Bounds on the Average Sensitivity of Nested Canalizing Functions

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Abstract

Nested canalizing Boolean functions (NCF) play an important role in biologically motivated regulatory networks and in signal processing, in particular describing stack filters. It has been conjectured that NCFs have a stabilizing effect on the network dynamics. It is well known that the average sensitivity plays a central role for the stability of (random) Boolean networks. Here we provide a tight upper bound on the average sensitivity of NCFs as a function of the number of relevant input variables. As conjectured in literature this bound is smaller than $\frac{4}{3}$. This shows that a large number of functions appearing in biological networks belong to a class that has low average sensitivity, which is even close to a tight lower bound.

Introduction

Boolean networks play an important role in modeling and understanding signal transduction and regulatory networks. Boolean networks have been widely studied under different points of view, e.g. [1–3]. One line of research focuses on the dynamical stability of randomly created networks. For example, random Boolean networks tend to be unstable, if the functions are chosen from the set of all Boolean functions with average number of variables (average in-degree) larger than two [4]. This can be attributed to the fact that the expected average sensitivity of random Boolean functions with an in-degree $\geq 2$ is larger than one. The expected average sensitivity is an appropriate measure for the stability of random Boolean networks [5,6].

If only functions from certain classes are chosen, stable behavior can be achieved for higher in-degrees. For instance, canalizing and nested canalizing functions, introduced in [7,8], have been conjectured [9] to have a stabilizing effect on network dynamics. In [10] it has been shown that Boolean networks can be stable, even if the average in-degree is high. Interestingly, studies of regulatory network models in Biology have shown that a large number of their functions are canalizing [11–16]. Canalizing functions are also important for the construction of stack filters used in signal processing [17].

A Boolean function $f(x_1, \ldots, x_n)$ is canalizing in variable $x_i$, if $f$ is constant as long as $x_i$ is set to its canalizing value. Nested canalizing functions are canalizing functions, whose restriction to the non-canalizing value is again a canalizing function and so on (a precise definition is given later). In this paper we analyze nested canalizing functions (NCFs), in particular their average sensitivities. The notion of sensitivity was first introduced by Cook et al. [18]. It was applied later to Boolean functions [19] and can be viewed as a measure of the impact of a permutation of the input variables on the output of the function. The average sensitivity was investigated in [20] in the context of monotone Boolean functions. An upper bound for locally monotone functions was presented in [15]. Here we give a tight upper bound on the average sensitivity of NCFs. Our result shows that the average sensitivity of NCFs is always smaller than $\frac{4}{3}$ as conjectured in [21]. We further provide a recursive expression of the average sensitivity and the zero Fourier coefficient of a NCF. Finally we discuss and compare our new bounds to bounds in literature.

Our main tool is the Fourier analysis [22,23] of Boolean functions, which is introduced in Section Notation, Basic Definitions and Fourier Analysis of Boolean Functions, where we also address further concepts needed. In Section Nested Canalizing Functions spectral properties of canalizing and NCFs are broached. Additionally we discuss functions, in which all variables are most dominant, as they turn out to minimize the average sensitivity. In Section Average Sensitivity new bounds on the average sensitivity are presented based on a recursive expression of the average sensitivity of NCFs. We conclude with a discussion of the results and some final remarks.

Methods

Notation, Basic Definitions and Fourier Analysis of Boolean Functions

A Boolean function (BF) $f \in \mathcal{F}_n = \{ f : \Omega^n \rightarrow \{0,1\} \}$ with $\Omega = \{ -1, +1 \}$ maps n-ary input tuples to a binary output. Note that we choose the $\{ -1, +1 \}$-representation of the Boolean states...
instead of the \{0,1\}-representation, since it will turn out to be advantageous as it simplifies our calculations in the Fourier domain. However, our results apply for all binary alphabets \(\Omega\). 

In general not all input variables have an impact on the output, i.e., are relevant. 

**Definition 1** [21] A variable \(i\) is relevant to a BF \(f\), if there exists an \(x_0\in\Omega^n\) such that 
\[
f(x) \neq f(x \oplus e_i),
\]
where \(x \oplus e_i\) is the vector obtained from \(x\) by flipping its \(i\)-th entry.

Further we define \(\text{rel}(f) \subseteq [n] = \{1,2,\ldots,n\}\) as the set containing all relevant variables of \(f\). 

