Analysing High-Dimensional Neuroscience Models: Neurovascular Coupling.

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July 12, 2018

Abstract

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1 INTRODUCTION

During the last two decades functional magnetic resonance imaging (fMRI) has proven to be an established tool in studying the human brain. This is especially true in the case of the blood-oxygen-level dependent (BOLD) signal, where changes in blood oxygen levels can

be detected via the magnetic signal [17]. However due to the constraint on the resolution of BOLD, fMRI methodology has not been used extensively to study the underlying cellular neural architecture and their associated cerebral functions. Complex models that address this important relationship and constructing a detailed compartmental model with the relevant cell types involved will allow simulations relating certain brain functions performed in a region to its fMRI BOLD response. The neurovascular coupling (NVC) mechanism, the cerebral metabolic rate of oxygen consumption, and the cerebral blood volume (CBV) are known to contribute to the fMRI BOLD response [3], however a thorough understanding of these factors has yet to be fully established.

The NVC response, the ability to locally adjust vascular resistance as a function of neuronal activity, is believed to be mediated by a number of different signalling mechanisms. Roy and Sherrington [19] first proposed a mechanism based on a metabolic negative feedback theory. According to this theory, neural activity leads to a drop in oxygen or glucose levels and increases in CO_2, adenosine, and lactate levels. All of these signals could dilate arterioles and hence were believed to be part of the neurovascular response. However, recent experiments illustrated that the NVC response is partially independent of these metabolic signals [10, 11, 16, 18, 13]. An alternative to this theory was proposed where the neuron releases signalling molecules to directly or indirectly affect the blood flow. Many mechanisms such as the potassium (K^+) signalling mechanism [8], the nitric oxide (NO) signalling mechanism or the arachidonic acid to epoxyeicosatrienoic acid (EET) pathway are found to contribute to the neurovascular response [2].

The K^+ signalling mechanism of NVC seems to be supported by significant evidence, although new evidence shows that the endfoot astrocytic calcium (Ca^{2+}) could play a significant role. The K^+ signalling hypothesis mainly utilises the astrocyte, positioned to enable the communication between the neurons and the local perfusing blood vessels. The astrocyte and the endothelial cells (ECs) surrounding the perfusing vessel lumen exhibit a striking similarity in ion channel expression and thus can enable control of the smooth muscle cell (SMC) from both the neuronal and blood vessel components [12]. Whenever there is neuronal activation K^+ ions are released into the extracellular space (ECS) and synaptic cleft (SC). The astrocyte is depolarised by taking up K^+ released by the neuron and releases it into the perivascular space (PVS) via the endfeet through the BK channels [7]. This increase in ECS K^+ concentration ($3 - 10$ mM) near the arteriole hyperpolarises the SMC through the inward rectifying K^+ (KIR) channel, effectively closing the voltage-gated Ca^{2+} channel, reducing smooth muscle cytosolic Ca^{2+} and thereby causing dilation. Higher K^+ concentrations in the PVS cause contraction due to the reverse flux of the KIR channel [6].

Amidst the difficulty in monitoring and measuring the rapid changes in metabolic demands in the highly heterogeneous brain, speculative estimates of the relative demands of the cerebral processes that require energy were given based on different experimental data by Ames [1]. As per the estimate, the vegetative processes that maintain the homeostasis including protein synthesis accounted for $10 - 15\%$ of the total energy consumption. The costliest function seems to be in restoring the ionic gradients during neural activation. The sodium potassium (Na^+/K^+) exchange pump is estimated to consume $40 - 50\%$, while the

Ca^{2+} influx from organelles and extracellular fluid consumes $3-7\%$. The processing of neurotransmitters such as uptake or synthesis consumes $10-20\%$, while the intracellular signalling systems which includes activation and inactivation of proteins consumes $20-30\%$. The rest of the energy is estimated to be consumed by the axonal and dendritic transport in both directions.

Previous work [**?**] has provided the construction of an experimentally validated numerical (*in silico*) model based on experimental data to simulate the fMRI BOLD signal associated with NVC along with the associated metabolic and blood volume responses. An existing neuron model [14, 15] has been extended to include an additional transient sodium (Na^+) ion channel (NaT) expressed in the neuron, and integrated into a complex NVC model [5, 4, 9]. This present model is based on the hypothesis that the K^+ signalling mechanism of NVC is the primary contributor to the vascular response and the Na^+/K^+ exchange pump in the neuron is the primary consumer of oxygen during neural activation. The model contains 160 parameters, most of which come from non-human experiments.

Such a complex model constructed with a high-dimensional parameter space is not easily amenable to sensitivity analyses considering the significant computing resource required. Indeed no formal theory exists which allows direct mathematical investigation of the variability of the large dimensional parameter vector and the resulting output. From a purely physiological perspective an understanding of the dominant cellular mechanisms resulting in cerebral tissue perfusion after neuronal stimulation would be of particular interest.

We have used the cerebral blood flow (CBF) change from the experimental data [20] taken from the rat barrel cortex.

2 Methodology

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2.1 Simulated Data

We use a square pulse of 10 seconds duration for stimulation such that the resulting output (after a substantial number of realizations) can be analysed in a formal manner. We assume that stimulation occurs for $t_1 \leq t \leq t_2$.

2.2 QoIs

We analyse 7 quantities of interest (QoIs) with respect to the 10 second square stimulation pulse. They are defined as follows.

1. As a representation of the volumetric flow rate in the cerebral tissue

$$\frac{1}{t_2 - t_1} \int_{t_1}^{t_2} \left(\frac{R(s)}{R_0} \right)^4 ds \tag{2.1}$$

2. ECS potassium has a distinct effect on the flux into the Neuron. Hence we look at the average and the maximum.

$$[K^+]_{max,ECS} \tag{2.2}$$

$$\frac{1}{t_2 - t_1} \int_{t_1}^{t_2} [K^+]_{ECS}(s) ds \tag{2.3}$$

3. ECS potassium has a distinct effect on the flux into the astrocyte. Hence we look at the average and the maximum.

$$[K^+]_{max,AC} \tag{2.4}$$

$$\frac{1}{t_2 - t_1} \int_{t_1}^{t_2} [K^+]_{AC}(s) ds \tag{2.5}$$

4. the combined concentration of the actin myosin complex, both phosphorylated and unphosphorylated, determines the effect stress due to the contraction for the smooth muscle cell.

$$[AM + AM_p]_{min} \tag{2.6}$$

5. The phase lag between neuronal stimulation and the radius changed effects a number of markers. Notably the BOLD signal, hence we choose to investigate the time, τ, to min value of AM_p

$$\tau = t_{min} - t_1 \tag{2.7}$$

2.3 Experimental Data

We repeat analysis of the 7 QoI's listed above

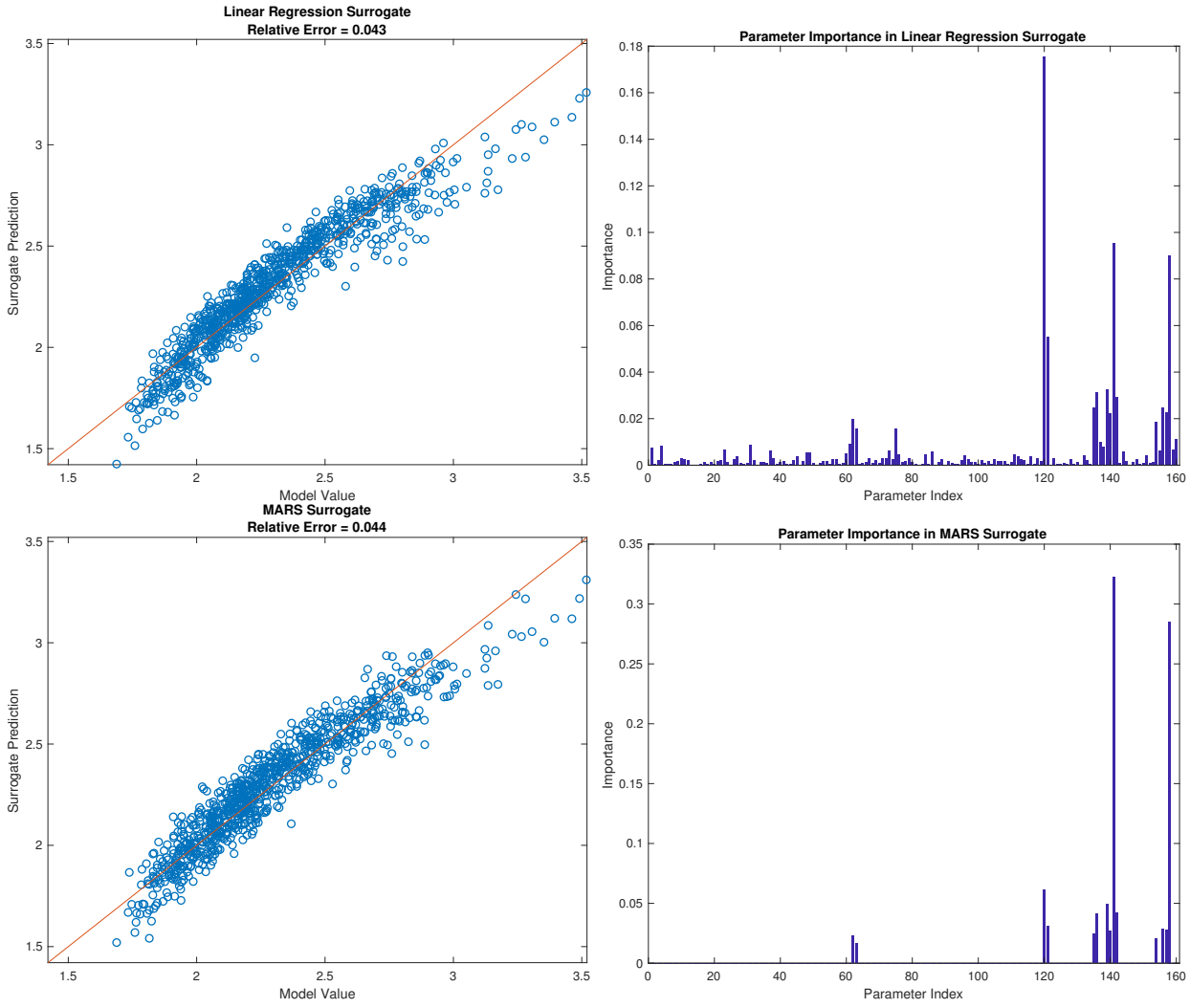
3 Results

This section contains numerical results for 14 QoI's, 7 using a square pulse stimulus and 7 using the experimental data stimulus. The section is organized into 7 subsection where each

subsection contains 2 sub-subsections with the results using the square pulse stimulus and experimental data stimulus. For each case we report results using a linear regression and Multivariate Adaptive Regression Splines surrogate models. The predictive capabilities and variable importance metrics are given for each surrogate and the results are compared.

