Modelling the compartmentalization of splicing factors

G. Carrero\textsuperscript{a}, M.J. Hendzel\textsuperscript{b}, G. de Vries\textsuperscript{a,*}

\textsuperscript{a}Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, AB, Canada T6G 2G1
\textsuperscript{b}Department of Oncology, University of Alberta, Cross Cancer Institute, 11560 University Avenue, Edmonton, AB, Canada T6G 1Z2

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Abstract

Splicing factor (SF) compartments, also known as speckles, are heterogeneously distributed compartments within the nucleus of eukaryotic cells that are enriched in pre-mRNA SFs. We derive a fourth-order aggregation–diffusion model that describes a possible mechanism underlying the organization of SFs into speckles. The model incorporates two hypotheses, namely (1) that self-organization of dephosphorylated SFs, modulated by a phosphorylation–dephosphorylation cycle, is responsible for the formation and disappearance of speckles, and (2) that an underlying nuclear structure plays a major role in the organization of SFs. A linear stability analysis about homogeneous steady-state solutions of the model reveals how the self-interaction among dephosphorylated SFs can result in the onset of spatial patterns. A detailed bifurcation analysis of the model describes how phosphorylation and dephosphorylation modulate the onset of the compartmentalization of SFs.

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1. Introduction

The structure of eukaryotic cells is characterized by the presence of two intracellular compartments, namely the cytoplasm and the nucleus. While the structural and functional organization of the cytoplasm is well defined, the nucleus has been more enigmatic. This is principally due to the absence of membranes that define compartments within the nucleoplasm. For example, cellular organelles in the cytoplasm such as the endoplasmic reticulum, the Golgi apparatus, and the mitochondria have been clearly identified, whereas the nature of structures and compartments within the nucleoplasm remains poorly understood. With recent advances in fluorescence microscopy techniques, and the visualization of specific proteins within the nucleus, the structural organization of the nucleus has started to unfold. In particular, fluorescence microscopy has allowed for the identification of subnuclear structures or compartments (Dundr and Misteli, 2001; Lamond and Earnshaw, 1998; Matera, 1999; Spector, 1993, 2001). These compartments differ from most cytoplasmic compartments in that they lack membrane boundaries. However, the identification of nuclear domains enriched in specific proteins has led to the conclusion that the nucleus itself is highly organized and dynamically compartmentalized (Dundr and Misteli, 2001; Hendzel et al., 2001; Lamond and Earnshaw, 1998; Lewis and Tollervey, 2000; Misteli, 2001b; Phair and Misteli, 2000; Spector, 2001).

The prototypical example of a non-nucleolar compartment is found in the spatial organization of splicing factors (SFs). SFs are nuclear proteins that remove introns (non-coding sequences in the genes) from precursor mRNA molecules in order to form the mature mRNA that will be transported to the cytoplasm. During the interphase of the cell cycle, SFs are concentrated in approximately 25–50 clusters; during mitosis, these clusters disassemble. These membraneless clusters or aggregates of SFs, which are heterogeneously distributed in a “speckled” pattern in the nucleus (see
are called Splicing Factor Compartments (SFCs) or nuclear speckles (Kruhlak et al., 2000; Lamond and Spector, 2003; Phair and Misteli, 1993, 2001).

One might infer that co-localized processes of splicing and transcription occur within the speckles, but this is not the case. In fact, splicing and transcription take place away from the speckles and predominantly at their periphery (Hendzel et al., 1998; Huang and Spector, 1996; Misteli, 2000; Misteli et al., 1997). This suggests the existence of a mechanism independent of interactions established during RNA splicing that is responsible for reversibly recruiting SFs. In other words, the organization of SFs must be highly dynamic. Indeed, fluorescence microscopy experiments have shown that (1) SFs are in continuous flux between the speckles and the nucleoplasm (Kruhlak et al., 2000; Misteli, 2001b; Misteli et al., 1997; Phair and Misteli, 2000), and (2) SFs move randomly throughout the cell nucleus (Pederson, 2000a; Phair and Misteli, 2000).

These dynamical aspects have brought forth two current biological hypotheses for SF compartmentalization, one relating to the role of phosphorylation and dephosphorylation in the formation and disassembly of SFCs, and the other relating to the existence of an underlying nuclear structure. First, recent experimental evidence obtained from SR proteins suggests that the flux between the speckles and the nucleoplasm is modulated by phosphorylation and dephosphorylation (Cáceres et al., 1997; Misteli and Spector, 1997, 1998; Xiao and Manley, 1998). SR proteins are a family of SFs containing a carboxy-terminal domain rich in arginine–serine dipeptides (RS-domain) (Fu, 1995; Manley and Tacke, 1996), and the phosphorylation status (phosphorylated or unphosphorylated) of this domain plays a major role in their localization. In particular, overexpression of kinases that phosphorylate the RS-domains results in the release of SFs from speckles and the disassembly of SFCs (Colwill et al., 1996; Duncan et al., 1998; Gui et al., 1994; Misteli et al., 1997; Misteli and Spector, 1997; Wang et al., 1998). In contrast, the reassociation of SFs to SFCs requires the presence of specific phosphatases responsible for the removal of a phosphate group (Misteli and Spector, 1996, 1997). Moreover, the unphosphorylated state of SFs enhances their self-interaction (binding), whereas the phosphorylated state diminishes it (Xiao and Manley, 1998). Understanding the role of phosphorylation in the location of SFs and the existence of self-interacting domains (RS-domains) (Cáceres et al., 1997; Xiao and Manley, 1997, 1998) has led to the following hypothesis for SF compartmentalization: self-organization is responsible for the formation of speckles, and phosphorylation and dephosphorylation modulate this organization.

Second, measurements of the mobility of SFs show that they move at a rate that is two orders of magnitude lower than expected based on their molecular weight (Phair and Misteli, 2000). A possible explanation for this apparent slow mobility of SFs is rapid transient binding to a relatively immobile nuclear scaffold or nuclear matrix (Capco et al., 1982; He et al., 1990; Hendzel et al., 1999; Kruhlak et al., 2000; Lasky, 2000; Nalepa and Harper, 2004; Nickerson, 2001; Wasser and Chia, 2000). This idea has led to the following hypothesis for SF compartmentalization: the existence of an underlying nuclear structure is a major determinant of the organization of SFs (Hendzel et al., 1999; Kumaran et al., 2002; Nickerson, 2001).

