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The DNA Conductor Hypothesis: Sequence-Dependent Electron Conduction as the Thermodynamic Basis of DNA-Centred Biological Function

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ABSTRACT

The prevailing description of deoxyribonucleic acid (DNA) treats the molecule primarily as an information-storage medium: a linear code that is replicated, transcribed and translated to build and operate a cell. This is not disputed here. Independently of this informational role, double-stranded DNA is also an established physical medium for charge transport: electrons move along its π -stacked bases by short-range superexchange and longer-range multi-step hopping, and DNA-bound redox-active proteins exchange electrons through the duplex over distances relevant to cellular biochemistry. This paper develops, as an explicit and falsifiable hypothesis rather than an established finding, the proposal that this sequence-dependent charge-transport property may constitute an additional physical layer of genome function, alongside DNA's informational, structural and regulatory roles. We hypothesise that the local charge-transport landscape of a genome - where the duplex preferentially opens, where it couples to donor or acceptor centres, and how it responds dielectrically - is set by local base sequence, so that this landscape is itself sequence-encoded and could, in principle, be partly predicted from sequence. We formalise this as four structural hypotheses (H1-H4) concerning directionality, base-stacking dependence, sequence-dependent local impedance, and dielectric response; We use a sign-consistent Marcus-type expression, written in terms of the donor-acceptor free energy ΔG° , to describe charge transfer along DNA. In the framework proposed here, the nucleotide sequence may determine not only genetic information but also the electronic landscape of the double helix. Because charge transfer can occur through the π -stacked bases, different sequences may create regions in which electron transfer is more or less favourable. We therefore ask whether sites used by cellular machinery - including replication origins, restriction-modification sites, and transcription-factor or RNA-polymerase binding regions in bacterial systems - may coincide with characteristic features of this electronic landscape. The corresponding question in eukaryotic chromatin is treated separately. No new experimental data are presented; the examples are intended to define measurements that could support or falsify the hypothesis and to identify the experiments that would most directly test it.

Keywords: DNA charge transport, sequence-dependent electron transfer, redox signalling, genome regulation, restriction-modification systems, theoretical biophysics.

1. Introduction

1.1. The physical question behind a familiar molecule

DNA is usually described in terms of its informational role: a sequence of four bases that encodes proteins and is copied during cell division. This description is fundamental, but it does not address another property of the molecule: double-stranded DNA is also a helically stacked polymer capable of supporting charge transport through its π -stacked bases [1]. Because the electronic properties of this structure vary with sequence and conformation, it is reasonable to ask whether the electronic landscape created by the nucleotide sequence might itself have a biological role. This paper takes that

question as its starting point and develops it as a testable hypothesis rather than an established conclusion.

1.2. The conventional account, briefly

The conventional, information-centric account of DNA function comprises: (i) storage of hereditary information in the linear sequence of bases; (ii) semi-conservative replication of that sequence at cell division; (iii) transcription of selected regions into RNA; and (iv) translation of messenger RNA into protein, modulated by an extensive regulatory apparatus (promoters, enhancers, silencers, chromatin state, non-coding RNAs). This account is empirically well supported and is not challenged here. This paper instead asks

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whether an additional, non-informational physical property of the molecule - its capacity for sequence-dependent charge transport - has physiological consequences beyond those already documented in DNA-repair signalling and in biosensor applications.

1.3. The proposed hypothesis

We propose that DNA may have, in addition to its established informational role, a physical role arising from charge transport through its stacked bases. The central point is that this property should not be uniform along the molecule. Because the bases differ electronically and because their order affects the structure and stacking of the double helix, the nucleotide sequence may create its own electronic landscape. Some regions may favour charge transfer, others may interrupt it, while local changes in base pairing, helix opening or protein binding may further modify this behaviour. If this is correct, sequence recognition by proteins may involve more than direct structural or chemical complementarity. Particular DNA sequences could generate local differences in charge distribution or electrostatic potential, creating sites that preferentially attract positively charged regions of DNA-binding proteins or associated metal centres. In this view, electrostatic attraction could help guide a protein towards a particular region of DNA, after which conventional sequence-specific contacts, conformational fitting or both would determine stable binding. Thus, electrostatic recognition and the classical 'lock-and-key' picture need not be mutually exclusive; they may represent successive or cooperating components of the same recognition process. Under this hypothesis, some sequence-specific biological events - including replication initiation, restriction-modification, transcription initiation and other protein-DNA interactions - may occur preferentially at positions with characteristic electronic properties. We do not propose that electrical behaviour replaces the known biochemical mechanisms of these processes, but that it may provide an additional physical component that has so far been underestimated. The hypothesis can therefore be tested by asking whether measurable charge-transport or electrostatic properties follow the nucleotide sequence, whether characteristic features recur at biologically relevant sites, and whether altering those features changes protein recruitment or activity. Such observations would need to be distinguished from the more limited possibility that DNA-mediated charge transport operates only locally and in specialised processes such as redox signalling associated with DNA repair.

1.4. Structure of the paper

Section 2 (Material and Methods) sets out the analytical approach used to construct and evaluate the hypothesis, including the evidence-classification scheme and the non-equilibrium thermodynamic and electron-transfer background against which it is built. Section 3 (Results) states the hypothesis formally as four structural hypotheses (H1-H4), gives a corrected mathematical formulation, and presents the corresponding structural-analogy and genome-as-network mappings. Section 4 (Discussion) reinterprets replication, restriction-modification and transcription in bacterial model systems in light of the hypothesis, separately addresses the eukaryotic/chromatin question, develops falsifiable

predictions split into physical-calibration and hypothesis-discriminating classes, proposes experimental tests, and critically discusses strengths, weaknesses and the conservative alternative explanation. Section 5 (Concluding Remarks) states the conclusions supported by this analysis and explicitly labels the central hypothesis as a new hypothesis for future testing, together with a prioritised research roadmap.

2. Material and Methods

This is a theoretical and hypothesis-generating study. No new experimental or bioinformatic data are presented. The purpose of this section is to define the physical framework used to formulate the hypothesis and to make clear which parts arise from established physical chemistry and which are proposed here as extensions of it.

