

Research Article

Reexamining The Pre-Metaphase Stretch.

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Abstract

The renowned cell researcher Sally Hughes Schrader originally used the phrase “pre-metaphase stretch” in 1950 to refer to the elongation of prometaphase chromosomes seen in the early spermatocytes of praying mantids and phasid insects. Numerous studies conducted since Hughes Schrader’s original discovery have provided explanations for why and how chromosomes may lengthen before metaphase. In this review, we outline Hughes-Schrader’s preliminary research and go over how more recent studies have shed light on and offered a mechanical explanation for this long-standing occurrence.

Keywords : *pre-metaphase stretch, prometaphase, bivalent, spindle, meiosis, mitosis, chromosomal architecture, and chromosome condensation.*

INTRODUCTION

Chromosome condensation starts in early prophase and reaches its peak condition in late prophase, according to C.D. Darlington’s 1937 seminal work *Recent Advances in Cytology* [1]. This early account of events is expanded upon by the biology classroom experience for students. Chromosome condensation occurs during prophase, and chromosomes remain condensed until they decondense during telophase. This is a concept that is taught to many students at various educational levels. The condensation process is not a uniform occurrence where chromosomes travel straight from an uncondensed state to a fully condensed state; rather, they continue to condense from prophase to late anaphase, according to several outstanding recent articles [2].

Certain systems undergo cycles of chromatin expansion and contraction through prophase and prometaphase, suggesting an even more intricate variation of chromosome architecture [3]. Sally Hughes-Schrader’s description of a phenomenon she and others saw when examining chromosomes in meiotic divisions—which Hughes-Schrader named the pre-metaphase stretch—foreshadowed these recent, intriguing investigations on chromosome structure and condensation [4]. We examine both older and more modern works that

shed light on the Hughes-Schrader phenomena in this study.

Meiosis and Mitosis Chromosomes A general understanding of the chromosomal construction process during meiosis I, meiosis II, and mitosis is necessary to comprehend the pre-metaphase stretch phenomena. Two pairs of sister chromatids that are joined by sister-chromatid bonds make up bivalents. Recombination and cohesiveness

One pair of sister chromatids associates with one spindle pole during meiosis I due to the fusion of sister kinetochores, whereas the homologous pair associates with the opposite pole during metaphase I. This makes it more likely that one sister chromatid pair will pass. the same spindle pole, but in anaphase I, the homologous pair travels to the opposite pole. One important characteristic of bivalent structures is that they are constructed so that homologous kinetochores have a significant chromatin length. Preliminary studies of living metaphase I spermatocytes of the praying mantid organism that display pre-metaphase stretchrows indicate that the space between homologous kinetochores can occasionally be the length of two chromosome arms.

In order to help sister chromatids split from one another during anaphase II, a meiosis II chromosome is made up of two sister chromatids with sister kinetochores now pointing in opposite directions (Figure 1B). Mitotic chromosomes,

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like those in meiosis II, are made up of two sister chromatids with oppositely oriented sister kinetochores (Figure 1C). This aids in ensuring that sister chromatids split apart during mitotic anaphase, just like in meiosis II. Sister kinetochores are separated by two chromosomal widths in both meiosis II and mitosis. According to our first observations, sister kinetochores in mantid spermatocytes undergo meiosis II at a distance of roughly 2 μm [5]. Although information on interkinetochore distances in mantid mitosis is lacking, interkinetochore distance.

Sister kinetochores in bivalents and meiosis II/mitosis chromosomes differ not only in distance but also in the chromatin that separates them. The inner centromere is a region of very elastic heterochromatin that separates sibling kinetochores during mitosis/meiosis II [7]. Highly condensed non-centromeric chromatin is part of the lengthy chromatin segment that separates homologous kinetochores in meiosis.

THE STRETCH BEFORE METAPHASE

Although chromosomes reach their greatest condensation in late prophase, according to Darlington [1] in his 1937 book *Recent Advances in Cytology*, other even earlier articles showed a more intricate sequence of events before metaphase in meiosis I. A thorough biological and anatomical description of multiple phasmid (stick insect) species, including cytological information, was published by de Sinéty in 1901 [8]. Several spermatocyte phases were depicted in camera-lucida drawings in De Sinéty's publication. Bivalents on a prometaphase I spindle were significantly longer than metaphase I bivalents, according to prometaphase I and metaphase I spermatocytes of the phasmid *Leptynia attenuata*. both in his footnotes and in the body of this lengthy essay.

