# Regeneration: Why junk DNA might matter

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**Abstract**

The ability of certain natural species to restore or regenerate missing structures has been a recurrent source of inspiration to forge our collective knowledge, from being used to adorn mythological figures with superhuman powers to permitting controlled reproducible observations that help setting the bases of entire research fields such as experimental biology and regenerative medicine. In spite of being one of the oldest natural phenomena under study, what makes certain species able or unable to regenerate missing parts is still largely a mystery. Recent advancements towards the highly detailed characterization of the sequence, the spatial organization, and the expression of genomes is offering a new standpoint to address the study of the natural variation in regenerative responses. An intriguing observation that has not yet conveniently pursued is that species with remarkable regenerative abilities tend to have genomes loaded with junk DNA (jDNA), *i.e.*, genetic elements presumed to be useless for the benefit of the individual, whereas species for taxa with limited regenerative abilities tend to have jDNA-poor genomes. Here, I use existing knowledge on the role of jDNA as genome evolution facilitator and its non-random chromosome and nuclear distributions to speculate about two non-excluding ways through which the variation in jDNA genomic content might end up enhancing or limiting regenerative responses. The present piece aims to go beyond the confines of correlational studies between biological variables and to lay sensible conceptual grounds for future hypothesis-driven attempts to substantiate the genomic determinants of the natural variation of regenerative responses.



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## Introduction

In recent years there has been an acceleration of the genomic characterization of species with remarkable regenerative abilities such as the cnidarians *Hydra magnipapillata* and *Nematostella vectensis*, the platyhelminths *Dugesia japonica*, *Macrostomum lignano*, and *Schmidtea mediterranea*, the crustacean *Parhyale hawaiensis*, the insect *Periplaneta americana* or the urodeles *Ambystoma mexicanum*, *Notophthalmus viridescens*, and *Pleurodeles waltl* [1-11]. Beyond their enhanced regenerative abilities, these species share another feature that hindered the assembly of their genome sequences and can be of great importance to understand the natural variation in regenerative abilities, *i.e.*, their genomes tend to be highly enriched in repetitive DNA [1-11]. Remarkably, not only species with enhanced regenerative abilities possess genomes with large amounts of repetitive DNA, but most species within taxa with remarkably limited regenerative abilities such as birds and nematodes have small compact genomes with reduced fractions of repetitive DNA [12-14]. These opposite trends hint to the possibility that the natural variation in repetitive DNA genomic content and regenerative abilities are somehow interrelated. Although some studies already explored the relationship between genomic properties such as general size, ploidy level, or intron size and the course of regenerative responses [15-19], little attention has been given to the covariation of regenerative abilities and the genomic content in repetitive DNA.

The study of the natural variation in regenerative responses is a particularly complex one. As it has been amply discussed, in spite of being simply defined upon a common outcome, *i.e.*, the restoration of missing parts upon injury, regenerative responses are very heterogenous [13, 20-25]. Very briefly, natural species differ in the organization level that they are able to regenerate,



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*i.e.*, tissue, organ, or whole body, the number of their parts that can regenerate, the temporal dynamics of the process, on whether they require or not the formation of specific structures such as the blastema, on the quantity and types of cells that are required to regenerate the missing part, and on whether intervening cells do proliferate or not [13, 20-25]. Such multilayered heterogeneity makes it very difficult to study the natural variation of regenerative responses by focusing on a particular trait shared by all of them.

Although at the cellular level regenerative responses are also considerable heterogeneous, they all seem to rely on the production of newly differentiated cells [22, 23, 26, 27]. Cells needed to restore missing complex structures might result from pre-existing cells exchanging specialized types, *i.e.*, transdifferentiation, or through the proliferation and differentiation of precursor cells that are actively maintained or regained a multipotent undifferentiated state, *i.e.*, stem cells and dedifferentiation respectively [22, 23, 26, 27]. Thus, regenerative responses ultimately rely on intervening cells inherent or regained multipotentiality. If this is truly the case, it could be argued that any factor that helped maintaining cells in multipotent states or mediated their irreversible specialization could respectively enhance or limit natural species regenerative abilities.

