

## S1 Supplementary Material for: Modeling Variability in Cardiac Electrophysiology: A Moment Matching Approach

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### Additional tables

**Table 1.** Statistics summary of the estimated parameters from the Decker model in control conditions (no drug block).

Parameter	$\mu$	$\mu_{ex}$	rel. err.	$\sigma$	$\sigma_{ex}$	rel. err.
$g_{Na}$	1.104	1.100	<b>0.4%</b>	0.155	0.150	<b>3.1%</b>
$g_{K1}$	1.099	1.100	<b>0.1%</b>	0.164	0.150	<b>9.2%</b>
$g_{to}$	1.103	1.100	<b>0.3%</b>	0.182	0.150	<b>21.2%</b>
$g_{Kr}$	1.091	1.100	<b>0.9%</b>	0.172	0.150	<b>14.4%</b>
$g_{Ks}$	1.264	1.100	<b>14.9%</b>	0.426	0.150	<b>184.0%</b>
$g_{CaL}$	1.102	1.100	<b>0.2%</b>	0.177	0.150	<b>17.8%</b>

**Table 2.** Statistics summary of the estimated parameters from the Decker model in drug block conditions (90% block for  $I_{to}$ ,  $I_{Kr}$  and  $I_{CaL}$ ).

Parameter	$\mu$	$\mu_{ex}$	rel. err.	$\sigma$	$\sigma_{ex}$	rel. err.
$g_{Na}$	1.104	1.100	<b>0.4%</b>	0.158	0.150	<b>5.5%</b>
$g_{K1}$	1.102	1.100	<b>0.1%</b>	0.154	0.150	<b>2.6%</b>
$g_{Ks}$	1.100	1.100	<b>0.0%</b>	0.158	0.150	<b>5.1%</b>

**Table 3.** Statistics summary of the estimated parameters from the Decker model in control conditions with moments constraints from drug block estimation.

Parameter	$\mu$	$\mu_{ex}$	rel. err.	$\sigma$	$\sigma_{ex}$	rel. err.
$g_{Na}$	1.104	1.100	<b>0.4%</b>	0.158	0.150	<b>5.5%</b>
$g_{K1}$	1.102	1.100	<b>0.1%</b>	0.154	0.150	<b>2.6%</b>
$g_{to}$	1.104	1.100	<b>0.4%</b>	0.182	0.150	<b>21.3%</b>
$g_{K\tau}$	1.101	1.100	<b>0.1%</b>	0.173	0.150	<b>15.6%</b>
$g_{Ks}$	1.100	1.100	<b>0.0%</b>	0.158	0.150	<b>5.1%</b>
$g_{CaL}$	1.102	1.100	<b>0.2%</b>	0.176	0.150	<b>17.1%</b>

**Table 4.** Statistics summary of the estimated parameters from the Courtemanche model in control conditions.

Parameter	$\mu$	$\mu_{ex}$	rel. err.	$\sigma$	$\sigma_{ex}$	rel. err.
$g_{Na}$	1.098	1.100	<b>0.2%</b>	0.149	0.150	<b>0.7%</b>
$g_{K1}$	1.102	1.100	<b>0.2%</b>	0.163	0.150	<b>9.1%</b>
$g_{to}$	1.109	1.100	<b>0.8%</b>	0.180	0.150	<b>20.1%</b>
$g_{K\tau}$	1.087	1.100	<b>1.0%</b>	0.302	0.150	<b>102%</b>
$g_{Ks}$	1.201	1.100	<b>9.2%</b>	0.426	0.150	<b>184%</b>
$g_{CaL}$	1.104	1.100	<b>0.4%</b>	0.178	0.150	<b>18.3%</b>

**Table 5.** Statistics summary of the estimated parameters from the Courtemanche model at 2Hz pacing frequency.

Parameter	$\mu$	$\mu_{ex}$	rel. err.	$\sigma$	$\sigma_{ex}$	rel. err.
$g_{Na}$	1.099	1.100	<b>0.1%</b>	0.151	0.150	<b>1.0%</b>
$g_{K1}$	1.110	1.100	<b>0.9%</b>	0.167	0.150	<b>11.6%</b>
$g_{to}$	1.109	1.100	<b>0.8%</b>	0.185	0.150	<b>23.3%</b>
$g_{K\tau}$	1.064	1.100	<b>3.2%</b>	0.366	0.150	<b>144%</b>
$g_{Ks}$	1.263	1.100	<b>14.9%</b>	0.424	0.150	<b>183%</b>
$g_{CaL}$	1.132	1.100	<b>2.9%</b>	0.208	0.150	<b>38.4%</b>