White was the first to state clearly in 1941 that certain species of praying mantids experience "violent stretching" of their chromosomes in prometaphase I spermatocytes [9]. White's account was extended by Sally Hughes-Schrader's groundbreaking research on chromosomal activities in meiosis I. Over the course of her more than 50-year career, Hughes-Schrader made groundbreaking findings that expanded our knowledge of the diverse ways chromosomes can interact with the spindle and be formed. She examined meiosis in a wide range of animals. In addition to providing evolutionary insight into the formation of various chromosome forms and behaviors, Hughes-Schrader was able to analyze the peculiarities of chromosomes by examining specific cytogenetic phenomena in many members of multiple taxonomic groupings. While researching meiosis in male praying mantids in the 1940s and 1950s, Hughes-Schrader focused on the stretching of prometaphase I bivalents, noting the same "violent stretching" of bivalents that M.J.D.

In his previous study, White observed [9, 10]. Hughes-Schrader dubbed this the "pre-metaphase stretch" when a further investigation of phasmids revealed that meiosis I bivalents also displayed this stretching behavior, which de Sinéty first noticed and briefly mentioned. Hughes-Schrader demonstrated that bivalents seem to unfold, isolating homologous kinetochores from one another, in both praying mantids and phasmids soon before nuclear envelope disintegration. In certain instances, an unbroken nuclear envelope at this time allows the bivalents to interact with the spindle poles as well [10].

Both phasmid and praying mantid bivalents attach to an existing bipolar spindle upon nuclear envelope disintegration (Figure 2A illustrates the activity of bivalents during meiosis, including the pre-metaphase stretch). The pre-metaphase stretch was most pronounced in bivalents positioned at the middle of the spindle; some only had a narrow chromatin segment connecting homologues (as seen in Figure 2B) [4,10]. Bivalents that formed a bipolar attachment displayed this stretch. All bivalents show "asynchronous" stretch, with some bivalents being un-stretched and others being heavily stretched (Figure 2A,B) [4,10]. Bivalents went through the pre-metaphase stretch and simultaneously congressed to the metaphase plate in mantids [10,11].

Bivalents underwent significant contraction upon reaching a metaphase I alignment (Figure 2A,B) [10,11]. In contrast to constricted, metaphase bivalents, Hughes Schrader observed that praying mantid bivalents undergoing the pre-metaphase stretch exhibited a rough shape [10]. In contrast to findings in praying mantids, certain species of phasmids showed stretching of the area between sister kinetochores during meiosis II, and the pre-metaphase stretch stage seemed to be finished before full alignment of metaphase I (Figure 2B) [4]. To expand on these findings, Matthey showed that blattids (cockroaches) also exhibit the pre-metaphase stretch, and Hughes-Schrader pointed out in his discussion of the phenomena that blattids experience chromosome congression and a pre-metaphase stretch simultaneously, just as praying mantids [4,12].

Importantly, Hughes-Schrader and others who reported on pre-metaphase stretch examined fixed, stained specimens in the spermatocytes of several species of praying mantids and phasmids at various stages of meiosis I [4,10]. Although Hughes-Schrader was unable to observe the stretch in living cells, it was possible to determine the exact duration of the stretch stage by carefully analyzing these fixed, stained images, which showed that the pre-metaphase stretch took place after nuclear envelope breakdown and before/during congression to the metaphase plate [4,10].

By calculating the number of cells in a certain region that were in each phase, Hughes-Schrader was able to estimate the relative amount of time spent in each stage of meiosis,

including stretch. Because more abundantly seen phases took longer, she reasoned, she would draw broad judgments about the relative timing of each phase [10]. Nevertheless, it is still unclear how the pre-metaphase stretch and chromosomal motions are arranged and timed.

Hughes-Schrader also talked about the taxonomy of various chromosomal activities. Phasmids, blattids, and praying mantids were all classified within the insect order Orthoptera at the time of these early publications. The taxonomy has been restructured so that the Mantodea, Phasmatodea, and Blattodea are now distinct orders that are part of the Polyneoptera, a monophyletic group [13]. The pre-metaphase stretch is not present in all Polyneoptera. It doesn't seem to be present in grasshoppers, and it hasn't even been seen in all of the mantid species that Hughes-Schrader has researched [10,11]. Therefore, the phenomena is neither clade-specific nor ubiquitous. However, Hughes-Schrader postulated that the stretch might have an ancient origin due to its existence in praying mantids, phasmids, and blattids [4].

