Molecular Motors in Bionanotechnology

James Youell
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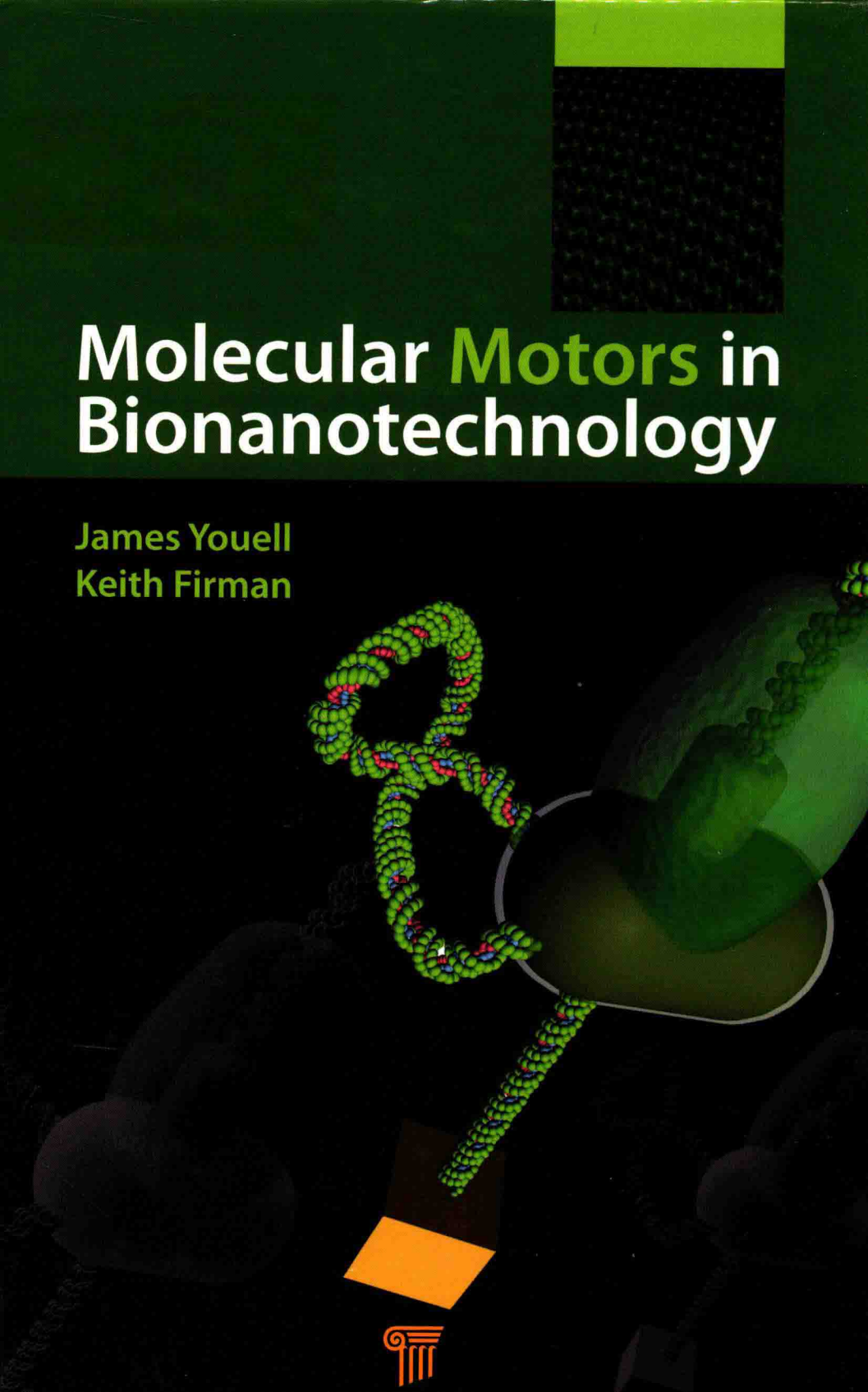

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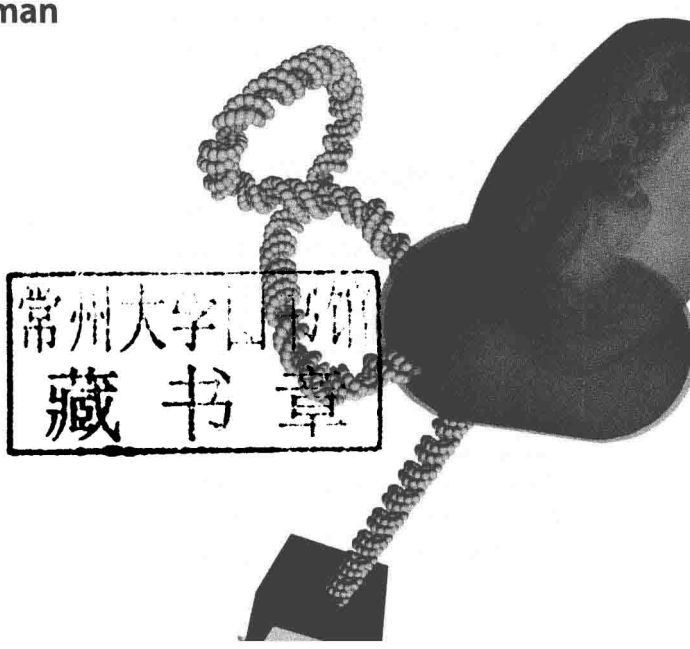

