Causality Analysis of Atrial Fibrillation Electrograms

David Luengo[1], Gonzalo Ríos Muñoz[2], Víctor Elvira[2]

[1] Universidad Politécnica de Madrid, Madrid, Spain
[2] Universidad Carlos III de Madrid, Madrid, Spain

Abstract

Multi-channel intracardiac electrocardiograms (electrograms) are sequentially acquired during heart surgery performed on patients with sustained atrial fibrillation (AF) to guide radio frequency catheter ablation. These electrograms are used by cardiologists to determine candidate areas for ablation (e.g., areas corresponding to high dominant frequencies or complex electrograms). In this paper, we introduce a novel hierarchical causality analysis method for the multi-output sequentially acquired electrograms. The causal model obtained provides important information regarding delays among signals as well as the direction and strength of their causal connections. The tool developed may ultimately serve to guide cardiologists towards candidate areas for catheter ablation. Preliminary results on synthetic signals are used to validate the proposed approach.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, but its underlying mechanisms are still not fully understood. One of the leading theories (rotor theory) maintains that specific areas of the myocardium are responsible for AF initiation and maintenance. RF catheter ablation is increasingly used to deal with AF, but requires identifying arrhythmogenetic areas. Sites with high dominant frequencies or complex electrograms have been proposed as candidate areas for ablation, but the success rate of these approaches still leaves room for improvement.

Several authors have investigated the inference of causality relationships among physiological signals. In particular, in electrocardiography the use of partial directed coherence to investigate propagation patterns in intra-cardiac signals was considered in [1], whereas Granger causality maps were built in [2, 3]. In this paper, we propose a novel *hierarchical causality* approach to guide cardiologists towards candidate areas for cathether ablation and discriminate between normal (sinus rhythm) and abnormal propagation (rotors).

2. Granger Causality (G-Causality)

Let us assume that we have N samples of a multi-variate time series composed of Q interrelated signals, $x_q[n]$ for $q = 1, \ldots, Q$ and $n = 0, 1, \ldots, N-1$. These signals correspond to unipolar intra-cardiac ECGs (electrograms) recorded at a single heart site during catheter ablation therapy. In the next two subsections we describe two standard approaches for causality inference, whereas in the following section we detail the proposed hierarchical approach.

2.1. Standard Pairwise Causality

In its standard (pairwise) formulation, Granger causality (G-causality) measures the increase in predictability on the future outcome of a given signal, $x_q[n]$ with $1 \leq q \leq Q$, given the past values of another signal, $x_\ell[n]$ with $1 \leq \ell \leq Q$, w.r.t. the predictability achieved by taking into account only past values of $x_q[n]$ [4]. The linear autoregressive (AR) predictor for $x_q[n]$ given its past samples (i.e., the q-th *self-predictor*) is given by

$$\hat{x}_q[n] = \sum_{m=1}^{M_{qq}} \alpha_{qq}[m] x_q[n-m] = \boldsymbol{\alpha}_{qq}^\top \mathbf{x}_q[n], \quad (1)$$

where M_{qq} is the order of the predictor (obtained typically using some penalization for model complexity to avoid overfitting [5]), $\alpha_{qq}[m]$ are the coefficients of the model, $\boldsymbol{\alpha}_{qq} = [\alpha_{qq}[1], \ldots, \alpha_{qq}[M_{qq}]]^\top$ and $\mathbf{x}_q[n] = [x_q[n-1], \ldots, x_q[n-M_{qq}]]^\top$. Similarly, let us define the linear AR predictor for $x_q[n]$ given the past samples of both $x_q[n]$ and $x_\ell[n]$ (i.e., the *cross-predictor* from the ℓ-th signal to the q-th signal) as

$$\hat{x}_{\ell\to q}[n] = \boldsymbol{\alpha}_{qq}^\top \mathbf{x}_q[n] + \boldsymbol{\alpha}_{\ell q}^\top \mathbf{x}_\ell[n], \quad (2)$$

where $M_{\ell q}$ is the order of the predictor from the ℓ-th signal to the q-th output (different from M_{qq} in general), $\alpha_{\ell q}[m]$ its coefficients, $\boldsymbol{\alpha}_{\ell q} = [\alpha_{\ell q}[1], \ldots, \alpha_{\ell q}[M_{\ell q}]]^\top$ and $\mathbf{x}_\ell[n] = [x_\ell[n-1], \ldots, x_\ell[n-M_{\ell q}]]^\top$. The *residual errors* of the two predictors in (1) and (2) are $\varepsilon_q[n] = x_q[n] - \hat{x}_q[n]$ and $\varepsilon_{\ell\to q}[n] = x_q[n] - \hat{x}_{\ell\to q}[n]$ respectively.