3.1 QoI (2.1) (volumetric flow rate)

3.1.1 Rectangular Pulse Stimulus

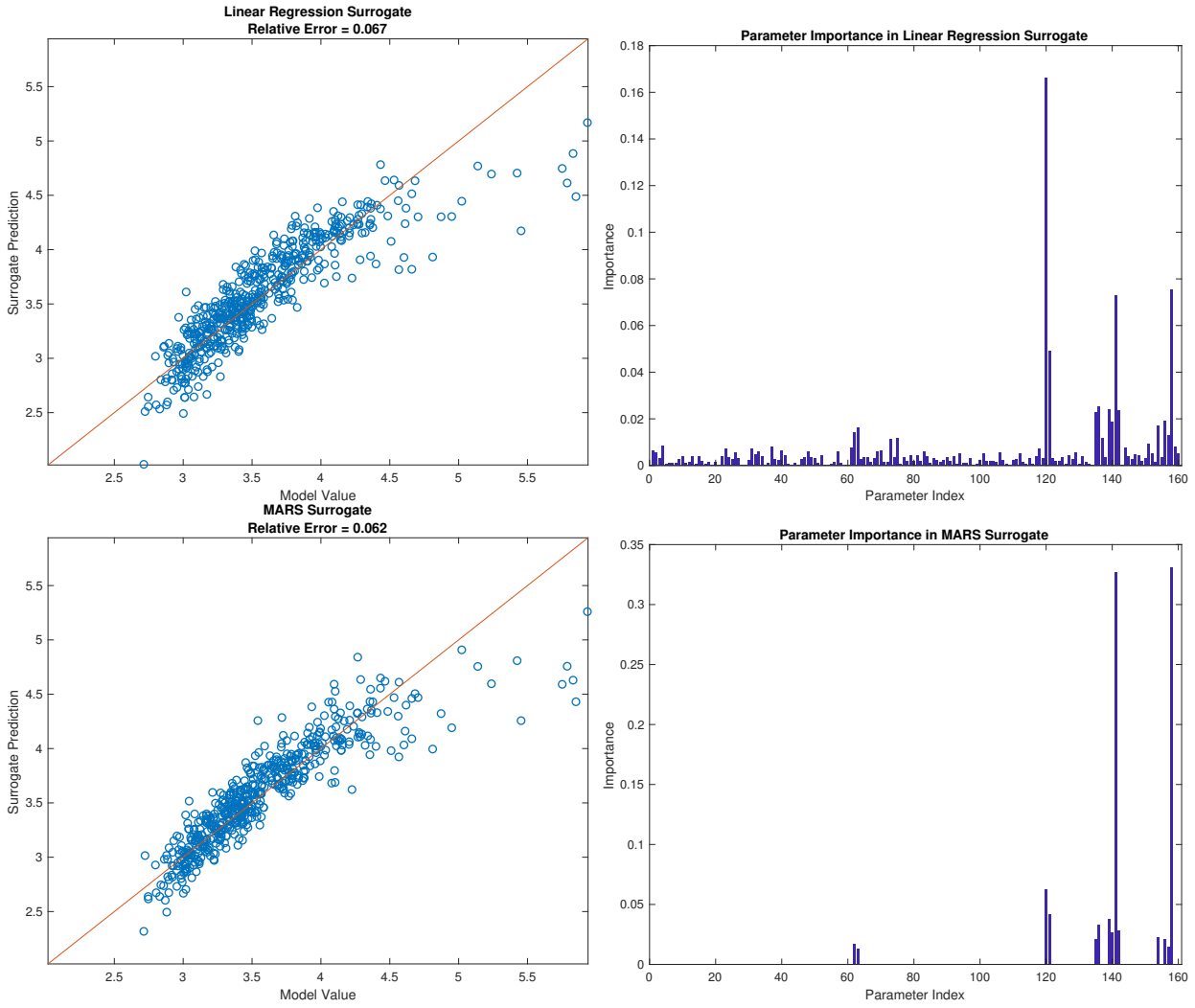


$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 7.2813$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.1360$$

Tabular data in Table 1.

3.1.2 Experimental Data Stimulus



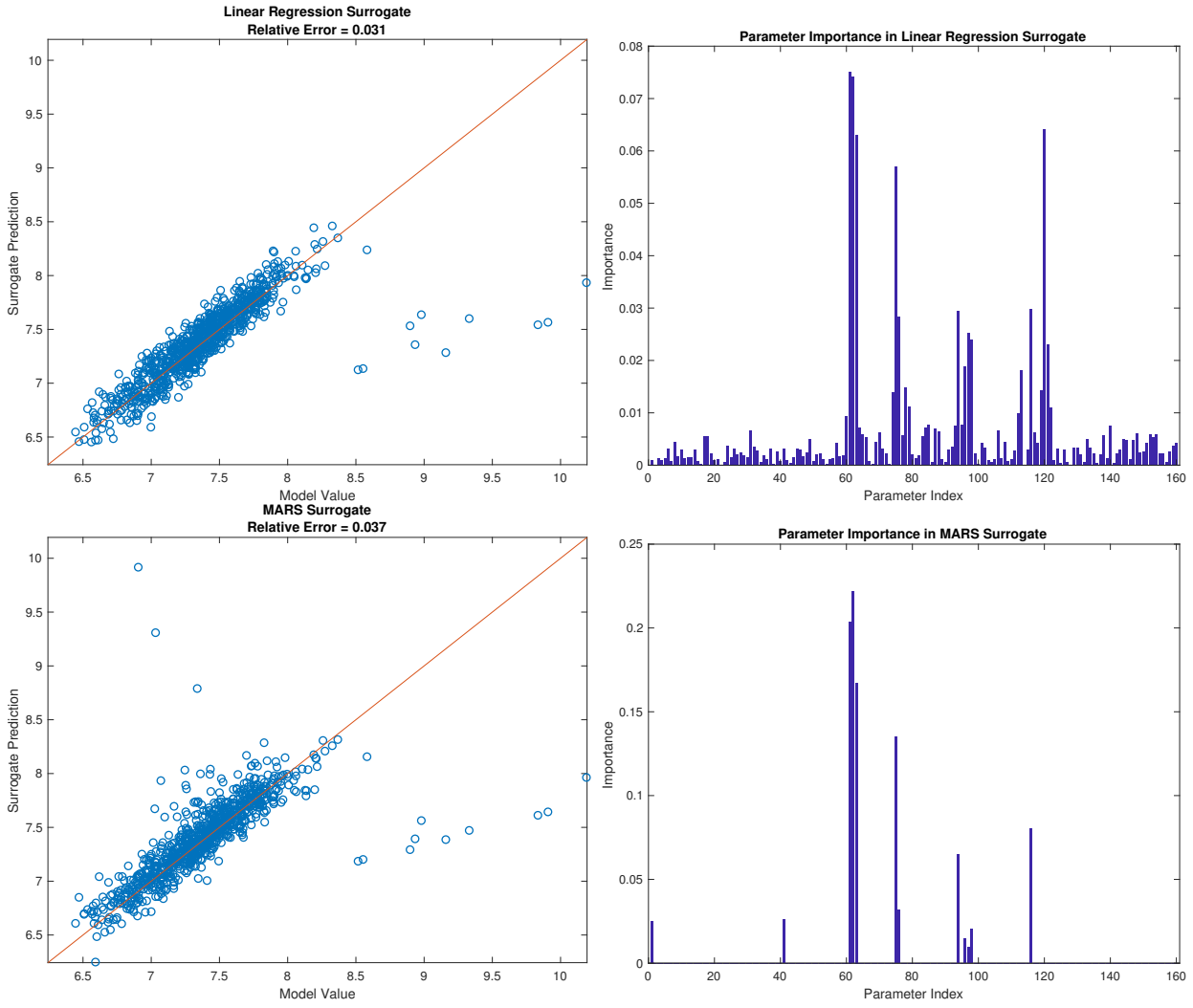
$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 7.0278$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.1407$$

Tabular data in Table 2.