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Preface

It has been recognised for a considerable time that nanotechnology and especially the manipulation of single molecules represent not only a major challenge but also a major opportunity for mankind. This is illustrated from early history, where the ability to manipulate "novel" materials has led to the inclusion of the name of the "novel" material in a description of the epoch during which the new technology was created — The Stone Age and the Bronze Age are the best examples, but the "industrial revolution" is similar. The manipulation of single molecules[1] (a possible definition of nanotechnology) presents a technical challenge, but the potential of using materials, produced at this scale, can be best understood from biology where most macro-sized materials are assembled using a "bottom-up" approach of organised self-assembly of single molecules. However, biological systems are usually dynamic, and many make use of molecular machines to manipulate the biomaterials they are produced from. Such machines provide ideal models of how to design nano-scale devices for nanotechnology and some will provide the machines for nanotechnology.

The writing of this book was, in part, inspired by our work with a specific molecular motor — the Type I Restriction-Modification enzyme EcoR124I[2] — and, in particular, our attempts to produce a nanoactuator device incorporating this motor. In addition, K.F.'s involvement in the "Productive Nanoscience Road-mapping exercise" in the USA and the "TESSY Project for Road-mapping Synthetic Biology" in Europe both contributed to ideas and background thoughts about the content of the book. The authors' background has also greatly influenced the content of the book, with J.Y. having a stronger interest in structural information and structure–function relationships, while K.F. has a more chemistry-driven interest in both function and organisation of molecular machines. Our original aim was an overview of molecular motors that would link to some novel ideas about how they might be used in bionanotechnology. However, several recent reviews[3–6] have also influenced the content

of the book and led to a different style and level of content from that first imagined. This final version is much longer than first imagined, but, we hope, provides an important overview of the various molecular motors that are well understood, or reasonably well described, and detailed in a way that helps understand structure–function relationships between the motors. However, we recognise that there can be an over-emphasis on the means for classifying biological systems. We are aware that this book suffers from this problem, and too much emphasis on such classifications can be misleading. Nature does not categorise, but we felt that the clarification of the classification of some systems was overdue.

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K.F. would like to thank Eric Drexler for his supportive comments about K.F.'s research, which led to the initial idea of a review and then this book. Much of the work described by the authors, from their own research, was supported by two EC-funded projects: MOL SWITCH and BIONANO-SWITCH.

Chapter 1

Mode of Activity of Molecular Motors

A simple dictionary definition of a motor is *"something, such as a machine or an engine that produces or imparts motion".** This definition works well in the macroscale world that we normally interact with. However, at the molecular scale, there is an immediate problem with this definition — the influence of thermal or Brownian motion. Brownian motion is random and can hardly be seen as motor activity; although, as we detail below it makes an important contribution to how a molecular motor works. The influence that Brownian motion has on the way a molecular motor works is elegantly summarised by Oster and Wang[7] with the phrase *"In such an environment you would not need to even pedal your bicycle: you would simply attach a ratchet to the wheel preventing it from going backwards and shake yourself forwards!"*. Therefore, we should rewrite the definition in a way that eliminates the problem of thermal motion and perhaps the simplest way is *"something, such as a machine or an engine that produces or imparts directional motion"*. Before discussing the wide variety of molecular motors that have been chemically synthesised, or exist in nature, it is important to describe the ways that motor activity can occur and discuss some of the problems molecular motors must overcome.

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Almost all chemical reactions are described by equations that detail the contribution of thermal motion towards the required energy for overcoming the energy barrier between chemical states (usually through an activated state for the chemical involved), and these equations provide a means for calculating (measuring) the rate constant. For biological macromolecules, thermal motion allows the molecules to adopt conformational changes that are separated by significant energy barriers, and these changes in conformation can often be measured in solution. Therefore, for directional motion, there needs to be a significant change to the energy landscape, separating the conformational states of the molecule, which also provides a bias towards a specific state such that the energy provided by thermal noise is just insufficient to allow the change back to the initial state, but sufficient to allow adoption of the preferred state for motion. The consequence of this is that thermal noise provides a significant contribution to motion, but fuel consumption biases the energy landscape in a way that overcomes the random nature of motion that thermal energy alone would produce.

