Stabilizing Turing patterns with subdiffusion in systems with low particle numbers

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The role of subdiffusion in the formation of spatial Turing patterns with particle number fluctuations is studied. It is demonstrated for a generic activator-inhibitor system that for normal diffusion the particle number fluctuations stabilize the homogenous steady state in a regime where the mean-field analysis already predicts stable spatial patterns. In contrast, pattern formation is stabilized considerably even for very low particle numbers when the activator moves subdiffusively while the inhibitor diffuses normally. In particular, this also holds true when the subdiffusive activator spreads faster than the inhibitor on small time scales. Possible applications to pattern formation in cell biology are discussed.

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Pattern formation is an ubiquitous phenomenon in nature and may be observed on various length and time scales. Since the pioneering work of Turing [1], who gave a criterion when the homogenous steady state of a chemical reaction can be expected to become instable due to diffusion, many studies have been devoted to reaction-diffusion models which are capable of exhibiting spatial, temporal, or spatiotemporal patterns. Depending on the kind of instability of the steady state, these patterns can be grouped into different universality classes (see Ref. [2] for review). Popular examples for the formation of spatiotemporal patterns are, e.g., the famous Belousov-Zhabotinskii reaction [3] and the self-organziation of the slime mold *Dictyostelium discoideum* [4]. Besides a deeper understanding of general principles of pattern formation, the investigation of reaction-diffusion systems also has shaped our current view on fundamental concepts in developmental biology [5,6] and cell biology [7,8].

However, the concept of Turing pattern formation, i.e., destabilizing the homogenous steady state by diffusion, typically requires strongly varying diffusion constants [6]. This condition is crucial in many applications, in particular with respect to pattern formation in living matter. For example, the diffusion coefficients of reaction partners in the cytoplasm of cells may possibly vary by an order of magnitude, however these high ratios of mobilities are almost impossible to obtain on membranes. This is due to the fact that in three dimensions the Einstein-Stokes equation $D \propto k_B T/R$ yields an inverse proportional dependence of the diffusion constant D on the radius R of the particle, whereas in two dimensions D only depends logarithmically on R [9].

A way out of the dilemma, to require strongly varying diffusion coefficients for pattern formation, could be to implicate subdiffusional motion, which has so far not been considered in the context of pattern formation. Subdiffusion is characterized by the nonlinear growth of the mean square displacement of particles, i.e., $(\Delta x)^2 \sim t^\alpha, \alpha < 1$, and may arise due to obstructed diffusion and/or a continuous time random walk (CTRW). While obstruction can easily give rise to transient subdiffusive motion with $\alpha \geqslant 0.7$ below and at the percolation threshold [10,11], the degree of anomality in the case of a CTRW is tunable in the range $0 < \alpha < 1$ (see Ref. [12] for a review on CTRW). This is achieved by imposing a singular distribution of resting/binding times, $p(\tau) \sim 1/\tau^{1+\alpha}$, between periods of free diffusional motion. In fact, subdiffusion has been reported in many areas of research, e.g., for intermittent chaotic systems [13], solute transport in porous media [14], soluble proteins in the nucleus [15] of living cells, as well as for integral membrane proteins in cellular organelles [16] and on the plasma membrane [17].

An additional problem arising in the context of pattern formation is the applicability of mean-field approaches when only low amounts of particles are involved. Especially in biological systems, only a few hundred or thousand particles may make up the reaction-diffusion system, leading to strong particle number fluctuations which are neglected in the mean-field description. If and to what extent (sub)diffusion mediated pattern formation is affected by particle number fluctuations is therefore a crucial, yet poorly explored problem.

Here, the ability to obtain spatial patterns for low numbers of particles is investigated for normal diffusion and subdiffusion. Using a well characterized reaction-diffusion (activator-inhibitor) system, it is shown that the ability to stabilize spatial patterns in both cases decreases with the particle number. Subdiffusion, however, yields a considerable enhancement to form patterns even when the number of particles involved in the reaction is low. This stabilization of pattern fomation is demonstrated to become stronger as the activator's movement becomes more subdiffusive. Even when the subdiffusive spreading of the activator is faster than the inhibitor on short time scales, a stable pattern emerges while this is impossible when invoking normal diffusion. Finally, possible applications to pattern formation in cell biology are discussed.

