A basic model of calcium homeostasis in non-excitable cells

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Supporting Information S9 Program

Oscillatory responses of the model

Calculations leading to Fig 18 with period 517.6 s

The folder "`fig18 (period=517.6s)`" contains the calculated results and files leading to Fig 18 and additional plots for j_{SOCC} (`CAREG65-205_jSOCC.pdf`) and the concentrations of STIM and STIM·Ca (`CAREG65-205_STIM.pdf`):

`CAREG65.f`: Fortran source file.
`careg65`, `careg65.exe`: precompiled binaries for Mac OSX and Windows.
`CAREG65.INP`: input file.
`CAREG65-205.INP`: copy of input file with runid in file name.
`careg65.sh`, `careg65.cmd`: Mac and Win scripts to automate calculation.
`CAREG65-205.txt`: data file for containing concentrations.
`CAREG65-205_ER.txt`: data file containing concentrations inside ER.
`CAREG65-205_fluxes.txt`: data file containing fluxes/velocities.
`copy_input.pl`: Perl script copying input file with runid in file name.
`graph_jPMCA.pl`: Perl script calling gnuplot for plotting.
`graph_NCX.pl`: Perl script calling gnuplot for plotting.
`graph_jSOCC.pl`: Perl script calling gnuplot for plotting.
`graph_jSERCA.pl`: Perl script calling gnuplot for plotting.
`graph_Ca_ER.pl`: Perl script calling gnuplot for plotting.
`graph_Ca_cyt.pl`: Perl script calling gnuplot for plotting.
`graph_STIM.pl`: Perl script calling gnuplot for plotting.
`graph_jIP3R.pl`: Perl script calling gnuplot for plotting.
`CAREG65-205_jPMCA.pdf`: plot in pdf format.
`CAREG65-205_NCX.pdf`: plot in pdf format.
`CAREG65-205_jSOCC.pdf`: plot in pdf format.
`CAREG65-205_jSERCA.pdf`: plot in pdf format.
`CAREG65-205_Ca_ER.pdf`: plot in pdf format.
`CAREG65-205_Ca_cyt.pdf`: plot in pdf format.
`CAREG65-205_STIM.pdf`: plot in pdf format.
`CAREG65-205_jIP3R.pdf`: plot in pdf format.
`CAREG65-205_summary.txt`: copy of Terminal or Command Prompt output.
`libV77.a`: 64-bits library for Mac OSX.
`vms.lib`: 64-bits library for Windows.
`tmp`: temporary file used for plot title/annotation.

The 64-bits binaries were created with `Absoft Pro Fortran` compilers for Mac OSX and Windows, by using the commands:

for Mac: `f77 -o careg65 -m64 -O2 CAREG65.f libV77.a`
for Win: `f77 -o careg65 -m64 -O2 CAREG65.f vms.lib`

To automatically execute the precompiled binaries `careg65` (Mac) or `careg65.exe` (Win) and to make the plots in Fig 18 do the following:

Win: Write in Command Prompt window: `careg65.cmd` and press RETURN.
Mac: Write in Terminal window: `./careg65.sh` and press RETURN.

If you should get `Permission denied` when using `careg65.sh`, write in Terminal window:
`chmod 755 careg65`

and

`chmod 755 careg65.sh`.
This will give execution rights to the files `careg65.sh` and `careg65`.

The period in seconds is written in the Terminal/Command Prompt output or can be found in the file `CAREG65-205_summary.txt` (outlined in red in Fig S1):

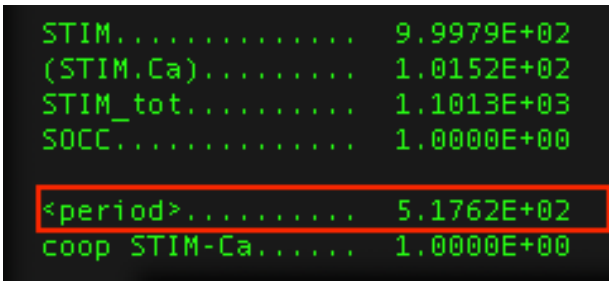

Figure S1. The period in seconds is written in the Terminal/Command Prompt output, or can be found in the file `CAREG65-205_summary.txt`.

Oscillations with a period of 30 hours

Reducing k_1 to $1\times10^{-5}\mu$M/s with k_{20}=50μM/s, k_{21}=0.1 s^{-1}, k_{23}=0.01 s^{-1}, and k_{38}= 1×10^{3} s^{-1} gives a period of 1.0971×10^{5} seconds or 30.5 hours (Fig S2).

