

Sensing and remembering IFNs concentrations

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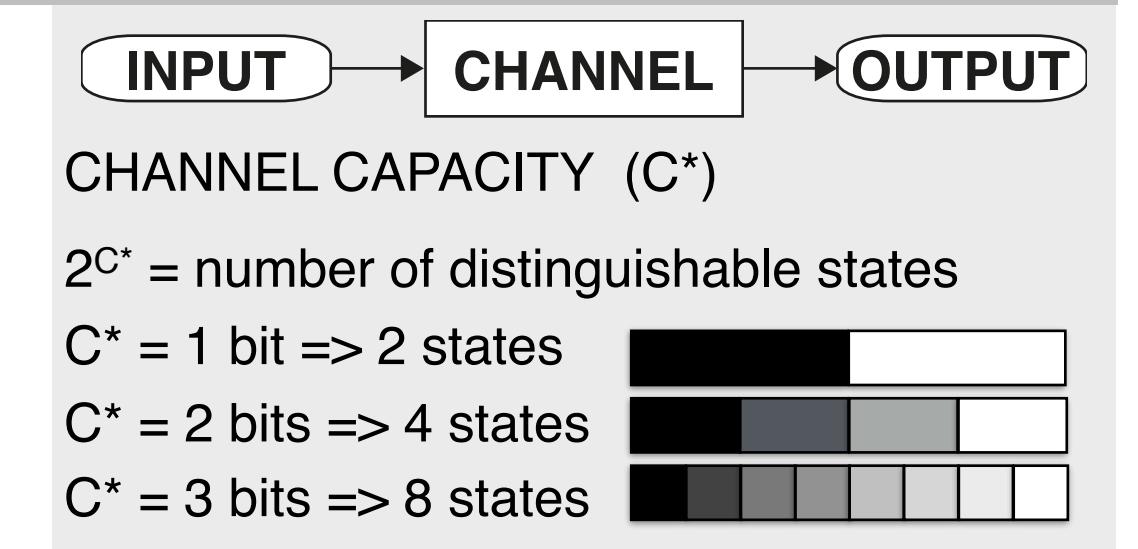
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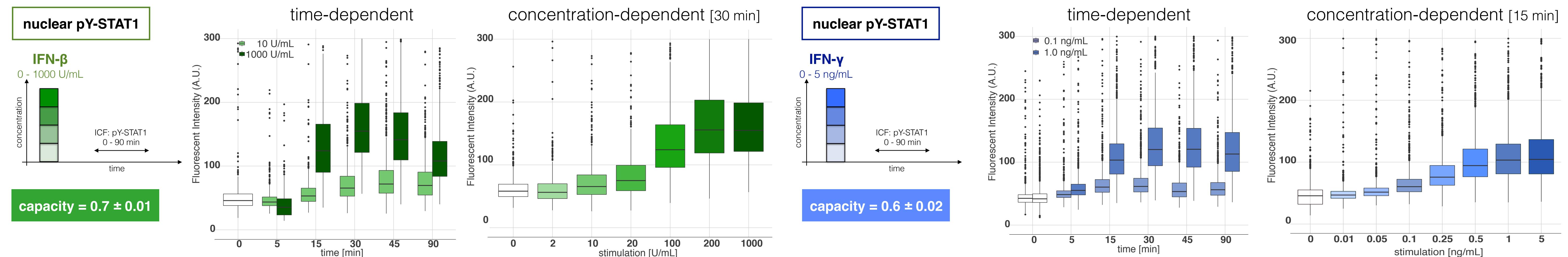
INTRODUCTION

Multiple different cell types of the immune system communicate with each other by releasing hundreds types of molecules such as cytokines, chemokines, or growth factors. Aberrations in signalling processes often have detrimental consequences and, therefore, reliable cell-to-cell communication appears to be essential for organism's survival. Yet, when exposed to the same stimulus, activities of signaling pathways can vary dramatically from cell to cell. This rises the question about fidelity of biochemical signalling. Specifically, **to what extent can an external stimulus control responses of individual cells?**

In response to IFN- β and IFN- γ heterodimers pY-STAT1/pY-STAT2 and homodimers pY-STAT1/pY-STAT1, respectively, enter the nucleus and induce transcription of several hundred genes, including STAT1 and IRF-1. We aimed to understand, to what extent the IFN signals can control protein levels of downstream genes in individual cells. Specifically, information theory has been deployed as an integrated measure of signaling accuracy, a term known as information capacity. Information capacity is expressed in bits, and broadly speaking, 2^C^* represents the maximal number of different ligand concentrations that a system can effectively resolve.