3.2 QoI (2.2) (K_{ECS} Max)

3.2.1 Rectangular Pulse Stimulus

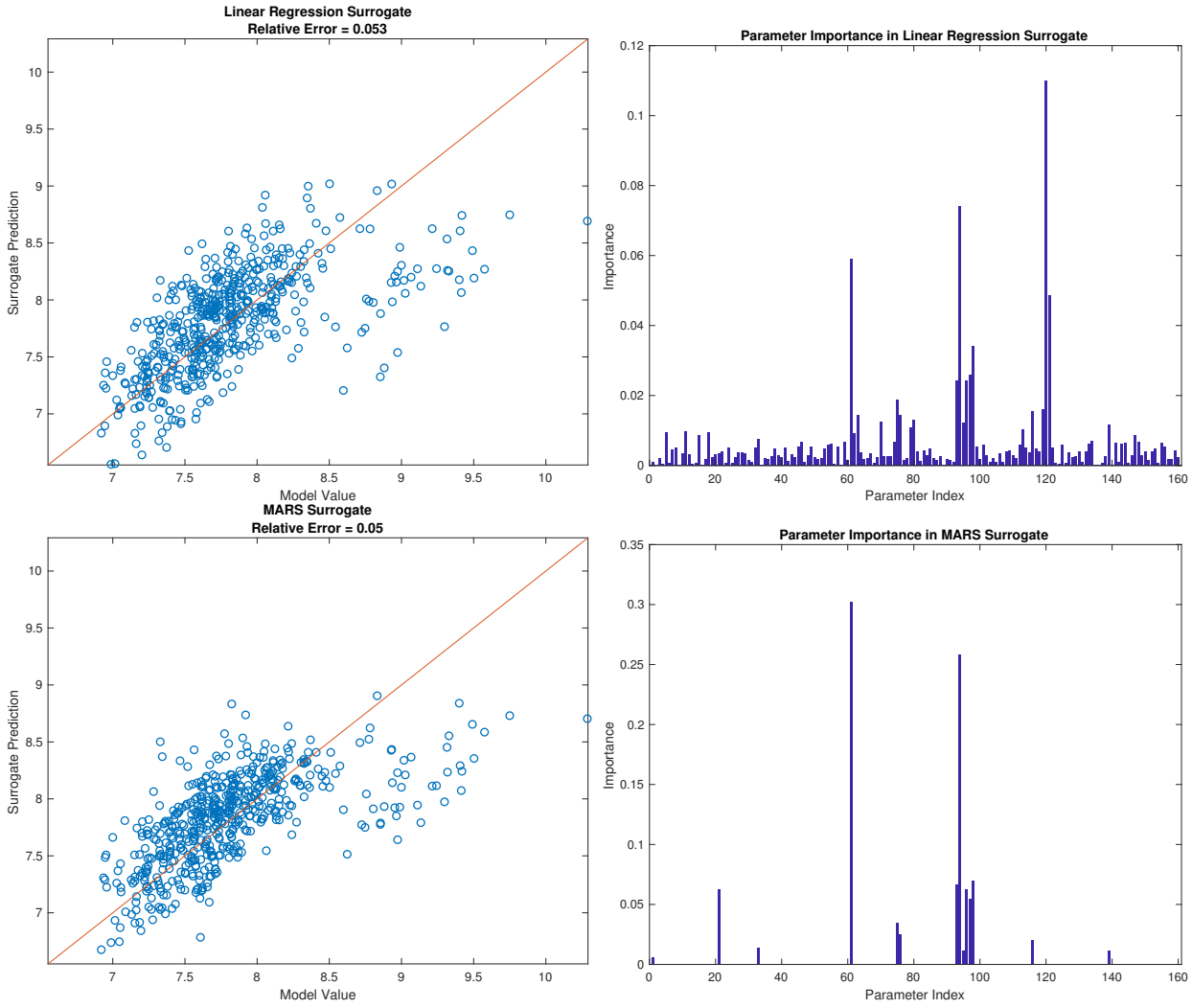


$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 18.7430$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.0532$$

Tabular data in Table 3.

3.2.2 Experimental Data Stimulus



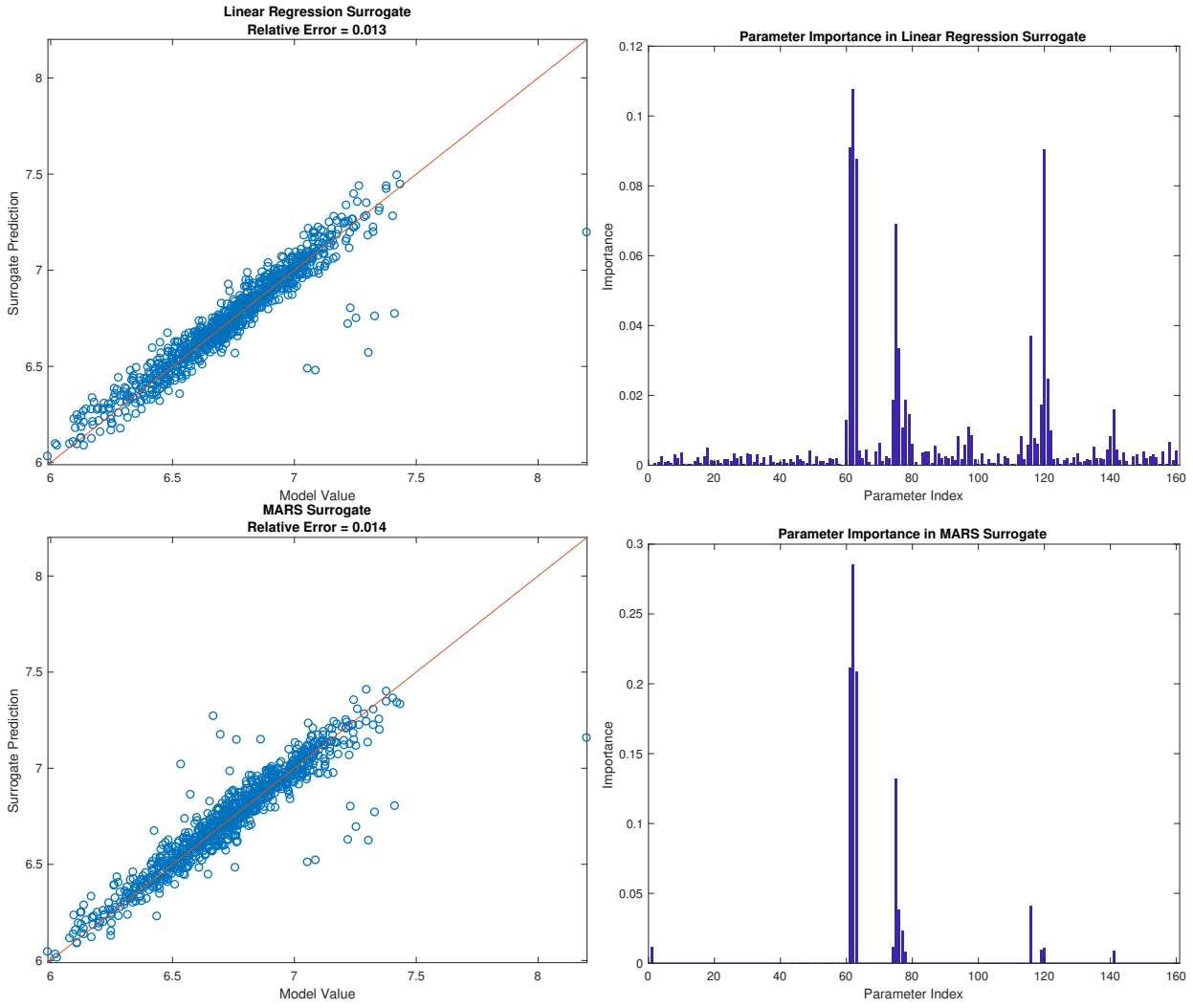
$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 15.5412$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.0642$$

Tabular data in Table 4.