**Fourier analysis of boolean functions.** In this section we recall basic concepts of Fourier analysis of BFs and some results from [13] concerning restrictions of BFs. Let \(X = (X_1,X_2,\ldots,X_n)\) be a random variable uniformly distributed on \(\Omega^n\), i.e., 
\[
\Pr[X=x] = \frac{1}{2^n},
\]
For \(U \subseteq [n]\) we define the basis functions \(\chi_U(x)\) by 
\[
\chi_U(x) = \begin{cases} 
\prod_{i \in U} x_i, & \text{if } U \neq \emptyset \\
1, & \text{if } U = \emptyset.
\end{cases}
\]
(1) 

Note that for \(A \subseteq U\) and \(A = U \setminus A\), 
\[
\chi_U(x) = \chi_A(x) \chi_{A^C}(x),
\]
which follows directly from the definition of \(\chi_U\) (Eq. (1)). 

Any BF \(f \in \mathcal{F}_n\) can be represented by its Fourier-expansion [22,23], i.e., 
\[
f(x) = \sum_{U \subseteq [n]} \hat{f}(U) \chi_U(x),
\]
where \(\hat{f}(U)\) are the Fourier coefficients, given by 
\[
\hat{f}(U) = 2^{-n} \sum_x f(x) \chi_U(x).
\]
(3) 

**Example 1** Table 1 and Table 2 contain the truth-table representation and the polynomial representation, i.e., Eq. (2), of AND, OR, and XOR.

**Remark 1** The polynomial representation in the previous example is different to the one used in [21], where the variables \(x_i\) are defined over \(\mathbb{GF}(2)\), i.e., \(\Omega = \{0,1\}\), where addition (\(\oplus\)) and multiplication are defined modulo 2. In this case, the AND function becomes \(x_1x_2\), the OR function is given by \(x_1 \oplus x_2 \oplus x_1x_2\) and XOR by \(x_1 \oplus x_2\).

**Restrictions of boolean functions.** We call a function \(f^{(i)} \in \mathcal{F}_n\) a restriction of \(f\), if it is obtained by setting the \(i\)-th input variable of \(f\) to some constant \(a_i\in\{-1,1\}\). Every BF can be decomposed in two unique restricted functions for each relevant variable, as stated by the following proposition:

**Proposition 1** For any \(f \in \mathcal{F}_n\) and each \(i \in [n]\) there exist unique functions \(f^{(i)}\), \(f^{(i)\neg}\) \(\in \mathcal{F}_n\), with \(i \in \text{rel}(f^{(i)})\) and \(i \notin \text{rel}(f^{(i)\neg})\), such that 
\[
f = g^{(i)}f^{(i)} + g^{(i)\neg}f^{(i)\neg},
\]
where the functions \(g^{(i)}\), \(g^{(i)\neg}\) \(\in \mathcal{F}_n\) are given by 
\[
g^{(i)}(x) = \begin{cases} 
1 & \text{if } x_i = 1 \\
0 & \text{else}
\end{cases}
\]
and 
\[
g^{(i)\neg}(x) = \begin{cases} 
1 & \text{if } x_i = -1 \\
0 & \text{else}
\end{cases}.
\]

Next we characterize the Fourier coefficients of \(f^{(i)}\) and \(f^{(i)\neg}\).

**Proposition 2** [13] Let \(f\) be a BF in \(n\) variables. The Fourier coefficients of \(f^{(i)}\) are given by 
\[
\hat{f}^{(i)}(U) = \hat{f}(U) + a_i \hat{f}(U \cup \{i\})
\]
where \(U \subseteq [n]\setminus\{i\}\).