2.1. Non-equilibrium thermodynamic background

Living systems exist far from thermodynamic equilibrium and maintain their organisation through a continuous exchange of energy and matter with their surroundings [2-6]. At the molecular level, electron transfer is one of the most fundamental processes by which this energy is channelled and controlled. Respiration, photosynthesis and many enzymatic redox reactions depend on electrons being transferred through ordered sequences of donors and acceptors rather than released through a single uncontrolled relaxation process [7-9]. This provides the physical starting point for the present hypothesis. Life already makes extensive use of organised electron-transfer pathways. The question raised here is whether DNA, a highly ordered polymer with documented capacity for charge transport, may also participate in such organisation at the molecular level. In this view, the double helix is considered not simply as a passive carrier of genetic information, but as a possible sequence-dependent pathway for charge transfer. The nucleotide sequence may determine where electron transfer is favoured, impeded or locally altered, thereby creating an electronic landscape along the molecule. This possibility does not follow from non-equilibrium thermodynamics itself; it is the specific hypothesis examined in this paper.

2.2. Sequence-dependent electronic pathway

The proposed model treats the stacked bases of double-stranded DNA as a molecular pathway through which charge transfer can occur. Because adenine, cytosine, guanine and thymine differ in their electronic properties, and because their order influences base stacking and local DNA structure, the efficiency of charge transfer is expected to vary along the sequence. The central proposition is therefore not merely that DNA can transport charge, but that the nucleotide sequence may define the path followed by that charge. Regions of favourable transfer, interruption, local charge redistribution or altered electrostatic potential could consequently arise at defined positions along DNA. A further possibility examined here is that these local electronic properties may influence interactions with DNA-binding proteins. Regions with a more negative local electrostatic potential could preferentially attract positively charged domains of proteins or associated metal

centres, potentially assisting molecular recognition before, or together with, conventional structural and chemical recognition.

2.3. Electron-transfer formalism

Electron transfer between donor and acceptor sites is described using the standard semiclassical non-adiabatic Marcus formalism [10-12]. The rate expression is written in terms of the donor-acceptor standard free-energy change, ΔG° , using a consistent sign convention for exergonic and endergonic processes. The Marcus framework is used here as a physical description of elementary transfer events. It is not taken to demonstrate the biological hypothesis. Rather, it provides a quantitative basis for asking how differences in sequence, distance, coupling and local molecular environment could alter the probability of charge transfer between positions along DNA.

2.4. Literature synthesis approach

The literature considered in this paper was selected to establish four points relevant to the hypothesis: first, that duplex DNA can support charge transport [1,13-15]; second, that DNA-mediated redox signalling has already been implicated in biological processes such as DNA repair [16-19]; third, that sequence and structure influence measurable electrochemical behaviour in DNA-based systems [20-23]; and fourth, that these processes occur within a wider cellular redox environment in which electron-transfer reactions are continuously coupled to metabolism and signalling [24]. Literature concerning DNA melting, replication, restriction-modification systems and transcription initiation is used to identify biological processes in which sequence-specific recognition is already established and in which the proposed electronic contribution can therefore be tested. This is not a systematic review. The literature is used to define the experimental facts on which the hypothesis rests and, equally importantly, to define the observations against which it may be rejected.

2.5. Scope of the hypothesis

The hypothesis is first considered in bacterial systems, where replication origins, restriction-modification sites and transcriptional regulatory regions provide relatively well-defined sequence-dependent processes that can be examined experimentally. The extension to eukaryotic genomes is treated separately. Chromatin, nucleosomes, DNA modifications and higher-order organisation introduce additional variables that may alter charge transport and electrostatic interactions. The bacterial model is therefore used as the simplest experimental setting in which the central proposition can first be tested, rather than as a basis for assuming that the same mechanism operates unchanged in eukaryotes.

3. Results

3.1. Established physical basis

Double-stranded DNA can support charge transport through the π -stacked bases of the duplex over distances greater than expected from simple through-space tunnelling [1,13-14]. Depending on distance, sequence and molecular environment, this transport can

involve short-range superexchange and longer-range hopping between bases. Direct electrical measurements through DNA molecules have also been reported using single-molecule and surface-based systems [15]. Importantly, this property is not limited to artificial electrical measurements. DNA-bound proteins containing redox-active cofactors can exchange electrons through the duplex. This has been studied particularly well for [4Fe-4S]-containing DNA-repair proteins such as EndoIII and MutY, where DNA-mediated electron transfer has been proposed to assist communication between proteins bound at different positions on the same molecule [16-18]. Disruption of normal base stacking, for example by a mismatch, reduces long-range charge transport, showing that the integrity and arrangement of the stacked bases are essential to the process [19]. The same property is already used in electrochemical DNA sensors, where changes in hybridisation or DNA structure alter electron transfer between the DNA and a redox reporter [20-23]. Taken together, these observations establish a simple but important point: DNA is not electrically inert. The double helix can provide a physical pathway for charge movement, and the efficiency of that pathway depends on its molecular structure. What remains open is whether this property has a broader biological significance.

3.2. From charge transport to the proposed model

The hypothesis developed here begins with a simple observation. DNA provides both a surface along which proteins can move and a stacked-base pathway through which charge can be transferred. These two properties are usually considered separately. We ask whether they may, in some circumstances, be physically coupled. Many DNA-binding proteins associate first with nonspecific DNA and then move along the duplex while searching for their target. Electrostatic interactions between positively charged regions of the protein and the negatively charged DNA backbone help maintain this association during sliding. The protein can therefore remain in close contact with the molecule while sampling successive regions of the sequence. We propose that this movement may occur over an electronic landscape that is itself determined, at least in part, by the nucleotide sequence. Charge transfer through the π -stacked bases need not be equally favourable at every position. Differences in sequence, stacking, local opening of the duplex and interaction with redox-active proteins may create regions with different charge-transfer properties and local electrostatic potentials. A sliding protein would consequently not encounter an electrically uniform DNA molecule. Regions in which charge redistribution produces a more favourable electrostatic environment could increase the residence time or binding probability of a positively charged DNA-binding surface. In this way, electrostatic attraction could assist the protein in locating particular regions of DNA, while direct base contacts and conformational recognition would provide the final specificity. The proposed mechanism therefore complements, rather than replaces, conventional molecular recognition. Under this model, the movement of charge and the movement of proteins along DNA become related phenomena. The stacked bases provide a pathway for charge transfer, while the DNA-bound protein samples the resulting sequence-dependent electronic landscape. We propose that this coupling may contribute to the localisation of

proteins involved in processes such as restriction–modification, replication and transcription. This does not require a continuous macroscopic electrical current through the genome. The relevant events may instead consist of transient electron-transfer and charge-redistribution processes between DNA-associated donor and acceptor centres. The testable proposition is that altering the charge-transport properties of a DNA region, without destroying its overall structure, should measurably alter the motion, residence time or recruitment of particular DNA-binding proteins.