The *pairwise G-causality* strength is then measured by the logarithm of the ratio of these two variances [6]:

$$G_{\ell\to q} = \ln \frac{\text{Var}(\varepsilon_q[n])}{\text{Var}(\varepsilon_{\ell\to q}[n])}. \quad (3)$$

Using these pairwise values, we can build a *pairwise G-causality strength matrix*, $\mathbf{G}$, whose (ℓ, q)-th entry is[1]

$$\mathbf{G}_{\ell,q} = \begin{cases} G_{\ell\to q}, & \ell \neq q; \\ 0, & \ell = q. \end{cases} \quad (4)$$

Finally, note that we should add a causality link from ℓ to q only when the decrease in the residual's noise variance from (1) to (2) is statistically significant. In order to construct this causality graph we may define the *pairwise G-causality connection matrix*, $\mathbf{C}$, whose (ℓ, q)-th element is $C_{\ell\to q} = \chi_p(G_{\ell\to q})$, where $\chi_p(\cdot)$ is an indicator function such that $\chi_p(G_{\ell\to q}) = 1$ when the causal link from ℓ to q is statistically significant (as indicated by its p-value for example) and $\chi_p(G_{\ell\to q}) = 0$ otherwise.

2.2. Conditional G-Causality

Pairwise causality is unable to discriminate between direct causal relationships (i.e., between parents and sons) and indirect relationships (e.g., between grandparents and grandchildren). In order to avoid the undesired extra edges introduced by these indirect relationships, [6] proposed the use of *conditional G-causality*. Let us define as $\mathcal{I}$ the set containing the indexes of the conditioning variables. Now we can define the *conditional self-predictor* as

$$\hat{x}_{q|\mathcal{I}}[n] = \boldsymbol{\alpha}_{qq}^\top \mathbf{x}_q[n] + \sum_{r\in\mathcal{I}} \boldsymbol{\alpha}_{rq}^\top \mathbf{x}_r[n], \quad (5)$$

where $\boldsymbol{\alpha}_{rq} = [\alpha_{rq}[1], \ldots, \alpha_{rq}[M_{rq}]]^\top$ and $\mathbf{x}_r[n] = [x_r[n-1], \ldots, x_r[n-M_{rq}]]^\top$ for all $r \in \mathcal{I}$, and the *conditional cross-predictor* from the ℓ-th signal (with $\ell \notin \mathcal{I}$) to the q-th output as

$$\hat{x}_{\ell\to q|\mathcal{I}}[n] = \boldsymbol{\alpha}_{qq}^\top \mathbf{x}_q[n] + \sum_{r\in\mathcal{I}} \boldsymbol{\alpha}_{rq}^\top \mathbf{x}_r[n] + \boldsymbol{\alpha}_{\ell q}^\top \mathbf{x}_\ell[n]. \quad (6)$$

Now, by defining the residual errors as $\varepsilon_{q|\mathcal{I}}[n] = x_q[n] - \hat{x}_{q|\mathcal{I}}[n]$ and $\varepsilon_{\ell\to q|\mathcal{I}}[n] = x_q[n] - \hat{x}_{\ell\to q|\mathcal{I}}[n]$, the conditional G-causality strength can be defined as

$$G_{\ell\to q|\mathcal{I}} = \ln \frac{\text{Var}(\varepsilon_{q|\mathcal{I}}[n])}{\text{Var}(\varepsilon_{\ell\to q|\mathcal{I}}[n])}. \quad (7)$$

Just like in the case of the pairwise causality, we may define two conditional connection/strength G-causality matrices, $\mathbf{G}_\mathcal{I}$ and $\mathbf{C}_\mathcal{I}$, whose (ℓ, q)-th elements are respectively $\mathbf{G}_{\ell,q|\mathcal{I}} = G_{\ell\to q|\mathcal{I}}$ and $C_{\ell\to q|\mathcal{I}} = \chi_p(G_{\ell\to q|\mathcal{I}})$.[2]

[1] Note that $\text{Var}(\varepsilon_{q\to q}[n]) = \text{Var}(\varepsilon_q[n])$, since $\hat{x}_{q\to q}[n] = \hat{x}_q[n]$, and thus $G_{q\to q}[n] = \ln 1 = 0$ and the definition in (4) is consistent with (3).