The reverse relation, i.e., the composition of a BF by two restricted functions, is described in terms of Fourier coefficients by the following proposition:

**Proposition 3** [13] The Fourier coefficients of a BF \(f\) with uniform distributed input variables can be composed in terms of the Fourier coefficients of its two restricted functions \(f^{(i)}\) and \(f^{(i)\neg}\) according to 
\[
\hat{f}(U) = \frac{1}{2} \left( \hat{f}^{(i)}(U \cup \{i\}) + (-1)^{U \cap \{i\}} \hat{f}^{(i)\neg}(U \setminus \{i\}) \right),
\]
or 

| Table 1. Truth-table representation. |
|---|
| \(x_1\) | \(x_2\) | AND | OR | XOR |
|---|---|---|---|---|
| +1 | +1 | +1 | +1 | +1 |
| +1 | -1 | +1 | -1 | -1 |
| -1 | +1 | +1 | -1 | -1 |
| -1 | -1 | -1 | -1 | +1 |

| Table 2. Polynomial representation (Eq. (2)). |
|---|---|---|
| AND | OR | XOR |
| \(\frac{1}{2} + \frac{1}{2}x_1 + \frac{1}{2}x_2 - \frac{1}{2}x_1x_2\) | \(-\frac{1}{2} + \frac{1}{2}x_1 + \frac{1}{2}x_2 + \frac{1}{2}x_1x_2\) | \(x_1x_2\) |
where $PLOS$ ONE | www.plosone.org 3 May 2013 | Volume 8 | Issue 5 | e64371

$2f(U) = \begin{cases} f^{(i>)}(U \setminus \{i\}) + f^{(i<)}(U \setminus \{i\}) & \text{if } i \in U \\ f^{(i>)}(U) - f^{(i<)}(U) & \text{if } i \not\in U \end{cases}$

An immediate corollary of Proposition 3 shows that the zero coefficient of a function only depends on the zero coefficients of the restricted functions:

**Corollary 1** The zero Fourier coefficient of any Boolean function $f$ can be written as:

$$f(0) = \frac{1}{2}f^{(i>)}(0) + \frac{1}{2}f^{(i<)}(0),$$

where $i \in [n]$ is the index of some variable.

If we restrict a function to more than one variable, namely to a set of variables $K$, we denote the restricted function with $f^{(K,a)}$, where $a$ is a vector containing the values to which the function is restricted. The Fourier coefficients of $f^{(K,a)}$ are given by the following proposition:

**Proposition 4** [15] Let $f$ be a Boolean function and $\hat{f}(U)$ its Fourier coefficients. Furthermore, let $K$ be a set containing the indices $i$ of the input variables $x_i$, which are fixed to certain values $a_i$. The Fourier coefficients of the restricted function $f^{(K,a)}$ are then given as:

$$\hat{f}^{(K,a)}(U) = \sum_{S \subseteq K} (f_S(a)) \hat{f}(U \cup S),$$

where $a$ is the vector with entries $a_i$, $i \in K$.

**Nested Canazilizing Functions**

In order to define NCFs we first need the following definition:

**Definition 2** A BF $f$ is called $a < b$-canalizing, if there exists a canalizing variable $x_i$ and a constant $a \in \{-1, +1\}$, such that:

$$f(x_{1}, \ldots, x_{i-1}, x_i = a, x_{i+1}, \ldots, x_n) = b,$$

for all $x_1, \ldots, x_{i-1}, x_{i+1}, \ldots, x_n$, where $b \in \{-1, +1\}$ is a constant.

Hence, $f$ is canalizing in variable $i$, if the decomposition according to Proposition 1 results in either $f^{(i>)}$ or $f^{(i<)}$ being a constant function.

As shown in [15] the Fourier coefficients of a canalizing function satisfy

$$\hat{f}(0) + a_j \hat{f}(\{i\}) = b_i,$$

where $\hat{f}(\{i\}) = \hat{f}(0) + a_j \hat{f}(\{i\})$.

A NCF can be described recursively as a canalizing function, whose restriction is again a NCF or more formally:

**Definition 3** For $k = 1$ and $k = 0$ any BF with $k \leq n$ relevant variables is a NCF. For $k > 1$ a BF is a NCF, if there exists at least one variable $i$ and constants $a_i, \beta_i \in \{+1, -1\}$, such that $f^{(i,\beta_i)} = \beta_i$ and $f^{(i,-\beta_i)}$ is a NCF with $k - 1$ relevant variables.

Let $x_{a(1)}, \ldots, x_{a(k)}$ be the variable order for which a NCFs fulfills the properties from Definition 3, then we call, following [21], a such function $\{\pi : \alpha : \beta\}$ nested canalizing.

