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Erratum

Erratum to: Stiffness Analysis of Cardiac Electrophysiological Models

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The authors wish to replace Tables 2–4 and Fig. 1 in the original publication with those shown below.

Table 2 shows corrected eigenvalue results for Jacobian matrices computed with ADiMat[1] or Matlab's symbolic toolkit and cross-checked against Matlab's symbolic toolkit or its `numjac` function. The units have been standardized to ms^{-1}. Figure 1 shows the corrected plot for the model of Pandit *et al.* (2003).[2] The model of Winslow *et al.* (1999) used in this paper is a reduced model of 31 variables,[3] obtained by removing the variables for the intracellular sodium concentration and one of the calcium concentration handling mechanisms from the full model.[4] These corrections do not materially affect the original analysis of the results.

Table 3 shows updated and corrected step-size and timing results for the forward Euler (FE), Rush–Larsen (RL), and second-order generalized Rush–Larsen (GRL2) methods. The timings reflect execution in Matlab Version 7.10.0.499 (R2010a) on an HP Z400 with an Intel Xeon W3520 2.66 GHz quad-core processor with 16 GB DDR3 RAM running 64-bit Ubuntu 9.04. Timings represent the minimum CPU time of 100 runs for all models. Reference solutions were computed using Matlab's `ode15s` with a decreasing set of tolerances; convergence to 7–10 significant digits was observed for all models at 100 equally spaced points in the interval of integration. The code JSim was able to verify 17 of the 37 models. Relative root mean square (RRMS) errors were computed at 100 equally spaced points, using appropriate interpolation when necessary. The results indicate that at 5% RRMS error, the RL method wins on 25 of the 37 cell models, while GRL2 wins 11 times, and FE wins once. This represents an increase of 7 wins for the RL method (and a corresponding decrease of 3 wins for the FE method and 4 wins for the GRL2 method, respectively) from the original report. At 1% RRMS error, the RL method wins 31 times, GRL2 wins 5 times, and FE wins once. This is an increase of 15 wins for the RL method (and a corresponding decrease of 6 wins for the FE method and 9 wins for the GRL2 method, respectively). The conclusion remains that GRL2 is most effective in only the stiffest situations, i.e., when the eigenvalues of the Jacobian and the accuracy required combine to restrict the time step size on the basis of stability. Otherwise, the RL method is the method of choice because it exhibits the best combination of stability and computational expense per step for moderately stiff situations, into which most cell models fall for typical accuracy requirements. The FE method is the most inexpensive per step; however its stability properties are so poor that it is only effective in the least stiff (and usually least realistic) situations, in this case, only the FitzHugh–Nagumo model.

The corrected results from the use of the backward Euler (BE) method are as follows. We find that the BE

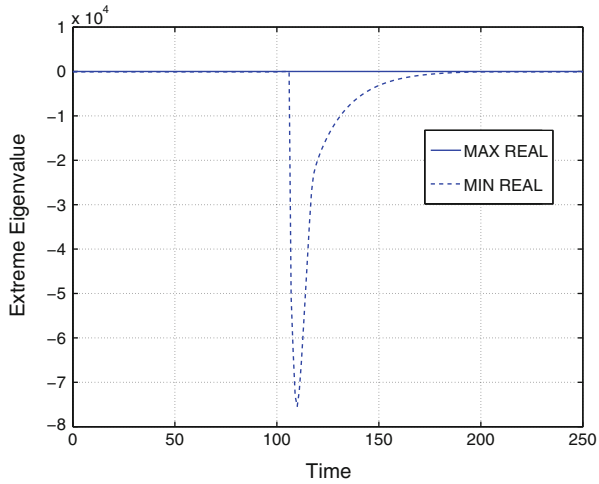

FIGURE 1. Extreme eigenvalues of the model of Pandit *et al.* (2003).

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TABLE 2. Extreme values of the eigenvalues for each model (in ms^{-1}).

