Physical theory of nucleo-cytoplasmic transport

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Short Abstract — **Proper functioning of all eukaryotic cells depends critically on the transport of macromolecules between the cell nucleus and the cytoplasm, which proceeds through the the nuclear pore complexes (NPC). Several characteristics of the NPC transport make it distinct from other common forms of biological transport. In addition to being central biological question, the transport through the NPC poses challenging physical problems. We develop a physical theory of transport through the NPC that explains its functional properties in terms of its structure. In particular, we propose a novel mechanism of selectivity enhancement that does not require input of metabolic energy. The theory can be extended to other signaling mechanisms, and suggests strategies for creation of artificial nano-molecular sorting devices.**

I. Background

Proper functioning of all eukaryotic cells depends critically on the transport of macromolecules between the cell nucleus and the cytoplasm, which proceeds through the the nuclear pore complexes (NPC). This transport is mediated by transport proteins that bind their cargo in the nucleus (or the cytoplasm), and transport it through the NPC [1,2]. In milliseconds time [1], the NPCs are able to selectively transmit - over the background of vast amount of non-specifically interacting macromolecules - only the cargoes that are bound to the transport proteins.

Remarkably, this fast and highly selective filtering does not require an active input of metabolic energy, and occurs purely by diffusion. Moreover, unlike common 'lock and key' transport gating mechanisms, the NPC is always in the 'open' state, known as 'virtual gating' [2].

Internal space of the pore and large parts of its nulclear and cytoplasmic surfaces, are filled by unfolded, flexible poly-peptide chains that create the permeability barrier[2]. A crucial component of the selective NPC transport is the transient binding of the transport proteins to this unfolded filaments[1]. Strikingly, the NPCs have been shown to function even when a large fraction of the material comprising the pore is deleted [1].

We have developed a physical theory of transport through the nuclear pore complex, which rigorously models the diffusion of the transport proteins through the meshwork of fluctuating filaments, controlled by the transient binding to the filaments [3].

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II. Results of the model

Using analytical theory, and computer simulations, we have modeled the transport through the NPC as diffusion in an effective potential, determined by the interactions of the transport factors with the meshwork of fluctuating filaments inside the pore.

The first question we address is how binding to the pore can enhance the transport efficiency. The theory shows that the macromolecules that do not interact with the pore have a very low probability of traversing it. By contrast, binding of the transport proteins to the pore *increases* the *time* they spend inside the pore, but also *increases* the *probability* to traverse it [3].

Limitations of space inside the pore lead to the competition between translocating cargoes, and at too high binding affinities, the pore becomes jammed. This leads to a preferential binding affinity that optimizes the transport, and provides the mechanism for the selectivity [3].

However, the predicted and measured optimal binding affinity is relatively low- of the order of 10-20 *kT*. The NPC, however, has to filter out non-specifically binding macromolecules whose binding affinity sometimes lies in the range of several *kT* from the optimal one. We have proposed a novel selectivity mechanism, and shown that in the case of *direct* competition between the cognate transport proteins, and non-specific cargoes, the selectivity increases far beyond the differences in the equilibrium binding affinities, and the non-specific cargoes are essentially filtered out [3].

Finally, we have shown how the flexibility of the filaments makes the transport relatively insensitive to their total number. Due to the thermal fluctuations of flexible filaments, the transport proteins can diffuse while still attached to a filament, and transfer to the next one. This makes the transport insensitive to the total number of filaments as long as the regions of their fluctuations overlap [3].

The proposed mechanisms of selectivity apply to other modes of biological signaling, e.g. transport through narrow channels, and cascades of enzymatic reactions, and suggest strategies for creation of artificial molecular sorting devices.

References

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