3.3. Four structural hypotheses

The model can be reduced to four physical propositions. They are not presented as established properties of DNA, but as consequences of treating the double helix as a sequence-dependent pathway for charge movement. (**Table 1**)

H1 - Direction of electron transfer. Where charge transfer occurs along DNA, its net direction should be determined by the energetic relationship between local electron donors and acceptors. The model therefore does not require a universal direction linked to the 5'→3' orientation of the strands. Instead, electron movement should depend on the local energetic landscape created by the sequence and by the redox centres interacting with it. Different regions of the

same DNA molecule could consequently favour transfer in different directions.

H2 - The stacked bases form the principal pathway. Charge transport is proposed to occur primarily through the π -stacked bases of the double helix, consistent with [19]. Anything that substantially disturbs this stacking - a mismatch, lesion, local opening of the duplex or other structural discontinuity - should therefore reduce or interrupt transfer. By contrast, a break confined to the sugar-phosphate backbone need not have the same effect if base stacking across that position remains largely preserved. In this model, it is the continuity of the stacked bases, rather than the continuity of the backbone alone, that defines the electronic pathway.

H3 - Local opening of the helix acts as an electronic gate. Some DNA sequences are more prone than others to local strand separation, particularly AT-rich regions [25–26]. We propose that such regions may behave as sequence-defined gates in the electronic pathway. In the closed duplex, stacked bases may allow charge to pass through the region. When the helix opens and stacking is disrupted, charge transfer should become less favourable.

Table 1 | Proposed mapping between sequence-dependent electronic properties of DNA and their possible biological consequences. The table summarises the working hypotheses developed in this paper; the terms describe proposed physical behaviour and do not imply that DNA is a manufactured electrical circuit.

Electronic/structural feature	Physical interpretation in the model	Possible biological consequence
π-stacked base pathway	Stacked bases provide the principal route for DNA-mediated charge transport. Sequence and local structure determine the efficiency of transfer.	Defines the underlying electronic pathway along which charge can move through the duplex.
Redox donor–acceptor coupling	DNA-associated redox-active proteins or cofactors can donate or accept electrons through the duplex. Direction and efficiency depend on local energetics, including ΔG° .	May couple separated DNA-bound proteins and create local or long-range redox communication.
Sequence-dependent electronic landscape	Different nucleotide sequences generate different charge-transfer efficiencies, local charge distributions and electrostatic potentials.	May create preferred regions for protein recruitment, retention or functional activity.
Local electronic gate	Partial melting, mismatches, lesions or other disruptions of base stacking reduce charge transport through that region. AT-rich, easily opened regions may therefore behave as switchable gates.	Could accompany or contribute to events requiring local DNA opening, including replication and transcription initiation.
Electrostatic recruitment zone	Charge redistribution may create a locally more negative electrostatic environment.	Positively charged regions of DNA-binding proteins may be preferentially attracted to, or retained at, such sites, potentially assisting target search before final sequence-specific recognition.
Directional charge-transfer bias	Net electron transfer depends on the energetic relationship between local donor and acceptor states rather than on a universal 5'→3' rule.	Different regions of DNA may favour different directions or probabilities of charge transfer depending on the molecules bound locally.
Local dielectric / polarisation response	Sequence, hydration, ionic environment, supercoiling and protein binding may alter the local ability of DNA to polarise and redistribute charge.	May modify the electrostatic environment experienced by proteins and influence local DNA–protein interactions.
Protein–DNA sliding over an electronic landscape	DNA-binding proteins may diffuse along DNA while continuously sampling sequence-dependent electrostatic and electronic properties.	Local electronic features could bias sliding, increase residence time or favour recognition at replication origins, restriction sites, promoters or other functional regions.

The sequence could therefore determine not only the electrical properties of a region, but also where the pathway is most easily switched between relatively conducting and poorly conducting states. This idea is close to the original model: local denaturation need not simply be a consequence of biological activity; it may itself alter the electrical state of the DNA and thereby participate in the process taking place at that site (**Figure 1**).

H4 - The sequence creates different local electrical environments.

The electrical behaviour of DNA is unlikely to be described by charge transport alone. We propose that different sequences may also differ in their local polarisation, dielectric response and capacity to redistribute charge, consistent with established dielectric characterisation of DNA in solution [27]. These properties will additionally depend on hydration, ionic environment, supercoiling and interaction with proteins.

The consequence is that DNA would not present a uniform electrical surface to a protein moving along it. Instead, the protein would encounter a succession of regions with different charge-transfer and electrostatic properties.

A region in which charge is redistributed towards a more negative local electrostatic potential could favour interaction with positively charged domains of a DNA-binding protein. This provides a possible physical connection between the electronic pathway of DNA and the sliding or recognition mechanisms discussed above. Taken together, H1-H4 describe DNA not as a homogeneous conductor, but as a sequence-defined molecular pathway whose direction of charge transfer, continuity, local gating and electrostatic behaviour vary from one region to another. The central experimental question is whether these variations correspond in a reproducible way to sites at which DNA-binding proteins act (**Figure 2**).

3.4. From local DNA properties to a genome-wide electrical map

The hypothesis can be represented using a simple circuit analogy. Three physical features are especially relevant. First, local opening of the double helix can interrupt base stacking and therefore increase resistance to charge transport. Such regions can be viewed as gates whose electrical state changes when the duplex opens or closes.

