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Observation of morphological and topological transitions within a wide range of natural phenomena has led to the general idea that development and transitions can be represented as a series of discrete steps determined by an initial set of predefined rules. Applying these rules and subjecting a system to parametric inputs from its environment will guide it through well-defined subsequent states and transitions. It may occur, however, that neither the initial set of rules nor the parametric inputs suffice to achieve this effect: at some critical point, there is not enough information available to decide whether a transition towards a new state is possible. In this article, we propose a new paradigm to describe such transitions. According to this paradigm, transitions are always preceded by a fundamental period of non-determinedness which is prolonged in a situation where a lack of information prevents a secure transition. The strain caused by the resulting contradiction may provoke an external informational input leading to a spontaneous decision that breaks the symmetry of the non-determined period. The result can be a new state which is not necessarily contained in the initial process.

The chronological development of physical systems, including state transitions and the concept of spontaneous symmetry breaking, has been intensively studied and is well understood for a large number of different systems. In developmental biology, a transition is usually well-defined by an appropriate balance of regulators enabling the cell to sense the direction of the next transition. This situation is often depicted as a road map starting from a stem cell to a highly specialized cell. In this context, the literature also employs the term *decision* to mark the «when» of a transition [1], for instance the moment at which a mammalian embryo transits from a symmetric to an asymmetric state during the first divisions [2, 3, 4, 5]. Here, the term decision refers to the selected direction of the embryonic-abembryonic axis*. An other example is the course of differentiation of embryonic stem cells* during which several crucial transitions have to decide which final fate, location and function the cells acquire through multiple divisions.

Hereafter, we will present a new paradigm to describe transitions in biological systems, in particular with the purpose of addressing the «when» and «how» of transitions. In this paradigm, we develop the understanding

of the term decision as employed in the cited literature. We conjecture that, besides the physical level, a need for an informational level exists in nature where decisions with respect to transitions are taken. At this informational level, a test is performed, whenever a transition is required by environmental factors, to determine if all conditions are met for the transition to take place. This test marks the beginning of a period of non-determinedness. If the amount and quality of information at the physical level is sufficient, a transition is automatically initiated upon which the period of non-determinedness ends. However, the amount and quality of information may not suffice to automatically initiate the next step leading to a secure transition, e.g. when the provided regulators are not well-balanced. As a result, still in terms of the proposed paradigm, the period of non-determinedness is prolonged and the system becomes subject to an internal contradiction between the current state and a subsequent state. At the physical level, this contradiction may become apparent from the emergence of chaotic behavior, when the set of system parameters neither contribute to the present, nor to a subsequent morphology or topology. We will argue that this internal contradiction cannot be resolved without an external input from the informational level, which is provoked by the mounting strain related to the internal contradiction. At the informational level, a decision in favor of one or another solution is strengthened, thereby breaking the «symmetry» of the non-determinedness. The decision is transposed back towards the physical level where a determined state is restored by entering an available morphology or topology. In the next section of this article, we develop a parametric model of transitions and argue why a system cannot be complete with respect to all possible situations. As an illustration of the ideas presented in the next section, we discuss the checkpoint signaling pathway within the mammalian cell cycle in the last section.

Parametric representation of transitions in incomplete systems

Hereafter, the term *system* denotes any organized ensemble, while the term *process* defines a set of ordered events or transitions through which the system shifts between different equilibrium states. The system and its environment produce a certain number of agents or regulators a_1, a_2, … , a_n having time-dependent parametric values $p_1(t)$, $p_2(t)$, … , $p_n(t)$, also written as p_1, p_2, … , p_n. The parametric values define the *information content* of the system. It is further assumed that at least one rule R, in the form of a condition C, exists that, when satisfied, leads to a transition T. A rule $R(C_1)$ provokes a transition T_1 if, for instance, $C_1 = C_1(p_1, p_2, \dots, p_n)$ is satisfied, with $(p_i)_{i=1, 2, \dots, n}$ assuming the values $(x_i)_{i=1, 2, \dots, n}$. Such a rule-based processing corresponds to performing a series of tests. The process information of the system contains the rule $R(C_1)$ and refers to the unitary

aspect of the process as a whole, which can be observed at the physical level. It encompasses all possible states of the system and defines the landscape that comprises the various equilibrium states accessed in the course of subsequent transitions.