The progressive characterization of genomes has shown that they encompassed large amounts of elements such as intergenic regions, introns, transposable elements or highly repetitive satellite DNA that were hard to categorize with the functional and/or selective criteria commonly used to define genes [28]. New concepts were coined to collectively refer to all or some of these elements in virtue of them not being transcribed and/or translated, *i.e.*, non-coding DNA, being of a repetitive nature, *i.e.*, repetitive DNA, their inherent abilities to change location within the genome and to propagate at the expense of the coding genome, *i.e.*, transposable elements and



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selfish DNA respectively, or their apparent uselessness for the well-being of biological systems, *i.e.*, junk DNA [28]. In particular, the utility of the junk DNA (jDNA) concept, the one among these concepts spanning the larger spectrum of elements, has been frequently called into question because of the stark heterogeneity of the elements it encompasses and the difficulty in definitely assessing the lack of function of any genetic element [28]. In spite of the debates on how to define jDNA or even the utility of this concept, it is widely acknowledged that jDNA elements act as evolutionary facilitators by directly participating in the causation of genetic changes, being exapted into new genes or regulatory elements, or tuning the expression gene expression [29-37]. In the present piece, I use existing knowledge on jDNA acting role as genome evolution facilitator and its non-random distribution within chromosomes and nuclei to explore two non-excluding avenues that would relate the natural variation in jDNA genomic content, the balance between cell multipotentiality and irreversible specialization, and regenerative abilities.

## Junk DNA-driven genetic diversification and cell specialization

In recent years it has been proposed that the jDNA genomic content itself is an important element driving the spatiotemporal and evolutionary dynamics of natural populations [35-37]. The heterochromatic jDNA (hjDNA)-based capacitance model spans organization levels to explain how the inherent ability of jDNA to vary within natural populations results in phenotypic heterogeneity, and how the ultimately hjDNA-based phenotypic heterogeneity permits natural populations better enduring variable environments and modulates genetic variation phenotypic exposure [35-37]. Very briefly, the idea that hjDNA genomic content promoting phenotypic heterogeneity in natural populations ultimately relies on four lines of evidence. First, chromosome elements such as centromeres, telomeres or the chromosome *Y*, originally referred



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to as heterochromatin because of their susceptibility to be stained with carmin acetic acid [38], tend to be gene-poor highly enriched in jDNA elements such as transposons and satellites [39]. Second, the amount of jDNA in large repositories of heterochromatin or hjDNA has been observed to be intrinsically variable resulting in obvious differences between closely-related species, natural populations of a single species, individuals of the same population or laboratory strain, or even between dizygotic human twins [40-60]. Third, the maternal-to-zygotic transition (MZT) refers to the time elapsed between oocyte fertilization and the transcriptional activation of the entire zygotic genome [61-63]. Along MZT there is a pressing need for chromatin-forming elements because of the intensive chromatin remodeling sperm chromosomes undergo just after fertilization and the formation of new chromatin after each zygotic division, both of which occur at the expense of limited mostly maternally-deposited material [61-63]. Fourth, there is an ample phenomenology showing that the variation in hjDNA correlates with the variation in expression of many genes along the genome [56, 64-69]. Based on all this knowledge, the hjDNA-based capacitance model proposes how the inherent variation in hjDNA within natural populations results proximately in a variation in chromatin dynamics early in embryogenesis which is ultimately manifested as a gene expression and phenotypic heterogeneity, even in the absence of genetic variation within the coding portion of the genome [35-37].