As shown in [15] $f$ is $\{\pi : \alpha : \beta\}$ nested canalizing, if for all $j \in \{1, \ldots, k\}$.

$$\hat{f}^{U,a}(T) = \sum_{S \subseteq U} (f_S(a)) \hat{f}(T \cup S),$$

and that $f$ is canalizing in any variable $k$, it follows that every

$$\sum_{S \subseteq [k]} (\hat{f}^{[S\setminus\{i\}],\beta_{S\cup\{a\}}} f(S)) = \beta_i,$$

where $a$ is a vector containing all negated $x_i$, i.e., $a_i = -x_i$ and $S$ is a set, which is retrieved by applying the permutation $\pi$ to the elements of $S$.

In order to illustrate the spectral properties of a NCF, consider the following example:

**Example 2** Let $f$ be a $\{\pi : \alpha : \beta\}$ NCF with $k = 2$ relevant variables and $\pi$ such that $S = \pi(S) = \{S\}$, then

$$\beta_1 = \hat{f}(0) + z_1 \hat{f}(\{1\})$$

$$\beta_2 = \hat{f}(0) - z_1 \hat{f}(\{1\}) + z_2 \hat{f}(\{2\}) - z_1 z_2 \hat{f}(\{1,2\}).$$

**Properties of nested canalizing functions.** In this section we state some properties of NCF. First we address most dominant variables, which are defined as follows:

**Definition 4** [21, Def 4.5] Variable $i$ is called a most dominant variable of $f$, if there exists a permutation $\pi$, such that $\pi(1) = i$, for which $f$ is $\{\pi : \alpha : \beta\}$ nested canalizing.

The set of most dominant variables has an impact on a number of Fourier coefficients, which is summarized in the following proposition:

**Proposition 5** Let $K$ be the set of most dominant variables of a $\{\pi : \alpha : \beta\}$ NCF $f$. Then the absolute values of the corresponding Fourier coefficients are all equal, i.e., $\forall U \subseteq K, U \neq \{\emptyset\}$.

$$|\hat{f}(U)| = c, \quad c > 0,$$

or, more general,

$$|\hat{f}(U)| = c \quad \forall U \subseteq K, U \neq \{\emptyset\} \text{ and } \forall j \in K.$$
restriction of \( f \) must also be canalizing in variable \( k \), i.e.,
\[
\hat{f}^{(U)}(\emptyset) + a_k \hat{f}^{(U)}(\{k\}) = b,
\]
we get:
\[
b = \sum_{S \subseteq U} \left( z_S(\emptyset) \hat{f}(S) \right) + a_k \sum_{S \subseteq U} \left( z_S(\emptyset) \hat{f}(\{k\} \cup S) \right),
\]
\[
b = \sum_{S \subseteq U, S \neq \emptyset} \left( -a_k z_S(\emptyset) \hat{f}(S) \right) + \hat{f}(\emptyset)
\]
\[
+ a_k \sum_{S \subseteq U, S \neq \emptyset} \left( z_S(\emptyset) \hat{f}(\{k\} \cup S) \right) + a_k \hat{f}(\{k\}).
\]
Using Eq. (5) and the induction hypothesis, we get
\[
0 = \sum_{S \subseteq U, S \neq \emptyset} \left( -c \right) + \sum_{S \subseteq U, S \neq \emptyset} \left( a_k z_S(\emptyset) \hat{f}(\{k\} \cup S) \right)
\]
\[
+ \left( a_k z_U(\emptyset) \hat{f}(\{k\} \cup U) \right).
\]
We again use that Eq. (6) holds for all \( S \subseteq U \), i.e., \(|S| < |U|\) and, hence:
\[
0 = -(2^{|U|} - 1) c + (2^{|U|} - 1) c + \left( a_k z_U(\emptyset) \hat{f}(\{k\} \cup U) \right)
\]
\[
c = a_k z_U(\emptyset) \hat{f}(\{k\} \cup U),
\]
which concludes the proof.
For the special case, in which all variables are most dominant, we derive the following corollaries:

**Corollary 2** Let \( f \) be a \( \{\pi : \alpha : \beta\} \) NCF with \( n \) variables of which \( k \) are relevant. All relevant variables are most canalizing, if the Fourier coefficients satisfy
\[
\left( \prod_{\alpha \in S, \beta \neq \emptyset} \bar{a}_\beta \right) f(S) = c \quad \forall S \subseteq [n], S \neq \emptyset \quad \text{and} \quad \forall \beta \in S \quad (7)
\]
with
\[
c = 2^{-(k-1)}. \quad (8)
\]
**Proof.** Eq. (7) follow, directly from Proposition 5, while Eq. (8) follows from Parseval’s theorem.

