Selectivity of Protein Interactions Stimulated by Terahertz Signals

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Abstract

It has been established that Terahertz (THz) band signals can interact with biomolecules through resonant modes. Specifically, of interest here, protein activation. Our research goal is to show how directing the mechanical signaling inside protein molecules using THz signals can control changes in their structure and activate associated biochemical and biomechanical events. To establish that, we formulate a selectivity metric that quantifies the system performance and captures the capability of the nanoantenna to induce a conformational change in the desired protein molecule/population. The metric provides a score between −1 and 1 that indicates the degree of control we have over the system to achieve targeted protein interactions.

System Model

- Our system is composed of a nanoantenna transmitter and a protein receiver, as shown in Fig. 1.
- The transmission from the nanoantenna impinges EM waves on the protein population to target distinct vibrational modes and trigger a functional conformational change.
- The application of an external EM field to biological entities induces a relative redistribution of internal charges within the molecule with respect to the field lines.
- According to structural mechanics, if an external harmonic excitation has a frequency which matches one of the natural frequencies of the system, then resonance occurs, and the vibrational amplitude of the structure increases.
- When two oscillators are in resonance, two important characteristics hold: high energy efficiency and rapidity.
- By triggering the protein to adopt a folding behavior, a series of downstream events occur within the cell, enabling a functional response.

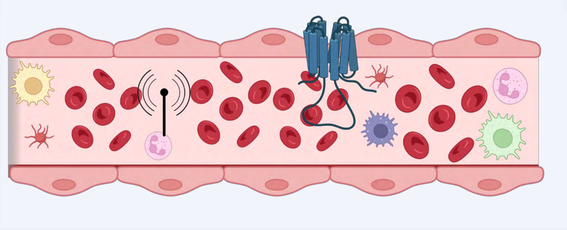

Fig.1. System Model. The figure was created using BioRender.com.

Selectivity

- Selectivity Metric

- To study and evaluate the impact of the nanoantenna-protein interaction, we formulate a selectivity metric to show the capability of the presented system in discriminating the desired response from adjacent inputs.
- The developed metric measures the capability of the nanoantenna to stimulate the desired protein molecule/population to change its conformation without impacting the conformation of other proteins in the system.
- Such a metric provides a powerful tool as it gives a single value to quantitatively decide whether or not an interaction is sufficiently controllable.
- It also dictates the frequency the nanoantenna must be tuned to, which could be the resonant frequency, or a frequency close to it.
- We propose a selectivity metric given by

$$S(p_{F,d}, p_{F,ud}) = \frac{p_{F,d} - p_{F,ud}}{\max(p_{F,d}, p_{F,ud})},$$

- where $p_{F,d}$ is the probability of the folded state of the desired protein, while $p_{F,ud}$ is the probability of the folded state of the undesired protein.

- Selectivity Metric Properties

- $S(p_{F,d}, p_{F,un})$ is bounded, such that $-1 \leq S(p_{F,d}, p_{F,un}) \leq 1$.
- $S(p_{F,d}, p_{F,un})$ has a ***maximum value*** of 1 indicating that **both** the targeted protein was selected **and** the untargeted protein was not selected.
- $S(p_{F,d}, p_{F,un})$ has a ***minimum value*** of -1 indicating that **both** the untargeted protein was selected **and** the targeted protein was not selected.
- $S(p_{F,d}, p_{F,un})$ is continuous and an increasing function of $p_{F,d}$ when $p_{F,un}$ is fixed.

- Optimal System Design Parameters

- To trigger a specific protein population to activate the desired system response, we must ensure that the system achieves maximum selectivity.
- We can notice that the nanoantenna frequency, ω, and the nanoantenna force, f_o, are the only system parameters that we can control.
- We formulate a joint optimization problem to maximize the selectivity with respect to those parameters.

$$\begin{aligned} \underset{f_o,\omega}{\text{maximize}} \quad & S(p_{F,d}, p_{F,ud}) \\ \text{subject to} \quad & 0 \leq p_{F,d} \leq 1 \\ & 0 \leq p_{F,ud} \leq 1 \end{aligned}$$

Numerical Results

- We consider two protein molecules in the vicinity of one other to mimic an intra-body environment.
- Those proteins are rhodopsin and bacteriorhodopsin.
- Rhodopsin is the light-activated G-protein coupled receptor involved in vision.
- Bacteriorhodopsin is a light-driven proton pump that is utilized to drive the synthesis of adenine triphosphate (ATP).
- We consider a population of size n=1000.
- The properties of the protein are found in Table 1.