[2] Note that the pairwise G-causality connection/strength matrices are unique, whereas many conditional G-causality connection/strength matrices can be constructed. The most usual situation in the literature is setting $\mathcal{I} = \mathcal{S}_{\neg\ell} = \{\infty, \ldots, \ell-\infty, \ell+\infty, \ldots, \mathcal{Q}\} = \{\infty, \ldots, \mathcal{Q}\} \setminus \{\ell\}$ and constructing the *full conditional* G-causality connection/strength matrices as $\mathbf{G}_{\ell,q|\mathcal{S}_{\neg\ell}} = G_{\ell\to q|\mathcal{S}_{\neg\ell}}$ and $C_{\ell\to q|\mathcal{S}_{\neg\ell}} = \chi_p(G_{\ell\to q|\mathcal{S}_{\neg\ell}})$ respectively.

3. Hierarchical Granger Causality

On the one hand, pairwise G-causality may provide misleading results. On the other hand, the "brute-force approach" to conditional causality (i.e., applying conditional causality on the whole data set all at once) is much more demanding from a computational point of view and may obscure some of the existing relationships. Hence, in this paper we propose a hierarchical approach that is able to exploit the advantages of both approaches while minimizing their drawbacks. The algorithm starts by searching for the node with the highest number of G-causality links to the other nodes and selecting it as the root node. Then, the sons of the root node are processed sequentially according to their strength, adding new causality links if they are significant conditioned on the previously added links. This process is repeated iteratively (on the grandsons of the root node and so on) until there are no more nodes to process and a *poly-tree* has been constructed. In the following, we describe the hierarchical causality algorithm in detail.

3.1. Initialization: Selecting the Root Node

The initialization stage seeks to find the optimal root node for the causal graph. This is done by calculating the pairwise G-causality among all nodes and selecting the one with the highest number of G-causality links to the other nodes. As a result, this stage returns the root node, i_1, and the set of its candidate sons, $\mathcal{C}_1 = \text{cand}\{i_1\}$. The detailed steps taken are the following:

1. Set $\mathbf{G} = \mathbf{0}$ and $\mathbf{C} = \mathbf{0}$. Initialize the sets of sons and parents as empty sets: $\mathcal{P}_q = \text{pa}\{q\} = \emptyset$ and $\mathcal{S}_q = \text{son}\{q\} = \emptyset$ for $q = 1, \ldots, Q$.
2. FOR $q = 1, \ldots, Q-1$ and $\ell = q+1, \ldots, Q$: Calculate $G_{q\to\ell}$ and $G_{\ell\to q}$, and set the corresponding entries in $\mathbf{G}$ and $\mathbf{C}$.
3. Calculate the G-causality strength of the q-th node ($q = 1, \ldots, Q-1$) as the sum of the strength of its causal links to the remaining nodes, $g_q = \sum_{\ell=1}^{Q} \mathbf{G}_{q,\ell} = \sum_{\ell=1}^{Q} G_{q\to\ell}$, and the number of links for each node as $K_q = \sum_{\ell=1}^{Q} \mathbf{C}_{q,\ell} = \sum_{\ell=1}^{Q} \chi_p(G_{q\to\ell})$.
4. Determine the node with the highest number of causal links stemming from it,

$$i_1 = \arg\max_{1\leq q\leq Q} K_q, \quad (8)$$

and set it as the root node, with g_q being used only to discriminate among nodes with identical values of K_q.
5. Obtain the set of candidate sons of the root node: $\mathcal{C}_{i_1} = \text{cand}\{i_1\} = \{\ell : \mathbf{C}_{i_1,\ell} = 1\}$.