The dynamical aspects of SFs and their heterogeneous distribution in speckles provide strong evidence that there is more to the spatio-temporal dynamics of SFs than just simple diffusion. To unravel the mechanism underlying the organization of SFs, we incorporate the two existing biological hypotheses for SF compartmentalization into a mathematical model. Unlike the current thinking that these two hypotheses are conflicting (Lamond and Spector, 2003), we will see that they can, indeed, complement each other in a possible mechanism responsible for the compartmentalization of SFs (see Fig. 2). We use the model to suggest answers to a number of fundamental questions about SFCs (Lamond and Spector, 2003; Misteli, 2000, 2001a). What is the detailed mechanism of SF compartmentalization? What controls the concentration of SFs inside and outside the speckles? Is speckle formation initiated randomly? What determines the number and size of SFCs?
The model we derive is a fourth-order aggregation–diffusion model that describes a possible mechanism underlying the organization of SFs in speckles (Section 2). Using linear stability analysis, we show how the onset of SF compartmentalization is captured by the model (Section 3), and using bifurcation analysis, we explain how the compartmentalization of SFs is modulated by the dynamical parameters of the model (Section 4). We conclude with a discussion of the relevance of the results and possible directions of future work (Section 5).

2. The model

In order to formulate a simple model that can capture the essence of SF compartmentalization, we accommodate the biological hypotheses stated in the previous section into the following general assumptions:

1. SFs transiently bind to an immobile underlying nuclear scaffold that is assumed to be homogeneously distributed throughout the nucleus.
2. Transient binding is rapid, and results in reduced diffusive behaviour in the context of Fluorescence Recovery After Photobleaching (FRAP) experiments (Carrero et al., 2004), or instantaneous reaction in the context of chemical kinetics (Crank, 1975). This assumption allows us to characterize the motion of SFs with an effective diffusion coefficient $D = (1 - k)D_b$, where $k$ is the proportion of SFs dynamically bound to the underlying structure, and $D_b$ is the actual diffusion coefficient of SFs based on their molecular weight.
3. There is no net growth of SFs, i.e., there is conservation of mass during the formation of speckles.
4. SFs density is divided into two classes, namely phosphorylated SFs, $v(x, t)$, and unphosphorylated SFs, $u(x, t)$, where $x$ denotes space and $t$ denotes time. It is worthwhile to mention that although there are different phosphorylated states of SFs, the simplification of considering two classes (phosphorylated and unphosphorylated) reflects the fact that net dephosphorylation promotes association with SFCs and net phosphorylation promotes dissociation (this does not mean that associated molecules are completely unphosphorylated or that a single phosphorylation is sufficient to promote dissociation from SFCs).
5. There is an exchange rate between phosphorylated SFs and unphosphorylated SFs given by a phosphorylation rate, $\rho$, and a dephosphorylation rate, $\delta$, caused by the activity of kinases or phosphatases, respectively.
6. Unphosphorylated SFs are capable of self-interaction.

On the basis of these general assumptions, and considering a one-dimensional space, the resulting system of equations for the dynamical organization of SFs takes the following form:

$$
\frac{\partial v}{\partial t} = D \frac{\partial^2 v}{\partial x^2} - \delta v + \rho u,
$$

$$
\frac{\partial u}{\partial t} = \text{(motion and self-interaction term)} + \delta v - \rho u,
$$

where the “motion and self-interaction term” for the density of unphosphorylated SFs needs to be fleshed out. To find an exact expression for this term, we follow a diffusion-approximation approach (Turchin, 1998), which is based on a random walk analysis that accounts for both the motion and self-interaction effects. This type of approach has been proven to be an effective tool when describing congregative behaviour in ecological systems (Lewis, 1994; Turchin, 1989).

Let us assume that unphosphorylated SF biomolecules move along a line that is discretized into small space intervals of length $\lambda$. Let us also discretize time into short intervals of length $\tau$, and assume that every time step $\tau$ a biomolecule located at position $x$ at time $t$ can move a distance of $\lambda$ either to the left with probability $L(x, t)$, to the right with probability $R(x, t)$, or remain in its current position with probability $N(x, t)$.
Thus, the probability of moving is given by

$$R(x, t) + L(x, t) = 1 - N(x, t). \quad (2)$$

We further assume that there is no bias in the movement, i.e. $R(x, t) = L(x, t)$. Following the procedure in Turchin (1998), we arrive to the following diffusion-approximation model for the density of unphosphorylated SFs

$$\frac{\partial u(x, t)}{\partial t} = D \frac{\partial^2 u}{\partial x^2} [(1 - N(x, t))u] = \frac{\partial^2 u}{\partial x^2} [\mu(x, t)u], \quad (3)$$

where $D = (1 - k)D_b = \lim_{t \to -\infty} \chi^2/2\pi$, and $\mu(x, t) = D(1 - N(x, t))$ represents the motility.

As a final step, we need to develop an expression for $N(x, t)$. For this purpose, we assume that the probability $N(x, t)$ for an unphosphorylated biomolecule to remain in its current position is proportional to the average density of unphosphorylated SFs bound to the underlying structure, and is given by

$$N(x, t) = \frac{k}{\sigma} \int_{-\infty}^{\infty} H(s)u(x + s, t) \, ds, \quad (4)$$

where $\omega$ represents a critical density of biomolecules dictated by space limitations, $k = k\chi$ is called the aggregative sensitivity, $k$ is the proportion of SFs dynamically bound to the underlying structure, $\sigma$ represents the binding affinity of SFs (probability of binding to each other), and the kernel function $H(s)$ is assumed to have the following form

$$H(s) = \begin{cases} \frac{1}{2\sigma} & \text{for } |s| \leq \sigma, \\ 0 & \text{for } |s| > \sigma, \end{cases} \quad (5)$$

where $\sigma$ denotes the range of influence of the self-interaction. Note that $N(x, t) \leq 1$ provided that $u(x, t) < \omega$,

$$u(x, t) < \omega, \quad (6)$$

i.e. $u(x, t)$ does not exceed the critical density $\omega$. We shall see that this condition is satisfied during the onset of the compartmentalization, but when aggregation is pronounced, the density may exceed $\omega$, and the model will no longer be valid. We will return to this issue in the discussion.

