Natural Nano-Machines

1. Alice in a Micro-Factory

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A popularized version of the introductory lecture in an undergraduate course on '*Natural Nano-machines*' taught at IIT, Kanpur.

Imagine an underwater factory which is about 10μm long in each direction. The factory is filled with machines, each typically a few tens of nanometers long, which perform specific tasks and operate in a well-coordinated manner. A cell, the structural and functional unit of life, is not very different from this micro-factory. In this two-part article, I begin with Alice's guided tour of this micro-factory in her dream during which the guide shows her wide varieties of nano-machines. The style of presentation of the first part is inspired by Lewis Carrol's *Alice in Wonderland*. In the second part, I introduce the methods of studying the materials and mechanisms of the molecular machines through dialogues. The three participants in this discussion are Alice, her elder brother Alex and her father Albert. The style of presentation of the second part is adapted from Galileo's *Dialogue Concerning the Two Chief World Systems*. Albert, a professor of biophysics, emphasizes the crucial differences between the mechanisms of the natural nano-machines and those of their macroscopic counterparts. He also points out some practical applications of this interdisciplinary research in biomedical science and nano-technology.

Keywords
Motor protein, intra-cellular transport, ion pump, ATP synthase.

1. Introduction

Alice was sitting on a window seat beside her father inside the aircraft. The departure was delayed because of bad weather. She was coming back to Delhi with her

parents after a two-week vacation with her grandparents. Soon her final year in school would begin. Her father, a professor of biophysics at a university in Delhi, had utilized the vacation to prepare his lecture notes for the next semester. Alice picked up the note book from her father's tray table and started reading the following paragraph from the notes.

"Three centuries ago Marcello Malpighi conjectured '*Nature, in order to carry out the marvelous operations in animals and plants, has been pleased to construct their organized bodies with a very large number of machines, which are of necessity made up of extremely minute parts so shaped and situated, such as to form a marvelous organ, the composition of which are usually invisible to the naked eye, without the aid of the microscope.*'[1]".

Alice had already learnt a lot about machines from her physics teacher in school. A machine is a device, having a unique purpose, that augments or replaces human or animal effort for the accomplishment of physical tasks. The operation of a machine may involve the transformation of chemical, thermal, electrical, or nuclear energy into mechanical energy or vice versa. All machines have an *input*, an *output*, and a *transforming* (or modifying) and a *transmitting* device (see *Figure* 1). A man-made complex macroscopic device is usually an assembly of simpler components, each of which is designed to achieve a specific function. For example, a hair dryer consists of a heater, a fan and a switch suitably connected by electric wires and assembled in a compact framework; combined and coordinated operation of these components gives rise to the function of the hairdryer – blowing hot air.

Figure 1. A schematic black-box like representation of a machine; only the input and the output are mentioned explicitly.

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Alice continued with the next paragraph in her father's note book. "Naturally, to understand how a machine works, one has to understand the structure and functions of its components. So, the belief in the role of organic machines in sustaining life led to intense anatomical investigations in the seventeenth century. Curiously, the emphasis shifted from organic machines during the eighteenth and nineteenth centuries; a critical analysis for plausible reasons has been carried out by Piccolino [1]. With the triumph of the molecular theory of matter in the beginning of the twentieth century, the molecule became the prime object of investigation in chemistry as well as in biology. Interestingly, as early as in 1906, Loeb (as quoted in [2]) referred to the cell as a "chemical machine".

Alice couldn't believe what she read. So, she asked her father, "Does a cell really function as a machine?". Her father replied, "Indeed, each of the cells in our body is like a 'factory that contains an elaborate network of interlocking assembly lines' [3], each of which is made up of an enormously large number of molecular machines. Just like macroscopic machines, these molecular machines also consist of 'highly coordinated moving parts' [3-7]. However, unlike man-made machines, these are products of Nature's *design perfected* over millions of years of evolution. The mechanisms underlying their function are often very different from that of their macroscopic counterparts in spite of many superficial similarities. The typical sizes of the molecular machines in our body cells range from tens to a few *nano-meters*. One of the biggest challenges of modern science is to determine the principles behind the *design* of these *natural nano-machines* and to understand their dynamics which help in elucidating the *mechanisms* of their functions in terms of the fundamental principles of physics". The aircraft now started moving along the runway of the airport. Alice's father said, "Alice, if you do not have

a lot of homework during the next weekend, I'll be glad to tell you some of the intellectual challenges posed by the unusual mechanisms of these nano-machines inside our cells, each of which is like a micron-sized factory".

