Medical & healthcare, Drug discovery, Materials

Find rare events at single-molecule level

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Abstract

Small-molecule drugs targeting DNA and RNA have recently been developed. To further develop small-molecule drugs, information on the interactions between the drug ligands and base molecules is indispensable, determined by the base molecule-ligand binding, selectivity, and hydrogen bonding mode. However, these parameters in the solution are unknown at the single-molecule level. Here we show that single-molecule counting based on combining single-molecule electrical measurements and artificial intelligence can quantify the abovementioned parameters. By analyzing a mixed solution of a ligand and base molecules, the binding selectivity of each of the five ligands to four different base molecules was quantitatively evaluated by the ratio of the number of the aggregates. Additionally, single-molecule counting and quantum chemical calculations showed that the mode and number of microscopic hydrogen bonds are ligand-dependent. Thus, single-molecule counting provided quantitative information about the properties of the aggregate in the solution without ligand incorporation into the DNA or RNA.

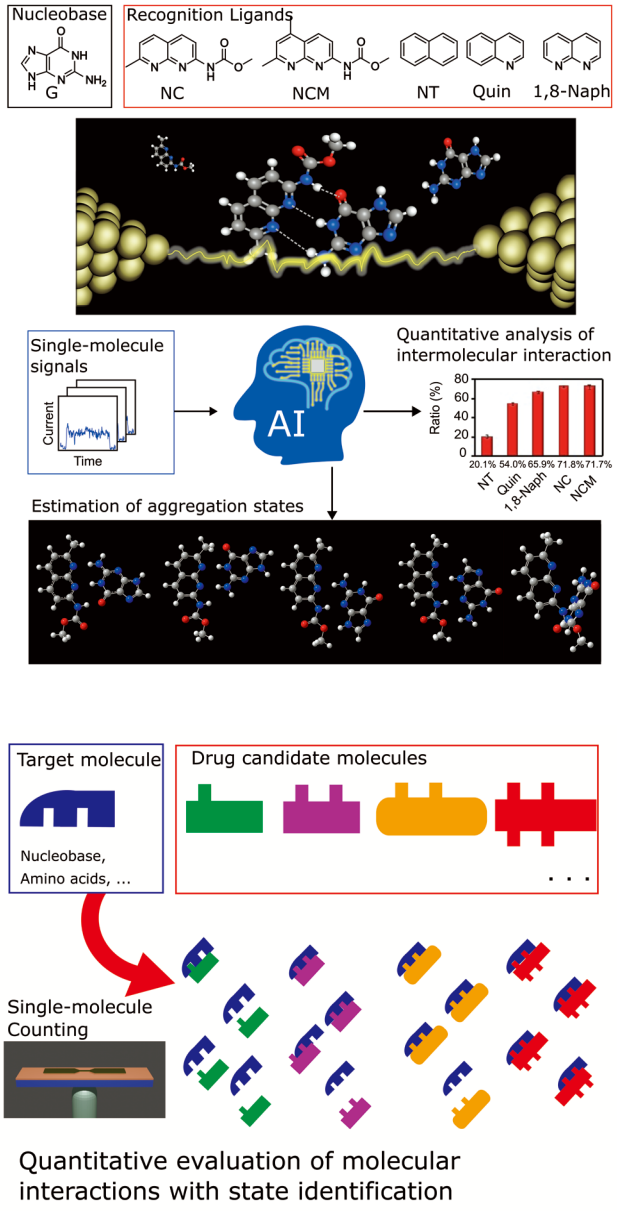
Background & Results

To date, numerous drugs have been developed by targeting proteins. However, the development of nucleic acid-targeted molecules aimed at DNA and RNA is expected to open new avenues for drug discovery. These molecules include not only DNA and RNA but also small molecules. The first step in drug discovery involves confirming that small molecules selectively and strongly bind to nucleic acids. However, the mode of hydrogen bonding between small molecules and nucleic acids has not been explored at the single-molecule level. Moreover, the rare binding mode, occurring at low probability, has never been explored.

In this study, we developed a single-molecule counting method, which identifies molecular species at the single-molecule level. This method combines a single-molecule measurement technique that identifies single molecules by measuring their electrical conductivity with AI that learns current waveforms obtained from the measurement. Additionally, employing this single-molecule counting method, we successfully quantified the binding strength between guanosine and ligand. Furthermore, this method can quantitatively evaluate the ligand's selectivity. By utilizing quantum calculations and statistical analysis of each signal, we estimated the metastable aggregation states. This enabled us to estimate the potential aggregation states of each signal group in solution at the single-molecule level. The estimated aggregation states revealed rare event aggregation states that differed from the predictions.

Significance of the research and Future perspective

Combining nucleic acid-targeted small-molecule drug discovery and single-molecule counting can create a powerful tool in drug discovery. This new nanotechnology can facilitate quantitative studies on the binding, selectivity, and hydrogen bonding modes between the base molecules and small-molecule ligands at the single-molecule level without using DNA or RNA.



Quantitative evaluation of molecular interactions with state identification

Patent JP7329806, JP6971499, JP6985687, JP6719773, JP662103

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Keyword single-molecule counting, single-molecule science, nanogap, ligand, DNA