Initially discovered in insect spermatocytes [4,10], the pre-metaphase stretch has now been seen in mollusk oocytes [14], antennid worms [15], and marsupial spermatocytes, notably those of the rat kangaroo *Potorous tridactylus* [16,17]. As a result, although not ubiquitous, the pre-metaphase stretch phenomena has been noted in several animal phyla.

Hughes-Schrader suggested several causes for the pre-metaphase stretch, including spindle fibers, elongation of the spindle with bivalents attached, early spindle development, and "repulsion" of homologous kinetochores, though she thought this implausible. Hughes-Schrader observed a connection between spindle elongation and chromosomal stretching extremities, and suggested that kinetochores are important in the pre-metaphase stretch [10]. However, Matthey [12] noted the pre-metaphase stretch within an intact nuclear envelope in cockroach primary spermatocytes, indicating that chromosome contact with the spindle cannot be the sole agent responsible for the stretch.

The pre-metaphase stretch: what produces it? Is it because the stresses exerted on the chromosomes during cell division vary? Do chromosomes that are stretched feel a temporary, stronger force? Or does the pre-metaphase stretch come from changes in the structure of the chromosomes when the cell divides? Does chromosomal stiffness as it approaches metaphase or variance in chromosome condensation correlate with the pre-metaphase stretch and subsequent contraction? We shall answer these questions below.

THE PROMETAPHASE SPINDLE AND KINETOCHORES

The nuclear membrane has completely dissolved, the spindle has formed, and the chromosomes have attached to it during prometaphase. Sadly, none of the meiotic systems that

Hughes-Schrader and others examined have been used as model systems to examine how chromosomes behave during prometaphase in recent years. Nonetheless, some meiotic and numerous mitotic cell types have had their prometaphase chromosomal activities examined.

Kinetochores bind spindle microtubules during prometaphase. In order for the chromosomes to generate bipolar attachments to the spindle, kinetochores and microtubules first engage in brief contacts before reorienting. Chromosomes oscillate on the spindle during mitotic prometaphase in a variety of systems, such as yeast, diatoms, human cells, newt lung cells, meiosis I cells of yeast, the flatworm *Mesostoma ehrenbergii*, and certain spiders [18–22].

One kinetochore's movement is typically well coordinated with that of its sister kinetochore in mitotic chromosome oscillations in systems like the Newt lung epithelial cell; both kinetochores move in the same direction most of the time (for example, when one chromosome's kinetochore moves poleward, its sister kinetochore moves antipoleward) [20]. Sister kinetochores are often uncoordinated in their motions in other systems, such as the two diatom species that Tippit et al. investigated and the meiotic cells in *M. ehrenbergii* [19,21]. This lack of coordination is linked to the stretching and contraction of the space between kinetochores.

Chromosomes move to the spindle equator during prometaphase, creating bipolar spindle attachments. King and Nicklas [23] demonstrated that when grasshopper primary spermatocytes get closer to metaphase I, there are more microtubules embedded in each kinetochore. As Hays and Salmon [24] shown by partially ablation of kinetochores in grasshopper primary spermatocytes, this increase in kinetochore occupation by microtubules is presumably linked to an increase in spindle forces applied to the kinetochore. Hays and Salmon demonstrated that the amount of microtubules attached to a kinetochore determines the forces the spindle applies to kinetochores; the more microtubule-kinetochore interactions there are, the greater the stresses on the kinetochore [24].

Although Hughes-Schrader suggested that the pre-metaphase stretch might have been caused by chromosomal interactions with the spindle [9], spindle forces are unlikely to be the whole picture. The fact that Matthey reported seeing the pre-metaphase stretch in an undamaged nuclear envelope is one evidence against the spindle forces' central role in the pre-metaphase stretch. Although spindle microtubules cannot reach the kinetochores due to the nuclear envelope, other cellular components may exert spindle stresses that are comparable to a kinetochore-spindle connection. The LINC complex has been linked to chromosomal stretching in early prophase I and binds portions of chromosomes to cytoskeletal components outside the nucleus during meiotic prophase. Forces that stretch chromosomes through an intact nuclear

membrane may be transmitted by this complex.

The strength of mitotic forces in prometaphase and metaphase is a second, and more significant, evidence in favor of extra participants in the pre-metaphase stretch beyond spindle forces. Forces acting on kinetochores during prometaphase must be greater than those during metaphase if attachment to the spindle were the sole reason for the “violent” stretching of bivalents during prometaphase I. Chromosomes experiencing forces related to full kinetochore occupancy with microtubules (i.e., metaphase chromosomes) should be stretched the greatest if the stretch is only caused by strong spindle forces. Chromosome architectural intrinsics must also contribute to pre-metaphase stretch.

