When off-target is right on

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Weizmann Institute scientists have developed a model showing that even though it appears counterintuitive, the observation that some molecular keys are not always an exact fit for their molecular locks actually helps them in discerning the right target.

All organisms perform intricate molecular computations to survive. Unlike man-made computer components that are meticulously ordered on a chip, the molecules that make up biological 'computers' are diffuse within the cell. Yet these must pinpoint and then bind to specific counterparts while swimming in the cell's thick, erratic molecular stew – something like finding a friend in a Tokyo subway station during rush hour.

In the classical view of molecular recognition, the binding molecules fit each other like a lock and key. Half a century of research has shown, however, that in numerous cases, the molecules need to deform in order to bind, as the key is not an exact fit for the molecular lock. Why would evolution choose such an inexact system"

The work of and Dr. Tsvi Tlusty and research student Yonatan Savir of the Weizmann Institute's Physics of Complex Systems Department suggests a possible answer. A simple biophysical model they developed indicates that in picking out the target molecule from a crowd of look-alikes, the recognizer has an advantage if it's slightly off-target. This may appear to be counterintuitive: Why search for a key that does not match its lock exactly, and then require that the imperfect key warp its shape to fit the lock"

The researchers' model shows that the key's deformation actually helps in discerning the right target. Although the energy required to deform the molecular key slightly lowers the probability of its binding to the right target, it also reduces the probability that it will bind to a wrong one by quite a bit. Thus, the quality of recognition – i.e. the ratio of the right to wrong binding probabilities – increases.

This simple mechanism is coined 'conformational proofreading' and may explain the observed deformations in many biological recognition systems. Furthermore, conformational proofreading may turn out be a crucial factor affecting the evolution of bio-logical systems, and it may also be useful in the design of artificial molecular recognition systems.

Source: Weizmann Institute of Science