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The landscape and flux theory for biological networks

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We developed a landscape and flux theory for biological networks. We identify the two global driving forces for biological network. One is the gradient of the underlying landscape and the other is from the curl flux. The underlying landscape is linked to the steady state probability distribution and provides a global picture for describing the networks. We found that the landscape can be used to quantify the global stability and robustness of the system. The non-zero flux breaks the detailed balance and therefore gives a quantitative measure of how far away the system is from the equilibrium state, reflecting the degree of the energy input to the system. Our decomposition of the driving forces of the complex systems into landscape gradient and curl flux establishes the link between the dynamics and the underlying thermodynamic non-equilibrium natures. We applied our theory to several biological systems such as cell cycle, stem cell differentiation and reprograming, cancer. For cell cycle oscillations, we found the underlying landscape has a Mexican hat ring shape topology. The height of the center island Mexican hat determines the global stability. The landscape gradient attracts the system down to the oscillation ring. The curl flux is the driving force for coherent oscillation on the ring. Along the cell cycle oscillation ring there are a few basins of attractions which can be identified and quantitatively described as the G1, SG2 and M phases. The barriers between these local basins become the check points of the cell cycle. The speed of the cycle is determined by the flux originated from nutrition and the barriers at the check points between the basins. Global sensitivity analysis on these two global factors gives us information on key genes and regulations determining the function. From this, new anti-cancer strategy can be designed aiming at reducing the speed of the cell cycle. We also applied our landscape and flux theory to stem cell differentiation and development. We quantify the Waddington landscape for differentiation and identify the stem cell and differentiation basins of attractions. We quantify the differentiation and reprograming path for a human embryonic stem cell network and identify the key genes and regulations. We also constructed a cancer gene network and quantify the landscape for cancer where we identify the normal, cancer and apoptosis basins of attractions. We quantify the major pathways of cancerization and identify the key genes and regulations responsible.

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Artificial RNA Synthesis Can Be Facilitated by a 5S rRNA Cassertte

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Small Artificial RNAs are being used in a variety of applications. Synthesis of such RNAs in large quantity by traditional means can be prohibitively expensive. An alternative approach has been devised in which the RNA of interest is embedded in a gene encoding a 5S ribosomal RNA variant that is very stable but is not incorporated into ribosomes. It is shown that a large variety of variants can be stabilized by inclusion in this cassette when expressed in *Eschericia coli*. The casette carrying the artificial RNA is expressed using the usual ribosomal RNA promoters and the product RNA accumulates in numbers comparable to those of wildtype 5S rRNA, which in the range of 50-100,000 copies per cell . The artificial RNA product degrades slowly allowing adequatetime for harvesting. Depending on the application, in some cases the RNA can be used without removal from the casette. If it is necessary to remove the artificial RNA this can be accomplished using specifically targeted DNAzymes, which can subsequently be recycled. Transcripsonal studies have shown that the only effect of the presence of the artificial RNA is an increase in the expression of genes involved in nucleotide degradation.

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