Functional Trade-offs in Allosteric Sensing

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***Short Abstract* — Cells use sensors to detect and measure changes in their environment. We used a quantitative approach to investigate the design principles of a generic allosteric sensor by defining a set of engineering-like characteristics. We calculated the characteristics using both analytical and numerical methods and determined the main trade-offs and relations between them to understand the constraints of this sensing mechanism. We found that high cooperativity requires high dynamic ranges and that cells can reduce intrinsic noise by increasing both the basal and saturation levels, amongst other results.**

***Keywords* — Allosteric sensors, MWC model, cellular sensing, engineering characteristics, noise.**

I. Background

CELLS can sense environmental changes by deploying allosteric molecular sensors, which are common in both eukaryotes and prokaryotes. Effective decision-making requires the cells to be able to convert graded inputs into discrete switch-like responses. The MWC model [1] describes how allosteric transitions generate such responses. It assumes sensors coexist in two conformational states with a strong bias towards one of them at equilibrium in the absence of ligand. Ligand binding favours the opposite state, such that adding the ligand disrupts the equilibrium towards the latter state, generating a sigmoidal response. The economy of the model lies in the variety of possible responses that depend on the tuning of only 3 parameters [1].

Our purpose is to determine the effectiveness of the design of a generic allosteric sensor under the MWC description, and thus gain a better understanding of how cells sense. We defined and computed a set of engineering-like characteristics [2-3] and analysed the trade-offs between these in both deterministic and stochastic frameworks.

II. Methods

Using equilibrium equations it is possible to derive the function of state, an input-output relation describing the proportion of sensor molecules in the active state. From it, and following Detwiler et al. [2], we derive the characteristics of the sensor, specifically, the dynamic range of responses (or amplitude), Hill number, local sensitivity, response time and, under a linear approximation, the cut-off frequency and transfer function. In addition, we derive the intrinsic noise from the stationary solution of the master equation [4]. We randomly sample the parameter space, calculating and comparing the characteristics for each set of parameters.

III. Results

For some purposes, a good allosteric switch should have, for example, high cooperativity and a fast response time or both small range and small intrinsic fluctuations at the threshold. However, we found that the system is constrained by its inherent design and there are regions of characteristic space that are inaccessible, i.e., optimising one characteristic may result in a less optimal response with regards to another.

Among some of the most important results related to trade-offs between characteristics, we found that: a high Hill number is accompanied by a high dynamic range, such that it is not possible to simultaneously have a high basal level of activity and a highly sigmoidal curve; the cut-off frequency (frequency of extrinsic fluctuations of the input that are filtered) seems to be well predicted by the response time; there is a positive correlation between the response time and the Hill number, especially for sensors with higher numbers of subunits (or binding sites); maximising the Hill number forces the intrinsic noise to an intermediate point within its interval of possible levels. Furthermore, we found that the solution of the master equation is approximated by a binomial distribution, resulting in maximal variance at the point where exactly 50% of the sensors are in each state. Increasing the basal level and moving the half saturation level away from the 50% point can thus globally reduce the intrinsic noise (but at the cost of reducing the Hill number).

This approach provides both quantitative and qualitative insights about the function and robustness of allosteric sensors. Understanding these characteristics is critical to the study of endogenous systems and the design of synthetic biology applications.

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