Humans SNPs, System Robustness, and Complex Disease Traits

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A key feature of complex adaptive systems is a balance between the appearance of complexity through the accumulation of change, and robustness of system function with respect to perturbation of the system components. On the one hand, any system that is overly sensitive to small changes will be short lived. On the other, excessive robustness damps the adaptive process. The severity of the robustness requirement depends on the effective population size of the system: At one extreme, ecosystems and economies have an effective population size of one, and must be relatively robust. At the other, many simple organisms, such as bacteria, have very large population sizes, and versions of the system will survive even if many individual instances fail. Humans have an intermediate effective population size, and so may be expected to have an intermediate level of robustness. Recent advances in our understanding of the link between human genetic change, biological macromolecules, and intra and extra cellular networks make this the first complex system where a detailed analysis of robustness mechanisms is becoming possible. An in-depth understanding of robustness in the human system may be expected to provide a general framework for robustness in all complex systems. In earlier work (1), we described a protein structure level model of the mechanisms by which the most common mechanism of genetic change, single nucleotide polymorphisms (SNPs), disrupt system function, and hence cause disease. A surprising finding was that few of the SNPs which significantly degrade performance at the protein molecule level have a clinical impact on human health. Examination of a set of these cases now shows how the larger scale system is robust with respect to component defects. We find the robustness arises through a variety of mechanisms. Some, such as simple feedback loops and component redundancy, are familiar from system engineering. Others, such as the use of 'fuzzy switches' in which control is distributed over multiple connections in the network, are novel. In this talk, I will survey the classes of robustness from a system perspective, and relate them to the 'complex trait' mechanisms by which susceptibility to disease is determined. I will also examine the extent to which the spontaneous emergence of robustness is a consequence of the properties of the adaptive landscape provided by protein based systems.

1. Z.Wang & J.Moult, 'SNPs, Protein Structure and Disease',
Human Mutation **17** 263-270 2001