The diffusion approximation model (3) falls into the class of integro-differential equations. Such equations have been shown to have rich dynamics, including potential for pattern-formation (Lewis, 1994; Mogilner and Edelstein-Keshet, 1995, 1996, 1999; Mogilner et al., 1996; Murray, 1993; Turchin, 1998). We will take the approach followed by Lewis (1994), Murray (1993), and Turchin (1998), namely to expand the integral term for the stability analysis of Eq. (3). However, this approach is not essential for the linear stability analysis (Mogilner and Edelstein-Keshet, 1996, 1999). Using the expansion in Taylor series

$$u(x + s, t) = u(x, t) + \frac{\partial u}{\partial x} s + \frac{\partial^2 u}{\partial x^2} \frac{s^2}{2} + \frac{\partial^3 u}{\partial x^3} \frac{s^3}{6} + O(s^4),$$

and the expression of the kernel (5), the probability of staying (4) becomes

$$N(x, t) = \frac{k\mu(x, t)}{\omega} + \frac{k\sigma^2}{6\omega} \frac{\partial^2 u}{\partial x^2} + O(\sigma^4). \quad (7)$$

Assuming that the range of influence $\sigma$ is small and neglecting the fourth-order and higher-order terms with respect to $\sigma$, the motility, $\mu(x, t) = D(1 - N(x, t))$, can be approximated by

$$\mu(x, t) = D - D \frac{k\mu(x, t)}{\omega} - D \frac{k\sigma^2}{6\omega} \frac{\partial^2 u}{\partial x^2} (x, t). \quad (8)$$

Substituting Eq. (8) into Eq. (3), the diffusion approximation for the density of unphosphorylated SFs can be written as the following fourth-order partial differential equation:

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} = \frac{\partial^2 u}{\partial x^2} \left[ \left( D - 2Dk \frac{\mu}{\omega} \right) \frac{\partial u}{\partial x} \right] - \frac{\partial^2 u}{\partial x^2} \left[ \left( \frac{Dk\sigma^2 u}{6\omega} \right) \frac{\partial^2 u}{\partial x^2} \right]. \quad (9)$$

which represents the motion and self-interaction term in Eq. (1). We refer to Eq. (9) as the aggregation–diffusion equation. Thus, the system of partial differential equations describing the compartmentalization of SFs becomes

$$\frac{\partial v}{\partial t} = D \frac{\partial^2 v}{\partial x^2} - \delta v + \rho u,$$

$$\frac{\partial u}{\partial t} = \frac{\partial}{\partial x} \left[ \left( D - 2Dk \frac{\mu}{\omega} \right) \frac{\partial u}{\partial x} \right] - \frac{\partial^2 u}{\partial x^2} \left[ \left( \frac{Dk\sigma^2 u}{6\omega} \right) \frac{\partial^2 u}{\partial x^2} \right] + \delta v - \rho u. \quad (10)$$

We refer to Eq. (10) as the aggregation–reaction–diffusion system.

The cell nucleus is a domain bounded by a membrane. For this reason, we assume a bounded domain, $0 \leq x \leq L$, with no net flux of SFs across the boundaries. This is achieved by considering the following no-flux boundary conditions:

$$\frac{\partial v}{\partial x}(0, t) = \frac{\partial v}{\partial x}(L, t) = \frac{\partial u}{\partial x}(0, t) = \frac{\partial u}{\partial x}(L, t) = 0,$$

$$\frac{\partial^3 u}{\partial x^3}(0, t) = \frac{\partial^3 u}{\partial x^3}(L, t) = 0. \quad (11)$$

In order to facilitate the analysis and reduce the number of parameters, we introduce the following
dimensionsless variables:
\[ x^* = \frac{x}{L}, \quad t^* = \frac{D}{L^2} t, \quad v^* = 2\kappa \frac{v}{\omega}, \quad u^* = 2\kappa \frac{u}{\omega}. \]
\[ \sigma^* = \frac{\sigma}{L}, \quad \delta^* = \frac{L^2}{D} \delta, \quad \rho^* = \frac{L^2}{D} \rho. \]  
(12)

After making these substitutions and dropping the asterisks, the aggregation–diffusion Eq. (9) becomes
\[ \frac{\partial u}{\partial t} = \frac{\partial}{\partial x} \left[ (1-u) \frac{\partial u}{\partial x} - \frac{\partial^3}{\partial x^3} \left( \frac{\sigma^2}{12} u \right) \frac{\partial^2 u}{\partial x^2} \right] + \delta v - \rho u, \]  
subject to the no-flux boundary condition
\[ \frac{\partial u}{\partial x}(0, t) = \frac{\partial u}{\partial x}(1, t) = 0, \]  
and the aggregation–reaction–diffusion system (10) can be rewritten in a dimensionless form as
\[ \frac{\partial v}{\partial t} = \frac{\partial^2 v}{\partial x^2} - \delta v + \rho u, \]
\[ \frac{\partial u}{\partial t} = \frac{\partial}{\partial x} \left[ (1-u) \frac{\partial u}{\partial x} - \frac{\partial^3}{\partial x^3} \left( \frac{\sigma^2}{12} u \right) \frac{\partial^2 u}{\partial x^2} \right] + \delta v - \rho u, \]
subject to the no-flux boundary conditions
\[ \frac{\partial v}{\partial x}(0, t) = \frac{\partial v}{\partial x}(1, t) = \frac{\partial u}{\partial x}(0, t) = \frac{\partial u}{\partial x}(1, t) = 0, \]
\[ \frac{\partial^3 u}{\partial x^3}(0, t) = \frac{\partial^3 u}{\partial x^3}(1, t) = 0. \]  
(15)

Since self-organization appears to be driven by the dynamics of the unphosphorylated SFs, described by the aggregation–diffusion equation (9), our first interest will be to demonstrate the potential of this equation for the spontaneous formation of spatial patterns (Section 3). These patterns, which are a consequence of the non-homogeneous distribution of biomolecules, can be interpreted as SF compartments or speckles, where the density of biomolecules is high. In Section 4, we focus on the aggregation–reaction–diffusion system (10), and study the modulating effect of phosphorylation on the compartmentalization of SFs. From the first equation in Eq. (10), we intuitively expect the modulation to be driven by the homogenizing effect of the spatial diffusion of phosphorylated SFs.

