Selective transport through nano-channels: from nucleo-cytoplasmic exchange to bio-sensors

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Short Abstract — **Nuclear Pore Complex (NPC) is a multi-protein cellular machine that gates the transport between the cell nucleus and the cytoplasm. NPC's are able to selectively transport hundreds of molecules per second in both directions, without a direct input of metabolic energy and without large scale transitions of the cnahhel from an 'open' to a 'closed' state. The transport selectivity is based not on high-affinity 'lock-and-key' interactions of the transported molecules with the channel but rather on a low-affinity transient binding of the transport factors that shuttle cargoes through the NPC. Despite extensive experimental and theoretical research, selectivity of the NPC is still not fully understood. We propose a model of the NPC selectivity that takes into account only the basic properties of the stochastic kinetics of transport through narrow channels. This minimal model provides insights into how the transient binding of the transport factors and their confinement in the limited space within the NPC combine to provide selective transport, even in the presence of large amounts of competing molecular species that may interact non-specifically with the NPC. Predictions of the theory have lead to the creation of an artificial nano-filter that mimics the selectivity of the NPC and confirms the theoretical predictions. Finally, I will discuss how the minimal model is applicable to the transport through a large class of biological and artificial selective nano-channels.**

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]. 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' [1].

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[1]. A crucial component of the selective NPC transport is the transient binding of the transport proteins to this unfolded filaments[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 [1,2].

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 [1,2]. 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 [1,2].

However the NPC, has to filter out non-specifically binding macromolecules whose binding affinity sometimes lies in the range of only 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 [1,3]. The theory explains the function of the selective nano-channels that are able to discriminate between single-mismatched DNA segments on the base of the binding energy differences [2]. The theoretical predictions have been employed in the creation of an artificial nano-sorting device that mimics the selectivity of the NPC [3]

The proposed selectivity mechanism 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.

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