The hjDNA-based capacitance model also proposes that hjDNA-based phenotypic heterogeneity can drive the spatiotemporal dynamics of natural populations in two ways [35-37]. First, hjDNA-based phenotypic heterogeneity in natural populations might be important for them to thrive in variable environments. Second, evolutionary or genetic capacitance can be defined as the ability of biological systems to promote the random fluctuation of cryptic genetic variation, *i.e.*, genetic variation with no phenotypic relevance [37]. hjDNA-based phenotypic heterogeneity could



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promote capacitance by shielding from selection those genetic variants that resulted in phenotypes indistinguishable from the phenotypic spectrum ultimately caused by hjDNA inherent variation. Such cryptic genetic variation could be of great adaptive value if it were to become phenotypically relevant following environmental changes and/or because of a reduction in the hjDNA genomic content that subsequently resulted in a narrower spectrum of hjDNA-based phenotypic heterogeneity.

Support for the validity of the hjDNA-based capacitance model has been accrued by directly testing expected trends for individuals differing largely in their hjDNA genomic content within and between species. On one hand, because *Y* and *W* chromosomes tend to be highly enriched in hjDNA [65, 70, 71], it has been argued that within a single species heterogametic individuals (*XY* or *ZW*) would show larger hjDNA-based capacitance than homogametic individuals (*XX* or *ZZ*)[35, 37]. Such proposal was directly tested and supported by studying gene expression and phenotypic heterogeneity for isogenic strains of *Drosophila melanogaster*, phenotypic heterogeneity for same-sex dizygotic and monozygotic human twins, and sex-biased dispersal for metazoan species [35, 37]. On the other hand, because the variation in genome size is mostly caused by the variation in the genomic content in jDNA [72, 73], it has been proposed that species with lower amounts of jDNA would show lower hjDNA-based capacitance than species with larger amounts of jDNA [36]. Since lower capacitance would be expected to be manifested by genetic variation being more often phenotypically relevant and therefore detectable by selection, it follows that natural populations of species with lower hjDNA genomic content would be prone to genetically diversify and become reproductively isolated faster than natural populations for species with larger hjDNA genomic content [36]. Such proposal was directly



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tested and supported by studying speciosity and measures of genetic diversification obtained using interspecific genetic crosses in the Drosophilidae family [36].

Could it be possible that the comparatively faster genetic diversification of species with lower hjDNA genomic content was perceivable at different complexity levels, *e.g.*, from faster speciation to more complex specialized cells and tissues (Figure 1A-D)? Were this the case, could ultimately hjDNA-based differences in tissue and cell specialization explained the natural variation in regenerative abilities? Interestingly, Anura and Urodela, *i.e.*, frogs and salamanders, the two largest orders within the Amphibia class probably epitomize the best the potential relationship between the natural variation in jDNA genomic content, the balance between cell multipotentiality and irreversible specialization, and regenerative abilities. First, the systematic study of comparable regenerative responses in adult stages of amphibian species showed that although both anurans and urodeles are able of regenerating amputated limbs during embryonic stages, and plenty of anurans are able of producing an outgrowth following adult limb amputation, only urodeles are able of fully regenerating adult amputated limbs [74, 75]. Second, extant anurans and urodeles dramatically differ in their genome size, being considerably larger in the latter [76-78]. In fact, phylogenomic reconstructions of genome size evolution suggest that Anura and Urodela differing genomic sizes are mostly driven by their jDNA content, and that since their last common ancestor the genomes of anuras and urodeles tended to shrink and bloat respectively [76-78]. Third, as it would be expected if lower hjDNA genomic content strongly favored genetic diversification leading to speciation, within the very diversified amphibians, Anura span almost nine time more species than Urodela [79, 80]. Finally, nervous and immune systems, and gene regulatory networks for mesoderm and mesendoderm specification have been shown to be considerably simpler in urodeles than in anurans [81-84]. Since the immune system



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plays an important role during regenerative responses, it has been suggested that the natural variation in regenerative responses could be secondary to the variation in the immune system complexity [85]. However, since Anura and Urodela show differences in the complexity of tissues and regulatory networks for lineage specification other than for the immune system, it is possible that Anura and Urodela regenerative abilities were not secondary to the complexity of their immune systems but their differences in both regenerative abilities and immune system complexity were consequence of a more general mechanism that promoted/limited cell specialization.