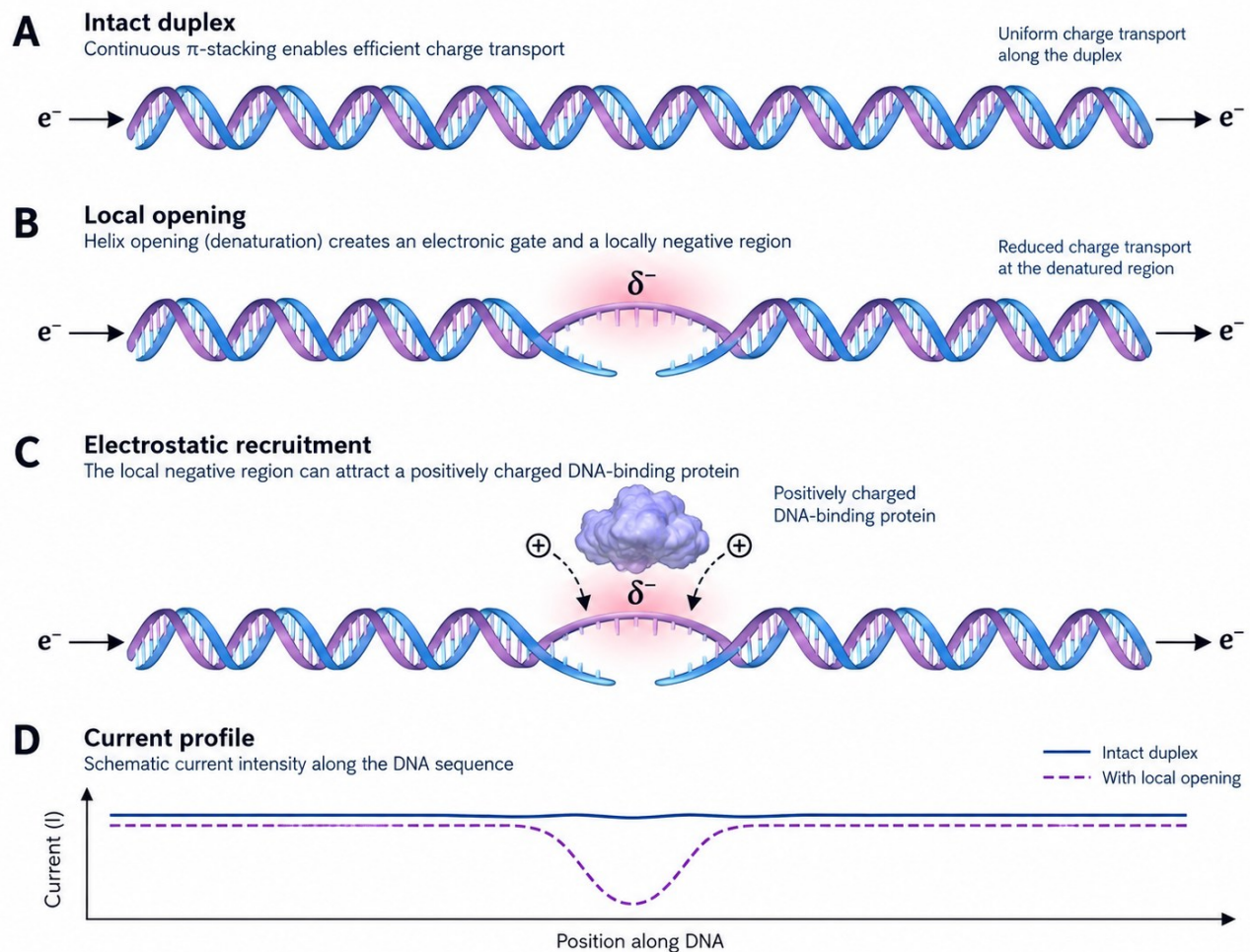


Figure 1 | Local helix opening as an electronic gate and electrostatic recruitment site. (A) Continuous base stacking in intact duplex DNA supports charge transport. (B) Local opening disrupts stacking and is proposed to reduce charge transfer at that position. (C) The associated charge redistribution may create a locally more negative electrostatic environment that favours interaction with positively charged DNA-binding proteins. (D) Idealised current profiles for intact and locally opened DNA.

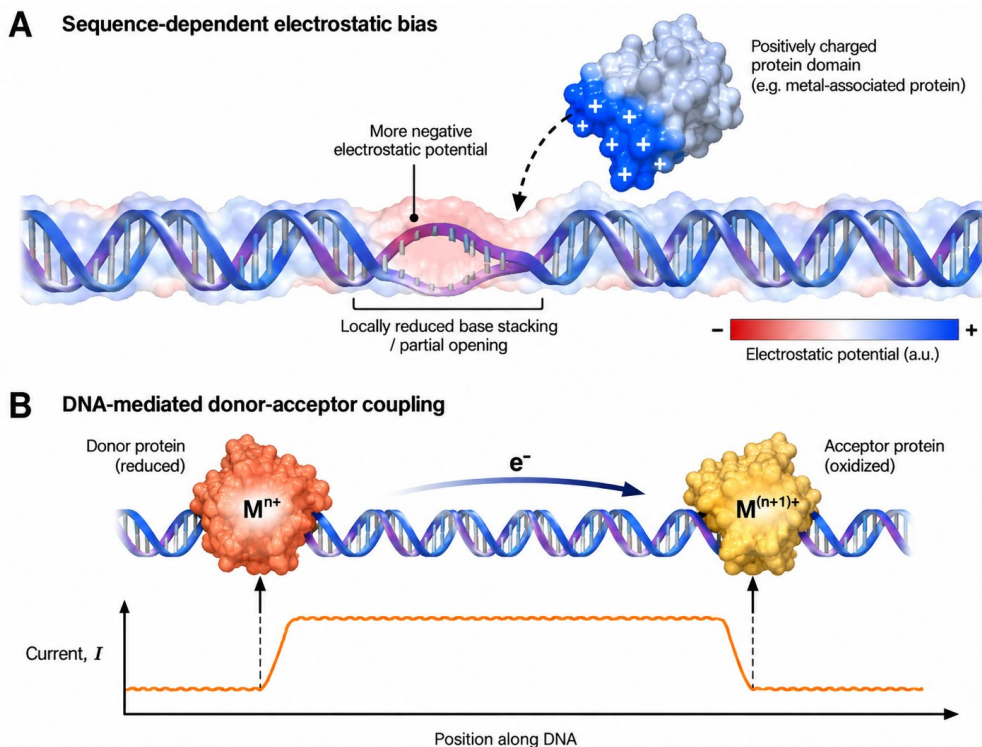


Figure 2 | Sequence-dependent electrostatic bias and DNA-mediated donor-acceptor coupling. (A) Proposed effect of sequence and local structural changes on DNA electrostatic potential and recruitment of positively charged protein domains. (B) Schematic DNA-mediated electron transfer between separated redox-active donor and acceptor proteins. Together, the panels illustrate the proposed connection between sequence-dependent charge transport, local electrostatics and protein–DNA interactions.

Second, redox-active proteins or cofactors bound to DNA may act as local electron donors or acceptors, creating preferred directions for charge transfer through the stacked bases. Third, different DNA regions may differ in their ability to polarise and redistribute charge, giving them different local capacitive or dielectric behaviour. These elements are not intended to imply that DNA is literally an electrical circuit. The analogy is used only to describe how sequence and structure may create regions with different electrical properties along the molecule. At the level of a gene, the sequence can therefore be represented as a succession of regions that differ in charge-transfer efficiency, local gating and interaction with electron donors or acceptors. A promoter, replication origin or protein-binding site may then be examined not only as a sequence motif, but also as a position within this electronic landscape. The same idea can be extended, more speculatively, to larger genomic networks. Genes, regulatory regions and DNA-binding proteins may be represented as interacting nodes, with conventional regulatory connections supplemented, where relevant, by a term describing DNA-mediated charge or redox coupling. The purpose of such a representation is not to claim that the genome is an electrical circuit, but to provide a framework in which the proposed electronic component can be measured and tested.