**Corollary 3** Let \( f \) be a \( \{\pi : \alpha : \beta\} \) NCF with \( n \) variables of which \( k \) are relevant. All variables are most canalizing, if the absolute values of the Fourier coefficients fulfill the following conditions,
\[
|\hat{f}(S)| = c \quad \forall S \subseteq K, S \neq \emptyset, \quad (9)
\]
\[
|\hat{f}(\emptyset)| = 1 - c
\]
with
\[
c = 2^{-(k-1)}.
\]

**Corollary 4** Let \( f \) be a \( \{\pi : \alpha : \beta\} \) NCF with \( k > 1 \) relevant input variables. All variables are most canalizing and \( \beta_i = b, \forall i \in \{1, \ldots, k\} \). All such NCFs are completely described by \( \pi \) and \( b \) and hence there are \( 2^{(k+1)} \) such functions.

**Proof.** The statement follows directly from the previous corollary.

Interestingly, we can describe the zero coefficients for NCFs in a recursive manner:

**Corollary 5** The zero coefficient of a \( \{\pi : \alpha : \beta\} \) NCF \( f \) can be recursively written as:
\[
\hat{f}(\emptyset) = \frac{1}{2} \hat{f}(\{\pi_1, \alpha_i\})(\emptyset) + \frac{1}{2} \beta_i.
\]
**Proof.** Follows directly from Corollary 1.

Further, the zero coefficient is upper bounded as shown by following proposition:

**Proposition 6** The absolute value of the zero coefficient of a NCF \( f \) with \( k > 1 \) relevant input variables can be bounded as:
\[
\frac{1}{2^{k-1}} \leq |\hat{f}(\emptyset)| \leq 1 - \frac{1}{2^{k-1}}.
\]
**Proof.** First, we prove the right hand side: Using the triangle inequality we get from Corollary 5:
\[
|\hat{f}(\emptyset)| \leq \frac{1}{2} \hat{f}(\{\pi_1, \alpha_i\})(\emptyset) + \frac{1}{2}.
\]

Obviously the zero coefficient of a function with only one relevant variable \( i \) is zero. The proposition now follows by induction. The left hand side can be easily shown using the inverse triangle inequality and induction.

As seen in Corollary 3, a NCF, whose variables are most dominant, fulfills the upper bound in Proposition 6 with equality. The following proposition follows directly from Corollary 5:

**Proposition 7** The absolute value of the zero coefficient of a NCF \( f \) with \( k \) relevant variables and alternating \( \beta_i \), i.e., with \( \beta = (-1, +1, -1, +1, \ldots) \) or \( \beta = (+1, -1, +1, -1, \ldots) \) is given as:
\[
|\hat{f}(\emptyset)| = \frac{1}{3} \left( \frac{1}{2^{k-1}} (-1)^k + 1 \right).
\]

**Average Sensitivity**

Before addressing the average sensitivity we first need to define the influence of a variable, which is a measure of the impact of a perturbation of this variable’s value.

**Definition 5** ([24,25]) The influence of variable \( i \) on the function \( f \) is defined as
\[
I_i(f) = \text{Pr}[f(X) \neq f(X \oplus e_i)].
\]
The influence can be related to the Fourier spectra as follows [26]:

\[ I(f) = \sum_{S \subseteq [n], |S| \neq 0} \hat{f}(S)^2. \]

The average sensitivity is a measure to quantify the impact of a random perturbation of the inputs of a Boolean function. It is defined as the sum of the influences of all input variables of \( f \).

**Definition 6** ([19,24]) The average sensitivity of \( f \) is defined as

\[ as(f) = \sum_{i \in [n]} I(f). \]

Consequently the average sensitivity can also be expressed in terms of the Fourier coefficients [24] as:

\[ as(f) = \sum_{S \subseteq [n], |S| \neq 0} \hat{f}(S)^2 |S|. \quad (11) \]

**Restricted functions.** To investigate the average sensitivity of restricted functions we first define \( \xi : \mathcal{F}_n \times \mathcal{F}_n \to \mathbb{R} \) by.

\[ \xi(f,g) = \frac{1}{2} \left( 1 - \sum_{U \subseteq [n]} \hat{f}(U) \hat{g}(U) \right). \quad (12) \]

Our next result shows the relation between the average sensitivity of a BF and the average sensitivity of its two restricted functions.

