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The Angel's staircase: Cell cycle, and the embryogenesis of vertebrates

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ABSTRACT

I present a simple model of vertebrate embryogenesis, coupling cell division, differentiation, and morphogenesis. The model relies on a gradient of cell cycle period, in a flat shell of tissue. When the cell cycle period varies linearly between two points, a cascade of cell division occurs in the tissue, which generates a staircase of cell sizes (the Angel's staircase). The variation in cell size is associated to a stepwise variation of mechanical properties, which induces a deterministic pattern of folds. The folded shell is recognized as an animal.

This short communication proposes a physical mechanism of morphogenesis for the vertebrates phylum. When an adult vertebrate is observed, it is difficult to imagine that a deterministic hierarchical, physical process may be the true cause at the root of morphogenesis of such an individual. However, when vertebrate embryogenesis is observed from start, one rapidly identifies a self-organized mechanism able to produce an animal of this sort.

Initially, animals emanate from a single, fertilized, gigantic cell. For many animals such as a frog, an individual is formed by reorganization of this mass, without even any mass increase. For other animals such as for example birds, the animal will grow by eating up the store of nutrients contained in the egg. However, at early stages, the fertilized ovocyte does not "eat" and the gigantic initial cell cleaves in a pattern of a cascade of splitting events, which reduces ever more the size of the individual cells. When such different vertebrates as a chicken or a frog are observed, one sees in the first steps of division a hierarchical process of cell cleavage (Fig. 1). Evidently, cells are bigger at one side of the initial mass and smaller at the opposite side. Fig. 1 shows the resulting cell texture in a frog, after a few rounds of division, and a few steps of cell cleavage in a chicken embryo. Looking carefully, one sees that cells are always smaller at one pole of the initial sphere (to the left in the image of the frog embryo), and much bigger at the other pole, whatever the level of cleavage in the hierarchy. It is obvious on a frog, which retains a spherical shape, that the cells are small at the so-called "Animal pole", and larger at the opposite pole [1]. The "Animal Pole" is where, actually, the animal forms. It is less obvious on a chicken, in which cells appear small centrally, and big at the periphery (Fig. 1 Right). But the chicken case can be viewed as a sphere flattened across the "Animal pole".

One may wonder why there should be a gradient of cell sizes from the center towards the edge (for animals having the shape of a flat shell), or between two poles of a spherical shell. During early stages of development, when there is no mass or volume increase, the cell cycle will be responsible for the cell size: at constant volume, cells that cleave more rapidly generate smaller cells. Cells having a delayed cell division, remain big. Classical work in developmental biology has ascribed the difference in cell cycle period between one pole and the other, inside the initial egg, to the presence of fat (yolk) [1–3]. There would exist a demixtion of lipids in the initial egg, such that fat is stored at one side, and there exists a gradient of lipid granules from one pole to the other (in the case of amphibians and the like), or from the center towards the periphery (for birds and the like, such as reptiles). It has been argued that the gradient of cell cycle period is flatly caused by the mere variation of physico-chemical parameters, in a more lipidic solution [1]. Recent work suggests that such a demixtion is a physical phase separation process but we shall not discuss this point further [4].

The facts presented above suggest to us a very simple model of hierarchical cleavage of a disk (for the simpler case of the avian embryo, taken as example). This hierarchical cleavage will lead to a structure in rings of the early embryo, and the ring structure will serve as "template" or "prepattern" or "blueprint" for the 3D morphogenesis of the animal proper [5].

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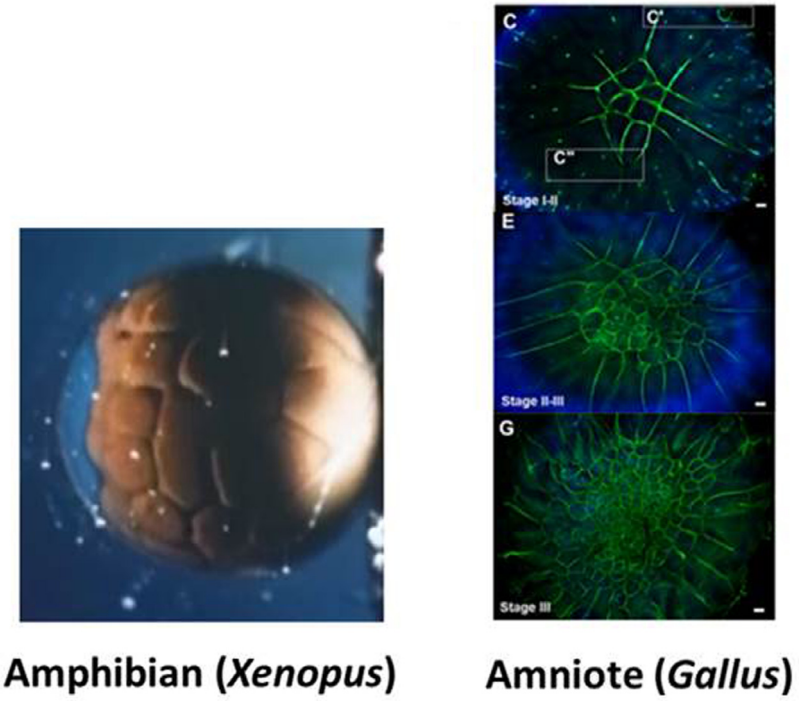

