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## Cellular Reorientation upon Cyclic Stretch can be due to the Instability of Focal Adhesions

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### Editorial

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### INTRODUCTION

Cellular reorientation upon cyclic stretch is an intriguing phenomenon, which has drawn intensive scientific attentions lately. When applying uni-axial cyclic stretches to cells on substrate, they gradually rotated themselves to almost perpendicular to the stretch direction <sup>[1]</sup>. The characteristic time of the cellular reorientation was quantified, which strongly depended on stretch amplitude and cyclic frequency. As revealed in experiments, this characteristic time decreased as the stretch amplitude increased and also decreased with increasing stretch frequency until it saturated at about 1 Hz <sup>[1]</sup>. Various models had been developed to provide an important insight into the underlying mechanism for cellular reorientation under cyclic stretch, which, however, remains elusive.

In our efforts to understand this phenomenon, we considered a mechanosensing system consisting of a stress fiber (SF) adhered to a substrate through two focal adhesions (FAs) at its both ends. In the simplification, the FAs were assumed to be composed of a cluster of molecular bonds, which could all be slip bonds or catch-slip bonds. For a slip bond, its lifetime monotonically decreases with the increasing applied force. For a catch-slip bond, its lifetime counter-intuitively increases with the increasing force at first and then decreases with the increasing force. The instability of this mechanosensing system upon cyclic loading was subsequently simulated with the utilization of a coupled method of finite element analysis and Monte Carlo method <sup>[2,3]</sup>.

In the simulation, we found that a cluster of slip bonds generally became unstable upon cyclic loadings <sup>[2]</sup>. The lifetime of the slip-bond cluster generally decreased with increasing stretch amplitude and also decreased with increasing cyclic frequency until it saturated at about 1 Hz <sup>[2]</sup>. These results were consistent with the experimental results <sup>[1]</sup>. In the simulation, the cluster of slip bonds might also manifest with "Unusual stability enhancement", where the stability of the cluster can be substantially enhanced. This occurred only when the cyclic loading had a relatively low frequency with relatively high amplitude, which seemed to contradict to the conventional fatigue theory of engineering materials.

In the investigation of a cluster of catch-slip bonds, we first probed the time-dependent behavior of a single catch bond based on the two-state model <sup>[3]</sup>. There could exist two types of catch-slip bonds with similar lifetime-force profile upon a force-clamp load <sup>[3]</sup>. However, when varied forces were applied to a single catch-slip bond of either type, they behaved very differently in terms of the force history dependence or bond strength <sup>[3]</sup>. In spite of the significant difference in the behaviors of two type of catch bonds at the level of a single molecule, we found that a cluster of catch-slip bonds of either type generally became unstable under cyclic loadings <sup>[3]</sup>, which was also consistent with experimental results <sup>[3]</sup>.

Our numerical simulation indicated a cluster of molecular bonds, either slip bonds or catch-slip bonds, could become unstable upon cyclic loadings, which supported the previous prediction by an ELSA model that we recently developed <sup>[4]</sup>. The ELSA model analytically predicted that cyclic loadings tended to destabilize FAs and the resulting slide or relocation of FAs would then cause the associated SFs to shorten and rotate to almost perpendicular to the loading direction <sup>[4]</sup>. Putting these works together <sup>[2-4]</sup>, we then suggest that the instability of the FAs can be essential in cellular reorientation upon cyclic stretch <sup>[1]</sup>.

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