As a model for the formation of spatial Turing patterns, the well studied dimensionless Schnakenberg model [6,18] is considered, i.e.,

$$\frac{\partial u}{\partial t} = a - u + v u^2 + d \Delta u, \qquad \frac{\partial v}{\partial t} = b - v u^2 + D \Delta v. \tag{1}$$

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This model is obtained when considering a simple trimolecular reaction, i.e., particles/molecules X and Y derive from different source pools ($X \rightleftharpoons A$, $Y \rightleftharpoons B$) and react to build new particles of species X ($2X+Y \rightarrow 3X$). Using the law of mass action and taking u, v as the dimensionless concentrations of X and Y, respectively, Eqs. (1) are obtained. While the species u can be interpreted as an autocatalytically generated activator, species v plays the role of an inhibitor. Consequently, the observed patterns for u and v are inverse to each other. For simplicity, the parameters a, b, d will be fixed to $a=0.1$, $b=0.9$, and $d=1$ in the remainder unless stated otherwise. Using these parameters, the steady state of the reaction is given by $u_0=a+b=1$ and $v_0=b/u_0^2=0.9$. A linear stability analysis of the mean-field equations (1) for these parameters shows that the homogenous steady state becomes instable beyond a bifurcation at $D_c \approx 8.5$.

Numerical investigations of Eqs. (1) were performed on a one-dimensional lattice with $m=100$ sites, periodic boundary conditions, and a lattice constant $\Delta x=0.2$. The total length of the environment is thus $L=m\Delta x=20$. To study the evolution of a random initial state, a fourth order Runge-Kutta scheme with time increment $\Delta t=10^{-4}$ was used. To include particle number fluctuations, the stochastic rate equations corresponding to Eq. (1) were considered, e.g., hopping of individual particles of species v between neighboring sites occurred with probability $D\Delta t/\Delta x^2$. The simulations were set up in such a way that the mean number of particles of species u on average was given by an integer N. For convenience, this number N was chosen to characterize the system while one equivalently could choose the total number of particles of both species u and v. For both the mean-field and the stochastic dynamics a maximum simulation time of $t_{\max}=10^6$ time steps was used, where the steady state had been reached [see Figs. 1(a–c)].

Before turning to subdiffusion and its effects on pattern formation, let us first focus on the role of particle number fluctuations in the case of normal diffusion. As anticipated from the linear stability analysis, the steady state of Eqs. (1) for $D=8.5$ already shows a periodic pattern for the mean-field equations [Figs. 1(a,d)]. In contrast, using $N=2000$ or $N=5000$ particles, rather fluctuations around a homogenous steady state, i.e., no stable pattern, are observed [Figs. 1(b-d)]. Increasing the number of particles to $N \gg 5000$ eventually leads to the convergence towards the inhomogenous steady state of Eqs. (1).

The most straightforward approach to quantify the ability to form a pattern at any given value of D is to monitor the time evolution of the leading mode of species u, i.e., the maximum ζ of the absolute square of the Fourier transform of u. If the leading mode decays ($d\zeta/dt<0$), the homogenous state is stable, while a growth indicates pattern formation. As can be seen in Fig. 2(a), smooth curves are obtained for ζ using Eqs. (1) with $D=8,10,12$ which confirm the anticipated stability of the homogenous state and the onset of pattern formation, respectively. For the stochastic counterpart ($N=2000,5000$), however, the curves for ζ fluctuate strongly and except for $N=5000$, $D=12$ do not yield a well criterion if a pattern indeed emerges [Fig. 2(b)]. In particular,

