A systems biology approach to the functional screening of genomes

Chiarugi D (1), Degano P (2), Marangoni R (2)

(1) Department of Mathematics and Informatics, University of Siena, Siena.
(2) Department of Informatics, University of Pisa, Pisa.

Motivation

Comparative genomics usually manages the functional aspects of genomes, simply by the comparison of gene-by-gene functions. Following this point of view Mushegian and Koonin (Mushegian A.R. and Koonin E.V. "A minimal gene set for cellular life derived by comparison of complete bacterial genomes." Proceedings of National Academy of Science USA, 93:10268-10273, 1996) proposed a hypothetical minimal genome, obtained by eliminating duplicate or apparently functionally identical genes from the genomes of very simple contemporary bacteria, with the aim to find a possible very ancestor genome. The Authors were unable to answer the fundamental question: is, such a hypothetical organism, able to live? We performed a dynamic simulation of the metabolic activities of this hypothetical organism in order to assess whether it is at least able to live virtually, or, in other words, if the dynamic simulation of a virtual cell with this genome will lead to some equilibrium state.

Methods

We specified all the enzymes encoded by the proposed gene set and wrote down all the metabolic reactions which could take place in that hypothetical cell. We represented all metabolites, enzymes and reactions using the enhanced pi-calculus formal language. We developed a simulator written in JAVA, and we used this simulator to test whether the formalized cell is able to reach an equilibrium state or not. Further details on the formalization method and procedure can be found in: Chiarugi D., Curti M., Degano P., Marangoni R., "ViCe: a Virtual Cell", Lect. Notes Comp. Sc., 3082: 207-220, 2005.

Contact email: marangon@di.unipi.it

Supplementary informations

Our simulation clearly shows that the minimal gene set (MGS) genome proposed by Mushegian and Koonin does not express an organism able to live. We proceeded by progressive functional replacements in order to find a genome composition able to give rise to an equilibrium. Among the original 256 genes in MGS, 75 of them have been ruled out because they are functionally duplicated. For example, some MGS genes encoding for proteins involved in the uptake of extracellular metabolites, as in the case of the uptake and phosphorilation of glucose. In this case we choose to maintain only the PTS system, because it is characteristic of Bacteria. Moreover, we needed to add 6 genes not present in MGS and coding for enzymes involved in critical nodes of the metabolic network, as in the case of ribulose-5-phosphate isomerase which leads to the synthesis of D-ribose-5-phosphate, a not dispensable metabolite for nucleotide synthesis. After these modifications, the 187-genes resulting genome is able to give rise to a virtual living organism. Moreover, the distribution of the concentrations of virtual metabolites, once the equilibrium is reached, is very similar to that experimentally measured in bacteria.