**Theorem 1** Let \( \tilde{f}^{(+)}, \tilde{f}^{(-)} \) be the restrictions of \( f \) to some relevant variable \( i \) of \( f \). Then

\[ as(f) = \frac{1}{2} as(f^{(+)}) + \frac{1}{2} as(f^{(-)}) + \xi(f^{(+)}, f^{(-)}). \]

**Proof:** Starting from Eq. (11), we can fractionize the Fourier coefficients according to Proposition 5. This yields:

\[
as(f) = \sum_{S \subseteq [n], |S| \neq 0} \left( \frac{1}{2} \hat{f}^{(+)}(S \setminus \{i\}) + \frac{1}{2} (-1)^{|S \cap \{i\}|} \hat{f}^{(-)}(S \setminus \{i\}) \right)^2 |S| + 2 \left( \frac{1}{2} \right)^2 |S| + \frac{1}{2} \sum_{S \subseteq [n], |S| \neq 0} \hat{f}^{(+)}(S \setminus \{i\})^2 |S| + \frac{1}{2} \sum_{S \subseteq [n], |S| \neq 0} \hat{f}^{(-)}(S \setminus \{i\})^2 |S|.
\]

which leads us to:

\[
as(f) = \frac{1}{4} \sum_{S \subseteq [n], |S| \neq 0} \left( \hat{f}^{(+)}(S \setminus \{i\}) \right)^2 |S| + \frac{1}{4} \sum_{S \subseteq [n], |S| \neq 0} \left( \hat{f}^{(-)}(S \setminus \{i\}) \right)^2 |S| + \frac{1}{2} \sum_{S \subseteq [n], |S| \neq 0} \left( (-1)^{|S \cap \{i\}|} \hat{f}^{(+)}(S \setminus \{i\}) \right)^2 |S| + \frac{1}{2} \sum_{S \subseteq [n], |S| \neq 0} \left( (-1)^{|S \cap \{i\}|} \hat{f}^{(-)}(S \setminus \{i\}) \right)^2 |S| + \frac{1}{2} \sum_{S \subseteq [n], |S| \neq 0} \hat{f}^{(+)}(S \setminus \{i\}) \hat{f}^{(-)}(S \setminus \{i\}) |S| + \frac{1}{2} \sum_{S \subseteq [n], |S| \neq 0} \hat{f}^{(+)}(S \setminus \{i\}) \hat{f}^{(-)}(S \setminus \{i\}) |S| + \frac{1}{4} \sum_{S \subseteq [n], |S| \neq 0} \hat{f}^{(+)}(S \setminus \{i\})^2 |S| + \frac{1}{4} \sum_{S \subseteq [n], |S| \neq 0} \hat{f}^{(-)}(S \setminus \{i\})^2 |S|.
\]

which concludes the proof.

For BF's we obtain:

**Corollary 6** The average sensitivity of a \( \{ \pi : \alpha : \beta \} \) BF can recursively be described as:
as(f) = \frac{1}{2} \left( as(f^{(z_1)}) + 1 - f^{(z_1)}(\emptyset)\beta_i \right),  \tag{13}

In [21] an upper bound on the average sensitivity of NCF has been conjectured. In the following theorem, we prove this conjecture to be correct.

**Theorem 2** The average sensitivity of a NCF with \( k = \text{rel}(f) \) relevant and uniformly distributed variables is bounded by

\[
\frac{k}{2^{k-1}} \leq as(f) \leq \frac{4}{3} \left( 2^{-k} - \frac{1}{3} \right) (\frac{1}{3})^{k}.  \tag{14}
\]

The bounds in Eq. (14) will turn out to be tight.