All these trends observed for the two closely related amphibian orders are indeed consistent with the possibility that their remarkable differences in jDNA genomic content drove them to differ in mechanisms that promote/limit cell specialization, which would subsequently enhance/limit their regenerative abilities. However, this might not be the only way jDNA variation influenced cell specialization and regenerative abilities.

**Subnuclear localization of jDNA and cell specialization**

The comparison of the natural variation in jDNA genomic content, speciosity, number of cell types, and regenerative abilities between animals and plants point to one more factor through which large differences in jDNA genomic content could modulate regenerative abilities. Since most of the elements used to assemble the hjDNA-based capacitance model are shared between animals and plants, it would be expected that plants differing in their jDNA genomic content showed similar patterns to those observed for animals. Indeed, a clear division between genome size and diversification similar to the one observed for Anura and Urodela is noticeable for the two main taxa within the clade Spermatophyta, *i.e.*, seed plants. In this case, and in accordance



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with what it would be inferable using the hjDNA-based capacitance model [35-37], gymnosperms tend to have considerably larger genomes and be less diversified than angiosperms [86-89]. Although further analyses are required, it is then possible that the hjDNA-based capacitance was a common mechanism driving genetic diversification for all eukaryotes.

Contrary to animals though, a high capacity to regenerate is observed widespread in plants, which has been key for the development of multiple strategies to induce their clonal propagation [21, 90-92]. The possibility of regenerating whole new plants out of simple explants was originally suggested to depend on plant cells being totipotent, which has been called into question [21, 90-92]. Regardless of whether all or only particular plant cells are multi- or totipotent, that the number of cell types identified in animals largely surpasses this of plants suggest it is possible that animals and plants differed in mechanisms that promoted cell specialization [93]. Furthermore, the difference between the respective patchy and widespread phylogenetic distribution of regenerative abilities in animals and plants could then relate with the existence in the former of specific mechanisms that promoted cell specialization.

The nuclear lamina refers to the filamentous meshwork that covers the inner side of eukaryotic nuclear envelope [94-97]. Originally believed to be a metazoan innovation, it is now acknowledged that some type of nuclear lamina mostly formed by the filamentous protein lamin might have been present in the last eukaryotic common ancestor (LECA) and become extremely dynamic evolutionarily later on [94-97]. The nuclear lamina became completely lost in fungi, had lamin replaced by other filamentous proteins in plants, and became considerably complicated due to the duplication and diversification of the ancestral lamin gene in animals [94-97]. Animal and plant nuclear laminas might not only differ in their composition, but also in the



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way they contact with the fraction of the genome that occupies the nuclear periphery, *i.e.*, peripherome [98]. Although in both cases it has been observed a peripheral distribution of silenced heterochromatic jDNA-enriched chromosome elements, in animals but not in plants the peripherome is characterized by being also AT-enriched and gene-poor [99-102].

Metazoan lamin is known to be important for cell specialization. First, the lamin type composition of the nuclear lamina and lamin posttranslational modifications are known to vary along cell differentiation and between cell types [103]. Second, laminopathies refer collectively to diseases caused by genetic mutations in lamin genes that course with degenerative alterations of one or more tissues formed by very specialized cells, *e.g.*, myocytes, cardiomyocytes, adipocytes, or neurons [103]. Third, it has been observed that the peripherome is enriched in tissue-specific genes, which upon differentiation are removed from the repressive nuclear periphery and become actively transcribed or poised for transcription [104, 105].