As was set out in the introduction, a test implies a period of fundamental non-determinedness which may end with a secure transition if the test shows that the parametric inputs correspond to the requirements of the rules. It is to be stressed that, in this case, the process evolves automatically and can be understood and followed without taking the informational level into account. However, the parameters $(p_i)_{i=1, 2, \dots, n}$ may not attain the required combination of values $(x_i)_{i=1, 2, \dots, n}$ at the same time. A prolonged test is now performed to determine if the present parametric configuration is sufficiently similar to an ideal rule-based situation. In general, this occurs when the information content of the system is not complete with respect to a changing environment.

To describe the relation between the information content of the system and a transition, we characterize the state of a system by its confinement in a parametric space, i.e. by its contour. The *contour* encloses the set of parameters $(p_i)_{i=1, 2, \dots, n}$ and their specific values $(x_i)_{i=1, 2, \dots, n}$ leading to a given morphology or a given topology that represents the state, whereby these parametric values belong to a statistical ensemble. Therefore, if we assume that the specific values are variables which are normally distributed, then the contour $c(x_i)_{i=1, 2, \dots, n}$ can be defined as a multivariate Gaussian distribution of the set of parameters and their respective variable x_i with mean values μ_i. The joint probability density function is given by [6]

$$f(\mathbf{x}) = f(x_1, x_2, \dots, x_n) = \frac{1}{\sqrt{(2\pi)^n \det(\Lambda)}} \exp\left(-\frac{1}{2}(\mathbf{x}-\mu)^T \Lambda^{-1} (\mathbf{x}-\mu)\right) \tag{1}$$

where Λ is the covariance matrix and $\det(\Lambda)$ its determinant. The coefficients of the covariance matrix are defined as $\lambda_{ij} = E[(x_i - \mu_i)(x_j - \mu_j)]$, E being the mathematical expectation. For $f(\mathbf{x})$ to exist, Λ must be positive definite. We also assume that the ranges within which the specific values of the parameters are variable, while still representing the state, lie in $[a_i, b_i]_{i=1, 2, \dots, n}$ which is included in $c(x_i)_{i=1, 2, \dots, n}$. Thus, the probability of finding the parameters $(p_i)_{i=1, 2, \dots, n}$ inside a contour can be calculated by integrating the joint probability density function over all these intervals

$$\Pr\Big(c(x_i)_{i=1,2,\dots,n}\Big) = \int_{a_1}^{b_1} \int_{a_2}^{b_2} \dots \int_{a_n}^{b_n} f(\mathbf{x})\, d\mathbf{x}. \tag{2}$$

In addition, the probability associated with the parameter p_i alone can be deduced from equation (1) by integrating the joint probability density function over all values of the *n-1* other parameters

$$f_{\mathbf{x}}(x_i) = \int f(\mathbf{x})\, dx_1 \,\ldots\, dx_{i-1}\, dx_{i+1} \,\ldots\, dx_n. \tag{3}$$

From equation (3), one can finally calculate the probability associated with the parameter p_i at a given point in time

$$\Pr\left(p_{i,t}^{c(x_i)_{i=1,2,\ldots,n}}\right) = \int_{a_i}^{b_i} f_{\mathbf{x}}(x_{i,t})\, dx_i. \tag{4}$$

During a transition, the system abandons its old contour and adopts a new one (figure 1). An orderly transition is characterised by the absence of an overlap between the two contours, i.e. the parametric values of the old and new state are variable within ranges that do not overlap. Now let $p_{i,t}$ be the *i*-th parametric value at a given time point, then the *difference* $d_t(c_1, c_2) \in [-1, 1]$ between two contours c_1 and c_2, can be defined by

$$d_t(c_1, c_2) = \frac{1}{n} \sum_{i=1}^{n} \Pr\left(p_{i,t}^{c_2}\right) - \Pr\left(p_{i,t}^{c_1}\right) \tag{5}$$

wherein $\Pr(p^{c_j}_{i,t})$ stands for the probability of the *i*-th parameter being in the domain of the *j*-th contour. In a well-defined state, the probability of the system assuming parametric values inside the contour is much higher than the probability of assuming parametric values outside this contour. For an orderly transition, the difference $d_t(c_1, c_2)$ between the two contours c_1 and c_2 should be large enough to make them distinguishable.