3.2. First Iteration: Processing the Sons of the Root Node

This stage is in charge of processing the set of candidate sons of the root node, determining which of them are true sons. This decision is taken by sorting the candidates according to their G-causality strength and processing them sequentially (with "stronger" candidates being processed first). At each iteration, a conditional G-causality strength is calculated using the current set of sons of the root node (initially empty). If the G-causality connection is deemed statistically significant, the candidate is added to the set of sons of the root node and the corresponding entry in the conditional G-causality connectivity/strength matrices is updated. The motivation for this approach is that true sons still provide statistically significant G-causality values after conditioning, whereas descendants further away along the family tree do not provide statistically significant G-causality values (as they are be masked by closer descendants of the root node). As a result, this stage sets the corresponding entries in the strength/connection G-causality matrices, $\mathbf{G}_{\ell,q|\mathcal{P}}$ and $\mathbf{C}_{\ell,q|\mathcal{P}}$, returns the set of sons of the root node, $\mathcal{S}_{i_1} = \text{son}\{i_1\}$, and sets the root node as the parent for the nodes in $\mathcal{S}_{i_1}$, i.e., $\mathcal{P}_q = \text{pa}\{q\} = \{i_1\}\ \forall q \in \mathcal{S}_{i_1}$. The procedure applied is the following:

1. Set $\mathbf{G}_{i_1,q|\mathcal{P}} = 0$ and $\mathbf{C}_{i_1,q|\mathcal{P}} = 0$ for $q = 1,\ \ldots,\ Q$. Set $\mathbf{G}_{\ell,q|\mathcal{P}} = \texttt{NaN}$ and $\mathbf{C}_{\ell,q|\mathcal{P}} = \texttt{NaN}$ for $1 \leq \ell, q \leq Q$ with $\ell \neq i_1$.[3]
2. Sort the elements in $\mathcal{C}_{i_1}$ according to their G-causality strength: $\mathcal{C}_{i_1}(j) \geq \mathcal{C}_{i_1}(k)\ \forall j < k\ (1 \leq j, k \leq |\mathcal{C}_{i_1}|)$.
3. Set $C_{i_1 \to \mathcal{C}_{i_1}(1)|\mathcal{P}} = 1$, $G_{i_1 \to \mathcal{C}_{i_1}(1)|\mathcal{P}} = G_{i_1 \to \mathcal{C}_{i_1}(1)}$ and $\mathcal{S}_{i_1} = \text{son}\{i_1\} = \{\mathcal{C}_{i_1}(1)\}$.
4. FOR $j = 2,\ \ldots,\ |\mathcal{C}_{i_1}|$:
   (a) Calculate $G_{i_1 \to \mathcal{C}_{i_1}(j)|\mathcal{S}_{i_1}}$ and $C_{i_1 \to \mathcal{C}_{i_1}(j)|\mathcal{S}_{i_1}} = \chi_p(G_{i_1 \to \mathcal{C}_{i_1}(j)|\mathcal{S}_{i_1}})$.
   (b) IF $C_{i_1 \to \mathcal{C}_{i_1}(j)|\mathcal{S}_{i_1}} = 1$: Set $C_{i_1 \to \mathcal{C}_{i_1}(j)|\mathcal{P}} = 1$, $G_{i_1 \to \mathcal{C}_{i_1}(j)|\mathcal{P}} = G_{i_1 \to \mathcal{C}_{i_1}(j)}$, $\mathcal{S}_{i_1} = \mathcal{S}_{i_1} \cup \{\mathcal{C}_{i_1}(j)\}$ and $\mathcal{P}_{\mathcal{C}_{i_1}(j)} = \text{pa}\{\mathcal{C}_{i_1}(j)\} = \{i_1\}$.

3.3. Main Algorithm: Processing the Remaining Nodes Iteratively

This final stage is in charge of processing the remaining roots iteratively in a hierarchical fashion. The process described in the previous section is repeated iteratively, processing the sons of each of the sons of the root node (i.e., the grandsons of the root node), starting again by the "strongest" one. The algorithm proceeds in this way (i.e., processing the great-grandsons of the root node, the great-great-grandsons of the root node and so on), until there are no more nodes to process. This stage returns the full strength/connection G-causality matrices, $\mathbf{G}_{\ell,q|\mathcal{P}}$ and $\mathbf{C}_{\ell,q|\mathcal{P}}$, defining a causal network with the corresponding sets of sons and parents, $\mathcal{S}_q = \text{son}\{q\}$ and $\mathcal{P}_q = \text{pa}\{q\}$ for $q = 1,\ \ldots,\ Q$. The steps taken are the following:

1. Set $t = 1, \mathcal{I}_t = \{i_1\}$ and $\mathcal{M}_t = \{1,\ \ldots,\ Q\} \setminus \mathcal{I}_t$.
2. WHILE $\mathcal{M}_t \neq \emptyset$:
   (a) FOR $k = 1,\ \ldots,\ |\mathcal{I}_t|$:
   • Set $\mathcal{S} = \mathcal{S}_{\mathcal{I}_t(k)}$ and sort its elements in decreasing order according to their G-causality strength (i.e., "strongest" elements placed first).
   • FOR $\ell = 1,\ \ldots,\ |\mathcal{S}|$ and $j = 1,\ \ldots,\ |\mathcal{C}|$: Set $\mathcal{C} = \mathcal{C}_{\mathcal{S}(\ell)} = \mathcal{M}_t \setminus \mathcal{S}(\ell)$, and calculate $G_{\mathcal{S}(\ell) \to \mathcal{C}(j)|\mathcal{I}_\sqcup}$ and $C_{\mathcal{S}(\ell) \to \mathcal{C}(j)|\mathcal{I}_t} = \chi_p(G_{\mathcal{S}(\ell) \to \mathcal{C}(j)|\mathcal{I}_t})$. IF $C_{\mathcal{S}(\ell) \to \mathcal{C}(j)|\mathcal{I}_t} = 1$, then set:

$$
\begin{aligned}
C_{\mathcal{S}(\ell) \to \mathcal{C}(j)|\mathcal{P}} &= 1, \\
G_{\mathcal{S}(\ell) \to \mathcal{C}(j)|\mathcal{P}} &= G_{\mathcal{S}(\ell) \to \mathcal{C}(j)|\mathcal{I}_t}, \\
\text{son}\{\mathcal{S}(\ell)\} &= \text{son}\{\mathcal{S}(\ell)\} \cup \{\mathcal{C}(j)\}, \\
\text{pa}\{\mathcal{C}(j)\} &= \text{pa}\{\mathcal{C}(j)\} \cup \{\mathcal{S}(\ell)\}.
\end{aligned}
$$

   (b) Set $\mathcal{I}_{t+1} = \cup_{k=1}^{|\mathcal{I}_t|} \mathcal{S}_{\mathcal{I}_t(k)}$, $\mathcal{M}_{t+1} = \mathcal{M}_t \setminus \mathcal{I}_{t+1}$ and $t = t + 1$.

4. Numerical Simulations

In this section, we validate the proposed approach by using synthetic signals generated using a grid of interconnected elements that simulate the behaviour of heart tissue using the FitzHugh-Nagumo model [7]. The Granger causal connectivity toolbox (see [8]) was used to obtain the basic pairwise and conditional causality relationships. A flat propagation wavefront is generated and a catheter with 9 sensors is placed inside the heart in such a way that the wavefront enters it through the eighth sensor and exits through the third sensor. An example of the noiseless signals and the true causal connectivity matrix, $\mathbf{C}$, is provided in Figure 1, whereas the ground truth causality network can be seen in Figure 2. The three approaches described in the paper (pairwise causality, full conditional causality and the novel hierarchical causality approach) are then applied (using $M = 16$ and $p = 5 \cdot 10^{-4}$) to infer the other causal networks shown in Figure 2. As expected, the pairwise approach includes a huge number of edges, since it does not discriminate between direct and indirect causal relationships. The full conditional approach does a much better job, but still provides some cross-connections across the nodes that may obscure the interpretation of the inferred network. Finally, the hiearchical scheme includes less cross-connections (always pointing in the right direction) and requires a lower computational effort.

[3] NaN is the IEEE arithmetic representation for "Not-a-Number", which is obtained as the result of mathematically undefined operations (e.g., $0/0$ or $\infty - \infty$). We use it here as a convenient way to indicate entries of $\mathbf{G}_{\mathcal{P}}$ and $\mathbf{C}_{\mathcal{P}}$ that have not been defined yet.