Since the animal nuclear lamina-peripherome ensemble conflates clear differences with plants, lots of jDNA, and genes related with cell specialization, it would make sense to explore how the natural variation in jDNA genomic content could drive peripheromal changes that subsequently modulated the balance between multipotentiality and irreversible specialization, and regenerative abilities. Possibly the simplest inference that can be made is that the fraction of coding genes within the confines of the repressive nuclear periphery might be respectively higher or lower for species with jDNA-poor compact or jDNA-rich bloated genomes (Figure 1E-F). Such differences in the gene density of the peripherome for species differing in jDNA genomic content could result in more or less genes being inaccessible for regulatory inputs ultimately dependent on regeneration-eliciting injuries, and therefore, a limited or enhanced ability to elicit



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regenerative responses. Regrettably, the precise characterization of the nuclear peripherome is still in its infancy having not yet reached those species with remarkable regenerative abilities and very recently sequenced genomes, and very little information exists to lend some support to this hypothesis. It is noteworthy that the mostly intergenic lamina-interacting domains (LADs) in human and *D. melanogaster* cells tend to be considerably larger in the former than in the latter, which parallels differences in jDNA-driven genome size between these two species [106, 107]. Although such differences would agree with the possibility that the gene density of the peripherome was larger in species with jDNA-poor compact or jDNA-rich bloated genomes, to our despair, neither *D. melanogaster* nor humans are particularly good regenerators [13, 20-25]. Another promising but insufficient piece of evidence comes from the recently sequenced genome of the salamander *A. mexicanum* or axolotl, a true regenerative champion [11]. jDNA elements such as introns are considerably smaller in humans than in the axolotl, again in parallel to differences in jDNA-driven genome sizes [11]. Unfortunately, no information exists on the composition of the axolotl peripherome to test whether different peripheromal gene densities for axolotl and human cells correlated with differences in traits related with cell specialization, and/or regenerative abilities.

Although at the present moment not enough information exists to test further whether jDNA genomic content variation result in differences in the peripheromal gene density that modulates the balance between cell multipotentiality and irreversible specialization and with it regenerative abilities, or to envision alternative hypothesis for that matter, already existing knowledge on the nuclear lamina-peripherome ensemble suggest this could be a key element to study the causal relationship that might actually exists between the natural variation in jDNA genomic content and regenerative abilities.



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## Conclusions and future perspectives

Here, I explored two potential non-excluding ways through which the amount of jDNA in the genome of a species might make it more prone or recalcitrant to respond to gross insults by regenerating missing structures (Figure 2). Because of the shared central role of cell potentiality/specialization for regeneration, cancer, development, or aging, it is possible that the thoughts barely sketched in here were of a much broader interest and will be explored further in future occasions. With regard to the study of regeneration, in recent years, an increasing number of voices are calling for a broadening of the exhaustively transited array of research models to gain a definitive corpus of knowledge concerning the natural variation of regenerative responses as a mandatory step to fulfill our long time will to enhance our own limited ability to regenerate [108-110]. Mainly, such voices advise for redoubling our efforts in studying species with already-known or newly appreciated enhanced regenerative abilities, which have been left behind mostly because of their unsuitability for simple genetic analyses [108-110]. The potential relationship between the natural variation in jDNA genomic content and regenerative abilities that motivated this piece, at the very least, suggests that the study of regeneration could also benefit from exploring non-gene-centric scenarios to reach a more complex understanding of the genomic determinants of regenerative development. Fortunately, a number of technical, analytical and conceptual advances are contributing to pave the way to fully comprehend the nature of the relationship between jDNA genomic content and regenerative abilities. In particular, of crucial importance would be, i) the increasing use of long-read sequencing methodologies and the elimination of filters to mask out repetitive DNA from genome annotations to have a fair representation of the historically overlooked jDNA fraction of genomes [111, 112], ii) the realization that genomes are three-dimensional structures with a



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complex organization and that such organization is highly relevant for gene expression dynamics through development and/or in response to external cues [35, 101, 113, 114], and, iii) the increasing appreciation that the use of high-throughput sequencing approaches for multiple closely related species spanning natural variation of interesting traits is far more valuable than genome sequencing individual model species [115]. In summary, the expansion of comparative genomic non-gene-centric approaches to groups such as amphibians, platyhelminths, or annelids, which show pertinent natural variation in regenerative responses, might be of definitive relevance to explain why some species can regenerate missing parts and others, mostly us, cannot.

