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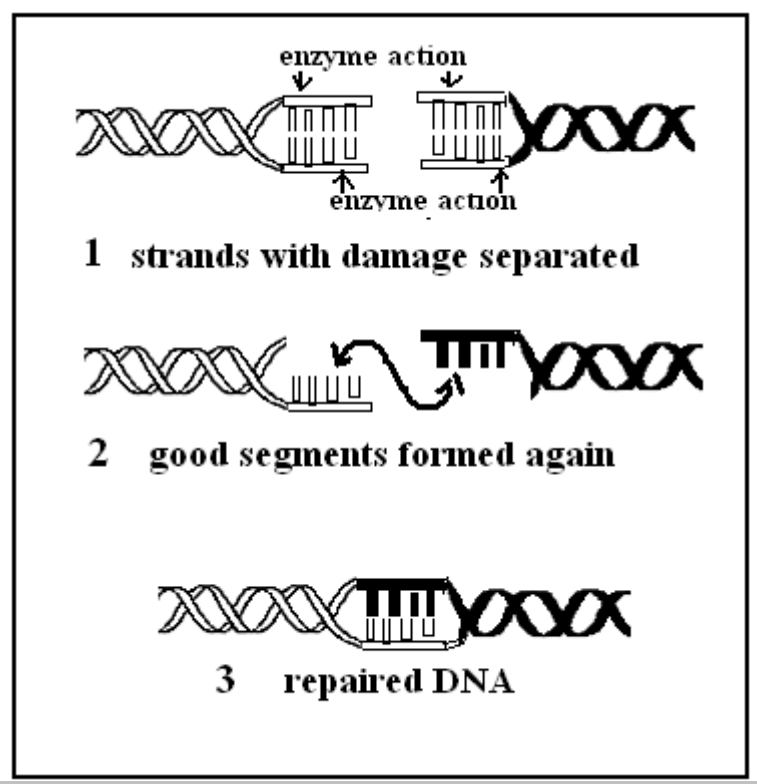
Enzymes ride the waves

There is a tide in the affairs of men which, taken at the flood, leads on to fortune

Natural systems pick random events to piggyback and save energy, says S.Ananthanarayanan.

Ralf Seidel and his team at the ***Technische Universität Dresden*** and researchers in the ***University of Bristol*** report in the journal, ***Science***, that a category of enzymes called ***helicases*** make use of the random buffets from moving molecules of the fluids in the cell to move them through the length of the DNA chain without expending their sparse fortune of energy.

Helicases are proteins which move from one end to the other of the millions-of-units-long DNA, double helix molecule to separate the two strands of the helix, as during replication, or for repair of damage to DNA. The DNA molecule consists of a pair of strings made up of sugar and phosphorus compounds, to which are attached chemical groups selected out of just 4 distinct kinds, which are called ***bases***. Each of these bases has a counterpart from among the remaining 3 kinds of bases and given one string of the DNA, the other string is nothing but the sequence of bases complementary to the bases in the first string. Any damage to one of the strands of the DNA results in a breakdown of the complementary nature of the two strands. In the repair of DNA the action of helicases is to unpin the DNA strands, for the damaged portion to be rebuilt by attachment of the correct complementary chemical groups to the strand that is intact.



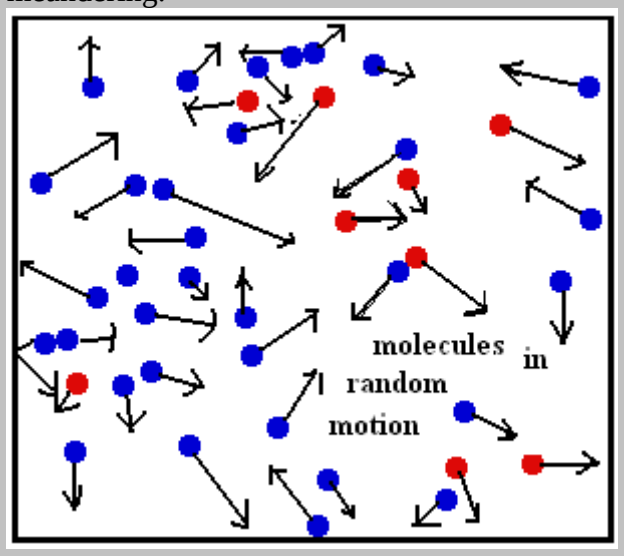
Energy to enable action within living things arises essentially from the oxidation of carbon, or sometimes from sunlight or heat. While nutrients need to move to and be consumed at the place where they are needed, energetic action is finally implemented by the transfer and expending of chemical units of energy, called ***ATP***. ATP stands ***Adenosine triphosphate*** and is a chemical unit that rapidly changes from its precursor form and back, with the absorption or release of energy. Within cells, it is used by enzymes and structural proteins for synthesis, movement and to bring about cell division.