ARCHITECTURE OF CHROMOSOMES

The pre-metaphase stretch may be caused by a variety of chromosomal architecture characteristics, such as compaction, condensation, and chromosome stiffness. Chromosomes undergo enormous architectural rearrangements as the spindle forms and the nuclear envelope disintegrates. Chromosomes compress to create unique chromosomes during mitotic prophase and late prophase I. Chromosome architectural changes are challenging to investigate and manifest differently in many systems. Early research by Bajer [27] showed that the triploid endosperm of two lily species, *Leucojum aestivum* and *Haemanthus katherinae*, had mitotic chromosomes that significantly shorten beginning in prophase. During late anaphase, these chromosomes continue to shorten. Numerous different mitotic systems are being studied by groups, such as fission, rat kidney (NRK) cells, chicken DT-40 cells, and human tissue culture cells (HeLa).

The condensin complexes, topoisomerase II α , and Aurora A and B kinases are among the proteins whose activity is linked to the chromosome architecture alterations seen during mitosis.

Condensins I and II are two complexes that regulate chromosomal layout during meiosis and mitosis. The Structural Maintenance of Chromosomes proteins SMC2 and SMC4 are lengthy, coiled coils that are shared by both condensins. CAP-D2, CAP-G, and CAP-H are likewise present in condensin I [31]. The components CAP-D3, CAP-G2, and CAP-H2 found in condensin II are linked to those found in condensin I. Despite having different but comparable components, the two condensin complexes also play diverse roles and have different localizations throughout cell division. In prophase, condensin II localizes to mitotic chromosomes, whereas condensin I is not present in the nucleus and begins to connect with chromosomes. Increased chromosomal stiffness is a result of chromatin architecture alterations linked to condensin I binding [34]. Furthermore, prometaphase cell stalling causes chromosome overloading with condensin,

which results in abnormally rigid chromosomes [35], demonstrating that increases in the chromosome-associated condensin complex are linked to time spent in a cell division state. Prometaphase marks the beginning of condensin I's attachment to chromosomes, which lasts until anaphase [36]. Condensin complex activity has also been investigated in *Drosophila melanogaster* male meiosis. It is interesting to note that *Drosophila* and several other insect lineages lack certain condensin II components, making it unclear how condensins function during the prophase of meiosis, when condensin II is linked to chromosomes in other systems. *D. melanogaster* contains every component of condensin I. Condensin I seems to follow the same pattern of localization during male *Drosophila* meiosis as it does during mitosis. In prometaphase I, it localizes to bivalents and is not found in the nucleus. For proper chromosomal segregation during meiosis I, condensin I is necessary. It's unclear how lessons learnt about male meiosis in *Drosophila* may be applied to systems with pre-metaphase stretch.

The presence of all condensin II components in praying mantids and phasmids, as well as its possible function in controlling chromosomal architecture during the pre-metaphase stretch, are unknown. All of the components of condensin II are present in cockroaches, which display pre-metaphase stretch [37], suggesting that both condensin complexes may be involved in controlling the pre-metaphase stretch.

The activity of several proteins is connected to the interaction of condensin I with mitotic chromosomes. The non-SMC subunits of condensin I are phosphorylated by the Aurora B kinase, which is necessary for condensin I to bind to chromosomes [34]. A significant connection between chromosome architectural alterations and chromosome congression is suggested by the interesting observation that the chromokinesin KIF4A also interacts with condensin I, and that this contact is necessary for proper and timely chromosome congression in prometaphase in HeLa cells [39]. The Aurora A kinase's activity determines how KIF4A interacts with condensin I [39]. Furthermore, as demonstrated in the human colorectal cancer cell line HCT116, topoisomerase II α is necessary for both chromosomal compaction and sister chromatid individualization during prometaphase [2].

We know that topoisomerase II α plays a crucial function in prometaphase based on data from trials where it is decreased. The transformed HCT116 cells were stopped in mitotic prometaphase using the microtubule toxin nocodazole. Chromatin volume decreased over time in these stopped prometaphase cells, suggesting that chromosomal condensation in prometaphase was progressive and ongoing. Chromatin volume did not diminish in these same prometaphase-arrested cells when topoisomerase II α was rapidly degraded. Since chromatin volume did not decrease

as cells moved through prometaphase, depletion topoisomerase II α in asynchronous cultures that were not treated with nocodazole produced comparable outcomes. These findings are consistent with topoisomerase II α playing a part in chromosomal condensation during prometaphase. As the quantity of condensin I on the prometaphase chromosome gradually rises, Nielsen et al. propose that topoisomerase II α functions in conjunction with condensin I.