4. Discussion

4.1. Replication, restriction–modification and transcription in bacterial systems

Replication. Bacterial replication begins at defined regions of the chromosome where the duplex is locally opened by initiator proteins. These regions often contain AT-rich sequences that are intrinsically easier to separate [26,28]. Within the present model, opening of the helix has an additional consequence. As base stacking is disrupted, the local pathway for charge transport should also change, effectively creating an electronic gate at the origin. The origin would therefore pass through two states: a more continuously stacked state and an opened state in which charge transport is reduced. A further possibility is that the electronic state of the origin contributes to protein recruitment. If sequence and charge transport produce a characteristic local electrostatic environment, positively charged regions of initiator proteins could preferentially interact with that region before or during stable sequence-specific binding. This would not replace the established roles of sequence recognition, supercoiling and initiator-protein assembly, but could provide an additional physical contribution to the process.

Restriction and modification. Restriction enzymes recognise defined DNA sequences and cleave the duplex at or near those sites, while corresponding methyltransferases protect the same sequences by modification [29] (Figure 3). The hypothesis developed here raises a simple question: does a recognition sequence have only a particular chemical and structural identity, or does it also produce a characteristic electronic state? For DNA-binding proteins that search the molecule through nonspecific association and facilitated movement along the duplex, the surrounding sequence may

Restriction enzyme recognition by electrostatically biased sliding

A dimeric restriction enzyme scans duplex DNA by one-dimensional diffusion, pausing at sites with a favorable electrostatic signature, leading to specific recognition and cleavage.

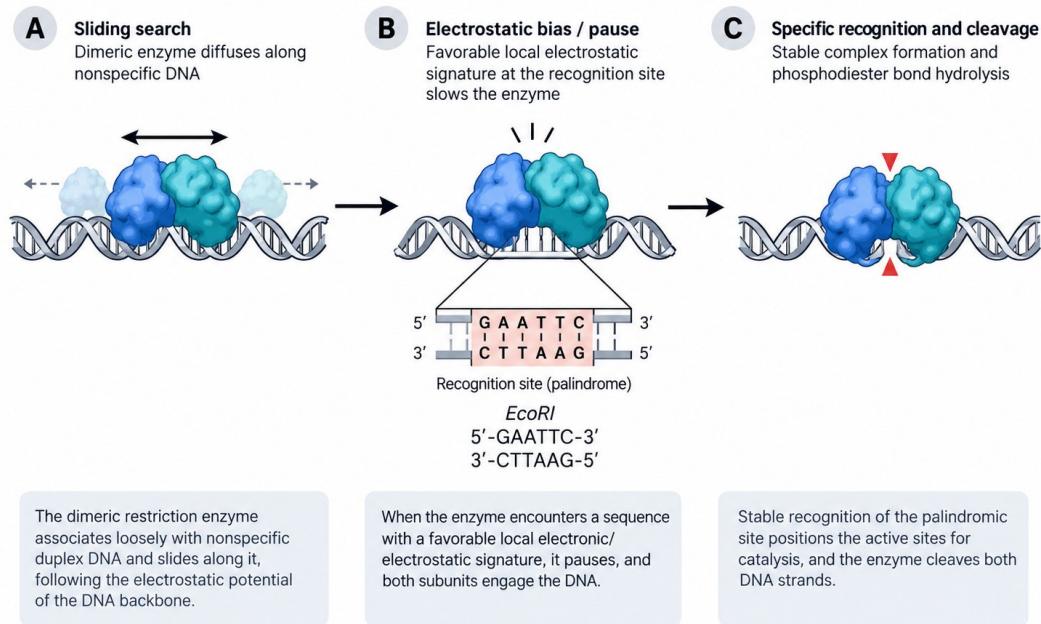


Figure 3 | Proposed electrostatic contribution to restriction-enzyme target search. (A) A restriction enzyme associates nonspecifically with DNA and searches along the duplex by one-dimensional sliding. (B) A favourable local electronic or electrostatic environment is proposed to increase residence time near the recognition sequence. (C) Conventional sequence-specific contacts then stabilise binding and permit cleavage. Electrostatic bias is proposed as complementary to established molecular recognition, not as its replacement.

influence the electrical environment encountered during that search. A recognition site with a distinctive charge distribution or electrostatic potential could increase the probability that a positively charged protein surface remains at that position long enough for direct molecular recognition to occur. In this view, electrostatic attraction and conventional sequence recognition are not alternatives. The first may help bring or retain the protein at the appropriate region, while direct contacts between protein and bases provide the final specificity.

Transcription. Bacterial transcription initiation also depends on defined DNA sequences and on local opening of the duplex, particularly around promoter elements such as the -10 region [30]. Under the present hypothesis, promoter sequences may therefore have two related properties: they encode the molecular information required for recognition by RNA polymerase and sigma factors, and they may also define a characteristic local electronic environment (see Figure 4). As the polymerase encounters DNA, sequence-dependent differences in charge distribution could influence its transient interaction with different regions of the molecule. A promoter could therefore be recognised not only through direct structural contacts but also, at an earlier stage, through an electrostatic environment that favours recruitment or longer residence of the protein complex. Once the promoter begins to open, disruption of base stacking would in turn alter the local charge-transport pathway. Transcription initiation may therefore involve a transition in both the structural and electronic state of the

DNA. These examples are not proposed as proof that charge transport controls replication, restriction or transcription. They identify biological processes in which sequence-specific recognition and local structural change already occur, and where an additional electronic contribution can therefore be tested experimentally.

4.2. DNA as an active component of cellular electron organisation

The hypothesis developed here concerns DNA itself and does not require, and does not currently propose, a specific mechanism linking DNA-mediated charge transport to translation or to ATP synthesis. Any suggestion that DNA-proximal redox events are coupled to whole-cell metabolic flux is treated here as speculation requiring a defined mechanism and a calibrated measurement before it can be evaluated. The hypothesis developed here invites a broader possibility: DNA may itself be an integral part of the cellular organisation of electron flow. The genome is an exceptionally large, ordered and sequence-defined molecular structure. Its bases are π -stacked, it is continuously contacted by proteins, ions and redox-active cofactors, and its conformation changes during replication, transcription, repair and regulation. It may therefore be misleading to regard most of the DNA molecule as electronically inactive whenever it is not being copied or transcribed. Instead, DNA may remain physically active as an extended pathway through which charge is transferred, redistributed or temporarily localised.

