New and Notable

Catch Me Because You Can: A Mathematical Model for Mechanosensing

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Most animal cell types sensitively react to the stiffness of their environment, with dramatic consequences for essential cellular processes such as adhesion, migration, differentiation, and cell fate. For example, many cell types migrate toward stiffer regions in their environment (durotaxis) (1). During the last decade, cell-matrix contacts based on the transmembrane adhesion receptors from the integrin family (focal adhesions) have emerged as the mechanosensitive organelles that collect, process, and integrate the information on extracellular stiffness (2); their mechanosensory function is thought to be an integral part of stiffness-dependent cellular processes. By actively pulling on the substrate through actomyosin contractility and focal adhesions, the cells are able to sense its stiffness. With >180 different components being reported in the literature (where this collection of components is collectively known as the "adhesome"), the molecular complexity of focal adhesions is overwhelming (3). Recent proteomic studies have not only found many more components, but also have revealed that many of them are recruited to focal adhesions in a force-dependent manner (4,5), supporting the view that focal adhesions harbor a network of mechanosensitive processes (6).

Despite the molecular complexity of focal adhesions, however, one expects that regulation of the integrin receptors through force would be at the core of the mechanosensitive function of focal adhesions. For focal adhesions of cultured tissue cells, the two most relevant of the 24 known integrin variants in humans are the $\alpha_5\beta_1$- and $\alpha_v\beta_3$-integrins. Recently it has been shown with single molecule force spectroscopy that the bonds mediated by $\alpha_5\beta_1$-integrins are so-called "catch bonds" (7). In contrast to the standard case of slip bonds, catch bonds possess the unusual physical property that at intermediate forces their lifetimes increase rather than decrease with increasing force (at high forces, they usually become slip bonds again). Other important examples for catch bonds are the bonds mediated by the selectin receptors capturing leukocytes in shear flow and the binding of myosin II to an actin filament during its motor cycle. In an article appearing in this issue of the *Biophysical Journal*, Novikova and Storm (8) present an elegant mathematical analysis of how stiffness-sensing at focal adhesions might arise from the interplay of catch-bond dynamics in the integrin layer and intracellular force generation through contractile fibers.

To put the analysis by Novikova and Storm into context, it is instructive to recall the classical treatment by Bell, who mathematically analyzed the statistics of an ensemble of N_t parallel slip bonds, each of which can be either open or closed (9,10). If we denote the number of closed bonds at time t by $N(t)$ $(0 \le N(t) \le N_t)$, it dynamically evolves according to the following kinetic equation:

$$\frac{dN}{dt} = -N\, e^{F/N} + \gamma(N_t - N). \quad (1)$$

The first term represents dissociation of the closed bonds and the second term describes rebinding of the open bonds with a dimension-less rebinding rate γ. For dissociation, it is assumed that the total force F (in units of an internal force scale of the order of pN) is shared equally between all closed bonds, and that single bonds dissociate more rapidly under larger force. For such slip bonds, the exponential relation between force and dissociation rate can be rationalized with Kramer's theory for thermally activated escape over a transition state barrier (11). Setting the time derivate in Eq. 1 to zero and solving for the steady-state number of closed bonds N as a function of force F reveals that the adhesion cluster is only stable up to a critical force $F_c = N_t\, p\log\,(\gamma/e)$, where the product logarithm $x = p\log(a)$ solves the equation $xe^x = a$ (linear for small arguments). Thus, a finite rebinding rate γ ensures that the adhesion cluster is stable under not-too-large values of mechanical loading. Mathematically, the critical force F_c corresponds to a saddle-node bifurcation, where a stable and an unstable branch annihilate each other. As shown in Fig. 1 *a*, the stable branch for the number of closed bonds N is a relatively weak and decreasing function of force F.

To extend this classical slip-bond analysis to the $\alpha_5\beta_1$-integrin catch-bond cluster, Novikova and Storm fitted its experimentally determined dissociation rate as a function of force to the two-pathway model for catch bonds (12). The resulting dissociation rate has a minimum at intermediate forces and can be used to appropriately modify the slip-bond dissociation term in Eq. 1. The kinetic equation then becomes

$$\frac{dN}{dt} = -2\,N\cosh\frac{(F/N - \phi_{max})}{\alpha + \gamma(N_{t-N})}, \quad (2)$$

and can be analyzed with the same methods as Eq. 1 (here $\phi_{max} = 5.9$ and $\alpha = 6.55$ are dimensionless numbers resulting from the data fit). One again finds a saddle-node bifurcation, thus also in this case the cluster is stable only up to a critical force F_c (this reflects the actual catch-slip bond character). However, in marked contrast to the slip-bond case first analyzed by