**Table 6.** Statistics summary of the estimated parameters from the Courtemanche model (combined 1Hz+2Hz data).

Parameter	$\mu$	$\mu_{ex}$	rel. err.	$\sigma$	$\sigma_{ex}$	rel. err.
$g_{Na}$	1.098	1.100	<b>0.2%</b>	0.149	0.150	<b>0.4%</b>
$g_{K1}$	1.103	1.100	<b>0.2%</b>	0.166	0.150	<b>11.0%</b>
$g_{to}$	1.106	1.100	<b>0.6%</b>	0.165	0.150	<b>9.7%</b>
$g_{Kr}$	1.096	1.100	<b>0.4%</b>	0.266	0.150	<b>77.2%</b>
$g_{Ks}$	1.150	1.100	<b>4.6%</b>	0.424	0.150	<b>183%</b>
$g_{CaL}$	1.102	1.100	<b>0.2%</b>	0.161	0.150	<b>7.4%</b>

**Table 7.** Davies model: experimental parameter calibration and observable moment matching results.

Conductance	OMM results		Reference values		
	$\mu$	$\sigma$	exp. calibration	literature	unit
$g_{Na}$	-	-	27.4	8.25	nS/pF
$g_{NaL}$	-	-	$7.26 \times 10^{-2}$	$1.1 \times 10^{-2}$	nS/pF
$g_{Kr}$	<b>0.96</b>	<b>0.03</b>	$4.82 \times 10^{-2}$	$1.39 \times 10^{-2}$	nS/pF
$g_{Ks}$	<b>1.06</b>	<b>0.12</b>	$1.38 \times 10^{-1}$	$7.47 \times 10^{-3}$	nS/pF
$g_{K1}$	-	-	$2.91 \times 10^{-1}$	$5.0 \times 10^{-1}$	nS/pF
$g_{Kp}$	-	-	$7.93 \times 10^{-3}$	$2.76 \times 10^{-3}$	nS/pF
$g_{to1}$	<b>1.03</b>	<b>0.11</b>	0.38	0.18	nS/pF
$g_{CaL}$	-	-	$2.0 \times 10^{-4}$	$9.7 \times 10^{-4}$	nS/pF
$g_{bCa}$	-	-	$5.88 \times 10^{-6}$	$7.98 \times 10^{-7}$	nS/pF
$g_{pCa}$	-	-	$9.84 \times 10^{-4}$	$5.75 \times 10^{-2}$	pA/pF
$g_{Clb}$	-	-	$9.45 \times 10^{-6}$	$2.25 \times 10^{-4}$	nS/pF
$g_{to2}$	-	-	$4.54 \times 10^{-9}$	$4 \times 10^{-7}$	L/F.ms
$g_{NaCa}$	-	-	$6.95 \times 10^{-2}$	5.85	pA/pF
$g_{NaK}$	-	-	$6.6 \times 10^{-3}$	$6.19 \times 10^{-1}$	pA/pF