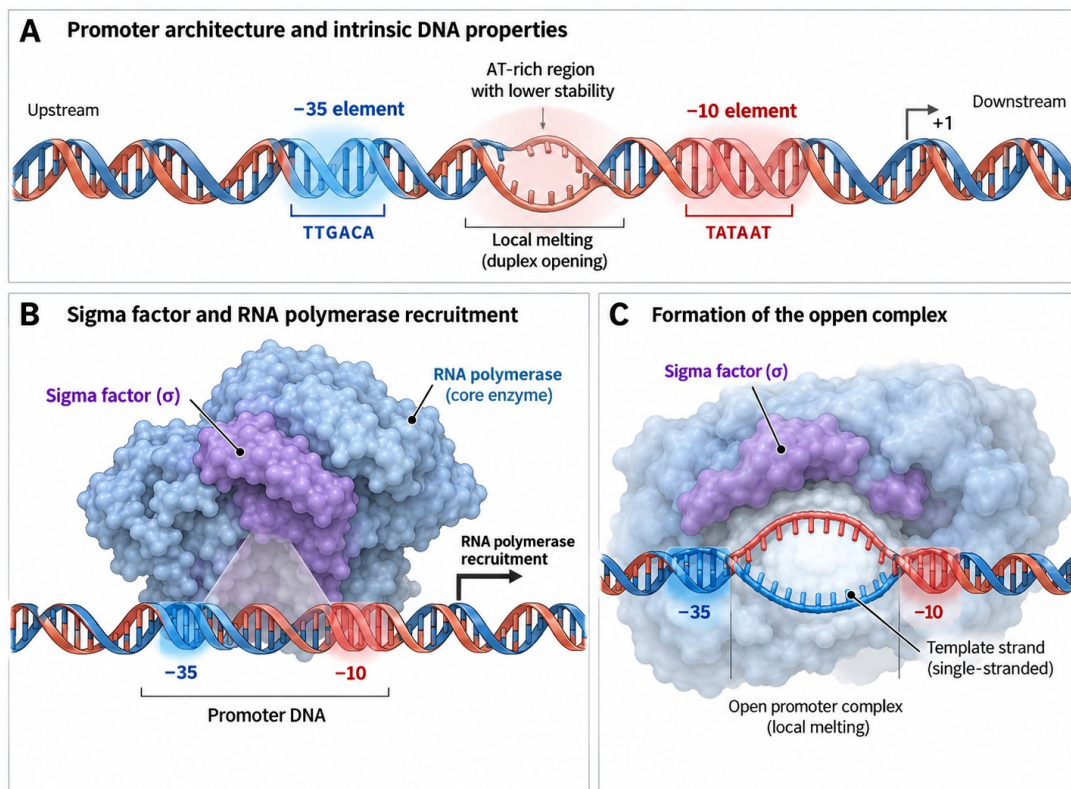


Figure 4 | Proposed transcription mechanism. Transcription initiation may involve a transition in both the structural and electronic state of the DNA.

In this view, the genome would not simply contain genetic instructions; its sequence and structure could also help determine where electrons can move, where transfer is slowed or interrupted, and where local electrostatic conditions favour interaction with proteins or other molecular partners. If such pathways exist *in vivo*, they would form part of the cellular redox environment and could indirectly connect genome activity with metabolic state. This possibility remains speculative. Its importance is that it makes the broader idea testable: changes in cellular redox state should, under the hypothesis, be capable of altering measurable DNA-associated charge-transfer events and perhaps the behaviour of proteins that depend on them.

4.3. Chromatin as a possible electronic switch

In eukaryotic cells, DNA is packaged into chromatin, and changes in chromatin organisation strongly influence access to genes [31]. The same structural changes could also influence the electronic behaviour of DNA. Wrapping around nucleosomes, changes in hydration, altered base geometry and the presence of chromatin-associated proteins may modify charge transport or local electrostatic properties. Chromatin could therefore act not only as a regulator of physical accessibility, but also as a modifier of the electronic state of a DNA region. Under this model, an open and a condensed chromatin region might differ both in their accessibility to proteins and in the way charge is transferred or redistributed through the underlying DNA. These effects would need to be measured independently: a change in transcription alone would not demonstrate an electronic mechanism.

4.4. From the DNA molecule to a genomic network

The circuit analogy introduced earlier can also be extended to larger scales. At the level of a single DNA molecule, the proposed model describes regions with different charge-transfer properties, electronic gates and interactions with redox-active proteins. At the level of the genome, these regions may be connected through proteins and other molecular interactions into a larger network. Genes, regulatory regions and DNA-binding proteins can therefore be represented as nodes linked by known biochemical interactions and, where appropriate, by a proposed DNA-mediated charge or redox coupling. A term such as J_{ij} may be used to represent the measurable rate of electron transfer or redox coupling between two defined sites. At present, however, this remains a conceptual quantity rather than a demonstrated genome-wide flux. The value of the network representation is therefore practical rather than metaphorical: it provides a way to ask where charge moves, between which molecular partners, and whether those pathways change when sequence or biological state changes.

4.5. Extension to eukaryotic regulation

The bacterial examples provide a relatively simple setting in which to test the hypothesis because DNA sequences, binding sites and protein interactions can often be defined directly. Eukaryotic regulation is more complex. DNA is wrapped around nucleosomes and influenced by histone modifications, DNA methylation, higher-order folding and long-range interactions. For this reason, the hypothesis should not simply be transferred unchanged from bacteria to eukaryotes. The relevant question is instead whether the

electronic landscape created by the nucleotide sequence remains detectable and biologically relevant after chromatin organisation is added to the system. It is also possible that chromatin itself modifies or even helps define that landscape. This makes eukaryotic regulation a separate experimental problem rather than merely an extension of the bacterial model (**Figure 5**).