As in the previous section, the calculations are performed by executing the precompiled binaries `careg66` (Mac) or `careg66.exe` (Win), which are found in the folder "`30 h oscillations`", i.e., direct the Terminal or Command Prompt to this folder and write:

Win: Write in Command Prompt window: `careg66.cmd` and press RETURN.
Mac: Write in Terminal window: `./careg66.sh` and press RETURN.

This will lead to the Terminal/Command Prompt output saved in the file `CAREG66-06_summary.txt` to the plots (in pdf format) shown in Fig S2. Fig S2 follows the same structure as Fig 18 with <Ca_{ER}> (outlined in red in panel C) being the calculated average of the (free) calcium concentration in the ER (Ca_{lum}, Fig 16).

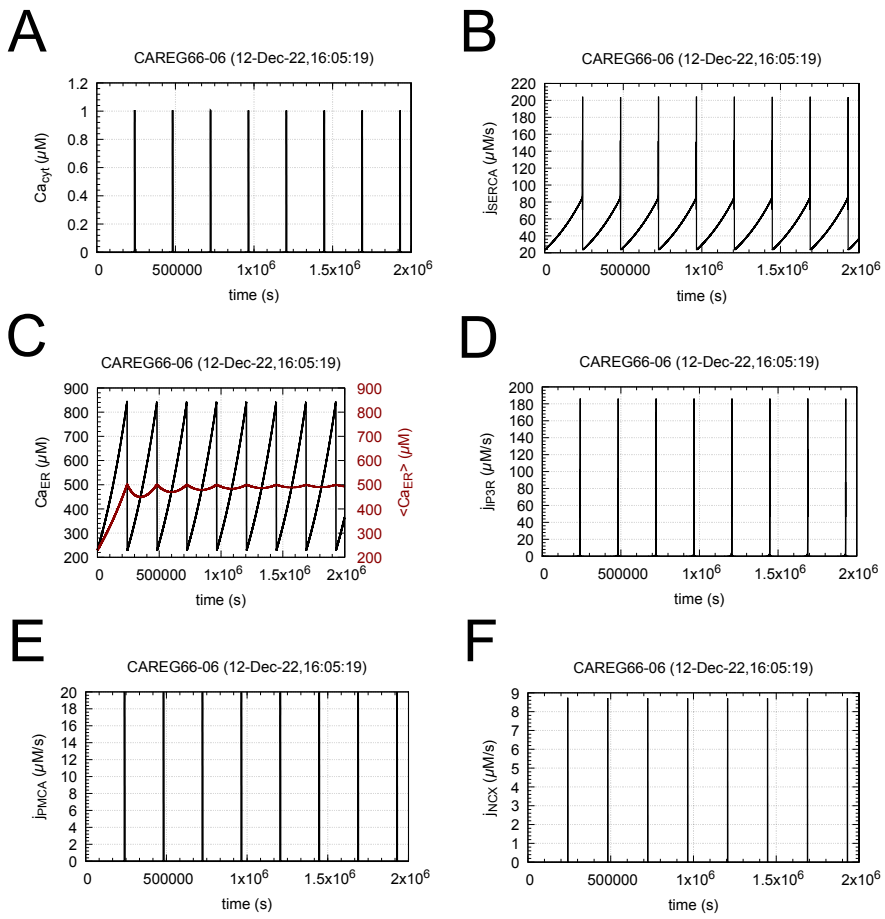

Figure S2. Oscillations with a period of 30.5 hours. For rate constants and initial concentrations, see the `CAREG66.INP` file in folder "`30 h oscillations`".

Oscillations with a period of approximately 2 seconds

Short period oscillations are promoted when the calcium concentration in the ER is decreased, the $IP_3R{\bullet}IP_3$ channel turnover number k_{38} is decreased, while the SERCA channel turnover number k_{23} is increased. In the calculations leading to the oscillations in Fig S3, we have k_{20}=10 μM/s, k_{21}=10 s^{-1} (defining the calcium set-point in the ER, see Eq 17), k_{23}=80.0 s^{-1}, and k_{38}= 10 s^{-1}.

Also here, the calculations can be performed by executing the precompiled binaries `careg65` (Mac) or `careg65.exe` (Win), which are found in the folder "`2.35 s oscillations`", i.e., direct the Terminal or Command Prompt to this folder and write:

Win: Write in Command Prompt window: `careg65.cmd` and press RETURN.
Mac: Write in Terminal window: `./careg65.sh` and press RETURN.