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## Figure legends

**Figure 1. Models for the covariation of jDNA and cell specialization.** A. The hjDNA-based capacitance model spans multiple levels of biological organization to propose that hjDNA can act as a genetic capacitor by modulating the phenotypic exposure of genetic variants. hjDNA-based capacitance can be better observed between species that differ in their jDNA genomic content. Such differences in jDNA genomic content will subsequently drive differences in capacitance and genetic diversification (See main text for further details). For the sake of continuity, large differences in jDNA genomic content are represented with a gradient of color



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where red represent jDNA-rich genomes and blue represents jDNA-poor genomes. In principle, ultimately jDNA-based differences in genetic diversification could be perceivable at multiple levels, from jDNA-dependent differences in speciosity (B) to jDNA-dependent differences in tissue complexity (C-D). B. Ideal representation of the phylogenetic relationships between species for closely related genera Rich and Poor. Species for the genus Rich tend to have jDNA-rich genomes, whereas species for the genus Poor tend to have jDNA-poor genomes. Such differences in jDNA genomic content ultimately drive genus Rich to be less specious than genus Poor. C-D. Ideal representation of cell composition for the ideal tissue X in species with jDNA-poor (C) and jDNA-rich (D) genomes. In this case, the inverse relationship between jDNA genomic content and genetic diversification causes that the number of cell types conforming tissue X is larger for species with jDNA-poor than jDNA-rich genomes. E-F. Ideal representation of the gene density for the fraction of the genome that occupies the nuclear periphery, *i.e.*, peripherome, for species with jDNA-rich (E) and jDNA-poor (F) genomes. The differences in jDNA all along chromosomes in general and in centromeres in particular are symbolized using thicker and thinner lines and symbols. Since, intergenic distances for jDNA-rich genomes are considerably larger than for jDNA-poor genomes, it is possible that the number of genes located within the confines of the repressive nuclear periphery was lower for jDNA-rich than for jDNA-poor genomes.

**Figure 2. Model for the covariation of jDNA and regeneration abilities.** Ideal representation of cell transitions through development for jDNA-rich (A) and jDNA-poor (B) species. The single totipotent zygote for each species is represented at the top, and the most specialized cells marked with colored symbols are represented closer to the bottom of each panel. According to the hjDNA-based capacitance model, jDNA-poor species would show a more diversified



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spectrum of specialized cells than jDNA-rich species, which is represented with a larger number of specialized cells in the former than in the latter. Also, here I speculate with the possibility that the nuclear peripherome gene density would be higher for species with jDNA-poor genomes than for species with jDNA-rich genomes. Considering that genes located within the repressive confines of the nuclear periphery tend to be tissue-specific, it is possible to predict how differences in peripheromal gene density might relate with differences in the balance between cell multipotentiality and specialization, and regenerative abilities. A lower number of peripheromal genes for cells with jDNA-rich genomes might make them less specialized, better prepared to respond to external stimuli like gross injury, and, therefore, prone to elicit regenerative responses or regeneration competent, whereas a larger number of peripheromal genes for cells with jDNA-poor genomes might make them more specialized, less able to respond to gross injury, and, therefore, less prone to elicit regenerative responses or regeneration recalcitrant. Differences in cell specialization between species with jDNA-rich and jDNA-poor genomes are symbolized by placing the more differentiated cells (colored symbols) closer to or further from the bottom of each panel. Also, it is possible that the lower level of specialization expected for terminally differentiated cells for species with jDNA-rich genomes permitted specialization transitions or reversions typical for regenerative responses, *i.e.*, transdifferentiation and dedifferentiation respectively. In panel A, transdifferentiations are symbolized using horizontal bidirectional arrows, and dedifferentiations are symbolized using ascending arrows.