Unlike man-made machines, cells are products of Nature's *design perfected* over millions of years of evolution. The mechanisms underlying their function are often very different from their macroscopic counterparts in spite of many superficial similarities.

2. A Guided Tour of the Living Cell

The aircraft lifted off the runway and was ascending. Alice looked out of the window and saw the busy vehicular traffic on the streets below. At one corner of the city she saw the high chimneys of the factories; this was the industrial area where her grandfather owned a small company that manufactured some chemicals. A few other high structures that she could recognise were huge water tanks that supplied drinking water to the adjoining residential areas. Several years ago she had seen one of the pumps which raised water up to those tanks from the water filtration plant below.

Alice recalled the days when she was still in her kindergarten and her grandmother used to narrate the stories of *Ramayana* and *Mahabharata* in the evening during the summer vacations. The story she liked the most was that of the underwater kingdom of snakes. She was so tired that, even before she realized, she was fast asleep in her seat and started dreaming.

Alice found herself at the entrance of the underwater kingdom. It was covered entirely by an approximately spherical membraneous soft wall. A water molecule greeted Alice with a smile: "Welcome Alice! Enjoy a guided tour of our kingdom which you call "cell". I'm Neera and I'll be your guide during the next ninety minutes of your tour of our kingdom".

The typical sizes of the molecular machines in our body cells range from tens to a few *nano-meters*.

Neera warned Alice that the "channel"-like passage of the entry gate was very narrow and Alice would have to squeeze through it. The wall of the kingdom actually consisted of two layers and the space in between was densely populated by what looked like two-tailed fish;

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Neera seemed to have a special dislike for these fish. When Alice asked the name of these unusual species of fish, Neera said they are called *lipids*. The peculiar feature of these lipids was that the ones at the outer layer had their heads facing water outside the kingdom and those in the inner layer had their heads staring inside the kingdom; Neera said that the two monolayers of the lipids always stay together forming a bilayer. The tails of these fish looked rather slippery and smelt like soap.

While Alice was looking at the wall, spellbound by what she saw, Neera had donned a special swimming suit, somewhat like the ones used by swimmers at the Olympics. Neera said, "I'll have a tough time swimming across that channel unless I put on this swim suit".

Just as they slipped in through the channel, Alice found a net of ropes which resembled fishing nets. First she thought that these were perhaps intended to prevent the two-tailed fish from entering the kingdom. But, immediately she realized her mistake; she had never seen such a dual-purpose net. While taking off her swim suit, Neera said that this special net is called *cytoskeleton*. The girders and cables together form a skeleton that gives strength to the architecture of the kingdom and, at the same time, also form the backbone of the transportation network of the kingdom [7].

There was water everywhere inside the kingdom. But, unlike the freely flowing transparent water Alice had always been familiar with, it was rather viscous and turbid because of the huge crowd swimming all around. Alice requested Neera for a brief pause as she wanted to watch the busy transportation system for a while before proceeding to their next destination.

Alice found that the motors were not moving smoothly; their jerky motion was similar to that of a person trying to move straight in a dust storm. The motors moving

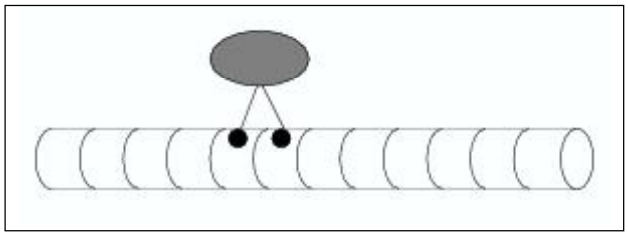


Figure 2. A cartoon of a two-headed molecular motor moving on a filamentary track.

along the cables and struts had no wheels. They looked more like two-legged humans than the four-wheeled vehicles Alice was familiar with. Each carried a heavy bundle of cargo on its head and moved like a porter. Neera pointed at the motor passing by and said it was a *kinesin*. Another coming from the opposite direction was a *dynein*. Neera said that these two brands are like trains of the rapid mass transit system that ran from the city centre to the peripheral suburbs. The kinesins transport cargo from the city centre to the peripheral suburbs while the dyneins move in exactly the opposite direction. The stiff struts that form the tracks for these motors are called *microtubules*. The shuttle buses that carried the passengers in these suburbs were mostly *myosins* and they moved on more flexible cables called *actin*.