3.3 QoI (2.3) (K_{ECS} Mean)

3.3.1 Rectangular Pulse Stimulus

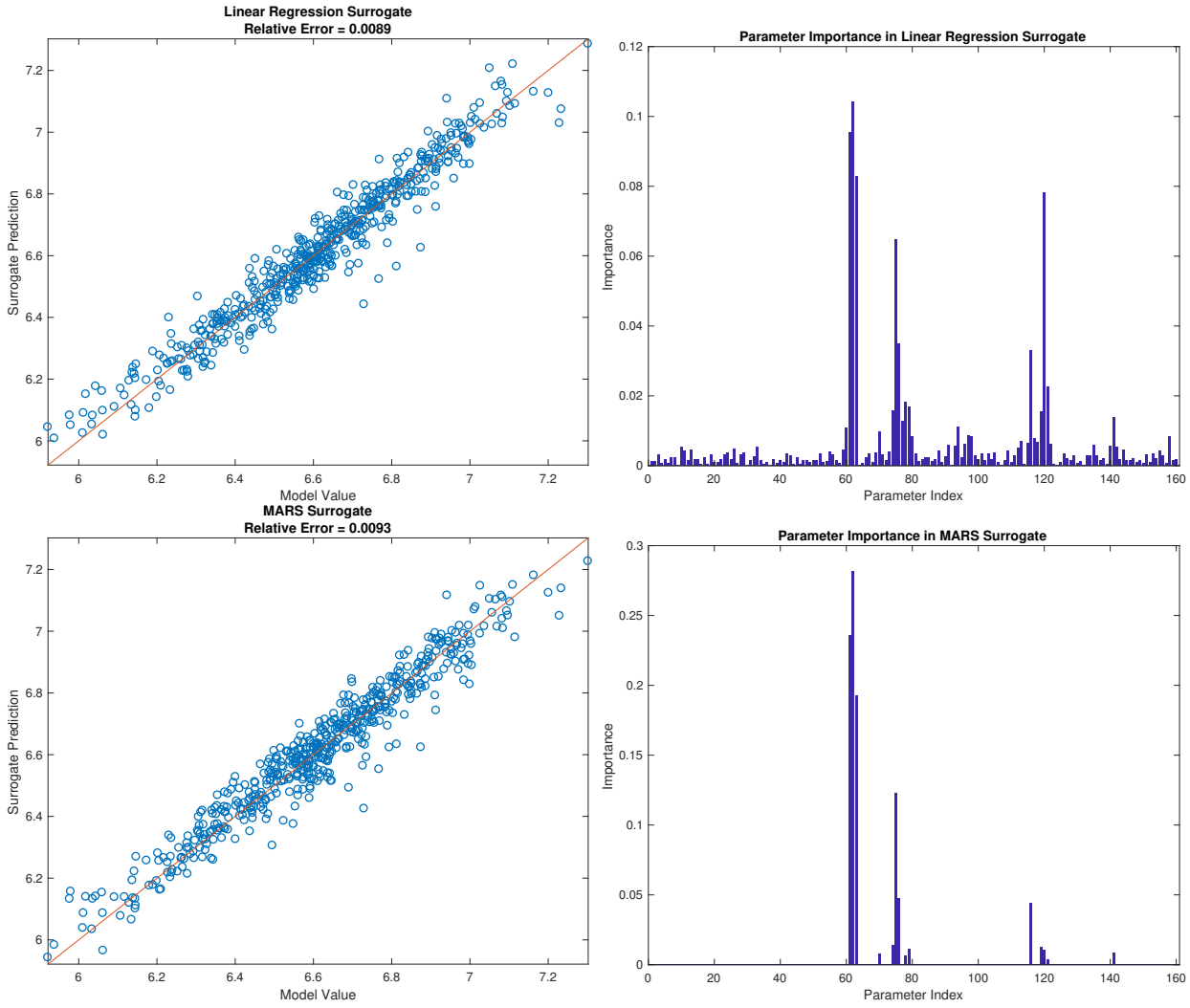


$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 25.2001$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.0396$$

Tabular data in Table 5.

3.3.2 Experimental Data Stimulus



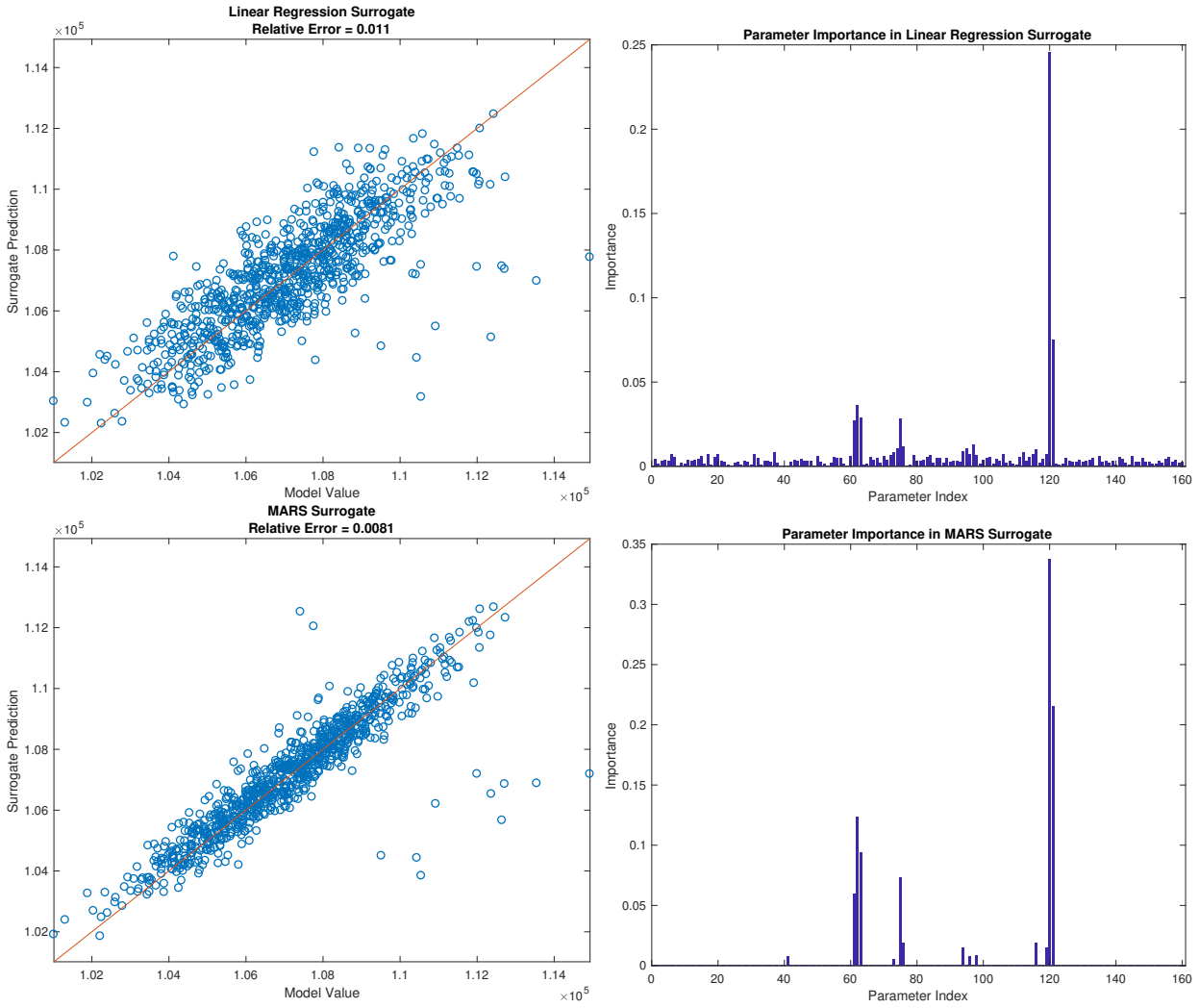
$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 26.9065$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.0371$$

Tabular data in Table 6.

3.4 QoI (2.4) (K_{AC} Max)

3.4.1 Rectangular Pulse Stimulus

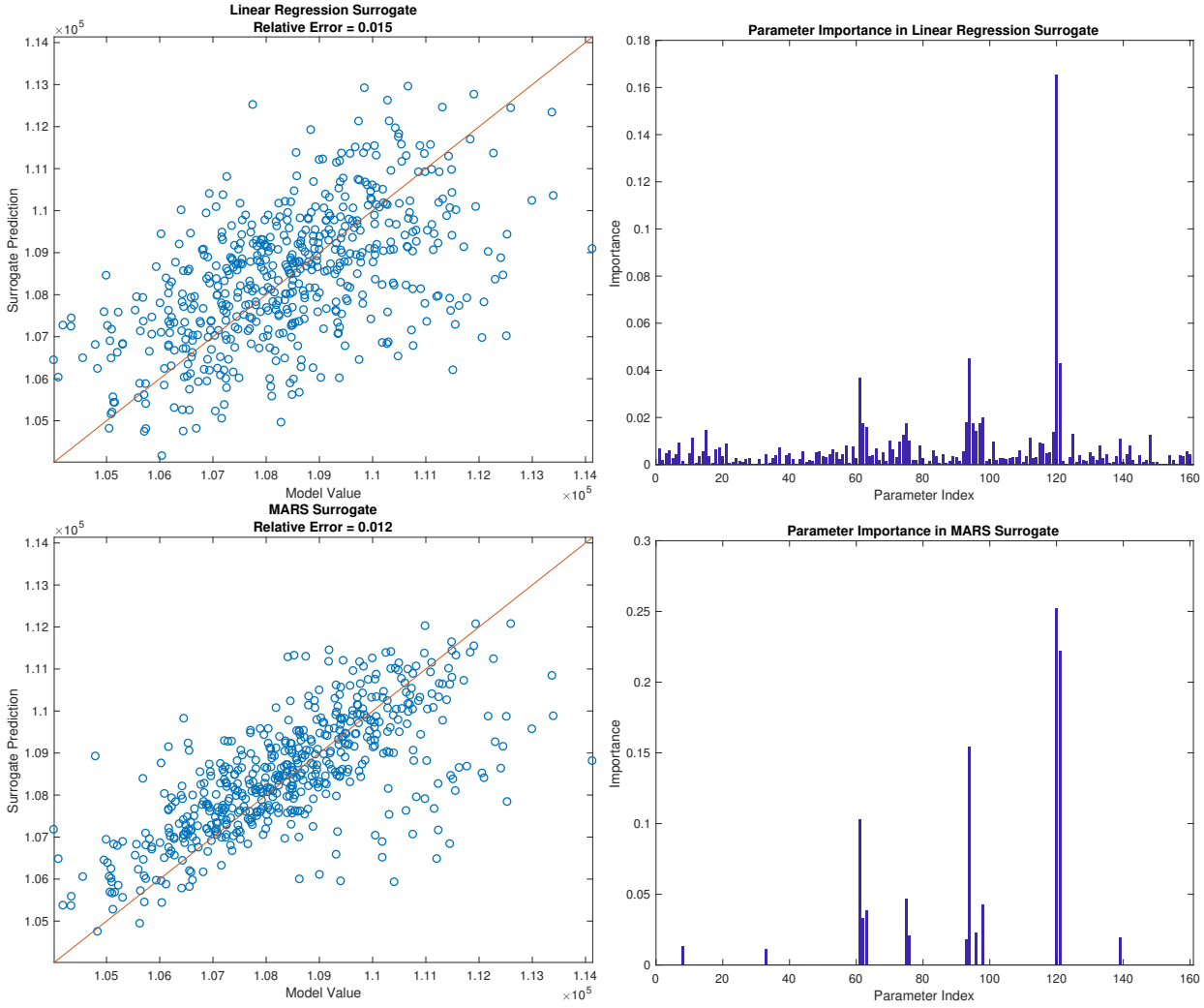


$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 52.9239$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.0189$$

Tabular data in Table 7.