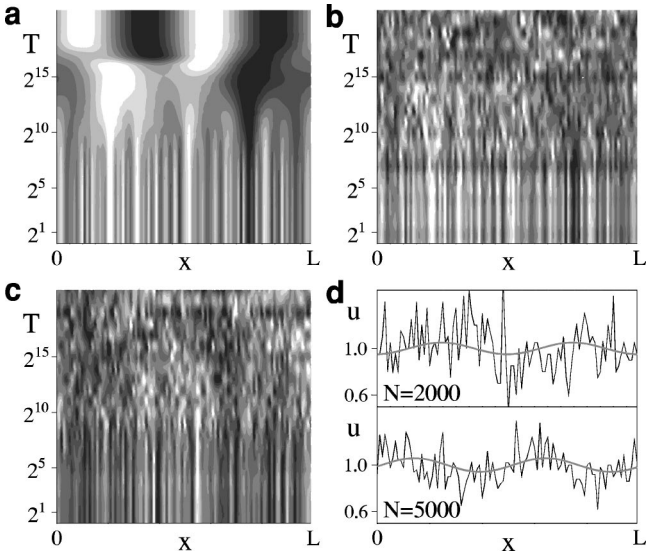

FIG. 1. (a) Time evolution of the activator species u according to Eqs. (1) for a random initial configuration at $D=8.5$. To highlight the emergence of a spatial pattern, u is scaled at each time step $T=t/\Delta t$ to the interval $[0,1]$ and displayed in gray scale. Using the corresponding stochastic rate equations with (b) $N=2000$ and (c) $N=5000$ particles instead, no pattern fomation is observed. (d) At $D=8.5$, the steady state of Eq. (1) shows a sinusoidal pattern along the one-dimensional lattice of length L for the activator u (thick gray line), while the corresponding stochastic dynamics (black line) for $N=2000$ and $N=5000$ particles hardly shows any signs of a spatial pattern.

the strong fluctuations do not allow one to extract a critical value D^* beyond which the homogenous steady state can be assumed to be instable. Therefore, in the following, an alternative, somewhat more simple and sensitive measure will be used to determine if a pattern is observed: the excursion of the steady state with respect to a homogenous density is determined for each simulation by the short range correlation

$$\sigma=\sum_i (u_i-\langle u\rangle)(u_{i+1}-\langle u\rangle). \tag{2}$$

Here, $\langle u\rangle$ is the mean of u over the entire length of the sample, $i=1,\ldots,m$ and $u_{i+1}=u_1$ is taken for $i=m$ to satisfy the imposed periodic boundary conditions. To avoid artifacts from individual realizations of the initial configuration, the data for σ were averaged over ten random initial conditions for all N's, D's. For the continuous and differentiable steady state of Eqs. (1), σ tends to zero if the steady state is homogenous, while it bifurcates at $D=D_c \approx 8.5$ and remains positive for the nonhomogenous steady states at $D>D_c$ [Fig. 2(c), full line]. Similarly, σ tends to a small number σ_0 for the homogenous steady state of the corresponding stochastic dynamics ($D<D_c$). However, due to the particle number fluctuations, σ_0 depends on N and does not tend to zero as observed for the mean-field equations [Fig. 2(c), symbols]. Concomitant to an increase of σ_0 for decreasing N, the onset of pattern formation appears to be shifted to the right, i.e., σ deviates from σ_0 significantly only for values $D>D_c$. To highlight this shift, the standard deviation $s(\sigma_0)$