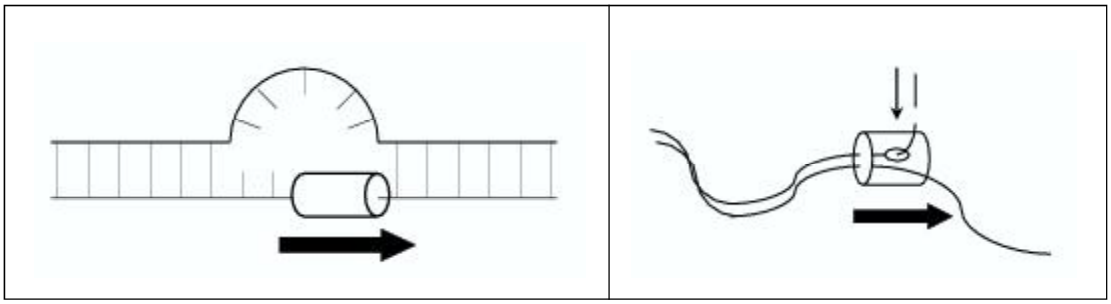
Alice did not find a single petrol pump (gas station) anywhere in the city and asked Neera how the motors were running without fuel. Neera corrected her mistake; the motors were consuming "chemical fuels". Each of the motors was utilizing the chemical energy released by a chemical reaction. The fuels, namely molecules of a compound called adenosine triphosphate (ATP), were abundant everywhere and the motors were using the energy released by their hydrolysis to generate the mechanical energy required for their directed movement. Alice was well aware of the environmental problems created by the emissions from the motor vehicles back at home. So, she asked Neera how they disposed of the spent fuel. Neera said that all of the spent fuel was recycled in their

kingdom; the spent fuel was recharged to manufacture fresh fuel. Neera also added that some other machines in their kingdom directly used sunlight and, therefore, were very eco-friendly as no waste product was generated by those machines. Moreover, another advantage of the machines running on light energy was that light can be switched on and off easily and rapidly.

As it was getting late, Alice resumed her sightseeing tour of the kingdom. Soon Alice and Neera were at the pore-like entrance to the palace, called *nucleus*, at the center of the kingdom. Alice was spellbound by the chemical factory inside the nucleus. A member of a special class of machines, called DNA *helicase*, was walking along a DNA fiber unwinding the two strands. This process resembled disentangling of two strands of fine thread that are snarled together. The local opening of the double stranded DNA (see *Figure* 3) is effectively an unzipping process that cuts the weak bonds which hold the two strands together. "Such openings form one step in the overall processes of DNA repair or polymerisation of DNA and RNA" explained Neera. RNA *polymerase*s (see *Figure* 4) also move on DNA and the main function of these machines is to polymerise the so-called messenger RNA joining nucleotides that are selected on the basis of the templates formed by a single-strand of DNA. The input energy for these machines comes from the condensation of nucleotide triphosphates (NTP) and the output is the work done by the machine against the opposing chemical force.

Figure 3 (left). A cartoon of a DNA helicase motor that moves on a nucleic acid track locally unzipping the double stranded DNA.

Figure 4 (right). A cartoon of an RNA polymerase motor that moves on a nucleic acid track synthesizing an m-RNA strand using DNA as the template.