Table 1: Protein Experimental Values

Protein	Frequency (THz)	Stiffness (N/m)	Mass (kg)
Rhodopsin	1.36	3	1.62×10^{-24}
Bacteriorhodopsin	1.13	1.9	1.48×10^{-24}

Fig. 2 presents the expected number of proteins in the folded state, $E[p_F] = np_F$, versus the nanoantenna force for both rhodopsin and bacteriorhodopsin, respectively. The driving frequency is fixed to the resonant frequency of rhodopsin (i.e. 1.36 THz).

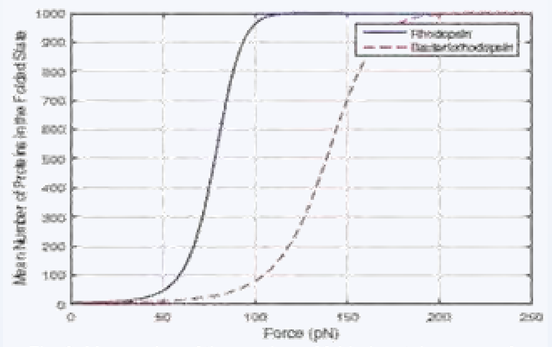

Fig. 2. Mean value of the number of folded proteins versus force.

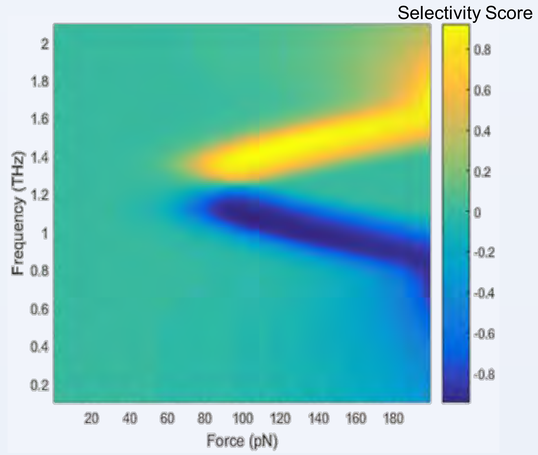

Fig. 3. Pseudo-color plot showing the optimal force and frequency for targeting rhodopsin in the presence of bacteriorhodopsin.

Fig. 3 and 4 present a pseudo-color plot indicating the optimal force and frequency values that must be used when targeting the desired protein population in the presence of the undesired population. The color map demonstrates the intensity of the selectivity value.

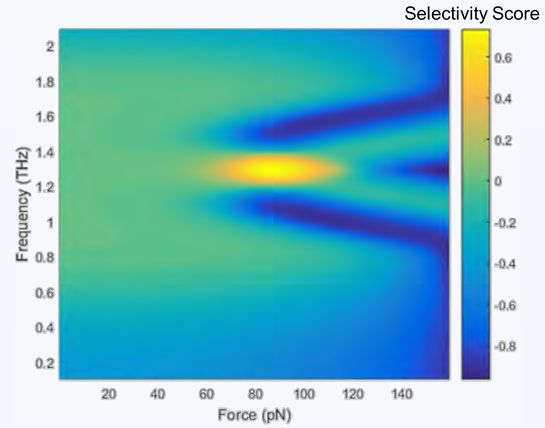

Fig. 4. Plot showing the optimal force and frequency for targeting protein population 2 (ω = 1.3 THz) in the presence of population 1 (ω = 1.1 THz) and population 3 (ω = 1.5 THz).

Conclusions

The selectivity analysis lays the grounds for directed signaling, where desired proteins are driven towards a conformation that evokes a particular response. It also paves the path toward a plethora of applications in the medical field. On the one hand, it allows us to recognize mechanisms for selectively targeting proteins involved in carcinogenesis, a procedure that can be utilized for the early diagnosis of cancer cells. On the other hand, it could further the understanding of neurodegenerative diseases, which are primarily caused due to the aggregation of misfolded proteins. Finally, the presented work has broad implications for improving our understanding of proteins, protein engineering and better drug design.

References

[1] R. Balu et al. Terahertz spectroscopy of bacteriorhodopsin and rhodopsin: Similarities and differences. Biophysical journal, 94(8):3217-3226, 2008.

[2] K. T. Sapra, P. S.-H. Park, K. Palczewski, and D. J. Muller. Mechanical Properties of Bovine Rhodopsin and Bacteriorhodopsin: Possible Roles in Folding and Function. Langmuir, 24(4):1330-1337, 2008.