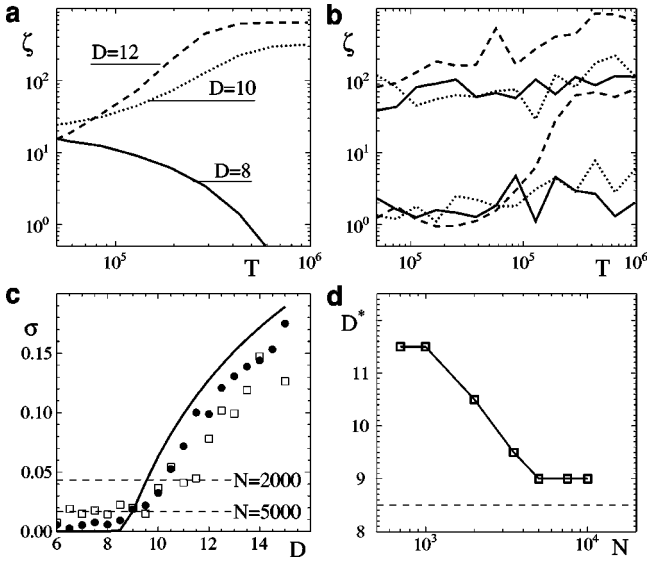

FIG. 2. (a) The maximum value ζ of the absolute square of the Fourier transform of the activator u as a function of time steps T. While the decrease of ζ for $D<D_c$ indicates the stability of the homogenous state, the increase in ζ for $D>D_c$ is a sign for pattern formation. (b) Same as in (a) when including particle number fluctuations (upper/lower set of curves: $N=2000/N=5000$, shifted up/down by a factor of 2/8 for better visibility). The strong fluctuations impair a decision if the homogenous state has become instable, except for $D=12$, $N=5000$ (lower dashed line) where pattern formation clearly has set in. (c) The short range correlation σ according to Eq. (2) shows the anticipated bifurcation at $D_c \approx 8.5$ for Eqs. (1) (full line) The emergence of a spatial pattern is indicated by $\sigma > 0$ for $D>D_c$. In contrast, the onset of pattern formation is shifted towards higher values of D when the particle number fluctuates (open/filled symbols: $N=2000/N=5000$). This also leads to a finite, but fluctuating σ_0 with standard deviation $s(\sigma_0)$ for $D<D_c$. Dashed lines indicate the value $\sigma^*=\sigma_0+7s(\sigma_0)$ from where σ can be expected to significantly reflect stable pattern formation (see text for details). (d) The onset value D^* for pattern formation, defined by the minimal D which fulfills $\sigma \geqslant \sigma^*$, tends towards D_c (dashed line) as N increases.

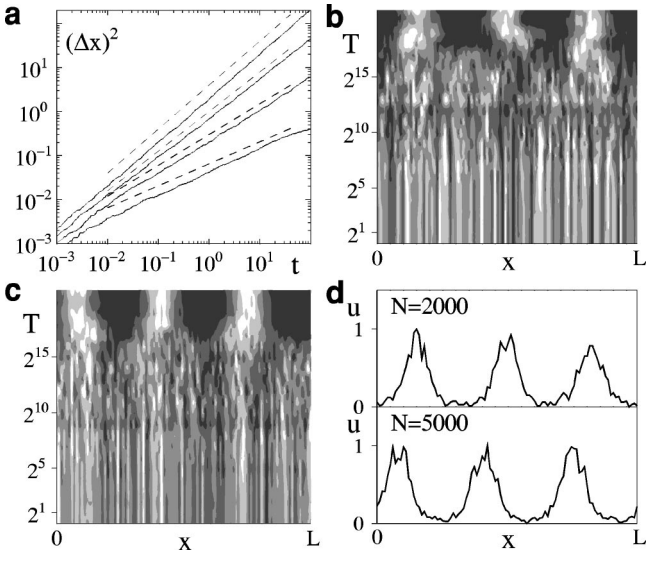

FIG. 3. (a) Mean square displacement $(\Delta x)^2$ of particles for normal diffusion ($\alpha=1$) and for various implementations of the CTRW ($\alpha=0.9,0.7,0.5$). Dashed lines highlight the anticipated (sub)diffusive behavior $(\Delta x)^2 \sim t^\alpha$. The time course of the activator u using the stochastic reaction-diffusion equation with (b) $N=2000$ and (c) $N=5000$ particles in the regime of subdiffusion (activator species u—$\alpha=0.9$, $d=1$; inhibitor species v—$\alpha=1$, $D=8.5$) shows the emergence of a pattern. These time courses and the corresponding steady states for the activator u in (d) are in strong contrast to the normal diffusive case [Figs. 1(b–d)] where no traces of pattern formation could be observed.

is calculated from the interval $D<D_c$ and used as a measure for the onset of pattern formation: when σ passes the threshold $\sigma^*=\sigma_0+7s(\sigma_0)$, this is taken as evidence that pattern formation has become stable. Dashed lines in Fig. 2(c) show this threshold for $N=2000$ and $N=5000$. The minimum value D^* fulfilling the condition $\sigma \geqslant \sigma^*$ thus determines the onset of pattern formation and is shown as a function of N in Fig. 2(d). Beyond $N=10^3$ no pattern could be detected any more and D^* appears to level off, while for large N a convergence of D^* towards D_c is observed.

It is tempting to conclude from these results that pattern formation with few particles and a low ratio D/d cannot be described by the usual activator-inhibitor systems. Obtaining stable patterns requires in the present example a ratio $D/d \sim 10$ and this ratio will have to increase even further when particle number fluctuations are taken into consideration. However, on biological membranes, for example, the ratio $D/d \approx 3$ typically cannot be overcome without additional mechanisms which constrain the diffusion. Also, the number of particles involved in the pattern formation may be fairly small (see Ref. [8] for an example and a nice discussion on that issue). In the remainder of the paper, subdiffusion will be shown to be a means to overcome these limitations.