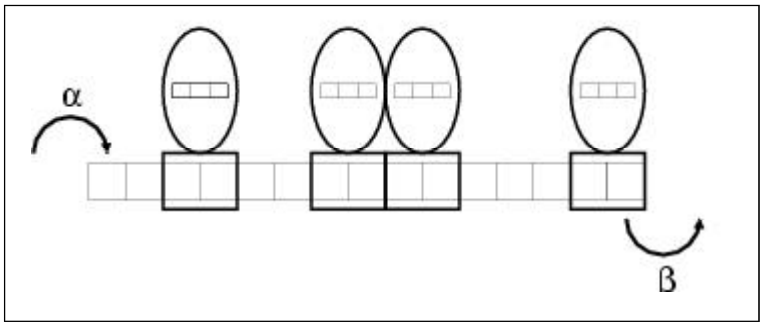


Figure 5. A cartoon of ribosomes that move simultaneously on an mRNA strand each synthesizing different copies of the same protein. The ribosome has two subunits; the larger subunit is represented schematically by the ellipse while the rectangular part represents the smaller subunit. The three small boxes on the larger subunit correspond to the three binding sites. The smaller subunit of the ribosome can cover simultaneously ℓ codons, i.e., ℓ triplets of nucleotides ($\ell = 2$ in this figure) on the mRNA. The parameters α and β capture the effective rates of initiation and termination of translation.

Alice saw the synthesis of one such mRNA strand in front of her eyes in a matter of seconds. Then the serpentine mRNA headed towards the nuclear pore. Neera said, "After moving out of the nucleus, the mRNA will serve as a template for the synthesis of a protein by another set of machines". Alice was excited and wanted to see the whole process. She rushed out of the nucleus behind the mRNA, closely followed by Neera. Alice saw that soon the mRNA got decorated by little ball-like machines. She looked at Neera. "Those are the *ribosomes*," explained Neera (see *Figure* 5). Alice saw a stiching-like action by each of the ribosomes, which also involved the mRNA, tRNA and amino acids, that finally gave birth to a fresh protein chain. However, almost instantaneously the nascent protein folded into a complex three-dimensional structure that Neera identified as the *tertiary* structure of the protein.

On the way back, Alice saw many buildings of wide variety of shapes and sizes; each of these was enclosed by a soft membranous wall. Neera pointed her finger at one and said, "Can you see that labyrinthine structure? That's *endoplasmic reticulum*. And, of course, the small balls sticking to its membranous wall are the ribosomes." Then Neera turned in another direction, "That one over there is called the *Golgi apparatus*". Alice could not control her curiosity. She asked, "Why do you need the Golgi apparatus?". Neera was brief, "The Golgi apparatus is like a letter sorting station of a postal system; the proteins are sorted here, packaged and forwarded to

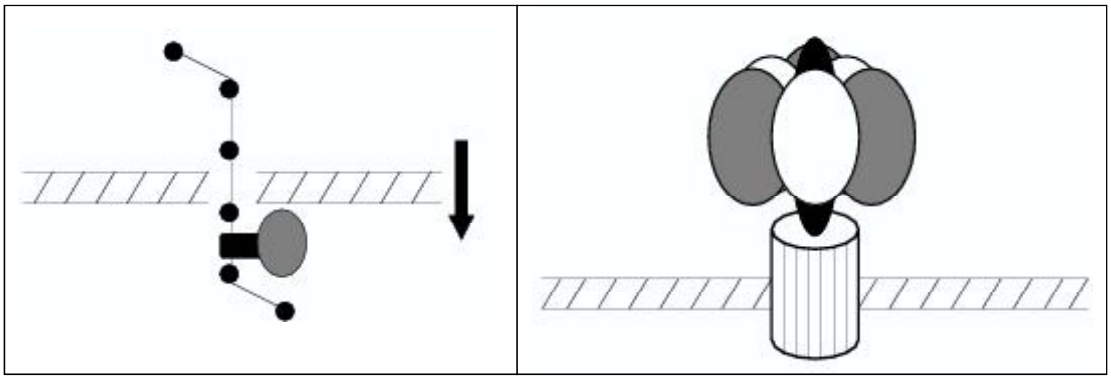


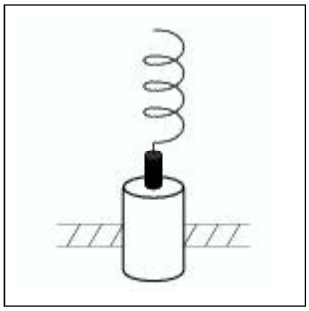
Figure 6 (left). A cartoon of a translocation machine that translocates a biological macromolecule across a membrane.