When the absence of information prevents a secure transition, and the period of non-determinedness is prolonged, the mobility and the kinetic energy content still continue to drive the system and the probability of finding the system at parametric values outside a given contour will increase. Every new parametric value realised outside the contour may increase the probability that the next parametric value will also be outside the contour. A fortiori, the system may gain kinetic energy through the loss of topological or structural information during the period of non-determinedness and may eventually become chaotic or ergodic. As a result of the «weakening» of the contours, the difference $d_t(c_1, c_2)$ between two contours decreases and the strain, defined as the absolute value of the inverse of this difference, $S_t(c_1, c_2) = |d_t(c_1, c_2)|^{-1}$, increases. The maximum strain and, at the same time, the maximum contradiction has been reached, when the probability to find parametric values inside the first contour is equal to the probability of finding these parametric values inside the second contour, in other words when

$$\Pr\left(p_{i,t}^{c_1}\right) = \Pr\left(p_{i,t}^{c_2}\right),\ i = 1, 2, \ldots, n. \tag{6}$$

Alternatively, the strain is also maximum when one half of the parameters lies inside the first contour and the other half inside the second contour,

$$\begin{cases} \Pr\left(p_{i,t}^{c_1}\right) \gg \Pr\left(p_{i,t}^{c_2}\right) & 1 \leq k \leq \dfrac{n}{2}, \\ \Pr\left(p_{i,t}^{c_1}\right) \ll \Pr\left(p_{i,t}^{c_2}\right) & \dfrac{n}{2} < k \leq n. \end{cases} \tag{7}$$

At this moment, the system can no longer be characterized by a single state and the informational identity of the system has vanished, even if it can still have a defined morphology or topology at the physical level. In this situation, the system is no longer complete in the sense that it cannot decide which state to realize. Any recovery of the system from this internal contradiction should therefore point to an external informational input. We conjecture that the strain $S_t(c_1, c_2)$, which is a measure of the internal contradiction, is responsible for provoking this informational input.

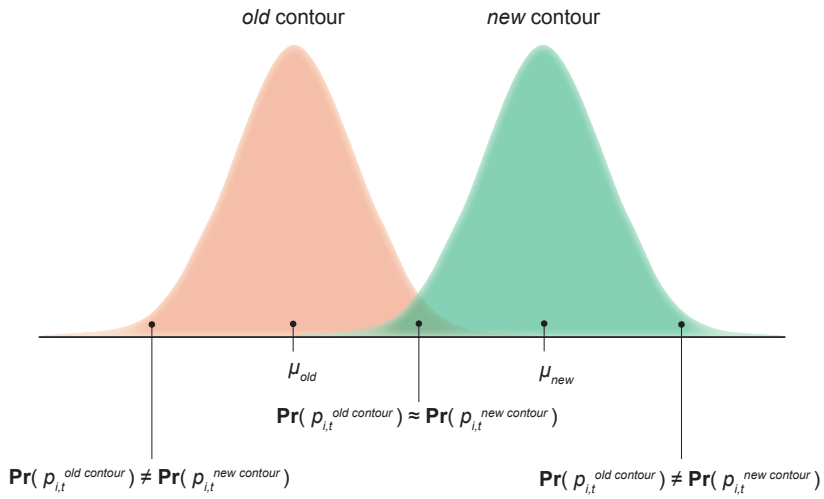

FIGURE 1 | GAUSSIAN DISTRIBUTION DEFINING AN *OLD* AND A *NEW* CONTOUR THE OVERLAP OF THE COUTOURS PREVENTS A SECURE TRANSITION BY LEADING TO A NON-DETERMINED SITUATION.