This will lead to the Terminal/Command Prompt output saved in the file `CAREG65-220_summary.txt` to the plots (in pdf format) shown in Fig S3.

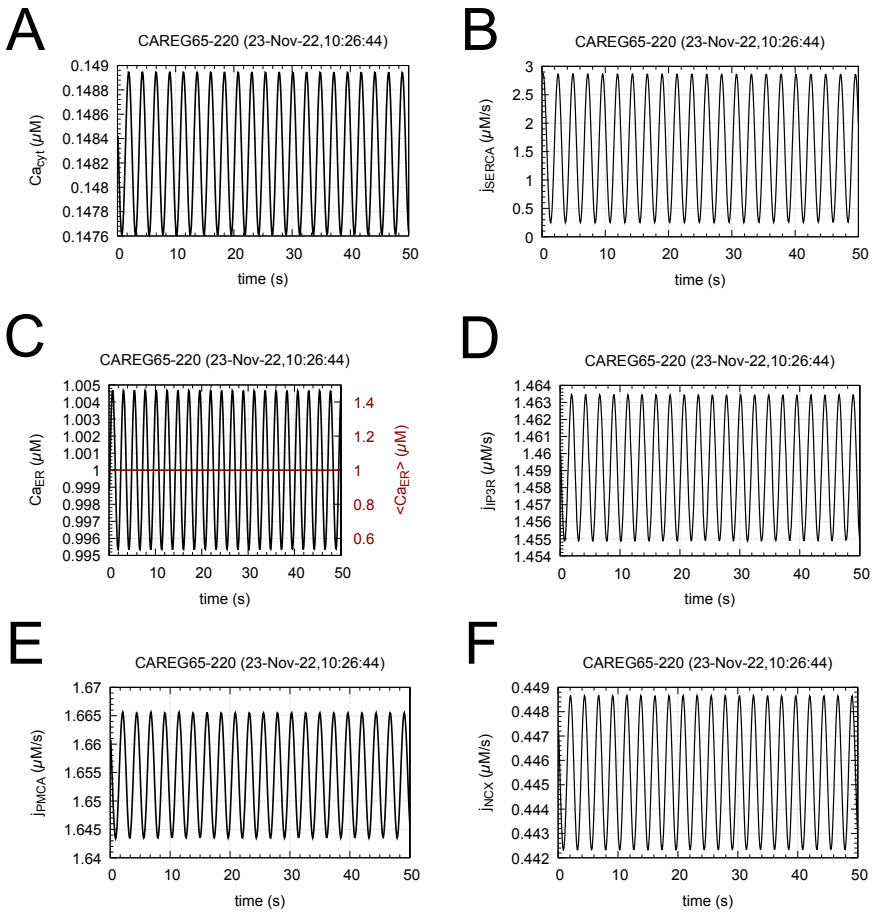

Figure S3. Oscillations with a period of 2.35 seconds. For rate constants, see the `CAREG65.INP` file in folder "`2.35 s oscillations`".

Influence of varying IP_3 and $IP_3R{\bullet}IP_3$ concentrations on amplitude

The calculations in Figs S1-S3 were done with constant $IP_3R{\bullet}IP_3$ and IP_3 concentrations by setting k_{77} and k_{78} to zero. In this case, the oscillations are not influenced by IP_3. On the other hand, the oscillations can be significantly affected in both period and amplitude when $IP_3R{\bullet}IP_3$ and IP_3 are allowed to vary by nonzero values of k_{77} and k_{78}.

Fig S4 shows a calculation where in phase 1 (0-200s) $IP_3R{\bullet}IP_3$ and IP_3 are kept constant by zero k_{77} and k_{78} values, while in phase 2 (200-600s) k_{77} and k_{78} are both set to 1 μMs^{-1}. In addition we assume that high cytosolic Ca^{2+} activates the dissociation of $IP_3R{\bullet}IP_3$ (condition (ii) in section "Effect of cytosolic calcium on the dissociation of $IP_3R{\bullet}IP_3$"). Once $IP_3R{\bullet}IP_3$ and IP_3 are allowed to vary in phase 2 this leads to a large increase in the oscillations' amplitude. The period length shows only a moderate increase from 21.1s in phase 1 to 28.7s in phase 2. The folder `CAREG67-02` contains the Fortran source file for this calculation,`CAREG67.f`, the input file `CAREG67.INP`, and the compiled binaries for Win (`careg67.exe`) and Mac (`careg67`). The Perl scripts generate the plots using `gnuplot`. To execute the binaries, point the Command Prompt (Win) or Terminal (Mac) to the folder `CAREG67-02` and write in the Command Prompt/Terminal window:

Win: `careg67.cmd` and press RETURN.
Mac: `./careg67.sh` and press RETURN.