The helicase protein too, for its work of separating the strands of the DNA, needs energy. As they are agents that use units of energy to do mechanical work, helicases have been regarded as ***motors*** at the molecular scale. Other ***molecular motor enzymes*** have been studied in some detail, but not yet the mechanism of the action of helicases. The work of the scientists at Dresden and Bristor has discovered that helicases do not actually consume ATP except for a small action of chemical rearrangement, but for motion, they piggyback on the thermal energy of the random motion of other molecules within the cell.

Random motion

There are literally billions of unattached molecules, including water molecules, within each living cell. Just as in any gas or liquid, these molecules create pressure against the cell wall through their motion. Given the large numbers, the pressure is uniform and the momentary state of motion of any given particle in the fluid is essentially random. Random motion of the molecules of a fluid were first studied by the English botanist Robert Brown, who noticed a rapic and random movment of lycopodium spores

suspended in water. The motion of such very small particles, while responding to random impacts by surrounding molecules has been mathematically studied and the probability of the particle being moved by a given distance, as a result of the random impacts, has been worked out. The conclusion is essentially that with the help of the Brownian ***random walk***, the helicase protein can hope to move some small distance, but this is in a random direction, not along the length of the DNA. For being able to work on the DNA, there has to be a mechanism for the helicase protein to recognize the part of the DNA and to act by causing cleavage, and then wait till it is in the right position again, through its random meandering.



That random processes cannot be used to do work has been generally accepted as being against the way of nature. A gas, for instance, consists of an exceedingly large number of molecules in random motion, such that no region within the gas can be distinguished from another. If any more gas, at a higher temperature and hence more energetic motion is introduced, the molecules rapidly rearrange themselves and the state of motion is again uniform. Now, consider a separator dividing the gas into two regions, with a small trapdoor that can allow molecules which have more than a minimum energy, on one side to move into the other side, but not the other way about. Could we expect that such more energetic molecules would then move to the other side and get trapped there? Would the result be that one side of the gas gets warmer, while the other side gets cooler, as its more energetic constituents have leaked?

That such a thing will not happen is well understood. There are different ways to explain why not. One is to recognize that if a molecule on the first side knocks the trapdoor open, then the door is open for that instant, for molecules to move in both directions. If the second side had collected more and faster moving molecules, then, more that one molecule may slip back to the first side during that brief open-door period. The temperature on both sides would thus tend to equalize, and given the vast numbers of molecules in real gases, changes in temperature through this process would be undetectable.

In the same way, one should expect that movement of the helicase protein because of Brownian motion cannot be of use for movement along a given path, as this would

amount to extracting energy from the environment. The difference in this case is that there is intelligence in recognition and action, which does consume energy, though small. As a result of this refinement, what we are looking for, at every event of contact with DNA, is the probability of movement of helicase by a short distance to the next point of contact. Again, given the very rapid change of position, albeit small, in the ***meso world***, or the intermediate world, neither of atomic or molecular structure nor of the scale of composite objects, it is a very short time before the helicase protein finds itself in the right spot!

Ralph Sidel and his team at Dresden developed a microscope that could view the length of the DNA molecule and also follow the movement of helicases, which had been rendered visible with a fluorescent label. The Bristol group, at the same time, used high speed photography to analyse the fluorescent light to make out changes in the protein structure and the pace of consumption of ATP in the helicases. What emerged is a motion picture of helicase protein molecules moving feverishly as they get knocked about by the environment, and periodically undergoing structural changes, with the ATP getting consumed only when that happens. "This enzyme uses the energy from ATP to force a change in protein conformation rather than to unwind DNA. The movement on DNA thereafter doesn't require an energy input from ATP. Although movement is random, it occurs very rapidly and the enzyme can cover long distances on DNA faster than many ATP-driven motors. This can be thought of as a more energy-efficient way to move along DNA and we suggest that this mechanism may be used in other genetic processes, such as DNA repair," says Mark Szczelkun, Professor of Biochemistry at Bristol.