulting in Suzhou City, PR China. The author is a theoretical scientist on neuroscience, aging/development and physics unification, and is also a social activist, independent publishing many papers abstracted in CNKI and Scopus.

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