3. The onset of the compartmentalization of SFs

The potential of Eq. (15) for spatial pattern formation is interpreted as the onset of SF compartmentalization during early G1. We can assert intuitively that no patterns will arise if there are no unphosphorylated SFs. For this reason, and to start the analysis as simple as possible, we will capture the essence of the onset of the compartmentalization by examining first the dynamics of just unphosphorylated SFs in the absence of phosphorylated ones. By carrying out a linear stability analysis about the homogeneous steady-state solutions of the aggregation–diffusion equation (13) subject to the boundary conditions (14), we will examine the behavior of perturbations, and determine whether there are wavenumbers with the ability to grow.

3.1. Dispersion relation for the aggregation–diffusion equation

The uniform steady states of Eq. (13) are given by any constant density \( u_{eq} \). Thus, using the assumption of conservation of mass, we can think of the uniform steady state \( u_{eq} \) as a parameter that varies according to the amount of biomolecules in the system. Let us consider small perturbations of the biomolecule density \( u(x, t) \) away from the spatially uniform steady state \( u_{eq} \), of the form
\[ u(x, t) = u_{eq} + \epsilon \eta(x, t), \quad \text{where} \quad \epsilon \ll 1. \]  
(17)

Substituting Eq. (17) into Eq. (13) yields
\[ \frac{\partial \eta}{\partial t} = \frac{\partial}{\partial x} \left[ (1-u_{eq} - \epsilon \eta) \frac{\partial \eta}{\partial x} \right] - \frac{\partial^2}{\partial x^2} \left( \frac{\sigma^2}{12} (u_{eq} + \epsilon \eta) \right) \frac{\partial \eta}{\partial x} \frac{\partial^2 \eta}{\partial x^2}. \]  
Dividing this expression by \( \epsilon \), dropping the bars, and noting that \( \epsilon \ll 1 \), we obtain the following linearization for the aggregation–diffusion equation (13):
\[ \frac{\partial u}{\partial t} = (1-u_{eq}) \frac{\partial^2 u}{\partial x^2} - \frac{\sigma^2}{12} u_{eq} \frac{\partial^4 u}{\partial x^4}. \]  
(18)

To investigate the behavior of solutions for the linearized equation (18), we study the normal mode solutions of the form
\[ u(x, t) \propto \exp(\lambda t + iqx), \]  
(19)
where \( \lambda \) is the growth rate corresponding to the wavenumber \( q \). Thus, wavenumbers \( q \) with a corresponding \( \lambda > 0 \) will grow with wavelength \( 2\pi/q \).

Substitution of Eq. (19) into the linearized equation (18) gives the following dispersion relation between \( \lambda \) and \( q^2 \):
\[ \lambda = (u_{eq} - 1)q^2 - \frac{\sigma^2}{12} u_{eq} q^4, \]  
(20)
which is shown as a function of \( q^2 \) in Fig. 3. The potential for pattern formation is determined simply by the fundamental condition \( \lambda > 0 \). Note that for the limit case \( \sigma = 0 \), the kernel (5) corresponds to a delta distribution centred at the current position of the biomolecule, and the dispersion relation increases or
decreases monotonically with respect to $q$, depending on whether $u_{eq} > 1$ or $u_{eq} < 1$. Therefore, the smaller the perturbation wavelengths the faster they will grow, which means that the problem is ill-posed in the sense of Hadamard (Zauderer, 1998). For this reason, we account for the realistic biological assumption that biomolecules can be influenced by nearby molecules of the same type and consider only the case $\sigma > 0$, in which small wavelengths, characterized by high $q$, do not grow. The main requirement for $\lambda$ to correspond to growing wavenumbers is that $u_{eq} < 1$ (see Fig. 3). In other words, the population of unphosphorylated SFs has to be large enough for pattern formation to occur. Otherwise, $u_{eq}$ becomes a stable steady state.

In order to illustrate these stability scenarios, we have performed two numerical simulations, one in which $u_{eq} < 1$, where stability is obtained (Fig. 4A), and another for $u_{eq} > 1$, where instability leads to a potential spatial pattern (Fig. 4B). Note that as a dimensionless parameter, $u_{eq}$ has buried the dimensional parameter $k$. Thus, the larger $k$ is, the more likely it is that pattern formation occurs; hence $k$ is called the aggregative sensitivity. Recalling that $k = ka$, the analysis suggests that the onset of the compartmentalization is enhanced by the affinity of the interaction, $a$, as well as by a large proportion $k$ of biomolecules bound to the underlying nuclear structure.

3.2. The onset of spatial patterns

In order to gain a better understanding on how the spatial patterns start to arise, we study the dispersion relation (20) in more depth and determine which is the fastest growing wavelength (or equivalently, the dominating wavenumber), and examine the effect of different values of the parameter $\sigma$ on the onset of the aggregation.

First, note that the only possible perturbations that satisfy the no-flux boundary conditions (14) on the domain $(0, 1)$ are those whose wavenumbers take the discrete values

$$q_n = \frac{n \pi}{a}, \quad \text{where } n = 0, 1, 2, \ldots .$$

(21)

From Fig. 3, we know that when $u_{eq} > 1$, $\lambda$ as a function of $q^2$ has two zeroes, namely

$$q_-^2 = 0 \quad \text{and} \quad q_+^2 = \frac{12(u_{eq} - 1)}{\sigma^2 u_{eq}}.$$  

(22)

Therefore, the modes with positive growth rate (modes of instability) are given by the wavenumbers $u_{eq} < 1$, where stability is obtained (Fig. 4A), and another for $u_{eq} > 1$, where instability leads to a potential spatial pattern (Fig. 4B). Note that as a dimensionless parameter, $u_{eq}$ has buried the dimensional parameter $k$. Thus, the larger $k$ is, the more likely it is that pattern formation occurs; hence $k$ is called the aggregative sensitivity. Recalling that $\kappa = ka$, the analysis suggests that the onset of the compartmentalization is enhanced by the affinity of the interaction, $a$, as well as by a large proportion $k$ of biomolecules bound to the underlying nuclear structure.