4.6. Strengths and limitations of the model

The main strength of the hypothesis is that it begins with an experimentally established physical property: DNA can mediate charge transfer through its stacked bases. The new proposition is not the existence of this phenomenon, but that its sequence dependence may carry biological significance. The model therefore makes several linked predictions. Charge transport should vary reproducibly with sequence; interruption of base stacking should alter that transport; local electronic properties should influence interactions with some DNA-binding proteins; and biologically important sites may display characteristic electrical behaviour. The model also has clear limitations. The π -stacked bases are treated as the principal charge-transfer pathway, while the phosphate backbone, hydration shell, ions and bound proteins are treated mainly as factors that modify that pathway. Local opening of the helix is expected to interrupt or weaken charge transport rather than create a permanently low-resistance region. Direction of electron transfer is expected to depend on the energetic relation between local donors and acceptors rather than on a universal 5'→3' rule. Mg^{2+} and Zn^{2+} should likewise not be treated as electron donors or acceptors under ordinary biological conditions. Their possible importance in this model is different: they can influence DNA structure, electrostatics and protein-DNA interactions. Proteins containing positively charged surfaces or metal-associated

structural centres may therefore respond to the local electrostatic environment of DNA without the metal ion itself undergoing redox chemistry. The most important uncertainty concerns biological causation. Demonstrating that a promoter, replication origin or restriction site has unusual charge-transport properties would not, by itself, prove that those properties are required for its function. The stronger test is whether changing the electronic properties of the surrounding DNA, while preserving the essential recognition sequence and overall structure, changes protein recruitment, residence time or biological activity. That experiment would directly address the central proposal of this paper: whether the electronic landscape of DNA is merely a physical consequence of nucleotide sequence, or whether cells also make use of it.

4.7. Proposed experimental approaches

The predictions in **Table 2** can be tested in two stages. Class A tests address the physical premises of the model. A1 can be examined with composition-matched synthetic duplexes whose base order is rearranged, using single-molecule conductance or electrochemical electron-transfer measurements. A2 compares backbone nicks with mismatches or other perturbations that disrupt base stacking. A3 requires controlled local helix opening combined with conductance, impedance or redox-transfer measurements. A4 can be tested in defined donor-DNA-acceptor systems in which donor and acceptor redox potentials are varied. A5 examines sequence, supercoiling, hydration and ionic-environment effects by electrochemical impedance spectroscopy or related dielectric measurements. Class B tests address biological consequences. B1 uses single-molecule tracking or binding measurements to compare identical recognition motifs embedded in flanking sequences with different predicted electronic properties.

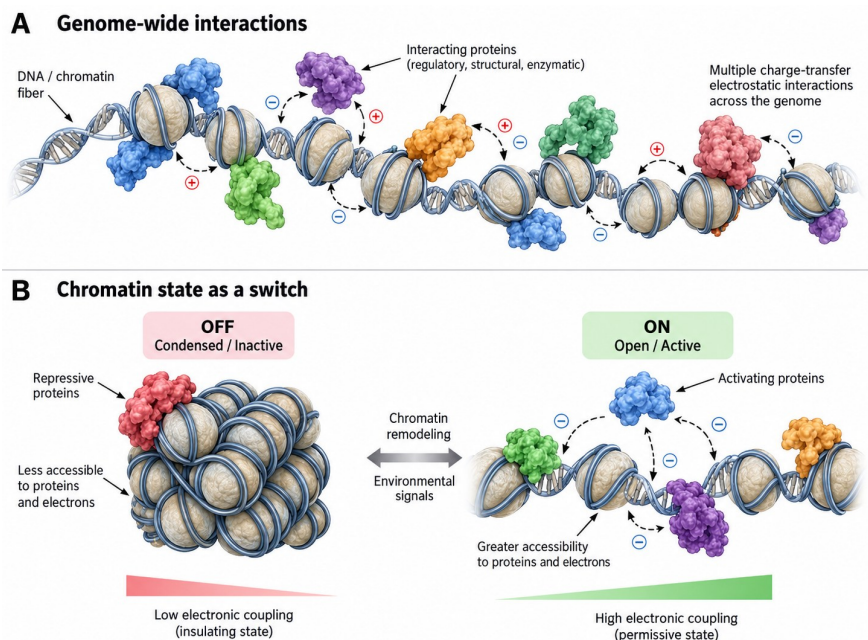


Figure 5 | Genome-wide interactions and chromatin state as a possible electronic switch. (A) Conceptual representation of multiple protein, electrostatic and charge-transfer interactions along chromatin. (B) Hypothetical influence of chromatin organisation on DNA-mediated electronic coupling: condensed chromatin is proposed to reduce accessibility and charge-transfer interactions, whereas open chromatin may favour them. This extension to eukaryotic chromatin remains a separately testable hypothesis.

Table 2 | Experimental predictions of the DNA charge-transport hypothesis. Class A tests the physical assumptions of the model; Class B asks whether sequence-dependent electronic properties of DNA contribute measurably to biological function. Each entry is a prospective test rather than a reported result.

ID	Prediction	Experimental test / readout	Supporting result	Result arguing against the
A1 - Sequence dependence	DNA molecules with the same length and base composition but different base order should show different charge-transfer properties.	Synthetic duplexes with matched composition but rearranged sequences; measure electron-transfer rate or conductance.	Reproducible differences associated with base order.	No detectable sequence-order effect when composition and structure are controlled.
A2 - Base-stacking pathway	Disruption of base stacking should affect charge transport more strongly than a backbone interruption that largely preserves stacking.	Compare matched duplexes containing a backbone nick, mismatch or other stacking-disrupting lesion.	Mismatch or stacking disruption strongly reduces transfer while an isolated nick has a smaller effect.	Both perturbations produce equivalent effects, or stacking disruption has no reproducible effect.
A3 - Electronic gating by helix opening	Local opening of the duplex should reduce charge transport through that region and alter its local electrostatic state.	Engineered melting-prone regions measure conductance, impedance or redox transfer before and after controlled opening.	Reversible reduction in transfer associated with local melting.	Opening produces no reproducible change in charge transport.
A4 - Donor-acceptor energetics	Direction and efficiency of charge transfer should depend on the energetic relation between DNA-associated donor and acceptor centres rather than on a universal strand direction.	Defined donor–DNA–acceptor systems with altered donor/acceptor redox potentials.	Transfer direction or rate changes predictably with donor–acceptor energetics.	Transfer remains independent of donor–acceptor energetics within the tested range.
A5 - Local electrical environment	Sequence, supercoiling and molecular environment should produce measurable differences in local dielectric or polarisation behaviour.	Defined DNA constructs differing in sequence, supercoiling, hydration or ionic environment impedance/dielectric measurements.	Reproducible differences associated with defined structural or sequence changes.	No measurable differences under controlled conditions.
B1 - Electrostatic bias of protein search	Altering the electronic properties surrounding a DNA recognition site, while leaving the recognition sequence unchanged, should influence the search behaviour of some DNA-binding proteins.	Single-molecule tracking or binding measurements using identical recognition motifs embedded in electronically different flanking sequences.	Changes in sliding, pausing, residence time or arrival frequency at the same recognition site.	Protein search kinetics remain unchanged despite substantial alteration of surrounding charge-transport properties.
B2 - Functional recognition	Sequence-dependent electronic properties may contribute to recognition or activity at restriction sites, promoters or replication origins.	Preserve the essential recognition motif while altering neighbouring sequence to modify predicted charge transport without substantially altering overall DNA structure.	Protein recruitment, binding or activity changes in association with the altered electronic environment.	Functional behaviour depends only on the recognition motif and is unaffected by surrounding electronic properties.
B3 - Coupling to cellular redox state	If DNA participates in cellular electron organisation, changes in cellular redox conditions should alter DNA-associated charge-transfer signals.	Controlled metabolic/redox perturbation combined with a validated DNA-proximal redox reporter.	Reproducible, dose-dependent change in DNA-associated redox signal.	Reporter remains unchanged despite substantial redox perturbation.
B4 - Chromatin modulation	Chromatin organisation should influence DNA-mediated charge transfer in addition to changing physical accessibility.	Compare controlled open and condensed chromatin states using an independent charge/redox reporter and transcriptional measurement.	Charge-transfer signal changes beyond that predicted by accessibility or transcription alone.	Electronic signal simply follows accessibility or show no independent change.
B5 - Genome-scale organisation	Functional DNA regions may occupy characteristic positions within a sequence-dependent electronic landscape.	Develop a sequence-based electronic/charge-transport model and compare predicted properties at promoters, origins and other defined sites against matched genomic controls.	Reproducible enrichment or characteristic electronic profiles at functional sites across independent datasets.	Functional sites show no difference from appropriately matched controls.