Figure 7 (right). A cartoon of ATP synthase, a rotary motor associated with a membrane. The cylindrical part is called the F_0 motor while the other part represents the F_1 motor. Both F_0 and F_1 are reversible and are tightly coupled to each other.

their onward destination." Neera added further, " We'll visit some endoplasmic reticulum and Golgi apparatus during your future visits and show you the functions of those. In particular, there are some *translocation machines* on and near their walls which pull and push proteins in and out of the building. Without the help of these membrane-bound machines, no protein would be able to cross the walls of the endoplasmic reticulum and Golgi apparatus" (see *Figure* 6).

Suddenly, Neera seemed very excited: "Alice, can you see that small sausage-shaped building over there? That is a *mitochondrion*, one of the power houses that convert the spent fuel ADP into fresh fuel ATP. It looks very different from the chemical factories in your world. This is achieved by a tiny machine, called ATP *synthase* [8], stuck on the wall of the mitochondrion. Perhaps you cannot see it from here (see *Figure* 7). But, I can assure you that this rotary motor currently holds the world record: it is the smallest rotary motor. This is, at least superficially, very similar to the motor of a hair dryer". "Is this the only rotary motor that exists in this kingdom?", asked Alice. "No. Bacteria also have a slightly larger rotary motor fixed on their skin [9]. This motor rotates a helical filament called a flagellum" (see *Figure* 8).

Figure 8. A cartoon of the flagellar motor of bacteria, a rotary motor associated with a membrane.



On their way back, Neera followed a shorter route and reached a gate different from the one through which they

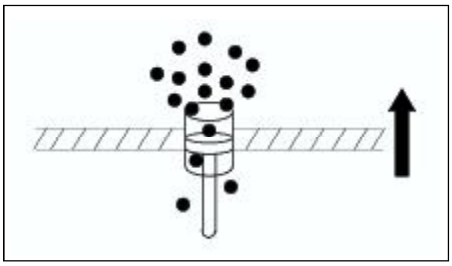


Figure 9. A cartoon of a molecular ion pump associated with a membrane.

had entered. Neera wanted to show Alice a pump in action [10]. It was fitted on the boundary wall. It was constantly pumping sodium ions from inside to outside while simultaneously, it was pumping potassium ions in the reverse direction. Neera emphasized, "The pump is continuously consuming energy to carry the ions against the concentration gradient, i.e., opposite to the direction of the spontaneous flow, just as a water pump consumes electrical energy to draw water upward against gravity".

Alice and Neera came out of the kingdom through another slippery channel close to the pump. Neera said to Alice, "I hope you liked our kingdom and will visit us again. Unfortunately, this kingdom of ours will not last long". This came as a shock to Alice, "Why will this cell perish?" Neera consoled her, "That's the rule in the world of cells; each goes through a life cycle and ultimately ends with a split into two daughter cells. This one is no exception and it will split into two daughter kingdoms in a few days. I'll be your guide during your next tour inside one of those two daughter kingdoms. Next time I'll also show you how cells use their machines to move from one place to another [11]. Some cells 'swim' in their aqueous environment while others 'crawl'; the piston-like action of some internal machines plays a crucial role in cell crawling".

Just as Alice and Neera were about to part ways, Alice saw a torpedo-shaped creature. It seemed as if it was looking for some way to sneak into the kingdom. It had a helical propeller attached to its skin that was rotating at an astonishingly high angular speed. Neera stopped

Acknowledgements
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Alice, "Beware! that is a bacterium". Alice immediately realized the rotating propeller must be the flagellum that Neera had mentioned earlier. Neera continued, "This bacterium is trying to invade the kingdom". Alice saw yet another object that looked like a mortar shell. "Oh my God, look at that virus", exclaimed Neera in a shaky voice, "This is another type of potential invader. If it succeeds, it will hijack our motors to get a free ride to the center of the town and then enter the nucleus. If it seizes control of the machines involved in the protein synthesis, the future of the kingdom is doomed". Suddenly the virus spotted Alice and, she thought, it was approaching her aggressively. Alice shrieked in fear... and her eyes opened. Her mother put her palm on Alice's head. "What happened Alice?", she asked. "Nothing mom, I just saw something in my dream". There was an announcement, the aircraft was going to land soon in Delhi.

As anticipated, Alice had very little homework during the next weekend. So she sat down with her father Albert and her elder brother Alex to hear the stories of molecular motors.

Suggested Reading

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