Model	min($Re(\lambda)$)	max($Re(\lambda)$)	min($Im(\lambda)$)	max($Im(\lambda)$)	% Complex
Beeler–Reuter (1977)	−8.20E+1	1.55E−2	−1.97E+0	1.97E+0	45
Bondarenko *et al.* (2004)	−8.49E+3	4.51E+0	−2.80E+0	2.80E+0	53
Courtemanche *et al.* (1998)	−1.29E+2	1.87E−1	−4.50E+0	4.50E+0	82
Demir *et al.* (1994)	−3.80E+1	4.79E−1	−7.95E−2	7.95E−2	74
Demir *et al.* (1999)	−3.82E+1	4.81E−1	−7.95E−2	7.95E−2	72
DiFrancesco–Noble (1985)	−2.63E+1	1.88E+0	−6.14E−1	6.14E−1	56
Dokos *et al.* (1996)	−2.99E+1	5.06E−1	−1.19E−1	1.19E−1	97
Faber–Rudy (2000)	−1.84E+2	1.37E−2	−5.61E−1	5.61E−1	58
FitzHugh–Nagumo (1961)	−4.39E−1	1.78E−1	−4.59E−2	4.59E−2	28
Fox *et al.* (2002)	−4.39E+2	4.44E−2	−4.19E−1	4.19E−1	65
Hilgemann–Noble (1987)	−3.25E+1	1.58E−1	−2.25E−1	2.25E−1	25
Hund–Rudy (2004)	−1.95E+2	9.22E−1	−3.74E+0	3.74E+0	62
Jafri *et al.* (1998)	−4.42E+3	4.82E+0	−2.35E−1	2.35E−1	47
Luo–Rudy (1991)	−1.51E+2	7.01E−2	−4.11E−2	4.11E−2	73
Maleckar *et al.* (2008)	−4.16E+1	2.42E−1	−3.43E−1	3.43E−1	28
McAllister *et al.* (1975)	−1.83E+2	1.49E+0	−3.02E+0	3.02E+0	68
Noble (1962)	−9.80E+0	1.74E+0	−1.28E−1	1.28E−1	24
Noble–Noble (1984)	−1.25E+1	4.77E−1	−1.03E−1	1.03E−1	92
Noble *et al.* (1991)	−3.89E+1	4.35E+0	−1.72E−1	1.72E−1	20
Noble *et al.* (1998)	−3.60E+1	5.71E+0	−2.35E−1	2.35E−1	47
Nygren *et al.* (1998)	−4.03E+1	2.05E+0	−3.88E−1	3.88E−1	24
Pandit *et al.* (2001)	−6.92E+3	4.30E+0	−1.43E+0	1.43E+0	12
Pandit *et al.* (2003)	−7.54E+4	3.87E+0	−9.11E−1	9.11E−1	35
Puglisi–Bers (2001)	−1.91E+2	2.22E+0	−1.07E−1	1.07E−1	41
Sakmann *et al.* (2000)—Endocardial	−2.97E+1	7.21E−1	−7.48E−2	7.48E−2	84
Sakmann *et al.* (2000)—Epicardial	−2.96E+1	6.98E−1	−7.47E−2	7.47E−2	75
Sakmann *et al.* (2000)—M-cell	−2.98E+1	1.98E+0	−7.58E−2	7.58E−2	72
Stewart *et al.* (2009)	−1.38E−1	3.34E−3	−1.57E−3	1.57E−3	92
Ten Tusscher *et al.* (2004)—Endocardial	−1.17E+3	1.01E−1	−4.64E+0	4.64E+0	17
Ten Tusscher *et al.* (2004)—Epicardial	−1.17E+3	9.74E−2	−4.70E+0	4.70E+0	18
Ten Tusscher *et al.* (2004)—M-cell	−1.17E+3	9.75E−2	−4.70E+0	4.70E+0	21
Ten Tusscher *et al.* (2006)—Endocardial	−1.26E+3	4.00E+0	−4.77E+0	−4.77E+0	50
Ten Tusscher *et al.* (2006)—Epicardial	−9.44E+2	2.84E+0	−5.01E+0	5.01E+0	51
Ten Tusscher *et al.* (2006)—M-cell	−9.81E+2	4.36E+0	−4.64E+0	4.64E+0	34
Wang–Sobie (2008)	−1.23E+2	1.23E+0	−1.24E+0	1.24E+0	46
Winslow *et al.* (1999) (31 variables)	−1.84E+4	1.53E+0	−4.22E−1	4.22E−1	63
Zhang *et al.* (2000)	−2.22E+1	1.29E−1	−1.00E−1	1.00E−1	89