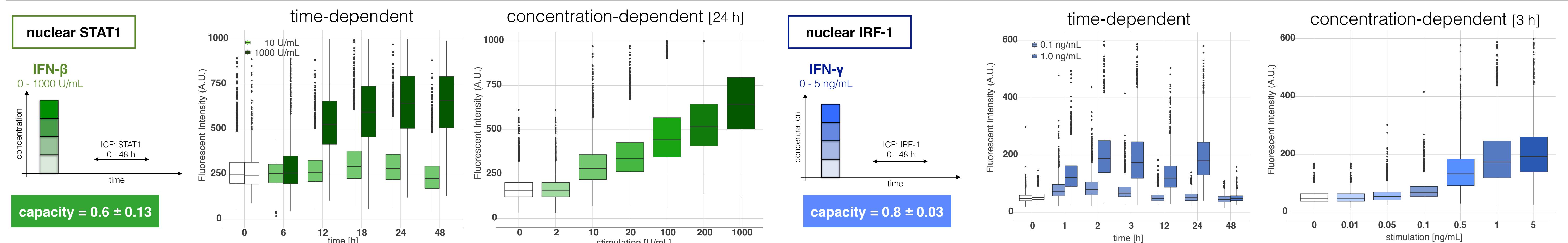


WHAT IS THE FIDELITY OF IFN SIGNALLING?



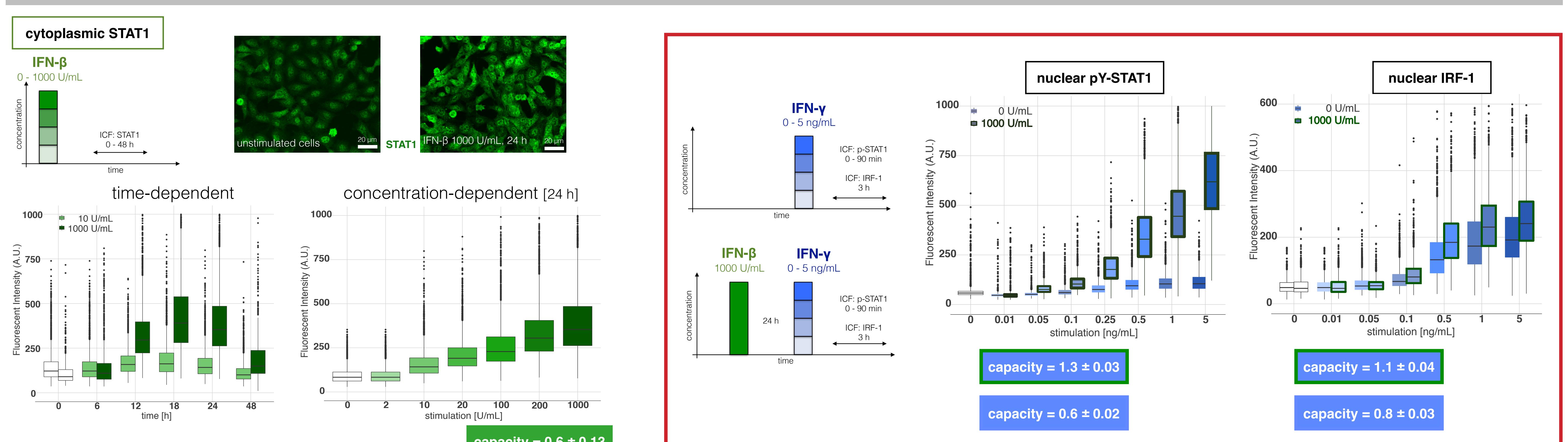
IFN signalling capacity is lower than 1 bit. This indicates that the downstream responses of individual cells cannot be fully controlled by IFN dose, i.e. some cells exposed to high doses IFNs can have the same levels of the downstream effector proteins as unstimulated cells. We have examined this prediction by measuring STAT1 and IRF-1 levels in individual cells.