A convenient way to model subdiffusive motion is the implementation of a CTRW [12], where particles take rests of duration τ during their diffusive motion. When the distribution of resting times decays asymptotically as $p(\tau) \sim 1/\tau^{\alpha+1}$, $0<\alpha<1$, the asymptotic behavior of the mean square displacement is characteristic for subdiffusion, i.e., $(\Delta x)^2 \sim t^\alpha$. To study the effects of subdiffusion on pattern formation, a CTRW was implemented where the particles try to perform a diffusive step to the next lattice site when the resting time has elapsed and then dice another resting time τ. As can be seen in Fig. 3(a), the mean square displacement obtained in that way indeed grows anomalously.

Figures 3(b–d) show the result when the activator species u moves subdiffusively with $\alpha=0.9$ (and $d=1$ for the random walk between the rests), while the inhibitor species v diffuses normally with a mobility determined by $D=8.5$. Although the motion of species u is only slightly anomalous, a stable pattern emerges even for low particle numbers, in contrast to the case of ordinary diffusion [cf. Figs. 1(b–d)]. Surprisingly, at low particle numbers even a mild subdiffusion stabilizes pattern formation dramatically. In fact, the range of values for D where patterns could be observed with $N=2000$ and $N=5000$ is shifted down to $D^* \approx 2.5$ [Fig. 4(a)] which is a major improvement as compared to $D^* \approx 10$ in the normal diffusive case [cf. Fig. 2(a)]. This pattern-

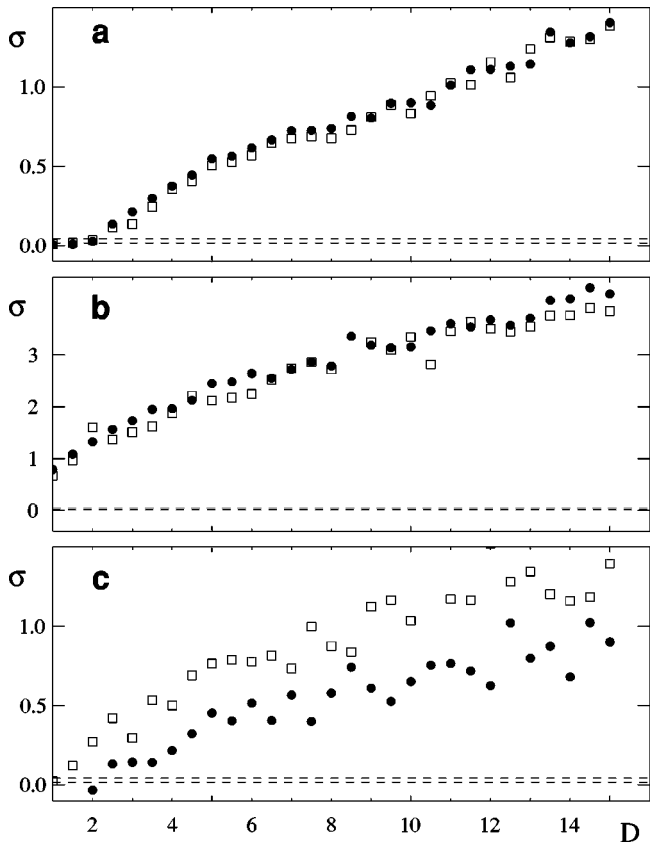

FIG. 4. Short range correlation σ [Eq. (2)] as a function of D for subdiffusive motion of the activator species u with (a) $\alpha=0.9$, (b) $\alpha=0.7$, (c) $\alpha=0.5$ (open/filled symbols: $N=2000/N=5000$). Despite the particle number fluctuations, the emergence of spatial patterns is shifted towards small values of D, i.e., $D^*<D_c$. This effect becomes more and more pronounced as α decreases and for $\alpha \leqslant 0.7$ stable patterns are obtained even for $D\approx 1$. Dashed lines indicate the value $\sigma^*=\sigma_0+7s(\sigma_0)$ (for $N=2000$, 5000) beyond which σ indicates stable patterns. For $\alpha=0.5$, σ becomes less well as a measure for pattern formation as the maxima become very sharp [see Fig. 5(b) for an example] and σ may even be negative although a pattern has emerged.

stabilizing effect of subdiffusion becomes even stronger when smaller α are used [Figs. 4(b,c)]. In particular, stable patterns are obtained even for $D\approx 1$ when $\alpha \leqslant 0.7$.