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satisfying
\[ q_+^2 < q_n^2 < q_+^2. \]  
(23)

Moreover, \( \lambda \) as a function of \( q^2 \) reaches a maximum at
\[ q_{\text{max}}^2 = \frac{6(\text{ueq} - 1)}{\sigma^2 \text{ueq}}. \]  
(24)

Thus, the dominating wavenumber \( q_m \), with \( m \in \mathbb{N} \), is a wavenumber of an unstable mode, such that
\[ |\lambda(q_m^2) - \lambda(q_{\text{max}}^2)| = \min_{q_+^2 < q_n^2 < q_+^2} \{ |\lambda(q_n^2) - \lambda(q_{\text{max}}^2)| \}, \]  
(25)

and the corresponding fastest growing wavelength of the spatial pattern that starts to evolve from the perturbation is
\[ l_m = \frac{2\pi}{q_m} = \frac{2}{m}. \]  
(26)

Note from Eqs. (24)–(26) that \( l_m \propto \sigma \), which means that initially after perturbation the longitude of the speckles or compartments is directly related to the scale of \( \sigma \). This is illustrated in the numerical simulations shown in Figs. 4B and 5. These figures show the evolution of a random perturbation about a homogeneous steady state for various values of \( \sigma \). The plot of the corresponding dispersion relations are shown in Fig. 6, and the numerical information gathered from them is arranged in Table 1. Notice that as \( \sigma \) decreases, the dominating wavelength \( l_m \) decreases (or equivalently, the dominating wavenumber \( q_m \) increases), and the growth rate increases. In other words, the larger \( \sigma \) is, the fewer the speckles or compartments.

### Table 1

<table>
<thead>
<tr>
<th>( \sigma )</th>
<th>Dominating wavenumber</th>
<th>Dominating wavelength</th>
<th>Growth rate</th>
<th>Expected # of peaks</th>
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<tr>
<td>0.04</td>
<td>6( \pi )</td>
<td>2/6 ( \approx 0.33 )</td>
<td>( \lambda(q_6^2) ) ( \approx 17 )</td>
<td>3</td>
</tr>
<tr>
<td>0.02</td>
<td>12( \pi )</td>
<td>2/12 ( \approx 0.16 )</td>
<td>( \lambda(q_{12}^2) ) ( \approx 68 )</td>
<td>6</td>
</tr>
<tr>
<td>0.012</td>
<td>20( \pi )</td>
<td>2/20 ( \approx 0.1 )</td>
<td>( \lambda(q_{20}^2) ) ( \approx 189 )</td>
<td>10</td>
</tr>
</tbody>
</table>

### 4. Modulating the compartmentalization

In this section, we incorporate the phosphorylated population into the analysis and study its modulating
effect on the compartmentalization of SFs. We carry out a linear stability analysis about the homogeneous steady-state solutions of the aggregation–reaction–diffusion system (15) and perform a bifurcation analysis to understand how the phosphorylation and dephosphorylation rates modulate the formation of speckles.

4.1. Dispersion relation for the aggregation–reaction–diffusion system

From Eq. (15), positive uniform steady states \((v_{eq}, u_{eq})\) are given by points in the first quadrant of the \(uv\)-plane satisfying

\[ u = \frac{\delta}{\rho} v. \]  

(27)

Moreover, by introducing a new parameter

\[ C = \int_0^1 (u_{eq} + v_{eq}) \, dx = u_{eq} + v_{eq}, \]  

(28)

representing the fixed amount of biomolecules in the system, the uniform steady \((v_{eq}, u_{eq})\) of Eq. (15) is determined by the intersection in the \(uv\)-plane of the straight line given by Eq. (27) and the straight line

\[ u + v = C. \]  

(29)

Therefore,

\[ (v_{eq}, u_{eq}) = \left( \frac{\rho}{\rho + \delta}, \frac{\delta}{\rho + \delta} \right) C. \]  

(30)

In order to assess the influence of the dynamical parameters of system (15) on the formation of speckles, we will consider small perturbations from the spatially homogeneous steady state \((v_{eq}, u_{eq})\) of the form

\[ v = v_{eq} + \epsilon \tau(x,t), \]  

\[ u = u_{eq} + \epsilon \eta(x,t), \]  

where \(\epsilon \ll 1\). Substitution of these perturbations into Eq. (15) yields

\[ \frac{\partial \tau}{\partial t} = \rho \frac{\partial^2 \tau}{\partial x^2} - \delta \epsilon \eta + \rho \epsilon \eta, \]  

\[ \frac{\partial \eta}{\partial t} = \frac{\delta}{\rho} \frac{\partial^2 \eta}{\partial x^2} - (1 - u_{eq} - \epsilon \eta) \frac{\partial \tau}{\partial x} \quad \text{and} \quad \frac{\partial^2 \tau}{\partial x^2} - \frac{\partial^2 \eta}{\partial x^2} = \frac{\sigma^2}{12} (u_{eq} + \epsilon \eta) \left( \frac{\partial^2 \eta}{\partial x^2} + \delta \epsilon \eta - \rho \epsilon \eta \right). \]  

(32)

Equating first-order terms with respect to \(\epsilon\), neglecting higher-order terms, and dropping the bars, we obtain the following linearized system for Eq. (15):

\[ \frac{\partial v}{\partial t} = \frac{\partial^2 v}{\partial x^2} - \delta v + \rho u, \]  

\[ \frac{\partial u}{\partial t} = (1 - u_{eq}) \frac{\partial^2 u}{\partial x^2} - \frac{\sigma^2}{12} u_{eq} \frac{\partial^4 u}{\partial x^4} + \delta v - \rho u. \]  

(33)

To find the dispersion relation between the growth rate \(\lambda\) and the wavenumber \(q\) and draw conclusions about the stability of uniform steady states of Eq. (15), we study the following normal mode solutions of the linear system (33):

\[ v(x,t) = A \exp(\lambda t + iqx), \]  

\[ u(x,t) = B \exp(\lambda t + iqx), \]  

(34)

where \(A\) and \(B\) are constants. Substitution of Eq. (34) into the linear system (33), cancellation of the factor \(\exp(\lambda t + iqx)\), and proper rearrangement leads to

\[ \lambda^2 + \beta(q) \lambda + \gamma(q) = 0, \]  

(36)

where

\[ \beta(q) = \frac{\sigma^2}{12} u_{eq} q^4 - (u_{eq} - 2) q^2 + \rho + \delta, \]  

\[ \gamma(q) = \frac{\sigma^2}{12} u_{eq} q^6 + \left( \frac{\sigma^2}{12} u_{eq} - u_{eq} + 1 \right) q^4 \]  

\[ + (\rho - \delta u_{eq} + \delta) q^2. \]  

(37)

The two roots of Eq. (36) are given by

\[ \lambda_{1,2} = \frac{-\beta \pm \sqrt{\beta^2 - 4\gamma}}{2}. \]  

(38)

The necessary and sufficient condition for the growth rate \(\lambda\) of the perturbations (34) to have positive real part is that \(\beta < 0\) or \(\gamma < 0\). Note that if \(\beta \leq 0\) then \(u_{eq} > 2\). In terms of the dimensional variables (see variables (12)), this implies that the density of unphosphorylated SFs exceeds the critical density \(\omega_0\), i.e. the restriction given by Eq. (6) is violated. For this reason we assume \(\beta > 0\). Therefore, one of the roots in Eq. (38) always has negative real part and the dispersion relation for possible growing modes is determined by the other root

\[ \lambda = \frac{-\beta + \sqrt{\beta^2 - 4\gamma}}{2}, \]  

(39)

which will have positive real part if and only if \(\gamma < 0\), where \(\gamma\) is as in Eq. (37).