B2 preserves the essential recognition site while altering neighbouring sequence and measures protein recruitment, residence time, binding or activity. B3 couples controlled metabolic or redox perturbation to a validated DNA-proximal redox reporter. B4 compares open and condensed chromatin states using an independent charge/redox reporter together with transcriptional measurements. B5 develops and calibrates a sequence-based electronic model and tests whether promoters, replication origins and other functional regions show reproducible electronic signatures relative to matched genomic controls. None of these experiments has been performed as part of this paper; they constitute a prospective research programme.

5. Concluding Remarks

The physical starting point of this work is established: double-stranded DNA can support charge transport through its stacked bases, and this transport depends on sequence, structure and molecular environment. What is proposed here is that this property may have a broader biological significance than is currently recognised. The central hypothesis is that the nucleotide sequence creates an electronic landscape along the DNA molecule. Different regions may favour, impede or redirect charge transfer; local opening of the helix may interrupt this pathway; and changes in charge distribution may alter the electrostatic environment encountered by DNA-binding proteins. In this way, the same sequence that carries genetic information may also define a physical pathway for electron movement and contribute to where proteins bind, where replication begins, where transcription is initiated and where other sequence-specific events occur. A stronger possibility follows from this idea. DNA may not be electronically silent except during a small number of specialised redox reactions.

The genome may form part of a much more extensive cellular system of electron organisation, remaining physically active as proteins bind, move along the duplex, open the helix and alter its local structure. If so, replication, transcription, repair and regulation would be accompanied not only by biochemical and structural changes, but also by changes in the electronic state of DNA. This model does not require electrostatic recognition to replace conventional molecular recognition. A protein may first be guided or retained by a favourable electrostatic environment and then achieve specificity through direct contacts with the bases and the structure of the duplex. Likewise, charge transport need not replace the established mechanisms of replication or transcription; it may represent an additional physical component of those processes. The critical question is therefore no longer simply whether DNA can transport charge, but whether cells make use of the electronic landscape created by DNA sequence and structure. The most direct tests of this hypothesis should compare DNA molecules in which conventional recognition elements are preserved while the surrounding charge-transport properties are altered. If changes in the electronic landscape modify protein sliding, residence time, binding, initiation or other biological activity, this would support a functional role for DNA-mediated charge transport beyond the specialised examples already known. Conversely, failure to detect such effects under well-controlled conditions would place clear limits on the model. A longer-term objective would be to construct a genome-scale map of charge-transfer properties and determine whether biologically active regions occupy characteristic positions within that map. Such a result would suggest that the genome is not only a sequence of instructions, but also a dynamic physical system in which genetic information, molecular structure and electron movement are coupled (see Figure 6).

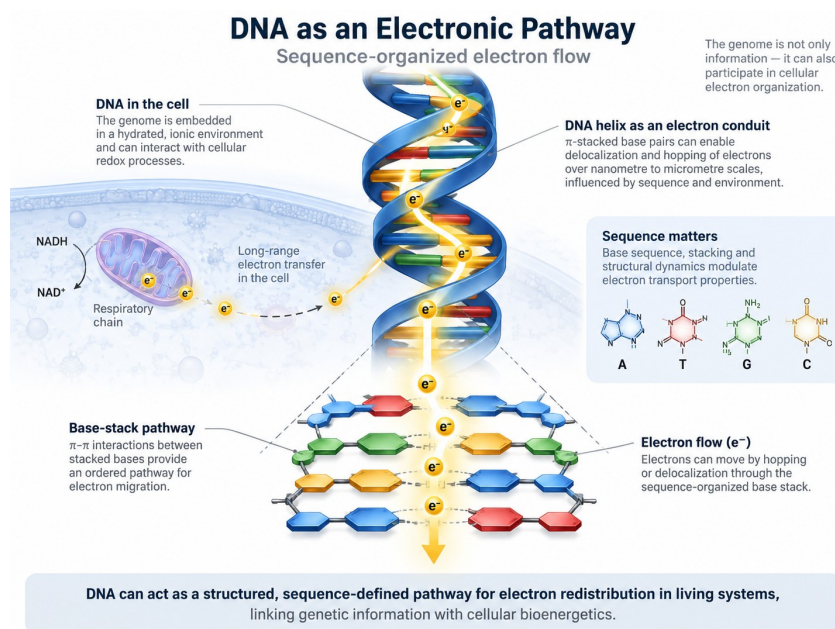


Figure 6 | DNA as a sequence-organized electronic pathway. Conceptual representation of DNA as a structured pathway for charge transport through π -stacked bases. Sequence, base stacking and molecular environment are proposed to shape electron-transfer properties along the duplex and may connect genetic information with cellular redox organisation. The figure illustrates the central hypothesis and does not imply replacement of established cellular bioenergetic pathways.

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