THE PRE-METAPHASE STRETCH, MEIOSIS II, AND THE STRETCH BETWEEN KINETOCHORES IN MITOSIS

As previously mentioned, chromosomal condensation causes chromosomes to shorten in length. Chromosome stiffening is another effect of the alterations in chromosome architecture brought on by the activity of condensin complexes, and this stiffening gets worse as the amount of bound condensin rises [35]. Stretching before metaphase could be the outcome of prometaphase I bivalents' stress cycling before their intense metaphase compaction.

One possible explanation for the pre-metaphase stretch is that prometaphase chromosomes in the systems under study are more elastic than metaphase chromosomes, making them more vulnerable to spindle stretching due to an early bipolar attachment. In prometaphase II spermatocytes, Hughes-Schrader noticed stretching between sister kinetochores, while in certain phasmids, there was no discernible prometaphase II length extension in chromosome length [4]. Hughes-Schrader regarded this as the pre-metaphase stretch equivalent of meiosis II [4]. The centromere may be more elastic, enabling the stretching, as evidenced by the absence of a discernible increase in prometaphase II chromosome length. In certain chromosomal systems during mitosis, centromere regions have been shown to extend similarly.

insights the architecture of mitotic chromosomes between prometaphase kinetochores in conjunction with spindle motions may provide some insights. As previously mentioned, chromosomes may oscillate and experience forces that expand the space between kinetochores during prometaphase, when they are compacting. In oscillating chromosomes, attachment to the spindle causes the centromere region between kinetochores to lengthen [19]. In order to properly segregate chromosomes in anaphase and fulfill the spindle checkpoint, centromere stretching seems to be required [44]. HeLa cells exhibit a behavior similar to the centromere stretch noted by Hughes-Schrader in prometaphase II spermatocytes in phasmids when condensin I is depleted, resulting in an increase in centromere stretch [36]. The closest analog to the pre-metaphase stretch observed during mitosis is variation in inter-kinetochore distance. Since there aren't many thorough investigations of the alterations in chromosome architecture and behavior

during meiosis, the stretched mitotic kinetochores may help to explain the pre-metaphase stretch since they resemble the static images seen during phasmid prometaphase II.

The meiosis I bivalents were found to exhibit the pre-metaphase stretch. A bivalent's two homologous kinetochores are separated by a significant amount of chromosome volume and distance; in certain cases, the homologous kinetochores are separated by two complete chromosome arm lengths (Figure 1A). A substantially smaller distance, two chromosome widths, separates the two sister kinetochores of a meiosis II or mitotic chromosome (Figure 1B,C). Systems exhibiting pre-metaphase stretch provide an excellent opportunity to study the fine details of prometaphase chromosome compaction, stiffening, and behavior because prometaphase I can take hours to complete [5] and the effects of stretching are more noticeable on a large bivalent than on a smaller mitotic chromosome.

A POTENTIAL REASON FOR THE PRE-METAPHASE LENGTH

As has already been seen in mitotic cells and *Drosophila melanogaster* spermatocytes, we suggest that condensin I is found in the cytoplasm of prophase I cells in systems with pre-metaphase stretch (condensin II, assuming both components exist, is associated with prophase I chromosomes in the nucleus). We contend that bivalents in pre-metaphase stretch systems take up condensin I very slowly, which explains the severe stretching of chromosomes in these systems. The bivalents are elastic and flexible immediately upon nuclear envelope collapse and can be stretched in early prometaphase I due to the sluggish uptake of condensin I. When bivalents first develop bipolar bonds, stretching takes place.

Condensin I concentrations on the bivalents rise during stretching, chromosomal adhesion, and congression. The localization of the chromokinesin KIF4A to the bivalent may also be linked to the rise in condensin I concentration, and both may facilitate progression. Higher concentrations of condensin I cause bivalents to become more stiff and compaction of the metaphase I bivalent, which helps to maintain proper bipolar attachments.

CONCLUSIONS

The pre-metaphase stretch is probably caused in large part by kinetochore forces. Another is probably changes in chromosomal architecture. Future research examining the role of chromosome architecture and spindle attachments in chromosome compaction and behavior during prometaphase would be ideal for systems where pre-metaphase stretching occurs due to the readily apparent changes in inter-kinetochore distance over prometaphase

I and the prolonged duration of prometaphase I.

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