For the purpose of simplifying the analysis of the dispersion relation, we will consider all the parameters in system (15) fixed except for the dephosphorylation rate \(\delta\). An analogous analysis could be carried out if the
free parameter were the phosphorylation rate \( \rho \). Note that varying \( \delta \) affects the slope of Eq. (27), and consequently the value of the steady state \( (v_{eq}, u_{eq}) \). Thus, the natural question that arises is whether or not this variation affects the stability of the uniform steady state. In other words, we want to understand the influence of the dynamical parameter \( d \) on the pattern forming potential of system (15).

The dispersion relation is visualized in Fig. 7 for two particular values of the dephosphorylation rate, namely \( d = 1.1 \), for which we obtain a dispersion relation defined by wavenumbers with positive growth rates (modes of instabilities), and \( d = 1 \), for which the dispersion relation is defined by negative growth rates for all wavenumbers. In other words, the uniform steady state \( (v_{eq}, u_{eq}) \) obtained with \( \delta = 1.1 \) is unstable and the evolving dynamics of its perturbation is characterized by the onset of spatial patterns, whereas the uniform steady state \( (v_{eq}, u_{eq}) \) obtained with \( \delta = 1 \) is stable and no spatial patterns will evolve. These stability results are corroborated by the numerical simulations shown in Figs. 8 and 9, respectively.

It is important to note that although self-interaction occurs between unphosphorylated SFs, the model predicts the aggregation for both phosphorylated and unphosphorylated populations. In fact, these populations aggregate in the same place. This results from the fact that the wavenumbers corresponding to unstable modes have an effect on both the normal mode solutions (34) for the phosphorylated and unphosphorylated SFs.

In the case of the aggregation–diffusion equation (13), we were able to use the dispersion relation (20) in order to find the dominating wavenumber \( q_m \) dictated by Eq. (24) and the fastest growing wavelength given by Eq. (26). But in the case of the aggregation–reaction–diffusion system (15), the complicated expression for the dispersion relation (39) has made the task of finding the dominating wavenumber very difficult. In spite of this, Hadeler and Hillen (2005) were able to estimate the dominating wavenumber for system (15). Under the assumption that the turnover rate of phosphorylated and unphosphorylated SFs is fast, the authors approximated system (15) with a limiting model that was linearized in order to obtain an estimate of the dominating wavenumber for system (15).

4.2. Bifurcation analysis: Instability and stability regions

We investigate the modulating effect of the phosphorylation and dephosphorylation rates on the onset of the
compartmentalization by addressing the question of how the transition from stability to instability takes place when the dephosphorylation rate is taken as the bifurcation parameter. We already know that this transition occurs when the real part of the dispersion relation \( \lambda \), given by Eq. (39), becomes positive. Equivalently, the transition occurs when \( \gamma \), given by Eq. (37), becomes negative. Therefore, this transition is described by a real bifurcation (Lewis, 1994). To simplify the analysis of this bifurcation problem, we let both \( \lambda \) and \( \gamma \) be functions of \( z = q^2 \). From Eqs. (30) and (37), it then follows that the roots of \( \lambda(z) \) are determined by the positive roots of

\[
\gamma(z) = zp(z) = z[a(\delta)z^2 + b(\delta)z + c(\delta)],
\]

where

\[
a(\delta) = C\frac{\sigma^2}{12\delta + \rho},
\]

\[
b(\delta) = C\frac{\delta}{\delta + \rho}\left(\frac{\delta\sigma^2}{12} - 1\right) + 1,
\]

\[
c(\delta) = \rho - C\frac{\delta^2}{\delta + \rho} + \delta,
\]

and \( C \) is as in Eq. (28). Thus, one of the roots of \( \gamma(z) \) is zero, and the other roots are given by the roots of \( p(z) \):

\[
r_{1,2} = \frac{-b(\delta) \pm \sqrt{b^2(\delta) - 4a(\delta)c(\delta)}}{2a(\delta)}.
\]

Since the coefficient \( a(\delta) > 0 \), the transition from a stable to an unstable steady state can only occur when \( f(\delta) = 0 \) or \( c(\delta) = 0 \), where

\[
f(\delta) = b^2(\delta) - 4a(\delta)c(\delta).
\]

To distinguish these two cases, we note first that the coefficient \( b(\delta) = 0 \) if and only if \( \rho = l(\delta) \), where

\[
l(\delta) = -\frac{C\sigma^2}{12}\delta^2 + (C - 1)\delta.
\]

Note as well that \( c(\delta) = 0 \) if and only if \( \rho = m_{\pm}(\delta) \), where

\[
m_{\pm}(\delta) = \frac{C - 1}{(1 \pm \sqrt{C})}\delta.
\]

For \( 0 < C \leq 1 \), \((v_{\text{eq}}, u_{\text{eq}})\) is stable. To see this, we note that the values of both Eqs. (44) and (45) are negative. On the one hand, \( l(\delta) < 0 \) implies that \( b(\delta) > 0 \). The bifurcation cannot take place at any root of \( f(\delta) \). If it did, the only root of \( p(z) \) at the bifurcation point, given by Eq. (42), would be negative. On the other hand, the bifurcation cannot occur when \( c(\delta) = 0 \), because \( \rho > 0 \) and \( m_{\pm}(\delta) < 0 \). Therefore, \((v_{\text{eq}}, u_{\text{eq}})\) is stable for \( 0 < C \leq 1 \).