Transitions within the mammalian cell cycle

One of the major tasks of a cell is the complete duplication of its genome (synthesis or S-phase) for further proliferation as well as for a proper segregation of each sister chromatid during cell division (mitosis or M-phase). These two major tasks are usually separated in mammalian cells by two gaps within the cell cycle, called G_1 and G_2. The first gap or G_1-phase corresponds to the period right after mitosis and before the next genome duplication. During this phase, the cells have temporarily withdrawn from the cell cycle and remain quiescent until they enter the S-phase. The

second gap or G_2-phase separates the period of DNA synthesis and chromatin condensation from the oncoming division of the cell. To ensure an accurate copy of the genome, the cell possesses a series of surveillance pathways called cell cycle checkpoints [7, 8]. Among the latter, the G_1 and the G_2 checkpoints both correspond to a moment in the cell cycle when a crucial decision has to be made with respect to the G_1 / S transition or the G_2 / M transition (figure 2), even if the G_1 / S transition can be triggered by the restriction point – the point after which cells no longer respond to extracellular inputs and have committed to carry out the cell cycle [9, 10].

The progression of the cell through the cell cycle is closely related to the balance between the concentration of cyclins and cyclin-dependent kinases (Cdk's). The binding of cyclins to the Cdk's enables the latter to phosphorylate different substrates. Signaling pathways regulate the oscillation in the level of cyclins as well as the activity of their associated Cdk's in response to events inside and outside the cell [11, 12].

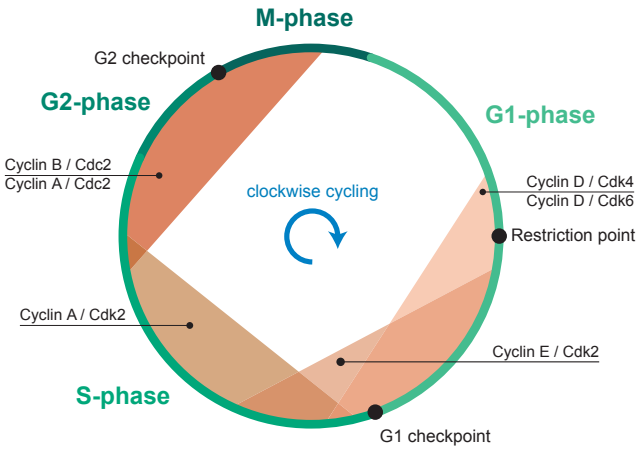

FIGURE 2 | PROGRESSION THROUGH THE MAMMALIAN CELL CYCLE
SCHEMATIC REPRESENTATION OF THE CELL CYCLE SHOWING THE POSITIONS OF THE TWO CRITICAL CHECKPOINTS, G_1 AND G_2, AS WELL AS THE RELATIVE ABUNDANCES OF THE INVOLVED CYCLINS AND CDK'S.

For the purpose of applying the ideas presented in the previous section to the cell cycle, we focus on the cyclin concentrations, especially during the G_1 / S transition. During the G_1 gap, information is collected from the cell's environment to see if all requirements for cell growth and DNA replication have been met. While assuming that the parameters defining the environment are constant (temperature, pH, salt concentration, nutrients and growth factors), we only take into account the molecular concentrations of cyclins within the cell. The cyclin D group is needed for the subsequent expression of cyclin E and A which are required for DNA replication in the S-phase. Cyclin B is associated with the M-phase and should be minimal [12].

Figure 3 illustrates four different situations during the G_1-phase, each with different relative cyclin concentrations. Although no accurate data are available for these concentrations during the entire cell cycle, it is approximately known what they should be for a normal transition from the G_1 to the S-phase to take place [12]. Firstly, the concentrations of D-type cyclins must reach a certain level during G_1 to ensure that the cell enters S-phase with sufficient amounts of cyclins E and A. Secondly, it is known that the concentrations of the S- and M-phase cyclins A and B must be reduced in G_1 cells, otherwise their expression in quiescent cells would lead to problems in DNA replication and cause genetic instability.