The minimum real part of the set of eigenvalues is denoted min($Re(\lambda)$), and the maximum real part of the set of eigenvalues is denoted max($Re(\lambda)$). Similarly, the minimum and maximum imaginary parts are denoted min($Im(\lambda)$) and max($Im(\lambda)$). The percentage of the solution interval in which there is at least one pair of complex eigenvalues is also reported.

method takes about 4.16 s to solve the model of Pandit *et al.* (2003). The fastest method, GRL2, is approximately 28 times faster than the BE method, at both 5% and 1% RRMS error. This is a significant departure from the speed of the BE method relative to the GRL2 method. As previously reported, the BE method also did not win on any of the remaining models attempted.

Table 4 shows updated results of various type-insensitive methods on four different models. A change was made in the intervals of stiffness and non-stiffness for the model of Bondarenko *et al.* (2004) to reflect the stimulus start time. The results show that the type-insensitive method that combines the GRL2 and FE methods (GRL2-FE) is always the best performing, with improvements ranging from 40% to over 6 times faster than the most efficient single method. Similar results hold at 1% RRMS error.

The data presented here continue to suggest that most of the cell models considered are moderately stiff for the typical accuracies required. A fully implicit stiff solver such as the BE method offers no efficiency improvement, even for the model of Pandit *et al.* (2003). As previously indicated, the RL method generally seems to strike the best balance between method stability and ease of implementation. Although its implementation is not entirely trivial, the GRL2 method strikes a similarly good balance for the stiffest cell models. The utility of the recently proposed GRL2 method can also be seen from its performance as part of a type-insensitive solver.

TABLE 3. Step size, in milliseconds, and execution time, in seconds, of the three numerical methods using the largest step size with less than 5% RRMS error.

