Constraint-based modeling method for analyzing neural connectivity

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Abstract

A constraint-based modeling technique is presented for analyzing neural connectivity networks. Drawing inspiration from metabolic modeling, the method considers all feasible connectivity states in a neural network based on fundamental connectivity constraints. The published connectivity network of *Caenorhabditis elegans* is used as an example of the method.

1 Introduction

Caenorhabditis elegans is a model organism for investigations in genetics [1] and neuroscience [2]. This nematode is an attractive organism for study due do its small size, transparency, fast life cycle, and simple neural system. The hermaphroditic *C. elegans* individual has 302 unique, recognizable neurons that are similar between specimen. Each neuron has been identified, and a reconstruction has been published with details of morphology and connectivity, including differentiation between chemical synapses and electrical junctions [3]. The connectivity data were gathered by analyzing electron micrographs. This reconstruction is an update of the seminal network publication by White *et al.* [4]. It should be noted that, according to the authors, this reconstruction "is only about 90% complete because of missing data and technical difficulties." [3] The network structure of the *C. elegans* connectivity network has been analyzed in the context of other networks [5]. It was concluded in that work that the neural network of *C. elegans* does fall into the class of scale-free network. This is in interesting observation, as scale-free network are seen in many self-assembling networks, including metabolic networks.

The network structure of this organism will be analyzed with a method known as constraint-based modeling. This modeling technique has been very successful for investigation the solution states of metabolic networks. Constraint-based models represent governing constraints based on physicochemical conservation laws, spatial limitations, and environmental parameters. Stoichiometric constraints are used to generate the stoichiometric matrix, and matrix representation of all metabolic reactions in the cell where each column is a reaction and each row is a metabolite [6]. By leveraging a steady-state assumption, the mathematical statement $S * v = 0$ can be made, where S is the stoichiometric matrix and v is a vector of all reaction fluxes. The solution spaces represented by this constrained mathematical statement can be examined by optimizing for objectives using flux balance analysis (FBA) [7]. The optimal solutions predicted by flux balance analysis will match in-vivo behavior if the regulatory network of the cell is optimized for the same objective (e.g. growth).

A constraint-based modeling approach to investigating neural behavior has been reported [8]. However, that work focused on the metabolic interactions of neurons—both between cell types and with the environment. That work built on the human metabolic network Recon1 to derive tissue-specific metabolic models of neurons. The approach taken here is fundamentally different from the work

by Lewis *et al.* and from metabolic modeling in general. Only the mathematical constraint-based modeling technique is similar.

In this work, a constraint-based modeling procedure is demonstrated for analyzing the solution space that represents all possible activities of a neural connectivity network based on just connectivity constraints and input and output constraints representing stimulus and response. A neural connectivity matrix is constructed for *Caenorhabditis elegans*, and analysis is performed on the matrix properties of the connectivity matrix. Linear optimization are performed on the network to find optimal flux-states for particular objective functions.

2 Methods

The constraint-based modeling procedure was adapted to the neural network based on the introductory assumption that all chemical synapses and electrical junctions can be excitatory. Because only connectivity information is available—synapse identities are not available on a whole-network scale—this assumption is necessary to build a whole-network model. The constraint-based technique is designed to constrain the solution space of a network based only on known factors. Thus, while it is overly permissive to say that all synapses can be excitatory, the method does not become false with this assumption. The lack of data only limits the predictive power of the model.

To build the network, sensory neurons, chemical synapses, electrical junctions, and neuro-muscular junctions were incorporated into a single connectivity matrix illustrated in Figures 2–1. Flux through the network is represented by a unit-less "neural activity" value which represents the percentage of electrical flux through any portion of the network. In these simulations, neural activity was constrained to values between 0 and 1.

	Sense1	Sense2	...	Neuron1	Neuron2	Neuron3	...	NMJ1	NMJ2	...
C1	-1			1						
C2		-1			1					
C3					-1	1				
C4						-1		1		
C5				-1		1			1	

Figure 1: A subset of the connectivity network matrix. The matrix includes one column for each sensory connection, neuron, and neuromuscular junction. Each row is a connectivity.