All four situations depicted in figure 3 can be characterized by a strain. The strain $S_t(S, G_1)$ at the G_1 checkpoint is obtained by rewriting equation (5) as

$$S_t^{-1}(S, G_1) = \left| \frac{1}{4} \sum_{i=\{A,B,D,E\}} \Pr\left(\rho_{i,t}^{S}\right) - \Pr\left(\rho_{i,t}^{G_1}\right) \right| \tag{8}$$

where ρ_i denotes the concentrations of cyclin A, cyclin B, cyclin D and cyclin E, respectively. The two different contours G_1 and S correspond to the two consecutive phases in the cell cycle. Obviously, a similar equation can be written for the G_2 / M transition.

In the ideal case, when the cyclins A, B, D and E reach their appropriate level during the checkpoint period, the situation is well-defined and the period of non-determinedness is minimal (figure 3A). If, on the other hand, the concentrations do not reach their appropriate level within the checkpoint period (figure 3B), or are too high (figure 3C), the result is a lengthening of the undetermined period with the corresponding increase of the strain. However, a well-defined state is still possible given the robustness of the cell mechanisms [12]. In the case depicted in figure 3D, the concentrations are located in an undetermined zone, such that

$$\begin{cases} \Pr\left(\rho_{A,t}^{S}\right) \gg \Pr\left(\rho_{A,t}^{G_1}\right), \\ \Pr\left(\rho_{B,t}^{S}\right) \ll \Pr\left(\rho_{B,t}^{G_1}\right), \\ \Pr\left(\rho_{D,t}^{S}\right) = \Pr\left(\rho_{D,t}^{G_1}\right), \\ \Pr\left(\rho_{E,t}^{S}\right) = \Pr\left(\rho_{E,t}^{G_1}\right), \end{cases} \tag{9}$$

hence creating an unresolved situation.

To our knowledge, the situation of figures 3B-D has not been reported as a result of controlled laboratory conditions. Both in nature and in laboratory, apoptosis and the onset of abnormal conditions like cancers [13] remain possible solutions to an unresolved situation. For instance, a relation between chromosomal instability and unmatched concentrations of regulators during the G_2/M transition was observed in cells in response to ionizing radiation [14]. How the equilibrium is maintained between a successful repair followed by a return into the cell cycle and apoptosis has not been satisfactorily clarified [15] and may be related to an external informational input.

In order to test the paradigm presented here, the reproduction of non-standard concentration ratios and the resulting cell states would be the aim of further laboratory investigations. Concentrations of cyclins can be manipulated by overexpression [16] or by depletion by using state-of-the-art techniques, while cyclin concentrations can be accurately measured [17]. The overexpression of G_1-cyclins (cyclin D and E) has been tested in laboratory (figure 3C) and has been observed to lead to a shortening of the G_1-phase with a compensatory lengthening of the S- and G_2-phase [16]. This compensatory phenomenon and a possible control of the cell cycle timing have been discussed in [18]. It has also been brought in relation with diverse types of cancers [13].

Finally, it is important to note that the ideal case, where all the concentrations are well-defined, may not exist, meaning that the strain is never equal to zero and the request for an external informational input can happen at any time.

We have shown that in some cases a system is incomplete and therefore cannot resolve an undetermined situation having two or more competing outcomes. In an attempt to escape this contradiction, we assumed the existence of an informational level apart from the physical level where a transition is decided. The outcome of this decision is then transposed back into the system.

Although information at the physical level is only observable through the material carriers, the informational level may contain elements that have no carrying counterpart at the physical level. This opens the possibility that a decision introduces new morphologies or topologies that had not been realized thus far. We claim that most transitions involving morphological and topological changes may be subject to such an internal contradiction and that nature may evolve through this path.The proposed paradigm is not limited to biological systems, but is applicable to transitions in other fields as well.