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Fig. 1.



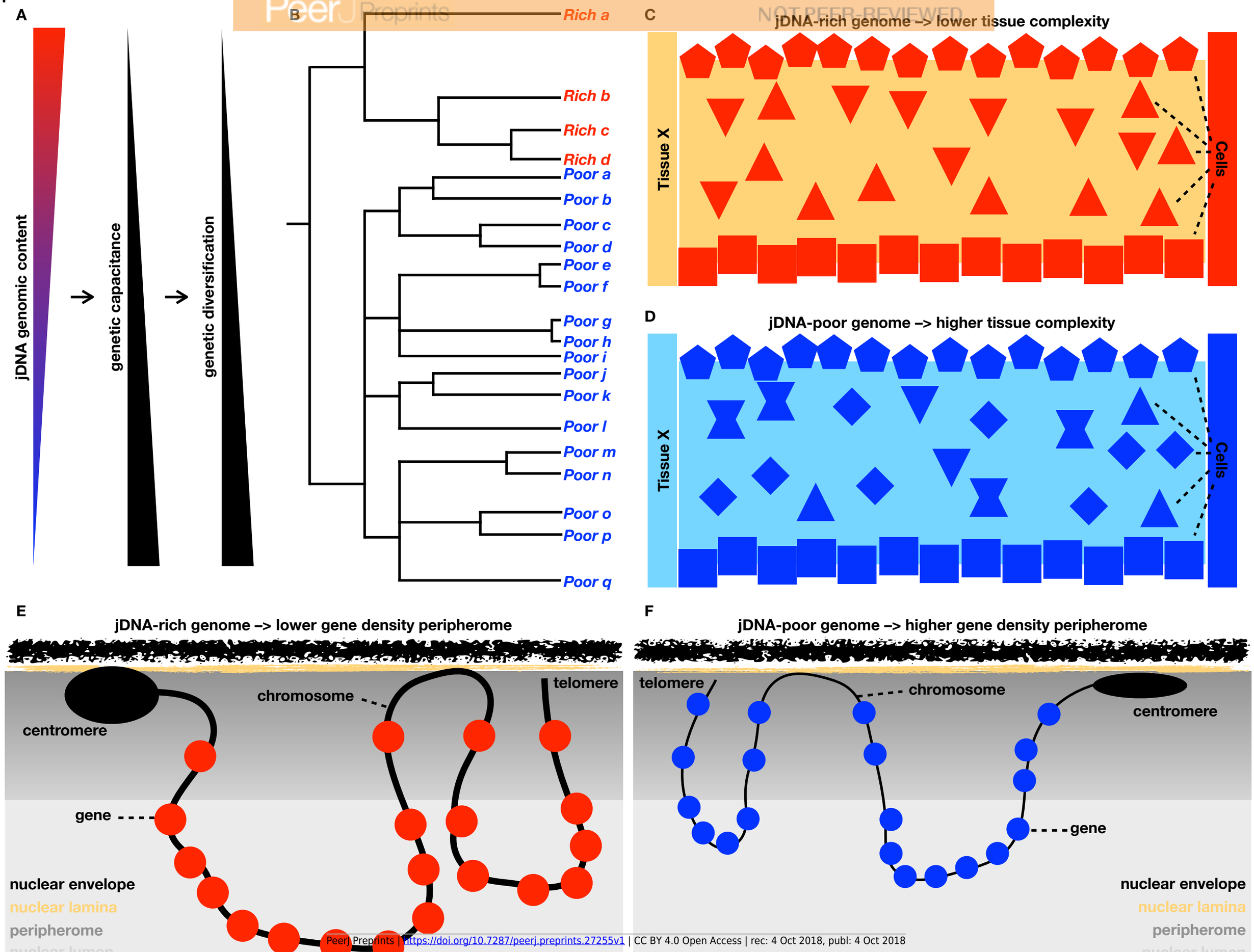