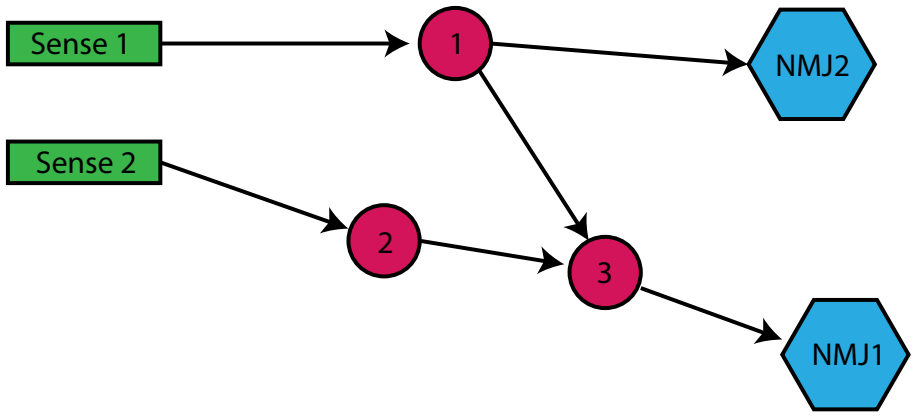

Figure 2: The corresponding network diagram.

In the neural connectivity matrix, each column represents a sensory connection, neuron, or neuromuscular junction. Thus, the flux vector, v, contains a flux value for each sensory connection, neuron, and neuromuscular junction. When the flux states are selected by optimization, the solution is a vector of activities for each of these components. Each row of the matrix is a connectivity and therefore corresponds to a matrix constraint. With a steady-state assumption, $S * v = 0$. For each row in the matrix, the sum of the 'stoichiometric values' (for the neural network, ones and zeros) multiplied by their corresponding fluxes must equal zero. Thus, if one unit of flux enters a neuron, one unit of flux must also exit that neuron, albeit divided among all neural connections.

Optimization was performed with a method analogous to flux balance analysis. For clarity, and in the spirit of academic neologism, I will refer to the optimization process as Neural Activity Balance Analysis (NABA). To optimize a linear problem, one must identify a matrix A (our connectivity matrix), and flux vector v (described above), a constraint vector b (a vector of zeros), upper and lower bound vectors (lower bound: zero, and upper bound: one, for each neural activity), and an objective function c. The objective function contains values corresponding to each column of the connectivity matrix, and a positive value represents a weight of desired minimization. Thus, the linear problem is to solve:

$$
\begin{aligned}
&\min c^T v \\
&s.t. \\
&\quad A\bar{v} = \bar{b} \\
&\quad v_{stimulus} = 1 \\
&\quad \bar{v}_{other\_sense} = \bar{0} \\
&\quad \bar{lb} \leq \bar{v} \leq \bar{ub}
\end{aligned}
$$

For these simulations, the objective function was selected as a single neuromuscular junction with a negative objective value in the c matrix, so that the problem is an maximization. The value $v_{stimulus}$ is the flux through the stimulation neuron—this value was set to one. The other sensory neurons (V_{other_sense}) were all held to zero.

All simulations were performed in MATLAB (Mathworks, Natick, MA) using the GLPK linear optimization toolkit (http://www.gnu.org/software/glpk/).

3 Results

The neural connectivity matrix was constructed. The matrix contains 464 rows and 463 columns. Singular value decomposition was performed on the matrix, and the magnitudes of the singular values are plotted in Figure 3. The values are also shown on a log scale (Fig. 3).

The singular values of medium magnitude decrease logarithmically. However, it is notable that the largest singular values (the left of both plots) have a noticeable spike, even in the logarithmic plot. This indicates that these modes are especially relevant to the network.

To investigate this result further, Figure 3 shows a heat map of the matrix produced by the first singular value of the matrix. A cluster of important neurons is seen in the center of the plot. These neurons correspond to the sensory neurons IL2DR, IL2DL, L1VR, IL1VL, IL1DR, IL1DL, FLPL, and URAVR. The neurons IL2 are though to be chemosensory and IL1 are mechanosensory neurons. FL are also mechanosensory neurons. This result points to the importance of these sensory mechanisms in the *C. elegans* network.

The flux through the network was analyzed after optimizing for stimulation of a motor neuron. It has been shown that the neurons ASJ, AWB, ASK, and ASH mediate a light response in *C. elegans* [9]. These neurons were stimulated with a magnitude 0.5 for each neuron. The corresponding activities in the network are 'ASJL_sense', 'ASJR_sense', 'ASKL_sense', 'ASKR_sense', 'AWBL_sense', 'AWBR_sense', 'ASHL_sense', and 'ASHR_sense'. Only the left side (those sensory neurons ending in 'L') were stimulated. The neural objective was to stimulate motor neurons MDR01 and MDL01.