The stabilization of pattern formation by subdiffusive motion of the activator can be understood when recalling that the major ingredient for the appearance of Turing instabilities is a fast spreading of the inhibitor as compared to the activator [6]. Thus, subdiffusion mimics the results of a lower diffusion coefficient, and does this also very effectively at low particle numbers. In fact, the reaction rate between few particles of species u and v may be too low to allow the reaction to happen fast enough before diffusion drives the particles apart. Subdiffusion on the contrary allows the particles to stay longer near each other and therefore enhances the probability for the reaction (see Ref. [11] for a detailed investigation), which eventually can stabilize pattern formation. However, the activator does not necessarily need to be slower on all time scales. In fact, one can also observe

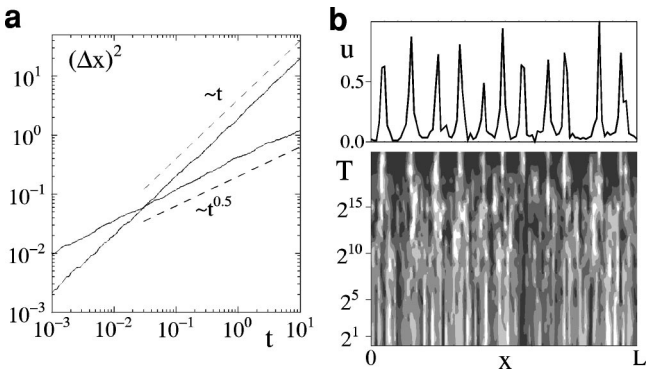

FIG. 5. (a) Anomalous mean square displacement obtained for a CTRW with $\alpha=0.5, d=10$ (activator species u), while the inhibitor v spreads normally with $\alpha=1, D=1$. Dashed lines highlight the respective (sub-)diffusive spreading. (b) Although the activator spreads faster on short time scales, still a Turing pattern emerges as steady state.

pattern formation when the activator moves subdiffusively with $\alpha=0.5$ and $d=10$, while the inhibitor diffuses normally with $D=1$ (Fig. 5). Here, also the shape is very distinct as not only two but many ''hot spots'' of the activator u are visible. Using normal diffusion, it is almost impossible to obtain a pattern which is as ''spiky'' as the one shown in Fig. 5(b) by simply tuning D/d. Therefore subdiffusion not only stabilizes the inhomogenous steady state, but also allows the emergence of patterns which often cannot be obtained by ordinary diffusion.

The stabilization of Turing patterns by subdiffusion, in particular for low particle numbers, is likely to be of importance for structure formation in cell biology. For example, the recently discussed model for bacterial cell divison [8] relies on the strongly decreased mobility of two involved proteins, when they attach from the cytoplasm to the bacterial cell wall. Even if these proteins aggregate on the membrane, the diffusion coefficient of about 10^{-3} μm^2/s used in Ref. [8] is extremely low as compared to the typical value 1 μm^2/s anticipated for membrane proteins [9]. Taking into account that especially membrane proteins have been reported to exhibit subdiffusive motion [16,17], the model proposed in Ref. [8] could be extended to employ this feature and thus to better satisfy possible biological constraints, e.g., obstructed diffusion. Similarly, the formation of membrane domains, so called rafts, which are crucial for cell signaling may be a result of subdiffusive stabilization of spatial patterns. Moreover, as shown here, even slightly anomalous diffusion, caused for example by obstructed diffusion, can enforce a Turing instability. Thus, steric hindrance due to the cytoskeleton in the cytoplasm or decondensed chromatin in the nucleus of living cells may be a means to trigger inhomogenous steady states. These patterns would change or vanish when the cell reaches another stage of the cell cycle where the obstruction of diffusion is released, e.g., when the cytoskeleton partly disassembles and the chromatin condenses to chromosomes.

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