**Table 8.** Human biomarkers dataset statistics.

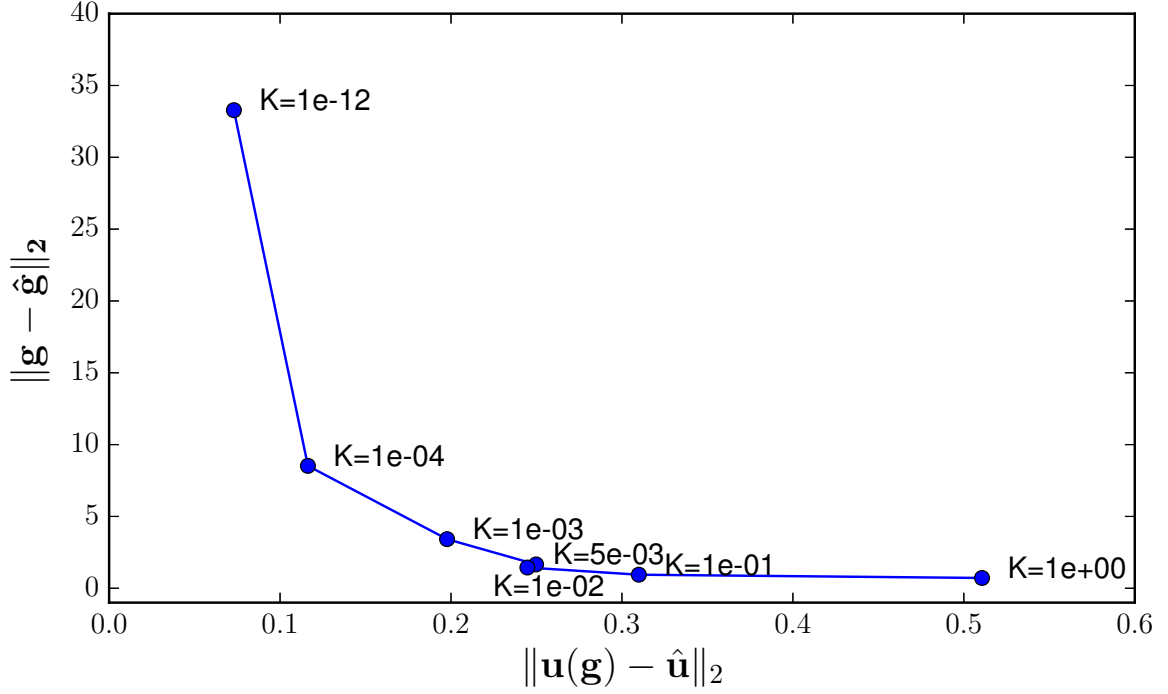
group		APD90	APD50	APD20	APA	RMP	$dV/dt_{max}$	V20
SR	representative (#163)	<b>324</b>	<b>142</b>	<b>5</b>	<b>93</b>	<b>-74</b>	<b>214</b>	<b>-19</b>
	median	319	151	5	95	-74	213	-16
	mean	317.7	138.7	7.1	94.8	-73.8	219.7	-16.1
	std	42.7	44.1	8.2	7.1	3.9	67.9	6.4
AF	representative (#131)	<b>213</b>	<b>105</b>	<b>38</b>	<b>98</b>	<b>-76</b>	<b>237</b>	<b>0</b>
	median	213	101	27	102	-77	229	-4
	mean	216.4	101.5	30.2	101.6	-76.8	232.0	-4.4
	std	34.4	27.7	17.9	7.6	3.6	70.3	10.9

**Table 9.** Courtemanche model: experimental parameter calibration.

Conductance	Experimentally calibrated (normalized)			Reference value	unit
	SR group	AF group	AF/SR rel. change		
$g_{Na}$	1.17	1.11	-5%	7.8	nS/pF
$g_{K1}$	0.45	1.45	<b>+220%</b>	$9.0 \times 10^{-2}$	nS/pF
$g_{to}$	1.12	$2.83 \times 10^{-3}$	<b>-100%</b>	$1.65 \times 10^{-1}$	nS/pF
$g_{Kr}$	1.15	1.41	+23%	$2.94 \times 10^{-2}$	nS/pF
$g_{Ks}$	1.10	1.21	+10%	$1.29 \times 10^{-1}$	nS/pF
$g_{CaL}$	0.87	0.32	<b>-63%</b>	$1.24 \times 10^{-1}$	nS/pF
$g_{bNa}$	1.26	1.31	+4%	$6.74 \times 10^{-4}$	nS/pF
$g_{bCa}$	1.14	1.85	+63%	$1.13 \times 10^{-3}$	nS/pF
$g_{NaK}$	0.78	0.80	+3%	0.6	pA/pF
$g_{NaCa}$	$4.65 \times 10^{-2}$	2.01	$\times 43$	$1.6 \times 10^3$	pA/pF
$g_{Kur}$	0.54	0.21	<b>-60%</b>	1.0	dimensionless

