Setting parameters for biological models with ANIMO

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ANIMO (Analysis of Networks with Interactive MOdeling) is a software for modeling biological networks, such as e.g. signaling, metabolic or gene networks. An ANIMO model is essentially the sum of a network topology and a number of interaction parameters. The topology describes the interactions between biological entities in form of a graph, while the parameters determine the speed of occurrence of such interactions.

When a mismatch is observed between the behavior of an ANIMO model and experimental data, we want to update the model so that it explains the new data. In general, the topology of a model can be expanded with new (known or hypothetical) players, and enable it to match experimental data. However, the unrestrained addition of new parts to a model causes two problems: models can become too complex too fast, to the point of being intractable, and too many parts marked as "hypothetical" or "not known" make a model unrealistic. Even if changing the topology is normally the easier task, these problems push us to try a better parameter fit as a first step, and resort to modifying the model topology only as a last resource.

In this paper we show the support added in ANIMO to ease the task of expanding the knowledge on biological networks, concentrating in particular on the parameter settings.

1 Introduction

The investigation of biological processes relies on computational support on a daily basis. This happens not only because of the extremely large amount of data generated in the *"-omics" era*, but also because many processes are simply too complex to be understood by the human brain alone. For this reason, systems biology has become more and more important in the last several years.

A single biological network such as a signaling or gene network, may involve up to hundreds of different players. As it would be very difficult to understand the dynamic behavior of such networks just by looking at their static representations, many tools were built to help the biologists in that sense. ANIMO (Analysis of Networks with Interactive MOdeling) is one of such tools. Its primary objective is to let the expert biologists work directly on the formalization of their knowledge, supporting the generation of new insights on the studied processes. An ANIMO model is formed by two main parts: the network topology and the parameters. The topology describes which biological components are included in the

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model, and which are the interactions we want to represent. The parameters define the rate of occurrence of such interactions, which are described based on simplified kinetic formulae.

Proteins are normally expressed at different concentrations in different individuals of the same species, and yet the overall behavior of their biological networks does not differ significantly. This phenomenon has led to the notion that biological networks are inherently *robust*. In modeling terms, this means that most of the parameters of a model can vary inside a certain interval without influencing the qualitative behavior of the whole network. The interactive approach of ANIMO is based on the assumption of robustness, as our tool is mainly aimed at the development of network models with a focus on the topology. Ideally, the biologist can "play" with the topology of a network, working more towards matching the qualitative behavior of experimental data, rather than precisely reproducing it. However, it is not our intention to concentrate exclusively on the network topology: in many cases a better parameter choice can improve the behavior of a network more than the addition of new components. Indeed, making an unnecessarily complex model could reduce its usefulness both in terms of analysis performances and closeness to reality. The first problem is simply due to the complexity of a network, which would require more and more computational resources to be analysed[1]. Realism of network models is more related to their ultimate usefulness: a model that explains a particular behavior very well but contains many nodes marked as "unknown" has little applicability, as its connection with known processes is very loose. Therefore, it desirable that a better parameter set is regularly sought for during the design cycle of a complex biological network model. Some support for parameter choice was already provided in the first versions of ANIMO. We present here an extended set of tools aimed at achieving a closer fit between ANIMO models and experimental data. A guideline on how to use these tools to get the best results will also be presented as an ideal workflow. Thanks to the better awareness on parameter choice gained through this new extension of ANIMO, the biologists will be able to judge more easily which are the most promising topologies for a network, and thus drive the experimental research more efficiently.

2 ANIMO models

The starting point of ANIMO is the traditional static representation of biological networks, which can be easily drawn and managed in softwares like Cytoscape. Indeed, ANIMO was implemented as a plug-in to Cytoscape, with the aim of adding dynamics to the static representation of biological networks, and thus allow for analysis on the behavior of such networks. The user interface of ANIMO can be seen in Figure **??**: at the center is the Network panel, where the network model is represented in the familiar nodes-edges form used in the domain of biology. Models in ANIMO are *activity-based*, in the sense that nodes have their activity as main property, and interactions among nodes change the activity of their targets. The concept of activity is to be intended for example as a generic post-translational modification a molecule can undergo to change its function. In the case of a kinase, the phosphorylated state is usually interpreted as active. However, in the context of a gene network the activity of a node standing for a gene represents its current transcriptional status. A basic type of analysis that can be performed with ANIMO is the generation of a simulation run, which is presented to the user in the form of a graph (to the right). The activity graphs generated by ANIMO show the variation in activity of selected nodes over the course of the simulation run. In addition to that, a slider placed under each graph allows the user to color the nodes in the Network panel with colors indicating their activity level at any point during the course of the simulation: the Legend panel on the left links colors to activity.

[1] We also refer to the problem of *state space explosion*: when a model contains too many loosely coupled components, the set of its possible evolutions grows exponentially, to the point of making it impossible to apply some analysis techniques.

Of the two main components of an ANIMO model, only the topology is immediately visible to the user in the Network panel; the parameters are accessed by double clicking the arcs representing node-node interactions. The dialog window that is shown for an interaction contains the details of the abstract reaction kinetic describing the interaction, together with the current value of its parameter k (see Fig. **??**). The unique parameter associated to any interaction in ANIMO is used as a scale factor to make the modelled reaction occur faster or slower. We also provided the user with pre-set values for k, encouraging an initial qualitative assignment of reaction rates as "slow", "fast" and so forth. This approach is based on the assumption that, being biological networks inherently robust, the role of parameters should be perceived as somewhat secondary with respect to the definition of the interactions in the network. However, as is explained in [**?**], we still recommend to pay attention to parameter settings, especially for those parts of a network that tend to be more sensitive to parameter variations. Such parts are usually involved in feed-back or feed-forward loops, where the ratio between the involved parameters plays a determinant role with respect to the behavior of the subnetwork.

3 Tools for parameter synthesis in ANIMO

4 Suggested ANIMO workflow

5 Conclusions

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