Abstract Submitted
for the MAR16 Meeting of
The American Physical Society

**Molecular Cooperativity Governs Diverse and Monoallelic Olfactory Receptor Expression**[1] JIANHUA XING, XIAOJUN TIAN, University of Pittsburgh, HANG ZHANG, Virginia Polytechnic Institute and State University, JENS SANNERUD, Brown University — Multiple-objective optimization is common in biological systems. In the mammalian olfactory system, each sensory neuron stochastically expresses only one out of up to thousands of olfactory receptor (OR) gene alleles; at organism level the types of expressed ORs need to be maximized. The molecular mechanism of this Nobel-Prize winning puzzle remains unresolved after decades of extensive studies. Existing models focus only on monoallele activation, and cannot explain recent observations in mutants, especially the reduced global diversity of expressed ORs in G9a/GLP knockouts. In this work we integrated existing information on OR expression, and proposed an evolutionarily optimized three-layer regulation mechanism, which includes zonal segregation, epigenetic and enhancer competition coupled to a negative feedback loop. This model not only recapitulates monoallelic OR expression, but also elucidates how the olfactory system maximizes and maintains the diversity of OR expression. The model is validated by several experimental results, and particularly underscores cooperativity and synergy as a general design principle of multi-objective optimization in biology.

[1]The work is supported by the NIGMS/DMS Mathematical Biology program

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Date submitted: 02 Nov 2015 Electronic form version 1.4