For \( C > 1 \), the stability of \((v_{\text{eq}}, u_{\text{eq}})\) depends on the value of \( \delta \). We let \( \delta_{h} \) be the bifurcation value at which the stability changes. For \( \delta < \delta_{h} \), \((v_{\text{eq}}, u_{\text{eq}})\) is stable, and for \( \delta > \delta_{h} \), \((v_{\text{eq}}, u_{\text{eq}})\) is unstable. The value of \( \delta_{h} \) depends on the choice of other model parameters. We give the details of \( \delta_{h} \) below. First, we note that the parabola \( l(\delta) \) reaches a maximum value \( \rho_{m} = \frac{3(C - 1)^2}{(C\sigma^2)} \) at \( \delta_{m} = 6(C - 1)/(C\sigma^2) \) (see Fig. 10) and \( c(\delta) = 0 \) if \( \rho = m(\delta) \), where

\[
m(\delta) = \frac{C - 1}{(1 + \sqrt{C})}\delta.
\]
Since the slope of \( m(\delta) \) is smaller than the slope of \( l(\delta) \) at \( \delta = 0 \) and \( m(\delta_m) < \rho_m \), the straight line \( m(\delta) \) is as shown in Fig. 10.

With Fig. 10 in mind, we conclude that if \( \rho > 3(C - 1)^2/(Cr^2) \), then \( b(\delta) > 0 \) for all \( \delta \), and the bifurcation cannot occur at any root of \( f(\delta) \). Thus, the bifurcation takes place when \( c(\delta) = 0 \), i.e., at \( \delta_b = (1 + \sqrt{C})\rho/(C - 1) \).

To study the case \( \rho \leq 3(C - 1)^2/(Cr^2) \), we observe that the roots of \( p(z) \), given by Eq. (42), are both negative when \( \delta \leq 1 \). As \( \delta \) increases, we note from Fig. 10 that there is at least one value \( \delta \) such that \( b(\delta) = 0 \) and \( c(\delta) \neq 0 \) for \( \delta \leq \delta_b \). This means that at \( \delta_b \), the roots (42) of \( p(z) \) have distinct signs or are conjugate complex numbers. Therefore, the only possible way for this transition in the roots of \( p(z) \) to happen as \( \delta \) increases is that there exists a \( \hat{\delta} < \delta_b \) such that \( f(\hat{\delta}) = 0 \), i.e. \( f(\delta) \) has at least one root. Moreover, it is not difficult to see that all the roots of \( f(\delta) \) are smaller than those of \( c(\delta) \). Since we are interested in the bifurcation from a stable to an unstable steady state, and \( f(\delta) \to \infty \) as \( \delta \to \infty \), we let \( \delta^* \) denote the largest root of \( f(\delta) \). Thus, if \( b(\delta^*) < 0 \), then the bifurcation occurs at \( \delta_b = \delta^* \), and if \( b(\delta^*) \geq 0 \), then the root of \( p(z) \) is negative and the bifurcation occurs when \( c(\delta) = 0 \), i.e., at \( \delta_b = (1 + \sqrt{C})\rho/(C - 1) \).

We have provided not only details on the real bifurcation, but also an algorithm to determine the bifurcation value. To illustrate this, we find the bifurcation value \( \delta_b \) for the example shown in Figs. 7–9, in which the dispersion relation becomes positive as the dephosphorylation rate \( \delta \) increases. For the particular choice of the parameter values in the example (\( \sigma = 0.05, \rho = 1, C = 2 \)), we note that \( \rho = 1 < 3(C - 1)^2/(Cr^2) = 600 \). The largest root of \( f(\delta) \), defined in Eq. (43), is \( \delta^* \approx 1.06 \). Since \( b(\delta^*) \approx -0.03 < 0 \), the bifurcation value is given by \( \delta_b = \delta^* \approx 1.06 \). The evolution of the dispersion relation (39) as \( \delta \) passes through \( \delta_b \) is shown in Fig. 11A, which is consistent with the results in Figs. 7–9.

Fig. 11B shows the bifurcation diagram for the steady state \((v_{eq}, u_{eq})\) obtained from the intersection of line (27), \( u = (\delta/\rho)v \), and (29), \( v + u = 2 \). When \( \delta \) is small, the steady state is stable (denoted by the solid portion of the line \( v + u = 2 \)). The slope of line (27) increases as \( \delta \) increases (or equivalently, decreases as \( \rho \) increases), and as it passes through the value \( \delta_b/\rho \), the resulting steady state becomes unstable (denoted by the dotted portion of the line \( v + u = 2 \)). The outcome is consistent with the biological fact that dephosphorylation (increased \( \delta \), or
decreased $\rho$) enhances the self-organization of SFs, and that phosphorylation (increased $\rho$, or decreased $\delta$) enhances the disassembly of speckles.

With the bifurcation diagram from Fig. 11B in mind, we can also obtain the bifurcation values for any value of $C$. In particular, we consider values of $0<C\leq 2$ to avoid breaking the restriction on the density of SFs given by Eq. (6). For each value of $C$, we obtain a bifurcation value $\delta_b(C)$, yielding the stability and instability regions for the steady state $(v_{eq}, u_{eq})$ shown in Fig. 12A. The uniform steady states that have the potential for pattern formation after perturbation lie in the instability region. The bifurcation curve

$$
(v_{eq}(C), u_{eq}(C)) = \left( C \left( \frac{\rho}{\rho + \delta_b} - \frac{\delta_b}{\rho + \delta_b} \right) \right)
$$  

(47)

that separates the regions of stability and instability in Fig. 12A lies slightly above the curve $u_{eq} = 1$. Thus, for the onset of the compartmentalization to take place, it is necessary to have enough biomolecules in the system ($C>1$), and to have enough unphosphorylated biomolecules, which is consistent with the results obtained in the analysis of the aggregation–diffusion equation (13), where it was required that $u_{eq}>1$ for instability to occur. The natural question that arises now is how the bifurcation curve changes as the phosphorylation rate increases. As expected, the stability region will increase, but only up to a certain point. Considering that the bifurcation curve is given by Eq. (47), we conclude that the curve that separates the regions when $\rho>3(2-1)^2/(2\sigma^2)$ is given by the intersection of the line $v_{eq} + u_{eq} = C$ and the line $u_{eq} = r(C)v_{eq}$, where

$$
\begin{align*}
\rho(C) &= \frac{1 + \sqrt{C}}{C - 1},
\end{align*}
$$  

(48)

i.e., by the parameterized curve

$$(v_{eq}(C), u_{eq}(C)) = \left( \frac{C(C - 1)}{C + \sqrt{C}}, \frac{3(C - 1)^2}{C\sigma^2} \right).$$  

(49)

Therefore, the largest region of stability, reached when $\rho>3(2-1)^2/(2\sigma^2)$, will be determined by Eq. (49) (see Fig. 12B). This implies that no matter how big the phosphorylation rate is, there will always be a region of instability, i.e., there exists a dephosphorylation rate that is high enough, such that the resulting uniform steady state $(v_{eq}, u_{eq})$ becomes unstable.

