Title : **The complexity of genotype-phenotype maps and its consequences for evolution**

Author : **Peter schuster**

Genotype-phenotype mappings are indispensable for a comprehensive understanding of evolutionary optimization. At the current state of the art only one example of a genotype-phenotype map is sufficiently well known in order to use it as a basis for modeling evolution: The sequence-structure map of RNA molecules, which can be investigated also experimentally, for example through the evolutionary design of RNA aptamers using the SELEX technique. Several evolutionarily relevant features of this mapping from sequence space into a space of structures, representing the phenotypes in RNA evolution experiments, have been discovered in the past: (i) High degree of neutrality leading to connected neutral networks spanning whole sequence space, (ii) shape space covering predicting that each common RNA structure can be reached from (almost) everywhere in sequence space through a fairly small number of point mutations, and (iii) the intersection theorem, which states that there exists at least one sequence for any arbitrarily chosen pair of structures that can fold into both._Modeling evolutionary optimization by computer simulation of replication, mutation, and selection of RNA molecules in a flow reactor revealed several characteristic features, among them: (i) The optimization process occurs in steps rather than continuously because fast adaptive phases are interrupted by long quasi-stationary epochs of neutral evolution, (ii) the evolution of a population in the stationary epochs corresponds to a diffusion process on a neutral network, and (iii) the exploration of sequence space by replication and mutation can be interpreted as a kind of primitive learning at the population level. This learning process has many features in common with the foraging strategies of ant colonies._The simple scenario assigning one structure to a given sequence becomes more realistic and more complex through considering suboptimal structures and explicit folding kinetics of RNA molecules. Comparing the set of suboptimal structures with the set of structures in the one-error neighborhood of a neutral network, called the shadow, allows for modeling the evolution of Boltzmann ensembles at different temperatures. Interaction between RNA molecules through cofolding provides another dimension of higher complexity within the RNA model. Several examples of multi-conformational RNA molecules will be presented. Such molecules have been designed and occur also in nature where they have important regulatory properties in molecular genetics.