Fig. 1. Two examples of "blastula" structure, in an anamniote (*Xenopus*, from *Youtube*), to the left, and an amniote (*Gallus* [10]), to the right. These blastulas show a scaling of cells from the periphery towards the central part where the body forms ("Animal" pole). In the frog we clearly see that cells at the Animal pole located to the left are small, while cells located at the opposite pole are enormous. In the chicken blastula, we see small cells in the center, and large cells at the periphery. To the right, the plate shows three stages of the pattern of early cleavages in a chicken embryo as seen from atop (the labels, irrelevant here, are from the orginal article); these views can be considered as the equivalent of seeing the amphibian egg by its "Animal" pole, at different times (developmental "stages" from I to III). We clearly see a more rapid cleavage in the central area and a less active cleavage by the edge. As time passes, cells become smaller, and the hierarchy slides down towards smaller sizes, with more steps in the staircase.

If we assume that cells have a cell cycle with a spatially varying period $T(x)$, because of the lipid gradient, we may write across the early chicken blastodisk (or similarly, from the so-called "Animal" towards the so-called "Vegetal" poles of the amphibian oocyte or "morula" [1].

$$T(x) = \tau_1 + x\tau_1/R \tag{1}$$

We simply assume that cells cleave twice as fast at an end (the more hydrophilic end $x=0$) than at the lipidic end ($x=R$), with a $T(x)$ varying between τ_1 and $2\tau_1$; we could take another parameter than 2, it does not change the argument. Now, cell cleavage occurs in a discrete fashion, with cleavage occurring brutally at the end of the cell cycle. The number of apparent cycles undergone by a cell at time t, and located at position x is $E(t/T(x))$, in which E is the integer part of the ratio $t/T(x)$. Whenever this ratio is increased by 1, a new cleavage is apparent. If we assume that cell division tends to be physically symmetrical with cells being in average divided by 2 at each round of cell division, then the volume $V(x,t)$ and size $D(x,t)$ of a cell at time t and position x write, as a function of their initial values:

$$V(x,t) = V_0(1/2)^{E[t/(\tau_1+x\tau_1/R)]} \tag{2}$$

$$D(x,t) = D_0\left\{(1/2)^{E[t/(\tau_1+x\tau_1/R)]}\right\}^{1/3} \tag{3}$$

This can be easily plotted for different times (Fig. 2). Fig. 2A shows the cell volume distribution across the disk, at a time when the central cells, the ones which cleave more rapidly, have already undergone 10 cell division cycles. Fig. 2B shows in semi-logarithmic units the subsequent states of splitting between 1 and 10 cleavages. In Fig. 2B, and, for the sake of clarity, the thickness of the line is proportional to time: we represent with the same thickness of the line a given temporal state of the morula, with cells positioned between $x/R=0$ and $x/R=1$ measured at the same time. Fig. 2C shows the scaling structure of the staircase for larger numbers of rounds: 10, 15, 20, 25.

Not surprisingly, the data show that discrete rounds of cell divisions in a gradient of inhibitor tend to generate a stepwise distribution of rings of isocycle cells (cells having performed the same number of cleavages). However there is a hierarchical shift as time passes by, towards smaller cells. The blueprint refines itself as more divisions occur, but a similar blueprint exists, at each round of the hierarchy. As time passes by the entire distribution slides towards smaller cells, but it keeps self-similarly a staircase structure, with rings of one level obtained by splitting of the previous. I nickname this hierarchical pattern the Angel's staircase, by opposition to the Cantor set nicknamed "Devil's staircase".

If we turn to actual embryos, we see that around the moment of embryo formation (1 day later than the states shown in Fig. 1), the reference configuration indeed exhibits a ring-like structure (Fig. 3, reprinted in part from [6]). Prior to the onset of morphogenetic movements, the "blastula" has a target structure, with a number of rings of order 6. It has been proven recently that