1.1 Power-Stroke Model of Motion

One can imagine two possible models for describing the type of motion produced by molecular motors, and these two models are often used to describe individual motors.[7] The first model is the "power-stroke", which is a viscoelastic model in which the motor is in a "tense" state following fuel consumption and moves to a "relaxed" state, through a number of conformational changes that occur in small (Å) steps, in a viscoelastic manner.[8] A model of a pure "power-stroke" is a charged rod (such as negatively charged DNA) passing through a polar trans-membrane pore under the influence of an applied electrical potential. The electrical potential drives the movement through the pore over a series of very small steps based on the distribution of the charge.

1.2 Brownian Ratchet Model of Motion

The second model is a Brownian ratchet in which the motor rectifies diffusion displacements over larger (nm) distances. A pure model of such a ratchet would be a charged rod (as above) passing

through a hydrophobic membrane pore in the presence of a high concentration (on the entry side of the membrane) of counter-charged ions, which bind and neutralise the charges on the rod allowing it to enter the pore. The low concentration of ions on the other side of the pore allows dissociation, but not rapid rebinding of the ions, therefore preventing backward movement of the rod. This is the process of rectification and involves attractive bonds between the solvent and the charges on the rod following passage through the pore.

Brownian motors and ratchets[9] can be described as motors that provide such a biased directionality to the random fluctuations produced by thermal motion. These motors make significant use of thermal motion during their motor activity,[8] usually through such a directionally biased conformational change in the motor protein. In effect the steps that lead to directional motion are one-dimensional thermally activated transitions. However, directed motion also requires asymmetries within the system[10,11] and a key aspect of such changes to symmetry, within molecular motors, is the presence of chiral elements.[12–14]

An example of such motion, driven by the chemical changes of ATP hydrolysis, is the translocation of DNA through a viral packaging motor into the viral capsid head, against the internal forces produced by the increasing pressure produced by this packaging. Both the change in available charge following hydrolysis and the chirality of the protein–fuel interactions provide a conformational change, which in turn influences the position of the motors on the DNA and leads to directional transport of the DNA through the motor complex. The most important aspect of this motion is the coupling of the chemical reaction of ATP hydrolysis with the conformational switches in the protein. This coupling provides a mechanism for directionality; although, as seen with ATP synthase, the chemical reaction is reversible and consequently so should be the directionality, which leads to ATP synthesis when the motor is mechanically wound in a specific direction. If ATP hydrolysis was in an equilibrium state, there would be no motion and, therefore, it is the value of ΔG for ATP hydrolysis, which must be greater than the energy required to "push" the motor backwards, that provides actual directionality.[8] This energy flow also drives directionality, and the chemical reaction can only proceed in a direction that results in chemical-free energy decrease.[15] Mathematical modelling of such

processes[15–18] shows that without thermal motion, a molecular motor would be trapped at a local minimum.

A key aspect of the above models for directed molecular motion is the need for fuel to drive the system, and molecular motors can use a variety of different fuels, including chemical fuel (as mentioned above for ATP), photons, and electrochemical energy. One ATP molecule is equivalent to approximately 20–24 kT of which ~8–9 kT is enthalpic, while the rest is entropic.[7] Hydrolysis of ATP in most motors is stored as 6–10 kT of elastic energy (although this elasticity is not flexibility of the binding site as this would waste energy). An important aspect of using chemical energy is that the fuel will produce by-products that will contaminate the system unless removed (as is the case for biological molecular motors).[19]

1.3 Motor Efficiency

One can readily imagine that there are two very different forces that act on molecular motors:

(a) Stall forces, which are often experimentally employed to determine the forces generated by a motor and can be illustrated by the application of a drag using an optical tweezer system.[20] These forces are often known as conservative forces and produce very different behaviour from the motor.

(b) Viscous forces in solution can be likened to friction for macroscale motors but are actually very different stochastic forces. Because molecular motors have negligible inertia and, as described above, the motor is mostly driven by Brownian force, the instantaneous velocity changes direction very rapidly and the absolute value can be of orders of magnitude greater than the average velocity of the motor.[21]

Stall forces applied to a molecular motor usually stop the motor and the chemical reaction that drives the motor (although there are cases where processivity of the motion is altered by such forces[22,23]). For a tightly coupled motor, where the step size is independent of the load force that produces stalling, and close to the stall point, the thermodynamic efficiency of the motor can approach 100%.[24,25]

However, without an external load, where the stochastic viscous forces apply, the motor will behave very differently. The

interactions that produce this force are intermolecular, which are particularly important in polar solvents such as water, and as the size of the motor approaches the nanometre scale and the geometry of these events becomes very significant at these small scales.[26] Efficiency under these circumstances is usually determined as Stokes efficiency[15] — the ratio of "mechanical performance" to energy supply and this can also approach 100% when the driving force is almost constant.