The Universal Sequence of Nested Canalizing Functions: Change of variables, symmetries, and direct impact on the phase space of a Boolean network

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The special class of Boolean functions $f : \mathbb{F}_2^n \to \mathbb{F}_2$ known as *nested canalizing functions (NCF)* has a long history, where mathematics, combinatorics, computer science, and theoretical/experimental systems biology are intertwined. We show that all NCFs form one universal sequence as a direct limit of the finite sets of NCFs in n variables (for $n \geq 2$). The most important symmetries of Boolean functions from a biological viewpoint are, arguably, those that stem from a *change of variables*: that is, a permutation of the input variables together with the negations of a subset of these variables. These symmetries represent the allotment of the same (or exactly opposite) roles to the genes in a gene regulatory network (GRN) in a different order, and are controlled by the *signed symmetric group* $S(2, n)$, where n is the number of variables (genes). Most importantly, $S(2, n)$ acts faithfully and transitively on the NCFs of a given *Hamming weight*, which also determines the *layering type* and *canalizing value* for this orbit (as defined by Li, Adeyeye, Murrugarra, Aguilar, and Laubenbacher 2013). Hence, we can generate all NCFs from "seed functions" and symmetries. We find that when the change of variables is performed simultaneously—but in opposite directions—on the input and output variables of a GRN update function from $\mathbb{F}_2^n$ to $\mathbb{F}_2^n$, the shape of the phase space remains invariant. Finally, we show that the largest functional-digraph automorphism groups attained by phase spaces of GRNs on n genes are S_N, S_{N-1}, $C_2 \times S_{N-2}$, and S_{N-2}, where $N = 2^n$, S_m denotes the symmetric group on m letters, and C_2 is the cyclic group of order two. If we require that all n Boolean functions of the GRN be NCFs, then the largest automorphism group is S_{N-2}. Relatively low symmetries were experimentally shown to be related to higher stability in our previous work.