3.4.2 Experimental Data Stimulus



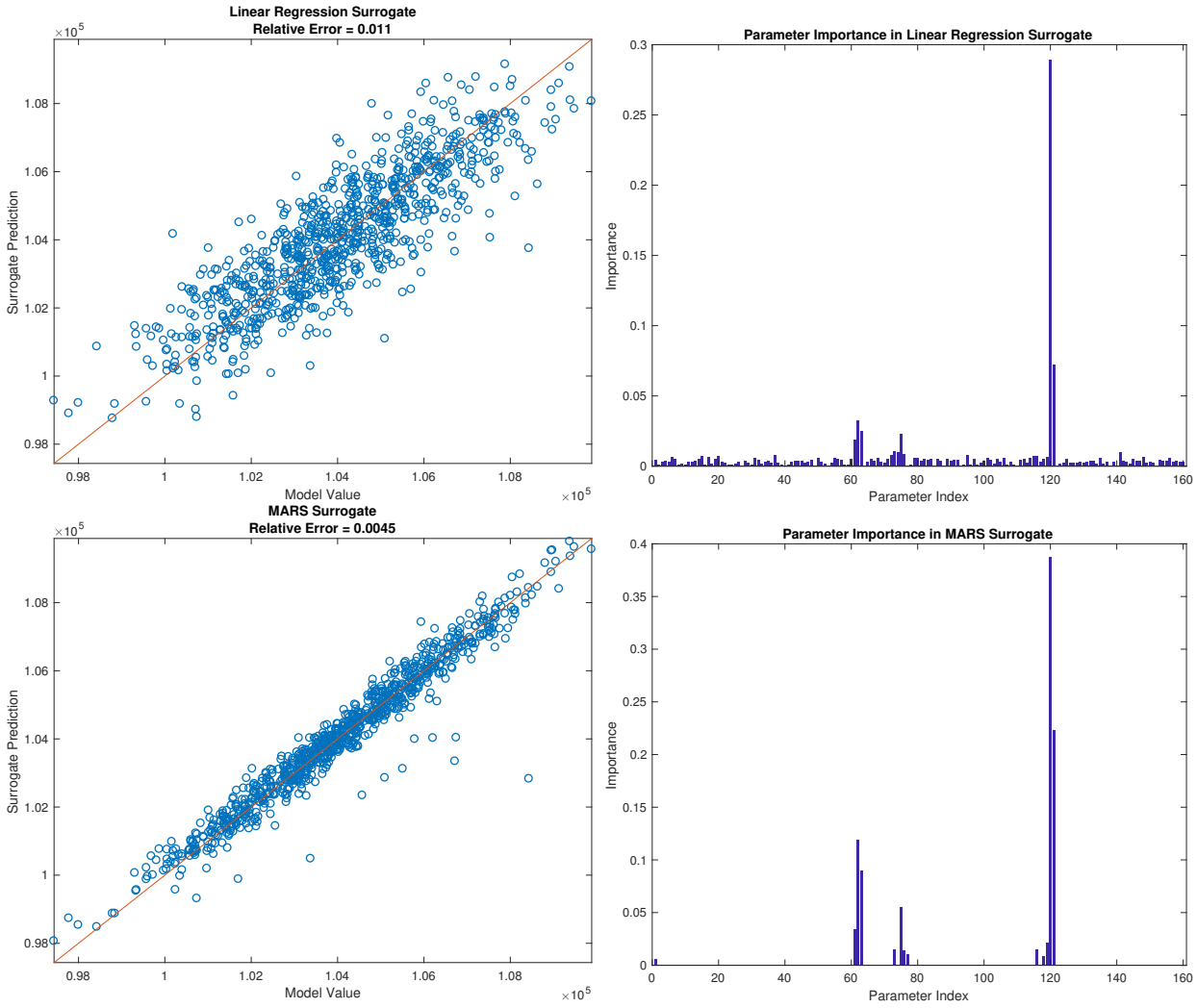
$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 61.0599$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.0164$$

Tabular data in Table 8.

3.5 QoI $(2.5)(K_{AC}$ Mean)

3.5.1 Rectangular Pulse Stimulus

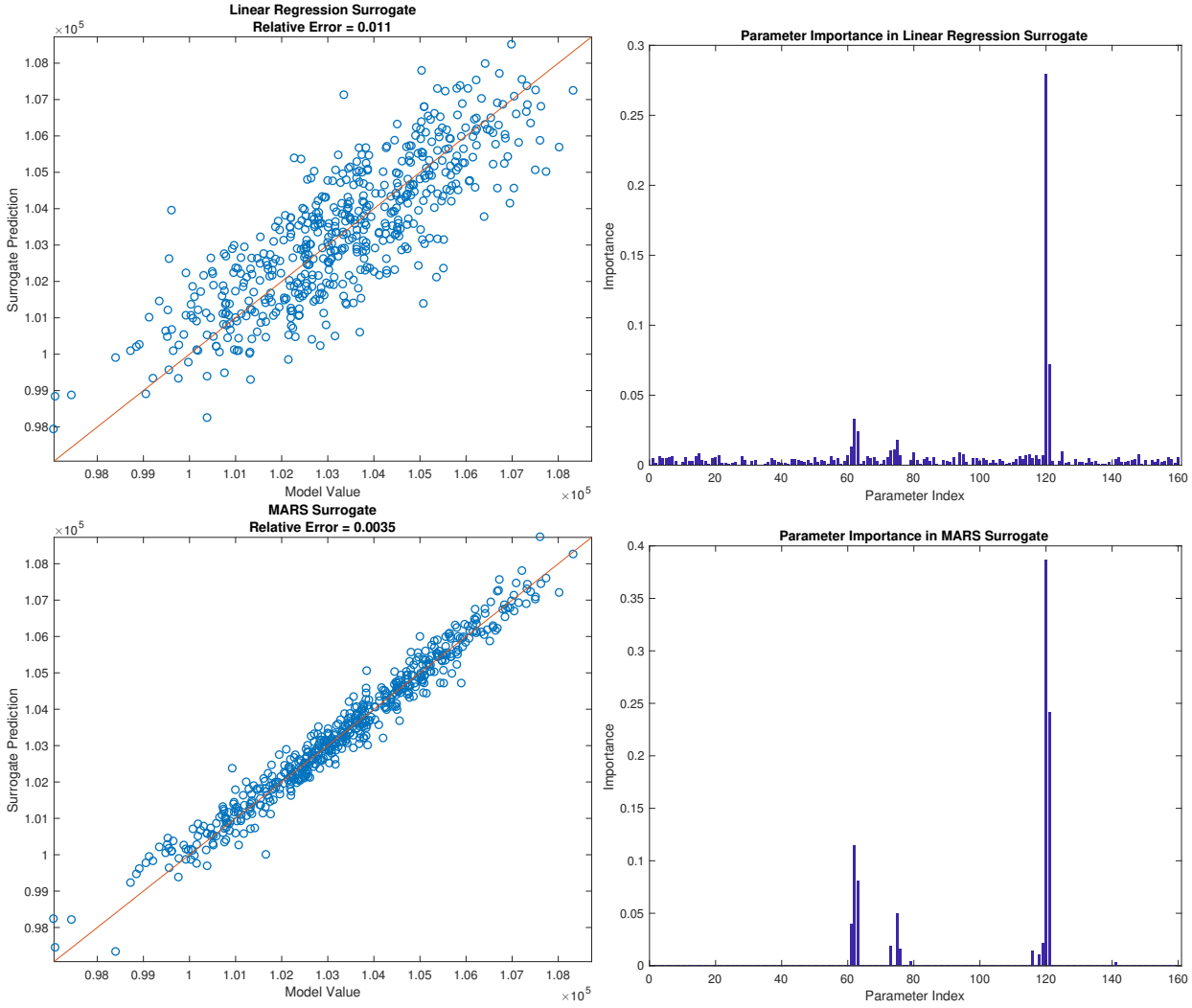


$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 50.1762$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.0199$$

Tabular data in Table 9.