HOW MUCH INFORMATION IS TRANSFERRED TO THE DOWNSTREAM EFFECTORS?



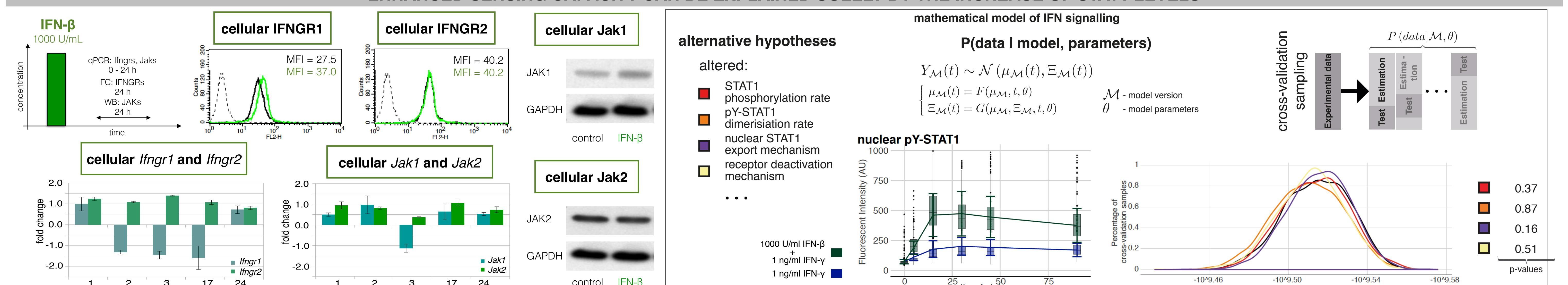
Information about IFNs concentrations contained in levels of the downstream signalling effectors is similar and even slightly higher than this contained in nuclear pY-STAT1 levels at 15 minutes upon stimulation. This seemingly paradoxical observation indicates that downstream responses depend not only on nuclear pY-STAT1 levels at a single time point but on other factors, including temporal profile of nuclear pY-STAT1, autocrine and paracrine signalling, as well as non-canonical signalling. Overall, however, the obtained values do not exceed 1 bit and some unstimulated cells have levels of downstream effectors as unstimulated cells. As high STAT1 levels persist for over 48 h after stimulation we interpret this as a memory of the system and examine its consequences for IFN signalling.

NON-TRANSCRIPTIONAL EFFECT OF MEMORY: ENHANCED SENSING FIDELITY



Exposure to IFNs increases both nuclear and cytoplasmic STAT1 levels that persists for at least 72 h. Increase in the cytoplasmic STAT1 level results in an enhanced sensing capacity for subsequent IFNs stimulation. This is an extension of the well known sensitisation phenomenon. Our experiments demonstrate that sensitisation not only makes cells respond to lower concentrations of IFNs but also increases the overall sensing fidelity. The enhanced sensing fidelity finds however only a limited effect in the expression levels of IRF1, rising the question how cells use the additional information.

ENHANCED SENSING CAPACITY CAN BE EXPLAINED SOLELY BY THE INCREASE OF STAT1 LEVELS



Experimental measurements of levels of the JAK1 and JAK2 kinases as well as IFNGR1/IFNGR2 receptor complexes suggests that the enhanced sensing fidelity is achieved solely by an increased STAT1 copy number. To verify this further, we have build a probabilistic model of IFN- γ signalling. The model allowed us to perform statistical test on whether the enhanced sensing results from other alterations in signalling kinetics. The model confirms that increased copy number is sufficient to achieve enhanced signalling fidelity.

SUMMARY

The measured information capacity of IFN sensing is surprisingly low. It is, in principle, insufficient to allow individual cells to distinguish between presence and absence of IFNs. Low capacity is reflected in the cell-to-cell variability of the downstream signalling i.e. some stimulated cells have levels of downstream signalling effectors as the unstimulated cells. Surprisingly, prior exposure to IFNs increases the information capacity for subsequent sensing to over 1 bit. Still, however, how cells achieve efficient cell-to-cell communication with such a low capacity remains to be determined.

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