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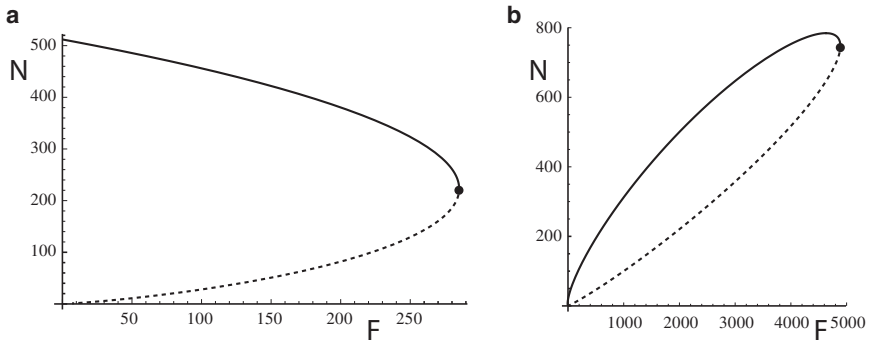

FIGURE 1 Steady-state values for the number of closed bonds N as a function of force F for (*a*) a slip-bond cluster versus (*b*) a catch-bond cluster. (*Solid* and *dashed lines*) Stable and unstable branches, respectively. They meet each other at the critical force F_c, where a saddle-node bifurcation takes place and stability is lost. For the slip-bond cluster in panel *a*, the stable value of N is a weak and decreasing function of F. For the catch-bond cluster in panel *b*, there is a strong increase of N with F over most of the range. Thus, for the catch-bond cluster, the number of closed bonds N is a better internal measure for the force F acting on the cluster than in the slip-bond case. Parameters: total number of bonds $N_t = 1024$, dimension-less rebinding rate $\gamma = 1$.

Bell (9), now the steady-state number N of closed bonds is a strongly increasing function of force, as shown in Fig. 1 *b*. Thus, in the catch-bond case the number of closed bonds N is a clear internal measure for the force F acting on the adhesion cluster, in contrast to the slip-bond case, where N is only weakly dependent on force and decays rather than increases with force. From Fig. 1 *b*, we also note that the number of closed bonds in the unstressed case is very low due to the large value of the unstressed dissociation rate, whereas the number of closed bonds reaches its maximum very close to the critical force. Novikova and Storm report that similar behavior can be found also for other catch-bond systems, suggesting that catch bonds have evolved to provide reinforcement mainly when acting in clusters.

How do these findings relate to stiffness-sensing through focal adhesions? To answer this question, the authors consider the composite system of an elastic environment with stiffness K, a focal adhesion of fixed size (N_t parallel catch bonds), and a contractile fiber pulling on it (with a linearized force-velocity relation for the myosin II motors). This model can be solved analytically and shows that the stiffer the environment, the faster the buildup of the force (13). Novikova and Strom show that if one assumes that the cells invest a constant amount of work W into pulling on the substrate through a given focal adhesion, it reaches the force level $F = (2WK)^{1/2}$. Because the number of closed bonds N in the catch-bond cluster increases roughly linearly with force (compare Fig. 1 *b*), this formula implies that it increases roughly as the square-root of external stiffness.

In summary, the authors have shown that the number of closed bonds N in the catch-bond cluster not only provides an internal measure of the force acting on the cluster, but also of the stiffness of the elastic environment. Their focus on the dynamical process of force generation agrees well with the recent finding that the correlation between force and size of focal adhesions is strongest during their growth phase (14). It also agrees with the finding that it is mainly the fibronectin-$\alpha_5\beta_1$-integrin bonds that support force in focal adhesions (15). The elegant and transparent analysis by Novikova and Storm nicely complements an earlier computational analysis of this situation (16) and shows that the $\alpha_5\beta_1$-integrin catch-bond cluster in combination with a contractile fiber leads to an effective response that resembles the mechanosensory function of single focal adhesions.

In the future, this simple model could be extended, with regard to several important aspects. On the one hand, a complete mathematical description of cellular mechanosensing through focal adhesions should go beyond a single focal adhesion in a stationary state and describe a population of dynamically growing, moving, and shrinking focal adhesions (17). On the other hand, the model for a catch-bond cluster should be extended to include more aspects of the molecular complexity of focal adhesions. For example, it remains to be seen whether the other most prominent integrin in the focal adhesions of tissue cells, $\alpha_v\beta_3$, is also a catch bond, as suggested by a recent cellular study (5). As it is obvious from Fig. 1 *b*, the $\alpha_5\beta_1$-integrin catch-bond cluster performs very badly in the unstressed situation, thus other adhesion receptors seem to be required to establish initial contacts. The exact spatiotemporal coordination of the different integrins is an open but very important issue (18). It is also clear that the mechanism studied here has to interact with many other mechanosensitive processes at focal adhesions, including recruitment of additional components under force, and signaling, e.g., through the small GTPases from the Rho-family (4,5). Irrespective of these future developments, however, the generic analysis presented here provides a very useful conceptual framework for the investigator to think about the way adhesion receptors under force collectively act together during stiffness sensing.

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Correction

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Equation (2) shown on page 1289 in the 105/6 issue of the Biophysical Journal as below:

$$\frac{dN}{dt} = -2N \cosh \frac{(F/N - \phi_{max})}{\alpha + \gamma(N_{t-N})} \tag{1}$$

is incorrect, and in fact should read

$$\frac{dN}{dt} = -\frac{2N}{\alpha} \cosh(F/N - \phi_{max}) + \gamma(N_t - N). \tag{2}$$

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