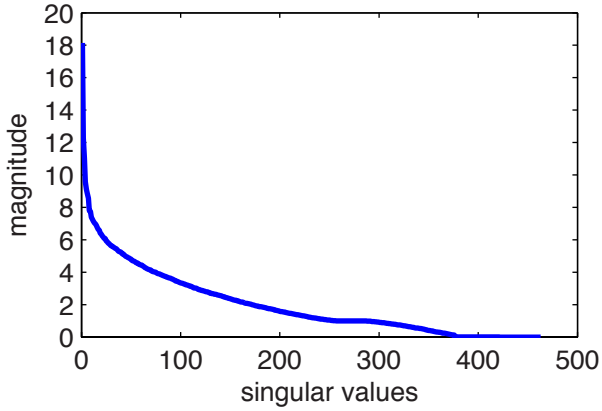

Figure 3: Singular values of the connectivity matrix—log scale.

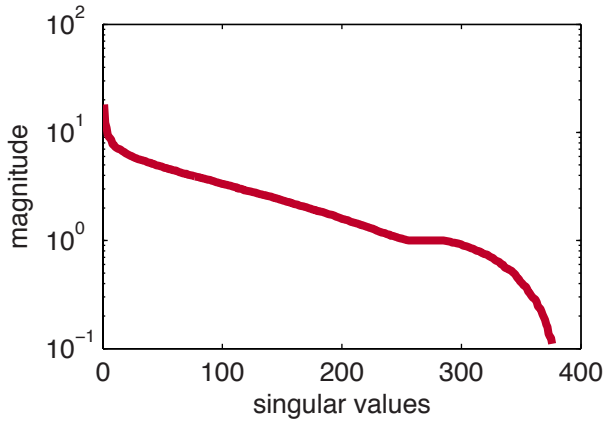

Figure 4: Singular values of the connectivity matrix—log scale.

Unfortunately, I was unable to get the optimization operational for this report. All solutions were zero valued. However, the code to produce a model and set up the optimization problem is included. It only requires some debugging and further network analysis to yield flux distributions through this network.

4 Conclusions

In this report, a whole-cell neural network was modeled for the nematode *C. elegans*. The model was prepared using constraint-based modeling techniques. Singular value decomposition was performed, and the most important network mode was elucidated. An important next step is to complete the Neural Balance Analysis Method so that neural activity flux optimizations can be calculated.

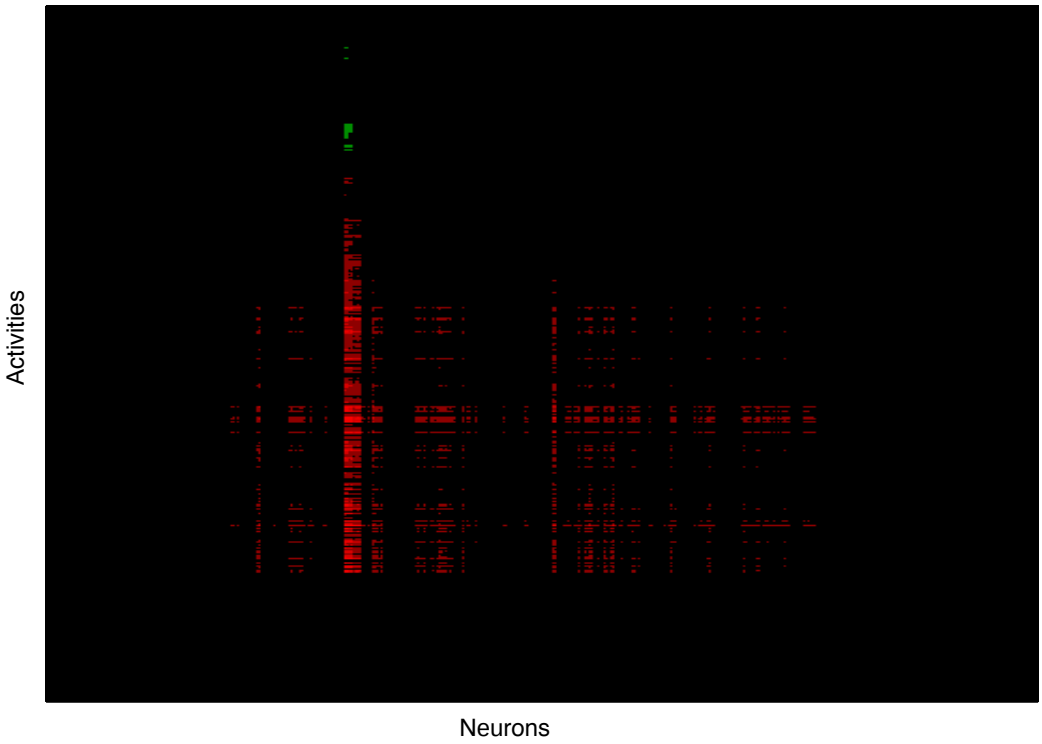

Figure 5: Heat map showing the array produced by the first singular value of the matrix

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