3.5.2 Experimental Data Stimulus



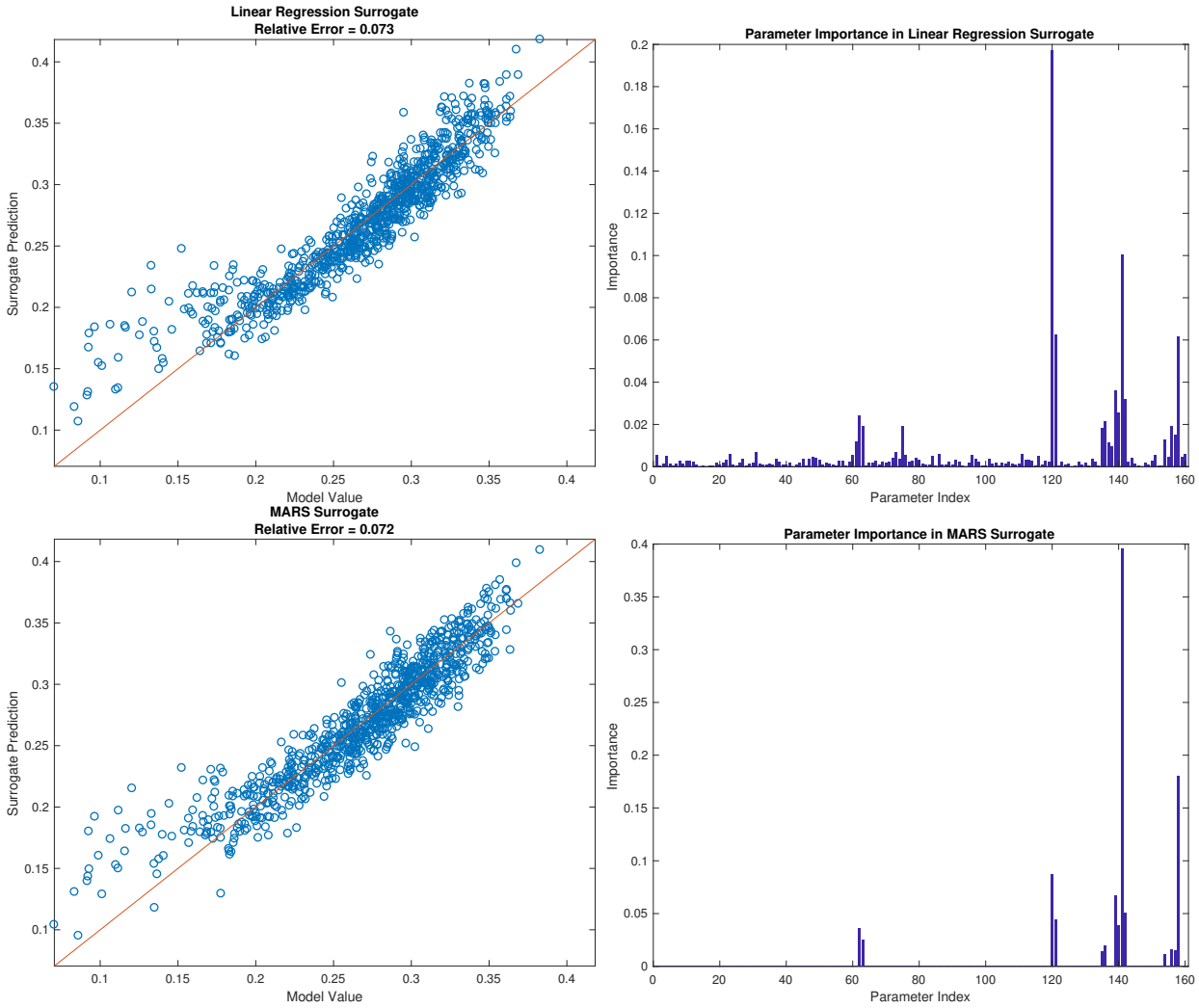
$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 52.0033$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.0192$$

Tabular data in Table 10.

3.6 QoI (2.6) ($AM + AM_p$ Min)

3.6.1 Rectangular Pulse Stimulus

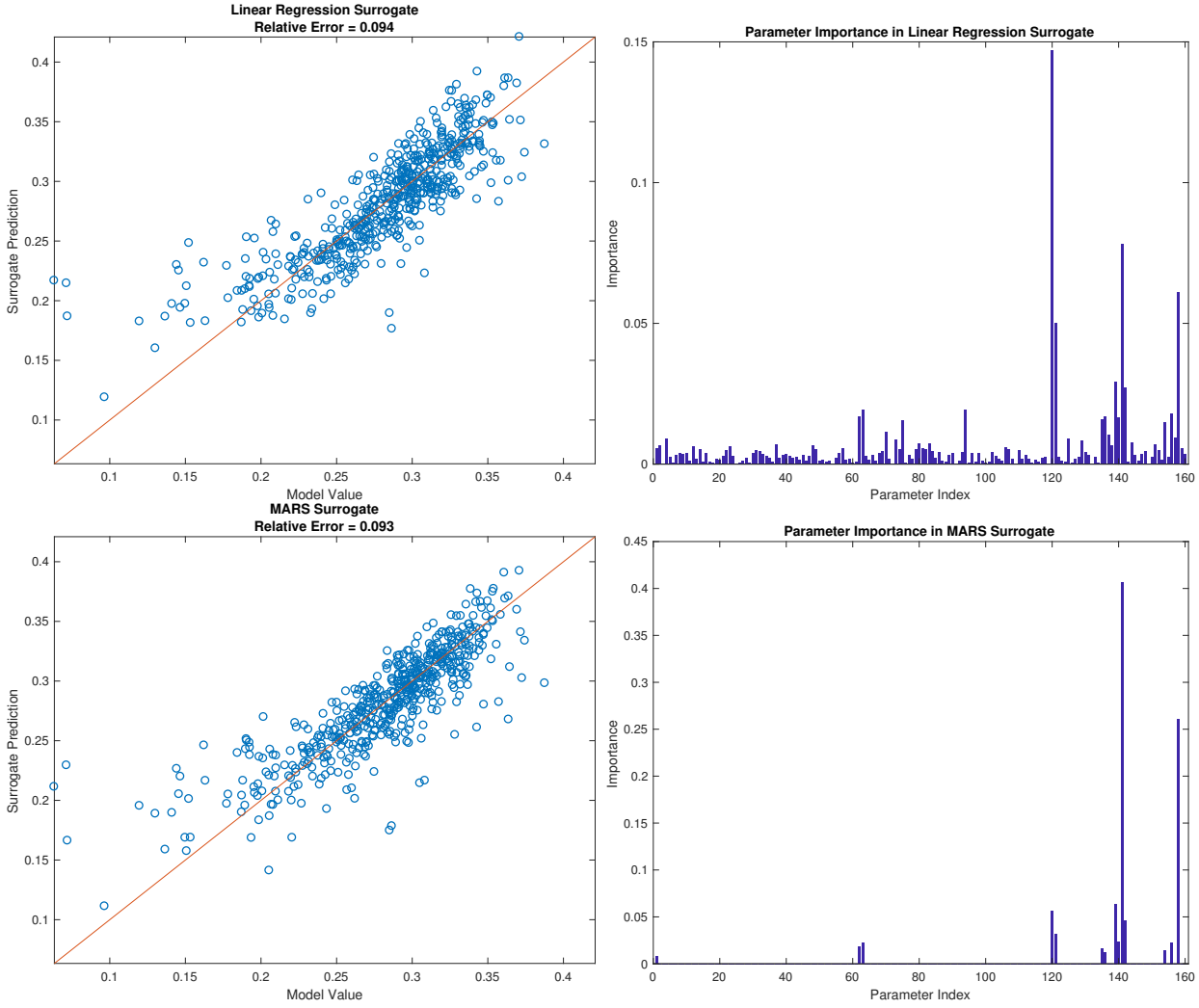


$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 4.9681$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.1972$$

Tabular data in Table 11.

3.6.2 Experimental Data Stimulus



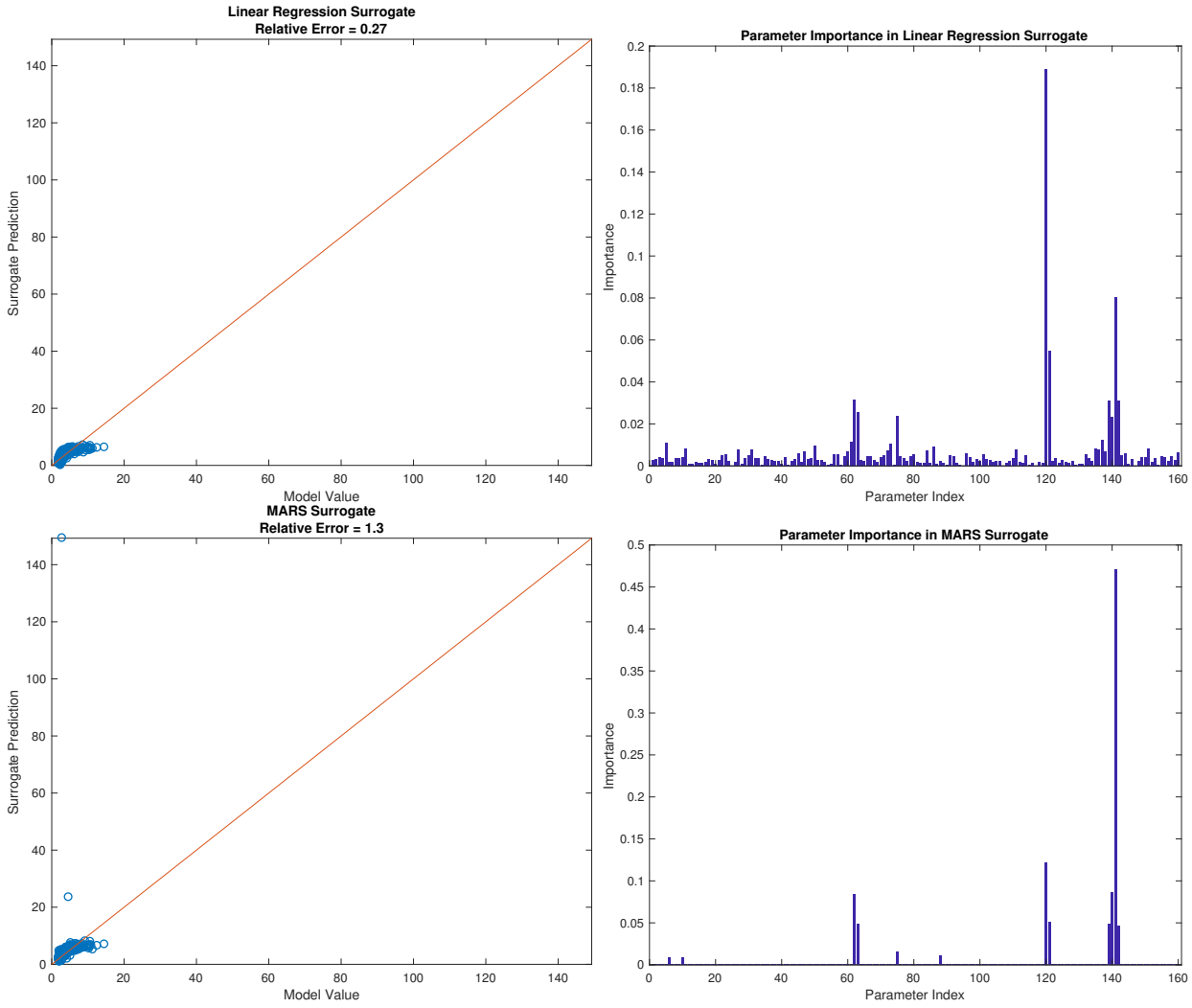
$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 5.7237$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.1720$$

Tabular data in Table 12.