If one wants to obtain information on the modulating effect of both the phosphorylation and dephosphorylation rates at the same time, one can portray the regions of stability in the $\rho\delta$-plane. By keeping all the parameters fixed except $\rho$ and $\delta$, we obtain the following bifurcation curve:

$$
\delta = \delta_b(\rho) = \begin{cases} 
1 + \sqrt{C} & \rho < \frac{3(C - 1)^2}{C\sigma^2}, \\
\frac{C}{C - 1} & \rho > \frac{3(C - 1)^2}{C\sigma^2} \text{ and } b(\delta^*) < 0, \\
\delta^* & \rho > \frac{3(C - 1)^2}{C\sigma^2} \text{ and } b(\delta^*) \geq 0,
\end{cases}
$$  

(50)

where $\delta^*$ denotes the largest root of $f(\delta)$ (Eq. (43)), and $b(\delta)$ is as in Eq. (41). Figs. 13A and B show this bifurcation curve and the resulting stability regions in the $\rho\delta$-plane when $\sigma = 0.05$, for $C = 2$ and 1.5, respectively. In Fig. 13B, note that decreasing the amount of biomolecules in the system, represented by $C$, has caused the region of instability to be reduced, i.e., there is a lower chance for the onset of compartmentalization of SFs.
In this section, we have demonstrated the existence of unstable uniform steady states of system (15), whose perturbation can result in the onset of the compartmentalization of SFs. Through the bifurcation analysis, we have concluded that the potential for the formation of compartments can be eliminated by increasing the phosphorylation rate or decreasing the amount of SFs in the system.

5. Discussion

Understanding the dynamical organization of SFs is an important step towards understanding the architecture of eukaryotic cell nuclei and the changes that take place under different physiological conditions or stresses. In this work, we have approached understanding nuclear compartmentalization using a mathematical model. In particular, we have proposed a model that describes a possible mechanism for the onset of SFs compartmentalization, i.e., for the formation of speckles. The model, namely the aggregation–reaction–diffusion equation (10), is based on the current biological hypotheses that self-organization of SFs is modulated by phosphorylation and dephosphorylation (Cáceres et al., 1997; Misteli and Spector, 1997, 1998; Xiao and Manley, 1998), and that the existence of an underlying nuclear structure plays a major role in the formation of speckles (Hendzel et al., 1999; Kumaran et al., 2002; Nickerson, 2001).

A linear stability analysis of the model and a study of its dispersion relation has brought to light a possible mechanism for the formation of speckles, in which slight perturbations of a uniform steady state of the system may lead to potential spatial patterns. This is possible so long as there are sufficient biomolecules in the cell nucleus. This result mimics the onset of the compartmentalization of SFs during the early stage of the cell interphase, when the distribution of SFs undergoes a transition from spatially homogeneous to heterogeneous (Lamond and Spector, 2003), and suggests that speckle formation can be initiated randomly. Moreover, the model illustrates how the ratio between the size of the domain (cell nucleus) and the size of the range of influence of the self-interaction, defined by the dimensionless parameter $\sigma$, can determine the number and size of SFCs. The larger $\sigma$ is, the fewer the speckles or compartments.

The bifurcation analysis illustrates that an appropriate ratio of phosphorylation–dephosphorylation rates is needed for speckles to form. An increase in the dephosphorylation rate leads to a larger region of instability, and therefore enhances the compartmentalization of SFs, whereas an increase in the phosphorylation rate leads to a small region of instability, and therefore has a homogenizing effect on the spatial distribution of SFs. This is consistent with naturally occurring processes that have been shown to lead to speckle disassembly, caused right before mitosis by an increase in kinases activity or induced experimentally by increasing the activity of specific kinases (Colwill et al., 1996; Duncan et al., 1998; Gui et al., 1994; Misteli et al., 1997; Misteli and Spector, 1997; Wang et al., 1998).

Throughout the paper, we have emphasized a qualitative mathematical description of the onset of the compartmentalization. For this purpose, we introduced the following dynamical parameters with biological significance that are of interest for the experimentalists: effective diffusion coefficient ($D$), phosphorylation and dephosphorylation rates ($\rho$ and $d$), aggregative sensitivity ($\kappa$), and range of self-interaction ($\sigma$). Except for the effective diffusion coefficient of
SFs, experimental estimates for these parameters are currently lacking. Although the estimation of parameters such as the phosphorylation and dephosphorylation rates, and the aggregative sensitivity represents a real challenge that may require the design of new experiments, the current biological information on SFs can be used to provide an idea of the magnitude of the range of self-interaction $\sigma$. In particular, we use the information on the dimensions of the cell nucleus and the number of speckles to estimate $\sigma$, as follows. We notice from Table 1 that on a one-dimensional space, a value of $\sigma = 0.012$ gives rise to ten speckles. If we were to introduce real dimensions, for example a longitude of 10 $\mu$m for the cell nucleus, this would mean that in order to obtain 10 speckles, the biological range of self-interaction is 0.12 $\mu$m, which is approximately a tenth to a third of the actual diameter of a speckle.

Although the model illustrates successfully a mechanism for the onset of the compartmentalization, the restriction given by Eq. (6) limits it from being able to describe the long-term behaviour for the aggregation of SFs. This has left us with an interesting modelling problem that is currently under investigation.

One of the basic assumptions of the aggregation–reaction–diffusion model is the existence of an underlying nuclear structure. Despite the existence of strong experimental evidence justifying this assumption (Capco et al., 1982; Hendzel et al., 1999; Kumaran et al., 2002; Nalepa and Harper, 2004; Nickerson, 2001), it remains a topic of controversy (Pederson, 2000b). For this reason, it would be worthwhile to develop alternative models for SFs compartmentalization, for example, models in which no underlying nuclear structure is considered. It is hoped that testing the predictions of a variety of models against experimental results ultimately will contribute towards determining the mechanism underlying the formation of nuclear speckles.

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