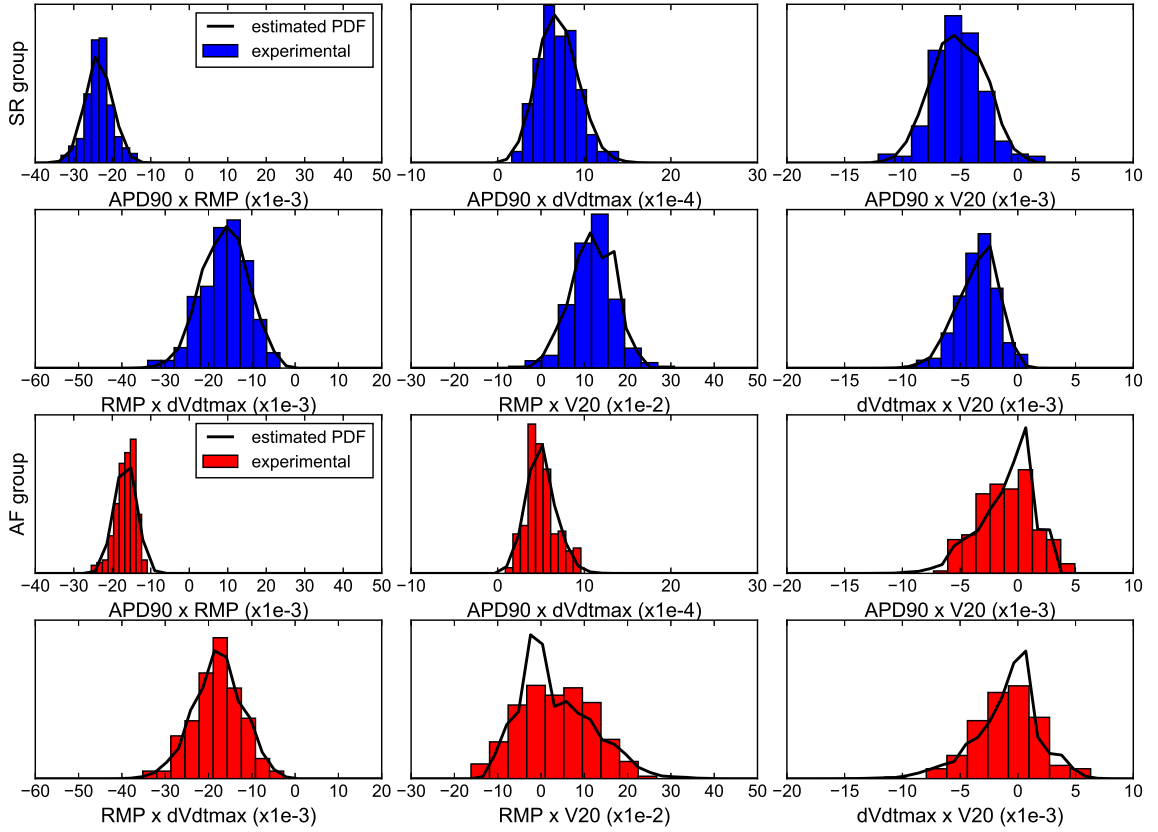
**Table 10.** Statistics summary of the estimated parameters from the Courtemanche model with experimental data (SR and AF group), normalized by the reference values.

Group	SR		AF	
	$\mu$	$\sigma$	$\mu$	$\sigma$
$g_{Na}$	1.464	0.652	1.310	0.533
$g_{K1}$	0.431	0.125	1.744	0.656
$g_{to}$	1.090	0.219	0.310	0.392
$g_{Kr}$	0.934	0.375	1.997	1.314



**Figure 1.** L-curve: calibration fitness plotted against the distance to reference conductances.

**Influence of  $K$  in the calibration step** We replicated the calibration procedure in Test Case 4 with the SR group representative several times by varying the regularization parameter  $K$ . In Figure 1, the fitness is plotted against the distance to the reference conductances values for different values of  $K$ .  $\mathbf{g}$  denotes the conductance values estimated by the CMA-ES algorithm,  $\hat{\mathbf{g}}$  are the reference values for these conductances,  $\mathbf{u}(\mathbf{g})$  are the simulated biomarkers and  $\hat{\mathbf{u}}$  are the experimental biomarkers to be fitted. We obtain a so-called “L-curve” which is typical of such hyper-parameter studies. We see that  $K=5e-3$  is a reasonable choice as it is close the curve’s elbow and therefore a good trade-off between goodness of fit and distance to the reference values.



**Figure 2.** Normalized histograms of the experimental biomarkers pairwise products for both SR (blue) and AF (red) groups. The black solid lines correspond to the PDF of each pairwise product estimated by the observable moment matching method. Biomarkers computed from an AP. This figure is an extension of Fig.7(C) in the main article.

## Appendix A: Illustration of the OMM method using the Davies model

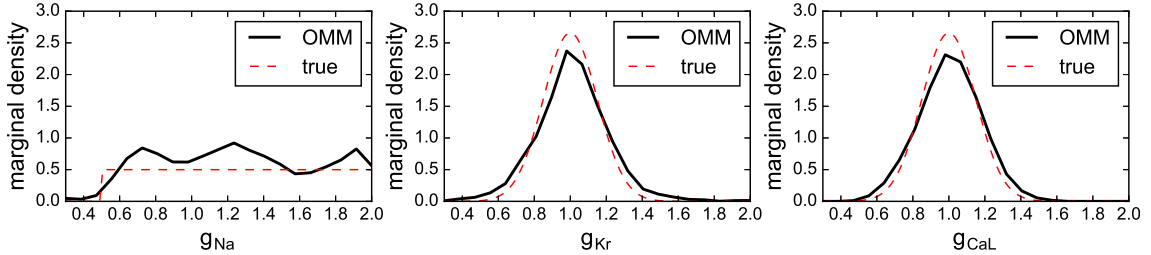
We propose to illustrate the OMM approach using a simple test case that highlights its non-parametric nature. Indeed, the PDF is estimated point-wise in the parameter space and therefore potentially any distribution may be recovered. We propose to study a test case where one of the parameters has a uniform distribution and two of them are correlated.