3.7 QoI (2.7) (AM_p Time Lag)

3.7.1 Rectangular Pulse Stimulus

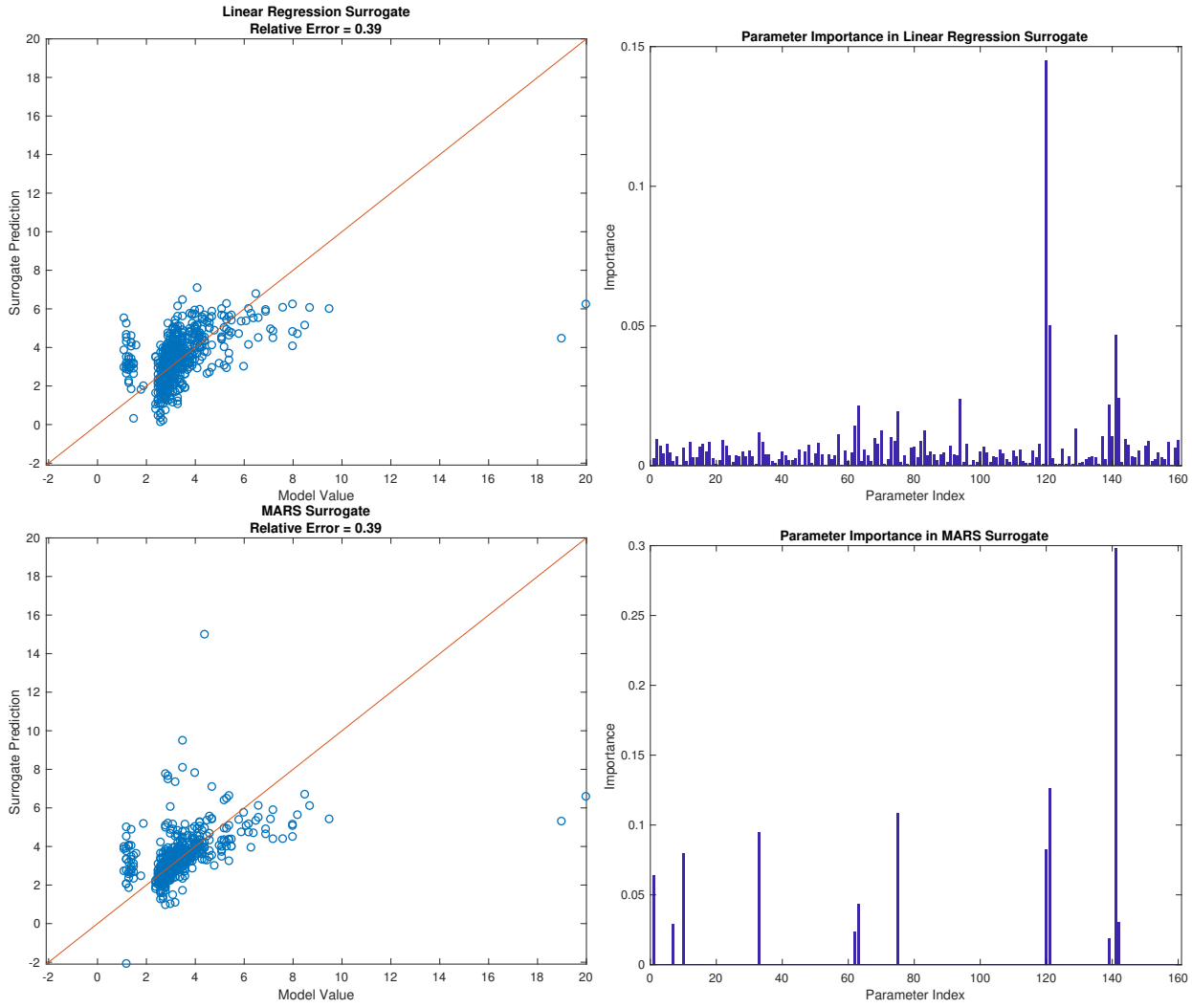


$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 2.3430$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.3924$$

The surrogate model is poor, I need to work more on this QoI.

3.7.2 Experimental Data Stimulus



$$\frac{\mu(\text{model})}{\sigma(\text{model})} = 2.2446$$

$$\frac{||\text{model} - \mu(\text{model})||_2}{||\text{model}||_2} = 0.4066$$

The surrogate model is poor, I need to work more on this QoI.

4 Discussion

5 Conclusion

References

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Index	Identification	LR Importance	MARS Importance	MARS Ranking
120	5.5 in Buff_e ODE	0.1755	0.0612	3
141	z_4 in SMCEC	0.0955	0.3226	1
158	n_cross in WallMechanics	0.0903	0.2854	2
121	1.09 in Buff_e ODE	0.0552	0.0311	7
139	z_2 in SMCEC	0.0326	0.0495	4
136	G_K_i in SMCEC	0.0313	0.0412	6
142	z_5 in SMCEC	0.0295	0.0418	5
135	F_NaK_i in SMCEC	0.0247	0.0244	11
156	K_7 in WallMechanics	0.0247	0.0284	8
157	gamma_cross in WallMechanics	0.0229	0.0275	9

Table 1: (volumetric flow rate rectangular pulse stimulus) The importance of the parameters is assessed in two ways; "LR Importance" is the absolute value of the linear regression coefficient normalized so that the sum of all indices equals 1 and "MARS Importance" is delGCV measure build in MARS normalized so that the sum of all indices equals 1. The parameters are ordered according to the results from linear regression and the ordering of parameters by MARS is given in the "MARS Ranking" column. The "Index" column is indexing of the parameters in the code (primarily for Joey's use) and the "Identification column" is the description of the parameter.

Index	Identification	LR Importance	MARS Importance	MARS Ranking
120	5.5 in Buff_e ODE	0.1663	0.0626	3
158	n_cross in WallMechanics	0.0755	0.3309	1
141	z_4 in SMCEC	0.0729	0.3270	2
121	1.09 in Buff_e ODE	0.0490	0.0423	4
136	G_K_i in SMCEC	0.0252	0.0335	6
139	z_2 in SMCEC	0.0239	0.0382	5
142	z_5 in SMCEC	0.0237	0.0285	7
135	F_NaK_i in SMCEC	0.0229	0.0212	10
156	K_7 in WallMechanics	0.0190	0.0212	11
140	z_3 in SMCEC	0.0186	0.0266	8

Table 2: (volumetric flow rate experimental data stimulus) The importance of the parameters is assessed in two ways; "LR Importance" is the absolute value of the linear regression coefficient normalized so that the sum of all indices equals 1 and "MARS Importance" is delGCV measure build in MARS normalized so that the sum of all indices equals 1. The parameters are ordered according to the results from linear regression and the ordering of parameters by MARS is given in the "MARS Ranking" column. The "Index" column is indexing of the parameters in the code (primarily for Joey's use) and the "Identification column" is the description of the parameter.

Index	Identification	LR Importance	MARS Importance	MARS Ranking
61	gKleak_d in Neuron	0.0752	0.2037	2
62	0.143 in m4alpha and m4 beta	0.0742	0.2218	1
120	5.5 in Buff_e ODE	0.0641	0	none
63	5.67 in m4alpha and m4 beta	0.0631	0.1673	3
75	34.9 in m6alpha	0.0570	0.1349	4
116	dhod in Neuron	0.0299	0.0802	5
94	34.9 in m2alpha	0.0295	0.0647	6
76	0.2 in m6alpha	0.0284	0.0317	7
97	0.025 in m2beta	0.0252	0.0097	12
98	1.25 in m2beta	0.0239	0.0203	10

Table 3: (K_{ECS} Max rectangular pulse stimulus) The importance of the parameters is assessed in two ways; "LR Importance" is the absolute value of the linear regression coefficient normalized so that the sum of all indices equals 1 and "MARS Importance" is delGCV measure build in MARS normalized so that the sum of all indices equals 1. The parameters are ordered according to the results from linear regression and the ordering of parameters by MARS is given in the "MARS Ranking" column. The "Index" column is indexing of the parameters in the code (primarily for Joey's use) and the "Identification column" is the description of the parameter.

Index	Identification	LR Importance	MARS Importance	MARS Ranking
120	5.5 in Buff_e ODE	0.1099	0	none
94	34.9 in m2alpha	0.0740	0.2584	2
61	gKleak_d in Neuron	0.0590	0.3023	1
121	1.09 in Buff_e ODE	0.0487	0	none
98	1.25 in m2beta	0.0341	0.0698	3
97	0.025 in m2beta	0.0258	0.0547	7
96	0.25 in m2beta	0.0243	0.0624	6
93	0.016 in m2alpha	0.0241	0.0670	4
75	34.9 in m6alpha	0.0187	0.0349	8
119	B0	0.0161	0	none

Table 4: (K_{ECS} Max experimental data stimulus) The importance of the parameters is assessed in two ways; "LR Importance" is the absolute value of the linear regression coefficient normalized so that the sum of all indices equals 1 and "MARS Importance" is delGCV measure build in MARS normalized so that the sum of all indices equals 1. The parameters are ordered according to the results from linear regression and the ordering of parameters by MARS is given in the "MARS Ranking" column. The "Index" column is indexing of the parameters in the code (primarily for Joey's use) and the "Identification column" is the description of the parameter.