	FE		RL		GRL2	
Model	Δt	Time	Δt	Time	Δt	Time
Beeler–Reuter (1977)	2.53E−2	4.39E−2	1.00E+0†	**1.02E−3**	1.00E+0†	5.90E−3
Bondarenko *et al.* (2004)	2.13E−4	2.64E+0	2.13E−4	2.30E+0	2.85E−2	**4.44E−1**
Courtemanche *et al.* (1998)	1.94E−2	2.35E−1	2.00E+0†	**2.25E−3**	2.00E+0†	2.64E−2
Demir *et al.* (1994)	5.95E−2	1.82E−2	1.53E−1	6.19E−3	7.30E+0	**3.30E−3**
Demir *et al.* (1999)	5.98E−2	1.93E−2	1.53E−1	8.69E−3	7.30E+0	**3.79E−3**
DiFrancesco–Noble (1985)	7.92E−2	9.57E−2	2.65E+1	3.33E−4	1.50E+3	**1.92E−4**
Dokos *et al.* (1996)	7.02E−2	3.33E−2	3.33E+0	**6.80E−4**	1.48E+1	3.74E−3
Faber–Rudy (2000)	1.12E−2	2.45E−1	5.00E−1†	**4.79E−3**	5.00E−1†	1.09E−1
FitzHugh–Nagumo (1961)	5.00E−1†	**3.73E−4**	N/A	N/A	5.00E−1†	1.26E−3
Fox *et al.* (2002)	4.62E−3	3.53E−1	1.00E+0†	**1.49E−3**	1.00E+0†	2.12E−2
Hilgemann–Noble (1987)	6.25E−2	2.49E−2	8.06E−2	1.51E−2	7.31E+0	**4.49E−3**
Hund–Rudy (2004)	1.11E−2	2.50E−1	1.90E−1	**1.37E−2**	3.89E−1	1.40E−1
Jafri *et al.* (1998)	5.76E−4	4.17E+0	5.33E−4	**3.88E+0**	1.03E−2	4.71E+0
Luo–Rudy (1991)	1.35E−2	1.50E−1	4.37E−1	**4.13E−3**	1.00E+0†	1.36E−2
Maleckar *et al.* (2008)	5.02E−2	9.49E−2	8.87E−2	4.60E−2	6.00E+0†	**1.85E−2**
McAllister *et al.* (1975)	2.76E−2	8.33E−2	4.50E+0	**5.23E−4**	2.19E+1	1.16E−3
Noble (1962)	2.12E−1	3.93E−3	2.05E+0	**3.23E−4**	3.93E+0	1.01E−3
Noble–Noble (1984)	2.04E−1	6.66E−3	9.72E+0	**2.02E−4**	3.23E+1	8.96E−4
Noble *et al.* (1991)	5.15E−2	2.57E−2	1.53E−1	**7.46E−3**	1.84E+0	1.37E−2
Noble *et al.* (1998)	5.58E−2	6.03E−2	1.57E−1	**1.97E−2**	2.76E+0	2.32E−2
Nygren *et al.* (1998)	5.36E−2	1.11E−1	8.88E−2	5.87E−2	5.00E+0†	**2.45E−2**
Pandit *et al.* (2001)	2.91E−4	5.90E+0	2.91E−4	5.13E+0	9.58E−2	**3.02E−1**
Pandit *et al.* (2003)	2.65E−5	6.34E+1	2.65E−5	5.68E+1	1.96E−1	**1.49E−1**
Puglisi–Bers (2001)	1.08E−1	1.00E+0	4.99E−1	**2.23E−2**	7.14E−1	9.86E−2
Sakmann *et al.* (2000)—Endocardial	6.90E−2	5.84E−2	2.36E−1	**1.48E−2**	3.00E+0†	2.58E−2
Sakmann *et al.* (2000)—Epicardial	6.90E−2	5.89E−2	2.36E−1	**1.48E−2**	3.00E+0†	2.58E−2
Sakmann *et al.* (2000)—M-cell	6.86E−2	5.87E−2	2.36E−1	**1.48E−2**	3.00E+0†	2.61E−2
Stewart *et al.* (2009)	1.54E+1	5.05E−1	1.18E+3	**6.13E−3**	1.49E+3	8.59E−2
Ten Tusscher *et al.* (2004)—Endocardial	1.78E−3	2.10E+0	1.00E+0†	**3.40E−3**	1.00E+0†	5.81E−2
Ten Tusscher *et al.* (2004)—Epicardial	1.78E−3	2.14E+0	1.00E+0†	**3.42E−3**	1.00E+0†	5.87E−2
Ten Tusscher *et al.* (2004)—M-cell	1.76E−3	1.58E+0	1.00E+0†	**2.54E−3**	1.00E+0†	4.35E−2
Ten Tusscher *et al.* (2006)—Endocardial	1.62E−3	1.54E+0	9.45E−1	**2.42E−3**	1.00E+0†	4.29E−2
Ten Tusscher *et al.* (2006)—Epicardial	2.14E−3	1.17E+0	1.00E+0†	**2.31E−3**	1.00E+0†	4.38E−2
Ten Tusscher *et al.* (2006)—M-cell	2.06E−3	1.22E+0	1.00E+0†	**2.25E−3**	1.00E+0†	4.20E−2
Wang–Sobie (2008)	1.66E−2	6.91E−2	5.27E−2	**1.89E−2**	6.14E−1	3.63E−2
Winslow *et al.* (1999) (31 variables)	1.07E−4	1.65E+1	1.07E−4	1.81E+1	5.27E−3	**7.68E+0**
Zhang *et al.* (2000)	9.97E−2	5.78E−2	3.77E+1	2.13E−4	1.00E+3	**1.85E−4**

Maximum allowable step sizes that were determined by the stimulus duration are indicated with a dagger.

TABLE 4. Stiffness intervals and execution time, in seconds, of type-insensitive methods using the largest step size with less than 5% RRMS error.

			Time		
Model	Stiff Interval	Non-stiff Interval	RL-FE	GRL2-FE	BE-FE
Bondarenko *et al.* (2004)	[20,30]	[0,20], [30,75]	7.10E−1	6.86E−2	1.01E+0
Jafri *et al.* (1998)	[0,50]	[50,300]	1.06E+0	1.04E+0	2.67E+0
Pandit *et al.* (2001)	[105,125]	[0,105], [125,250]	9.16E+0	9.94E−2	2.88E−1
Winslow *et al.* (1999) (31 variables)	[0,50]	[50,300]	3.02E+0	1.54E+0	4.38E+0

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