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Force-balance model of suppression of multipolar division in cancer cells with extra centrosomes[1]

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Cancer cells often possess extra centrosomes which have the potential to cause cell death due to catastrophic multipolar division. Many cancer cells, however, are able to escape multipolar mitosis by clustering the extra centrosomes to form bipolar spindles. The mechanism of centrosome clustering is therefore of great interest to the development of anti-cancer drugs because the de-clustering of extra centrosomes provides an appealing way to eliminate cancer cells while keeping healthy cells intact. We present a physical model assuming 1) dynamic centrosomal microtubules interact with chromosomes by both pushing on chromosome arms and pulling along kinetochores; 2) these microtubules interact with force generators associated with actin/adhesion structures at the cell boundary; and 3) motors act on anti-parallel microtubules from different centrosomes. We find via computer simulations that chromosomes tend to aggregate near the cell center while centrosomes can be either clustered to form bipolar spindles or scattered to form multipolar spindles, depending on the strengths of relative forces, cell shape and adhesion geometry. The model predictions agree with data from cells plated on adhesive micropatterns and from biochemically or genetically perturbed cells. Furthermore, our model is able to explain various microtubule distributions in interphase cells on patterned substrates.

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