Postgraduate student: **Dimitris Christodoulou**

Thesis Title:

Computational Modeling of the Dynamics of the IFNβ transcription mechanism through its Enhanceosome Assembly

Abstract:

In recent years, important findings regarding the human IFNβ gene expression have appeared in literature. Among them, the elucidation of the Enhanceosome Assembly process, which works in a stochastic manner and plays a crucial role in the transcription of the IFNβ gene, has been considered a great success. The activation of Interferon – β transcription is a highly ordered process, which involves many proteins that bind to the enhancer of the gene in a highly cooperative fashion. The assembled "Enhanceosome" serves as a switch, leading to the transcription of the IFNβ gene. If a cell does not have all the necessary proteins in abundance, it does not manage to turn the switch on and thus transcribe IFNβ. The stochasticity of the phenomenon is thus both intrinsic and extrinsic: the Enhanceosome assembly process is intrinsically stochastic, whilst each cell in a population seems to have a different concentration – regarding the main transcription factors contributing to the stochasticity of the system. Only a small fraction of cells (~20%-25%) manages to transcribe IFNβ initially. This percentage is almost doubled after a few hours, suggesting that the initially expressing cells induce their neighbor cells. The importance of this procedure is great, since IFNβ plays a very important role in the timing of the immune system's response, while it seems to have a certain – protective – role against cancer.

In this Master's thesis, we took the first steps towards creating a Systems Biology based computational model, able to capture the dynamics and function of the IFNβ transcription mechanism both in single-cell and population level, upon virus infection. The single-cell level model we developed is capable of simulating the IFNβ transcription, through the Enhanceosome Assembly mechanism. This model formed our basis, in order to move towards a useful and powerful population level computational model, able to capture not only the dynamics but also the stochasticity of the system, the auto and paracrine induction mechanisms between the cells and the effects they have in a population of interacting cells.

The single-cell level computational model was developed as a biomolecular/biochemical reactions kinetics model, and was trained by using available experimental data from the laboratory. Despite the limited amount of data used, the model simulates particularly well the observed phenomena. However, it is the population level computational model we developed – based on the single cell model – that stands out. A very important accomplishment is the ability of the population level model to predict the dynamic and stochastic behavior in a population of cells, in many different cases, managing to verify some of the most interesting hypotheses that have been only recently verified experimentally. It manages to do so although no parameter learning procedure has been applied specific to these cases. These results are very positive indications for the trustworthiness of both models and for their predictive capabilities. Our computational models are not only capable of reproducing the dynamic characteristics of the IFNβ transcription mechanism, but, of more importance, provide a tool for understanding and exploring the mechanisms behind

such complex dynamics, a tool for generating and testing new hypotheses in silico that can be then validated experimentally.

SUBJECT AREA: Systems Biology
KEYWORDS: IFNβ transcription, Enhanceosome Assembly, computational modeling, biochemical reaction kinetic networks, in-silico experiments, parameter estimation

Examining Committee

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