Index	Identification	LR Importance	MARS Importance	MARS Ranking
62	0.143 in m4alpha and m4 beta	0.1078	0.2854	1
61	gKleak_d in Neuron	0.0912	0.2117	2
120	5.5 in Buff_e ODE	0.0906	0.0107	10
63	5.67 in m4alpha and m4 beta	0.0878	0.2088	3
75	34.9 in m6alpha	0.0691	0.1320	4
116	dhod in Neuron	0.0372	0.0409	5
76	0.2 in m6alpha	0.0335	0.0380	6
121	1.09 in Buff_e ODE	0.0249	none	
74	0.016 in m6alpha	0.0188	0.0114	9
78	0.025 in m6beta	0.0186	0.0079	13

Table 5: (K_{ECS} Mean rectangular pulse stimulus) The importance of the parameters is assessed in two ways; "LR Importance" is the absolute value of the linear regression coefficient normalized so that the sum of all indices equals 1 and "MARS Importance" is delGCV measure build in MARS normalized so that the sum of all indices equals 1. The parameters are ordered according to the results from linear regression and the ordering of parameters by MARS is given in the "MARS Ranking" column. The "Index" column is indexing of the parameters in the code (primarily for Joey's use) and the "Identification column" is the description of the parameter.

Index	Identification	LR Importance	MARS Importance	MARS Ranking
62	0.143 in m4alpha and m4 beta	0.1043	0.2817	1
61	gKleak_d in Neuron	0.0954	0.2357	2
63	5.67 in m4alpha and m4 beta	0.0827	0.1929	3
120	5.5 in Buff_e ODE	0.0781	0.0105	10
75	34.9 in m6alpha	0.0648	0.1232	4
76	0.2 in m6alpha	0.0349	0.0473	5
116	dhod in Neuron	0.0331	0.0040	6
121	1.09 in Buff_e ODE	0.0227	0.0040	14
78	0.025 in m6beta	0.0183	0.0065	13
79	1.25 in m6beta	0.0168	0.0110	9

Table 6: (K_{ECS} Mean experimental data stimulus) The importance of the parameters is assessed in two ways; "LR Importance" is the absolute value of the linear regression coefficient normalized so that the sum of all indices equals 1 and "MARS Importance" is delGCV measure build in MARS normalized so that the sum of all indices equals 1. The parameters are ordered according to the results from linear regression and the ordering of parameters by MARS is given in the "MARS Ranking" column. The "Index" column is indexing of the parameters in the code (primarily for Joey's use) and the "Identification column" is the description of the parameter.

Index	Identification	LR Importance	MARS Importance	MARS Ranking
120	5.5 in Buff_e ODE	0.2455	0.3379	1
121	1.09 in Buff_e ODE	0.0749	0.2155	2
62	0.143 in m4alpha and m4 beta	0.0362	0.1237	3
63	5.67 in m4alpha and m4 beta	0.0286	0.0941	4
75	34.9 in m6alpha	0.0285	0.0732	5
61	gKleak_d in Neuron	0.0270	0.0595	6
97	0.025 in m2beta	0.0126	0	none
76	0.2 in m6alpha	0.0117	0.0186	8
74	0.016 in m6alpha	0.0106	0	none
95	0.2 in m2alpha	0.0104	0	none

Table 7: (K_{AC} Max rectangular pulse stimulus) The importance of the parameters is assessed in two ways; "LR Importance" is the absolute value of the linear regression coefficient normalized so that the sum of all indices equals 1 and "MARS Importance" is delGCV measure build in MARS normalized so that the sum of all indices equals 1. The parameters are ordered according to the results from linear regression and the ordering of parameters by MARS is given in the "MARS Ranking" column. The "Index" column is indexing of the parameters in the code (primarily for Joey's use) and the "Identification column" is the description of the parameter.

Index	Identification	LR Importance	MARS Importance	MARS Ranking
120	5.5 in Buff_e ODE	0.1654	0.2521	1
94	34.9 in m2alpha	0.0450	0.1545	3
121	1.09 in Buff_e ODE	0.0427	0.2221	2
61	gKleak_d in Neuron	0.0366	0.1032	4
98	1.25 in m2beta	0.0197	0.0430	6
93	0.016 in m2alpha	0.0180	0.0182	12
97	0.025 in m2beta	0.0176	0	none
75	34.9 in m6alpha	0.0176	0.0470	5
95	0.2 in m2alpha	0.0176	0	none
62	0.143 in m4alpha and m4 beta	0.0174	0.0329	8

Table 8: (K_{AC} Max experimental data stimulus) The importance of the parameters is assessed in two ways; "LR Importance" is the absolute value of the linear regression coefficient normalized so that the sum of all indices equals 1 and "MARS Importance" is delGCV measure build in MARS normalized so that the sum of all indices equals 1. The parameters are ordered according to the results from linear regression and the ordering of parameters by MARS is given in the "MARS Ranking" column. The "Index" column is indexing of the parameters in the code (primarily for Joey's use) and the "Identification column" is the description of the parameter.

Index	Identification	LR Importance	MARS Importance	MARS Ranking
120	5.5 in Buff_e ODE	0.2892	0.3871	1
121	1.09 in Buff_e ODE	0.0724	0.2228	2
62	0.143 in m4alpha and m4 beta	0.0328	0.1194	3
63	5.67 in m4alpha and m4 beta	0.0250	0.0900	4
75	34.9 in m6alpha	0.0230	0.0550	5
61	gKleak_d in Neuron	0.0188	0.0345	6
73	0.07 in J_NMDA_K_d	0.0104	0.0153	8
141	z_4 in SMCEC	0.0099	0	none
74	0.016 in m6alpha	0.0099	0	none
76	0.2 in m6alpha	0.0083	0.0146	10

Table 9: (K_{AC} Mean rectangular pulse stimulus) The importance of the parameters is assessed in two ways; "LR Importance" is the absolute value of the linear regression coefficient normalized so that the sum of all indices equals 1 and "MARS Importance" is delGCV measure build in MARS normalized so that the sum of all indices equals 1. The parameters are ordered according to the results from linear regression and the ordering of parameters by MARS is given in the "MARS Ranking" column. The "Index" column is indexing of the parameters in the code (primarily for Joey's use) and the "Identification column" is the description of the parameter.

Index	Identification	LR Importance	MARS Importance	MARS Ranking
120	5.5 in Buff_e ODE	0.2799	0.3867	1
121	1.09 in Buff_e ODE	0.0720	0.2413	2
62	0.143 in m4alpha and m4 beta	0.0335	0.1141	3
63	5.67 in m4alpha and m4 beta	0.0242	0.0805	4
75	34.9 in m6alpha	0.0181	0.0499	5
61	gKleak_d in Neuron	0.0131	0.0396	6
74	0.016 in m6alpha	0.0114	0	none
73	0.07 in J_NMDA_K_d	0.0103	0.0184	8
125	v_6 in Astrocyte	0.0096	0	none
94	34.9 in m2alpha	0.0093	0	none

Table 10: (K_{AC} Mean experimental data stimulus) The importance of the parameters is assessed in two ways; "LR Importance" is the absolute value of the linear regression coefficient normalized so that the sum of all indices equals 1 and "MARS Importance" is delGCV measure build in MARS normalized so that the sum of all indices equals 1. The parameters are ordered according to the results from linear regression and the ordering of parameters by MARS is given in the "MARS Ranking" column. The "Index" column is indexing of the parameters in the code (primarily for Joey's use) and the "Identification column" is the description of the parameter.

Index	Identification	LR Importance	MARS Importance	MARS Ranking
120	5.5 in Buff_e ODE	0.1970	0.0871	3
141	z_4 in SMCEC	0.1005	0.3960	1
121	1.09 in Buff_e ODE	0.0627	0.0442	6
158	n_cross in WallMechanics	0.0617	0.1801	2
139	z_2 in SMCEC	0.0362	0.0671	4
142	z_5 in SMCEC	0.0320	0.0503	5
140	z_3 in SMCEC	0.0253	0.0385	7
62	0.143 in m4alpha and m4 beta	0.0243	0.0358	8
136	G_K_i in SMCEC	0.0215	0.0200	10
75	34.9 in m6alpha	0.0194	0	none

Table 11: ($AM + AM_p$ Min rectangular pulse stimulus) The importance of the parameters is assessed in two ways; "LR Importance" is the absolute value of the linear regression coefficient normalized so that the sum of all indices equals 1 and "MARS Importance" is delGCV measure build in MARS normalized so that the sum of all indices equals 1. The parameters are ordered according to the results from linear regression and the ordering of parameters by MARS is given in the "MARS Ranking" column. The "Index" column is indexing of the parameters in the code (primarily for Joey's use) and the "Identification column" is the description of the parameter.

Index	Identification	LR Importance	MARS Importance	MARS Ranking
120	5.5 in Buff_e ODE	0.1470	0.0565	4
141	z_4 in SMCEC	0.0783	0.4063	1
158	n_cross in WallMechanics	0.0612	0.2605	2
121	1.09 in Buff_e ODE	0.0503	0.0312	6
139	z_2 in SMCEC	0.0293	0.0638	3
142	z_5 in SMCEC	0.0272	0.0456	5
94	34.9 in m2alpha	0.0195	0	none
63	5.67 in m4alpha and m4 beta	0.0193	0.0224	9
156	K_7 in WallMechanics	0.0179	0.0227	8
62	0.143 in m4alpha and m4 beta	0.0171	0.0182	10

Table 12: ($AM + AM_p$ Min experimental data stimulus) The importance of the parameters is assessed in two ways; "LR Importance" is the absolute value of the linear regression coefficient normalized so that the sum of all indices equals 1 and "MARS Importance" is delGCV measure build in MARS normalized so that the sum of all indices equals 1. The parameters are ordered according to the results from linear regression and the ordering of parameters by MARS is given in the "MARS Ranking" column. The "Index" column is indexing of the parameters in the code (primarily for Joey's use) and the "Identification column" is the description of the parameter.