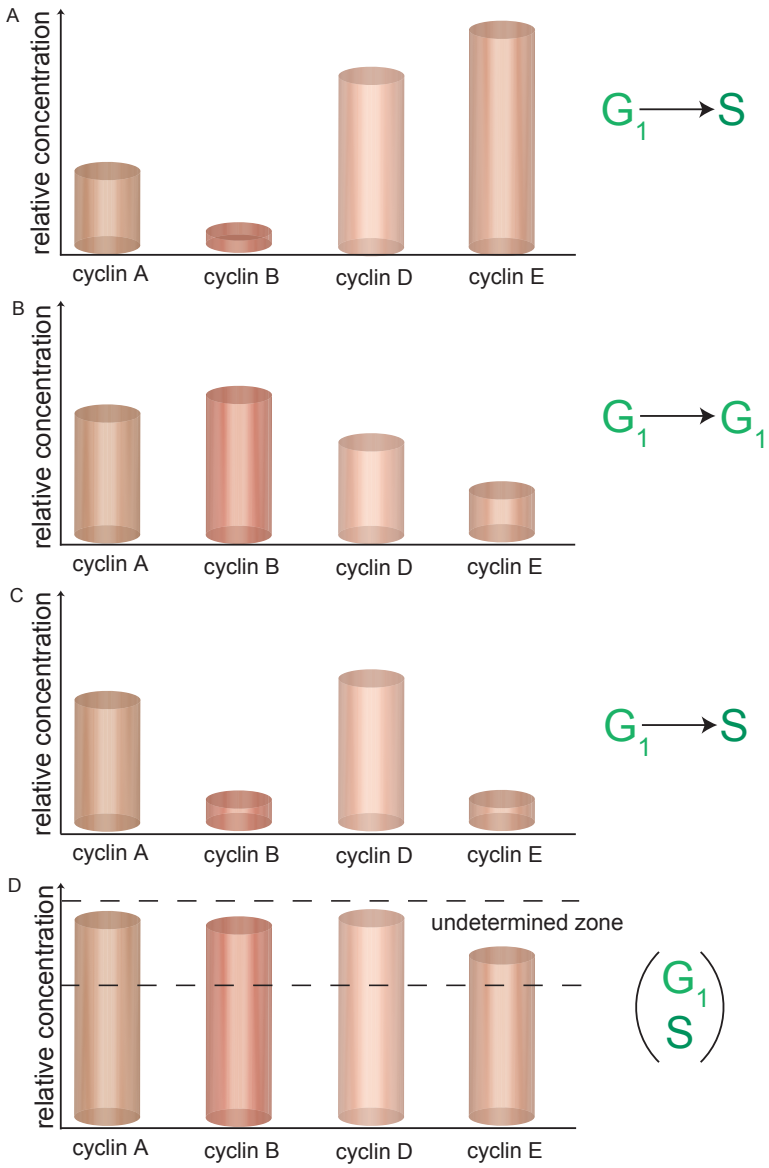

FIGURE 3 | CYCLIN CONCENTRATION IN RESPECT TO THE G_1 / S TRANSITION FOUR DIFFERENT SITUATIONS RELATED TO THE CYCLIN CONCENTRATIONS THAT MAY BE ENCOUNTERED DURING A PHASE TRANSITION IN THE CELL CYCLE: WITH ALL FOUR CYCLINS BEING WELL-BALANCED, ENSURING A SECURE TRANSITION INTO S-PHASE (A), WITH THE CELL TO STAY IN G_1-PHASE (B), WITH THE CELL TO ENTER INTO THE S-PHASE (C) AND WITH NONE OF THE CYCLINS BEING WELL-BALANCED (D). NOTE THAT THE CONCENTRATIONS ARE NOT QUANTIFIED, BUT RATHER REPRODUCE THE RELATIVE ABUNDANCE OF CYCLINS DURING G_1/S TRANSITION.

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Lexicon

embryonic-abembryonic axis
About one week after fertilization, a mammalian embryo consists of a few dozen cells. At this stage of the development, the embryo is called a blastocyst. At least two types of cells are present in the blastocyst: the inner cell mass which will form the fetus as well as some parts of the placenta and surrounding tissues, and the trophoblast cells, which will form most of the placenta but will not contribute to the developing fetus. The inner cell mass proliferates at one end of the blastocyst, called the embryonic side, while the other half of the blastocyst, the so-called abembryonic side, contains a hollow cavity, called the blastocoel.

embryonic stem cell
Stem cells are present in multi-cellular organisms and are characterized by their ability to renew themselves through mitotic cell division and to differentiate into a wide range of specialized cell types. Among mammals, embryonic stem cells are found in blastocysts, while adult stem cells are found in tissues.