**Proof.** We first prove the upper bound in Eq. (14). Let us recall Corollary 6:

as(f) = \frac{1}{2} \left( as(f^{(z_1)}) + 1 - f^{(z_1)}(\emptyset)\beta_i \right).  \tag{15}

If we apply Corollary 6 again on as(f^{(z_1)}) and use Corollary 5 on \( f^{(z_1)}(\emptyset) \), Eq. (15) becomes:

\[
as(f) = \frac{1}{2} \left( \frac{1}{2} \left( as(f^{(z_1)}) + 1 - f^{(z_1)}(\emptyset)\beta_i \right) \right) + 1 - \frac{1}{2} \left( f^{(z_1)}(\emptyset) + \frac{1}{2} \beta_i \right) \beta_i
\]
\[
= \frac{1}{4} as(f^{(z_1)}) + 1 - \frac{3}{4} f^{(z_1)}(\emptyset)\beta_i + \frac{1}{2} \beta_i \beta_i
\]
\[
= \frac{1}{4} as(f^{(z_1)}) + \frac{3}{4} f^{(z_1)}(\emptyset)\beta_i + \beta_i
\]
\[
= \frac{1}{4} \beta_i \beta_i + \frac{3}{4}
\]

Since \( \beta_i \beta_i \in \{-1, +1\} \) and \( f^{(z_1)}(\emptyset) \leq 1, \)
\[
- \frac{1}{4} f^{(z_1)}(\emptyset)\beta_i + \beta_i \leq \frac{1}{4} \beta_i \beta_i + \frac{3}{4}
\]

Thus we obtain

\[
as(f) \leq \frac{1}{4} as(f^{(z_1)}) + 1 \tag{16}
\]

where \( f^{(z_1)}(\emptyset) \) has \( k - 2 \) relevant variables. We will now show the theorem by induction. For \( k = 1 \) the upper bound in Eq. (14) simplifies to

\[
as(f) \leq 1,
\]

which is obviously true by definition. For \( k = 2 \) the upper bound in Eq. (14) results in

\[
as(f) \leq \frac{1}{4} \left( \frac{4}{3} - 2^{-2} - \frac{1}{3} \right) + 1
\]
\[
= \frac{1}{3} - 2^{-2} + \frac{1}{3} - 2^{-2} + \frac{1}{3} - 2^{-2}
\]

which is also true and can be verified by inspecting all possible functions.

Using Eq. (14) as the induction hypothesis, and applying it on \( f^{(z_1, z_2)}(\emptyset, 1) \) in Eq. (16), which has \( k - 2 \) relevant variables, yields:

\[
as(f) \leq \frac{1}{4} \left( \frac{4}{3} - 2^{-2} - \frac{1}{3} \right) + 1
\]
\[
= \frac{1}{3} - 2^{-2} + \frac{1}{3} - 2^{-2} + \frac{1}{3} - 2^{-2}
\]

The lower bound in Eq. (14) can be proven along the lines of the proof of the upper bound, using the following inequality, which follows from Corollary 6 and Proposition 6:

\[
as(f) \geq \frac{1}{2} \left( as(f^{(z_1)}) + \frac{1}{2^{k-2}} \right)
\]

The tightness of the bounds in Eq. (14) is shown in Propositions 8 and 9.

We can further upper bound the right hand side of Theorem 2 in order to make it independent of the number of relevant variables \( k \):

**Corollary 7** The average sensitivity of a NCF with uniformly distributed variables satisfies

\[
as(f) \leq \frac{4}{3}
\]

Next we show that the bounds in Theorem 2 are tight.

**Proposition 8** Let \( f \) be a NCF, whose variables are all dominant. Then \( f \) satisfies the upper bound in Theorem 2 with equality.

**Proof.** Starting from Corollary 6 and using that, by Corollary 3, \( \| f(\emptyset) \| = 1 - \frac{1}{2^{k-1}} \) and \( \beta_i = \text{sgn}(f(\emptyset)) \) for all \( i \), we get:

\[
as(f) = \frac{1}{2} \left( as(f^{(z_1)}) + 1 - (1 - \frac{1}{2^{k-2}}) \right)
\]
\[
= \frac{1}{2} \left( as(f^{(z_1)}) + \frac{1}{2^{k-2}} \right)
\]

Since as(f) depends on \( k \) relevant variables, while as(f^{(z_1)}) depends only on \( k - 1 \) relevant variables, Eq. (17) becomes:

\[
as(k) = \frac{1}{2} \left( as(k - 1) + \frac{1}{2^{k-2}} \right)
\]
The proof is concluded by solving this recursion using induction.