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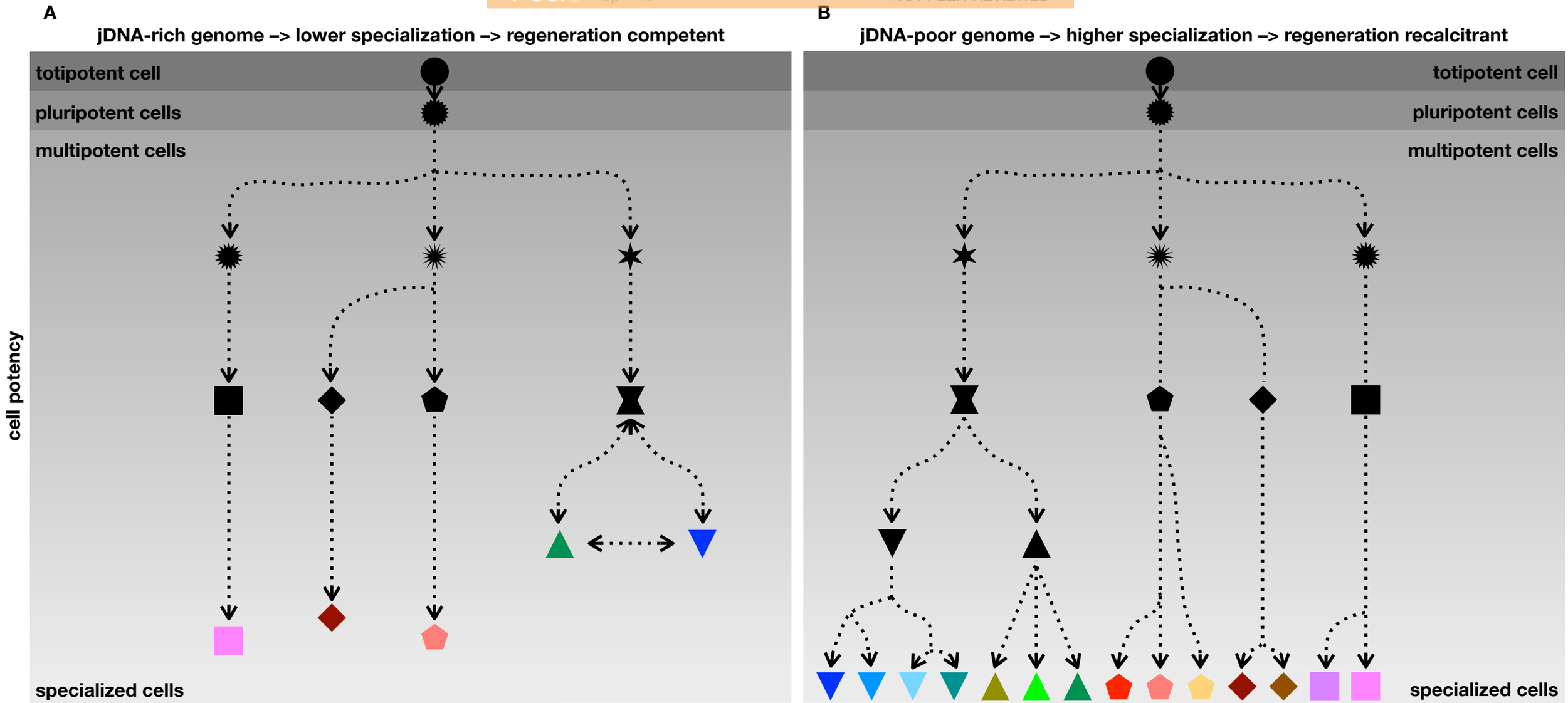
Fig. 2.



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