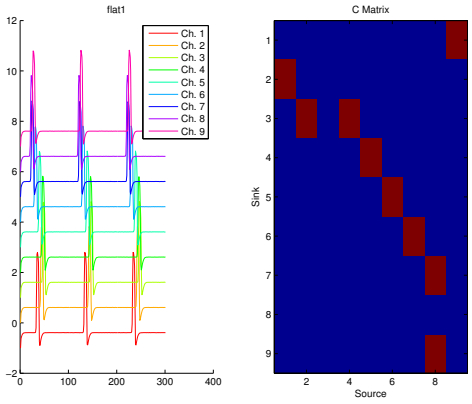

Figure 1. Example of the synthetic signals **(left)** and the true causal connectivity matrix **(right)**

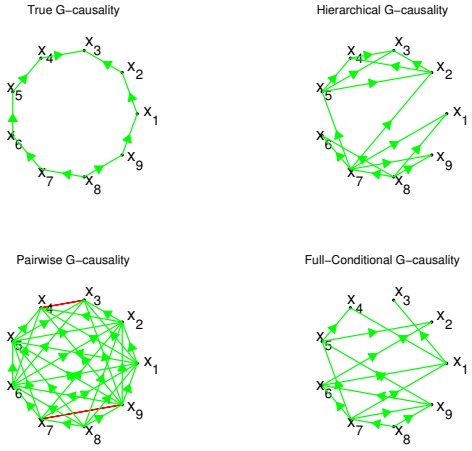

Figure 2. True map and causality maps provided by the tested methods (hierarchical, pairwise and full)

Table 4 provides some numerical results in terms of accuracy ($\frac{TP+TN}{P+N}$), sensitivity ($\frac{TP}{P}$) and specificity ($\frac{TN}{N}$).[4] On the one hand, the pairwise technique provides very good results in terms of sensitivity (detecting all the edges), but very poor results in terms of specificity (introducing many false edges). On the other hand, the full conditional scheme obtains very good results in terms of specificity, but very poor sensitivity results. Finally, the hierarchical approach provides the best accuracy and specificity results, performing well also in terms of sensitivity.

Method	Accuracy	Sensitivity	Specificity
Hierarchical	0.85185	0.66667	0.87500
Pairwise	0.69136	1.00000	0.65278
Full Cond.	0.81481	0.44444	0.86111

[4] P denotes the number of positive instances (i.e., existing edges), N the number of negative instances, TP the number of correctly detected existing edges and TN the number of correctly detected missing edges.

5. Conclusions and Future Lines

In this paper, we have introduced a novel hierarchical approach to infer Granger causality relationships among multi-channel intra-cardiac electrocardiograms. The proposed scheme avoids detecting indirect causal links (as in pairwise approaches), and has a better performance and less computational cost than the full conditional causality method. Synthetic signals, generated using the FitzHugh-Nagumo model, have been used to validate our method.

Acknowledgements

This work has been supported by the Spanish government's projects ALCIT (TEC2012-38800-C03-01), AGES (S2010/BMD-2422), and OTOSiS (TEC2013-41718-R), and COMPREHENSION (TEC2012-38883-C02-01). D. Luengo has also been funded by the BBVA Foundation's "I Convocatoria de Ayudas Fundación BBVA a Investigadores, Innovadores y Creadores Culturales".

Address for correspondence:

David Luengo
Universidad Politécnica de Madrid, ETSIS de Telecomunicación, Desp. 7009, Ctra. de Valencia, Km. 7, 28031 Madrid (Spain)
E-Mail: luengod@ieee.org

References

[1] Richter U, Faes L, Cristoforetti A, Masè M, Ravelli F, Stridh M, Sörnmo L. A novel approach to propagation pattern analysis in intracardiac atrial fibrillation signals. Annals of biomedical engineering 2011;39(1):310–323.

[2] Rodrigo M, Liberos A, Guillem M, Millet J, Climent AM. Causality relation map: a novel methodology for the identification of hierarchical fibrillatory processes. In Computing in Cardiology, 2011. IEEE, 2011; 173–176.

[3] Rodrigo M, Guillem MS, Liberos A, Millet J, Berenfeld O, Climent AM. Identification of fibrillatory sources by measuring causal relationships. In Computing in Cardiology (CinC), 2012. IEEE, 2012; 705–708.

[4] Granger CWJ. Investigating causal relations by econometric models and cross-spectral methods. Econometrica 1969; 37:424–438.

[5] Stoica P, Selen Y. Model-order selection: a review of information criterion rules. Signal Processing Magazine IEEE 2004;21(4):36–47.

[6] Geweke J. Measures of conditional linear dependence and feedback between time series. Journal of the American Statistical Association 1984;79:907–915.

[7] Keener JP, Sneyd J. Mathematical physiology, volume 1. Springer, 1998.

[8] Seth AK. A matlab toolbox for granger causal connectivity analysis. Journal of neuroscience methods 2010;186(2):262–273.