**Proposition 9** Let $f$ be a NCF with alternating $\beta_i$, i.e., $\beta = (-1,+1,-1,+1,\ldots)$ or $\beta = (+1,-1,+1,-1,\ldots)$. Then $f$ fulfills the upper bound in Eq. (14) of Theorem 2 with equality.

**Proof.** Similar to the proof of the previous proposition we start from Corollary 6 and use $|f(0)| = \frac{1}{3} \left( \frac{1}{3^k} (-1)^k + 1 \right)$. The proof is established by solving the recursion.

Propositions 8 and 9 show that the maximal and minimal average sensitivity is achieved, if the absolute value of the zero coefficient is minimal and maximal, respectively. The following proposition gives a bound on the average sensitivity for fixed $|f(0)|$.

**Proposition 10** Let $f$ be a NCF with uniform distributed inputs. Then

$$as(f) \leq \frac{5}{3} |f(0)|.$$

**Proof.** Combining Corollaries 6 and 7, we get:

$$as(f^{(e_i,\alpha_i)}) - \beta_i f^{(e_i,\alpha_i)}(0) \leq \frac{5}{3},$$

and since $\beta_i \in \{-1, +1\}$:

$$as(f^{(e_i,\alpha_i)}) + |f^{(e_i,\alpha_i)}(0)| \leq \frac{5}{3}.$$

Substituting $f^{(e_i,\alpha_i)}$ by $f$ concludes the proof.

**Discussion**

In Figure 1 we summarize the bounds from the previous section. Specifically, we plot the average sensitivity versus the zero coefficient. Additionally, we include a lower bound on the average sensitivity that is independent of the number of relevant variables and applies for any $f \in \mathbb{F}^n$ and can be found in [27]. One can see that this bound intersects with our lower bound (which we plotted for $k = 5$), though we stated that our bound is tight. However, this is not a contradiction, since the lower bound in Theorem 2 is achieved for functions with large absolute zero coefficients, which are located outside the intersection.

For $k = 5$ our lower bound forms a triangle with the upper bound as formulated in Proposition 10. The NCFs with all variables being most dominant are located in the left and right corners of that triangle. However the lower bound decreases in $k$ and with it the most dominant NCFs.

The upper bound in Corollary 7 also intersects with the bound of Proposition 10. Again, this is not a contradiction, since NCFs reach this bound only for small absolute zero coefficients.

In general the average sensitivity is upper bounded by $k$, i.e., $as(f) \leq k$. As shown in [28] for monotone and in [15] for unate, i.e., locally monotone, functions, the average sensitivity is upper bounded by $as(f) \leq \sqrt{(1 - f(0))k}$. This bound is tight up to a multiplicative constant, see e.g. [29]. A function is unate, if it is monotone in each variable. In a regulatory network, where each regulator acts either inhibitory or exhibitory towards a certain gene, each function is unate. NCFs form a subclass of unate functions. Thus, our results show, that even within the class of unate functions, the average sensitivity of NCFs is remarkably low.

Since a low average sensitivity has a positive effect on the stability of Boolean networks [2], our result gives an explanation for the remarkable stability of BNs with NCFs.

**Conclusion**

In this paper we investigated canalizing and nested canalizing Boolean functions using Fourier analysis. We gave recursive representations for the zero coefficient and the average sensitivity based on the concept of restricted BFs.

We addressed the average sensitivity of nested canalizing functions and provided a tight upper and lower bound on the average sensitivity. We showed that the lower bound is achieved by functions whose input variables are all most dominant and which maximize the absolute zero coefficient. The upper bound is reached by functions, whose canalized values are alternating.

We provided an upper bound on the average sensitivity, namely $as(f) \leq \frac{1}{3}$, which has been conjectured in literature [21]. Finally, we derived a bound on the absolute zero coefficient and the average sensitivity and discussed the stabilizing effect of nested canalizing functions on the network dynamics.

It is worth noting that all those results rely on the assumption of uniformly distributed inputs. This rises the question, if the results can be generalized to other distributions. The recursive representations can easily be extended to product distributed input variables. But without further constraints there always exists a distribution, which maximizes the average sensitivity, i.e., for any function with $k$ relevant variables the average sensitivity can be $k$.

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**Author Contributions**

Wrote the paper: JK SS. Did important preliminary work and commented on the manuscript: RH.
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