For the synthetic data set,  $N = 10^4$  APs were generated using the Davies model with three uncertain parameters:  $g_{Na}$ ,  $g_{Kr}$ ,  $g_{CaL}$ .  $g_{Kr}$  and  $g_{CaL}$  were drawn from a bivariate normal distribution of mean vector  $\boldsymbol{\mu} = (1, 1)$  and of covariance matrix:

$$A = 10^{-2} \times \begin{pmatrix} 2.25 & 2.03 \\ 2.03 & 2.25 \end{pmatrix}$$

which means  $g_{Kr}$  and  $g_{CaL}$  have a standard deviation of 0.15 and a Pearson correlation coefficient of 90%.  $g_{Na}$  is sampled from an uncorrelated uniform distribution over  $[0.5, 2.]$ . The simulation database was built by sampling the same three parameters over the domain  $\Theta = [0.3, 2.0]^3$ .  $N_c = 2^{12}$  samples were drawn and the number of moments to be matched was set to  $N_m = 3$ . The estimated marginals are shown in Fig. 3. We also plotted the estimated correlation matrix of the three conductances in Fig. 4. The correlation between  $g_{Kr}$  and  $g_{CaL}$  is captured by the method even though it is under-estimated at 60% instead of the 90% of the true distribution.

The discrepancy observed between the true and estimated correlation would not be observed when using Bayesian inference techniques. This is a limitation of the proposed method. In this particular case, the observable quantities could be enriched with auto-correlation quantities to be able to correctly estimate the parameters correlation.



**Figure 3.** Conductances estimated marginal densities.

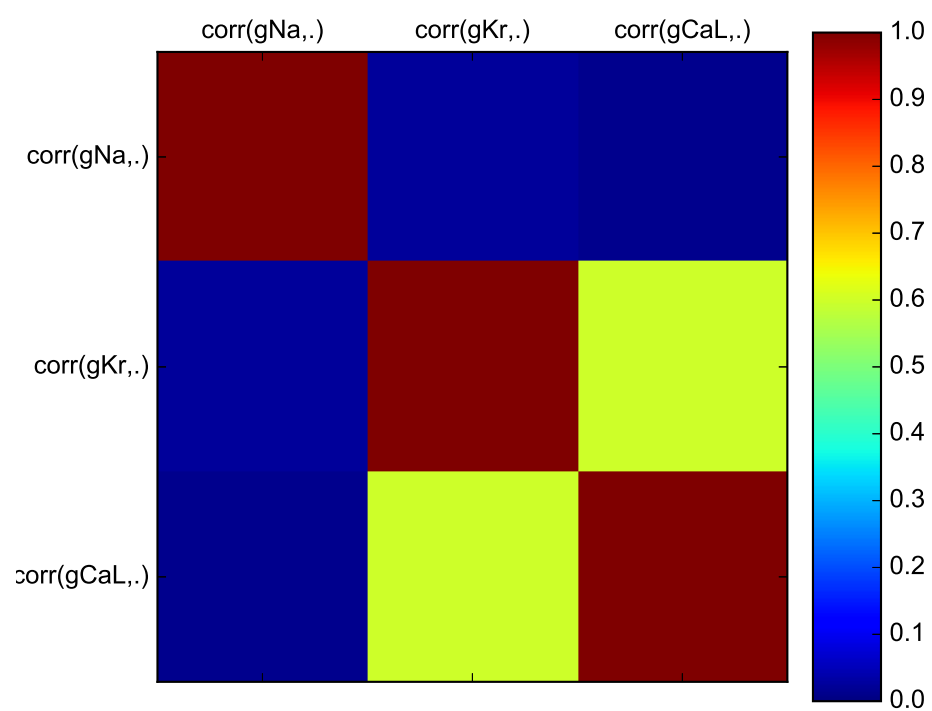


Figure 4. Estimated correlation matrix.