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Simulation of signaling and regulatory networks in B. subtilis

B. subtilis is a Gram-positive bacterium commonly found in the soil. This bacterium has been studied extensively especially for the way it manages to induce itself to sporulate [1-4]. Sporulation, the creation of a spore is a last resort alternative a bacterium chooses to undertake when the resources in the environment are not compatible with maintaining a normal metabolism, especially when there is shortage of glucose, the input of cellular respiration.

In such condition the behaviour of an isogenic population of B.subtilis is not uniform. Some bacteria sporulate, some faster than others, some do not. This kind of behaviour is called bet hedging, and it is understood as a differentiation strategy which maximize the survival of the colony. In facts if the shortage of resources is long lasting, sporulation truly gives an advantage to individuals producing spores. Spores have very strong endurance and almost a frozen metabolism. These spores can reactivate their metabolism when the conditions turn to be more favourable. On the other hand if the shortage of resource is only temporary the process of producing a spore is not advantageous because it is energetically expensive and it is not reversible; from an early stage of sporulation any quick reappearance of resources would have not been exploited by the new born spore.

Sporulation is a quite complex process which entails the activity of more than 500 genes in a period of about 10 hours.

In this work we want to consider the phase which trigger the sporulation, a phase where the cell produces the protein σ^H, a sigma factor which plays a key role in triggering sporulation in B. subtilis.

Few parameters of this regulatory network are available in the literature, these are mostly the length of genes of proteins involved in the network. Statistical description about chemical reactions rates, spatial dynamics of molecules and synthesis production are almost totally unknown.

Estimation of order of magnitude of some parameters can be made by looking at the correspondent parameters in other species like E. choli.

We combine this comparison with a rigorous approach. We have developed a software which perform a stochastic simulation of the network which produces σ^H. We then identify unknown parameters of the network by comparing the output of our simulation with experimental data.

The available experimental data is in the form of time series of proteins KinA, Spo0A, Spo0B, Spo0F and sigmaH in arbitrary unit. The measurement has been performed in bacterial colonies by using green fluorescent protein (GFP). The measurement of each protein occurred in different experiments (one for protein) where a gene of GFP was insert in a suitable location to keep track of the production of the protein. The amount of luminescence is proportional to the amount of GFP present in the cell which can be assumed proportional to the rate of synthesis of the protein.

The simulation produces as output time series for each protein in a form homogeneous to the experimental data. We compare the two time series with the root square mean error. We use evolutionary strategies [5] to perform a black box optimization in order to find the parameters which minimize this error.

In our talk we are going to discuss the results we obtained and we compare them with the present literature.

References

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