If you should get "`Permission denied`" when using a Mac, see above on how to get the rights to execute the binary `careg67` and the shell script `careg67.sh`.

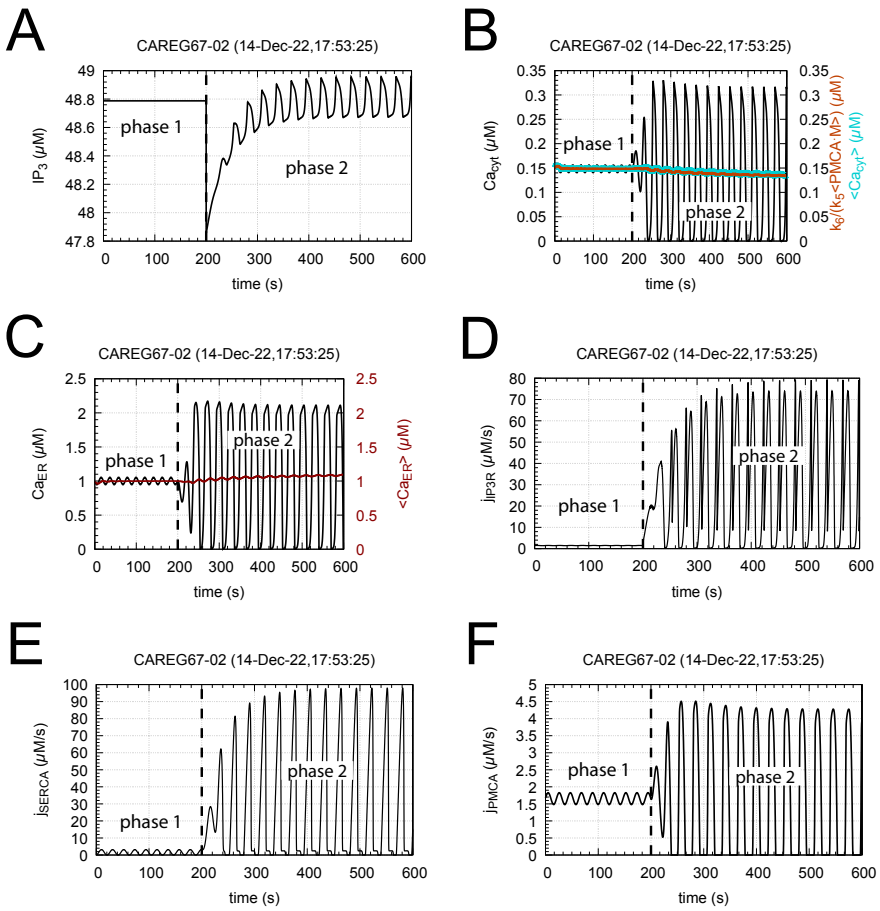

Figure S4. Influence of varying IP_3 and $IP_3R{\bullet}IP_3$ concentrations on amplitude. In phase 1 IP_3 and $IP_3R{\bullet}IP_3$ concentrations are kept constant by setting k_{77} and k_{78} to zero. In phase 2 k_{77} and k_{78} are both set to 1 μMs^{-1}. The right orange-colored ordinate label in panel B shows the calculated set-point of cytosolic calcium as $k_6/(k_5{<}PMCA{\bullet}M{>})$ in analogy to Eq 5. The cyan-colored ordinate label shows the calculated average concentration of cytosolic calcium, $<Ca_{cyt}>$. The right red-colored label in panel C shows the calculated average concentration of calcium inside the ER. Averages <X> are time dependent and calculated as $<X(t)>=(1/t)\cdot\int_0^t X(t')dt'$, where t is time. Rate constant values and initial concentrations are found in the input file `CAREG67.INP`.

Influence of varying IP_3 concentration on period

Fig S5 shows an increase in period length from 29.3s (phase 1) to 38.5s (phase 2) when the synthesis of IP_3 is increased by k_{46} (activated by PLC). In the calculation k_{46} is increased from $50s^{-1}$ (phase 1) to $100s^{-1}$. In both phases we have that $k_{77}{=}k_{78}{=}1\mu Ms^{-1}$. The results are consistent with an accompanied increase of $IP_3R{\bullet}IP_3$,

which leads to an increased (average) j_{IP3R} flux and an increased j_{IP3R} amplitude.

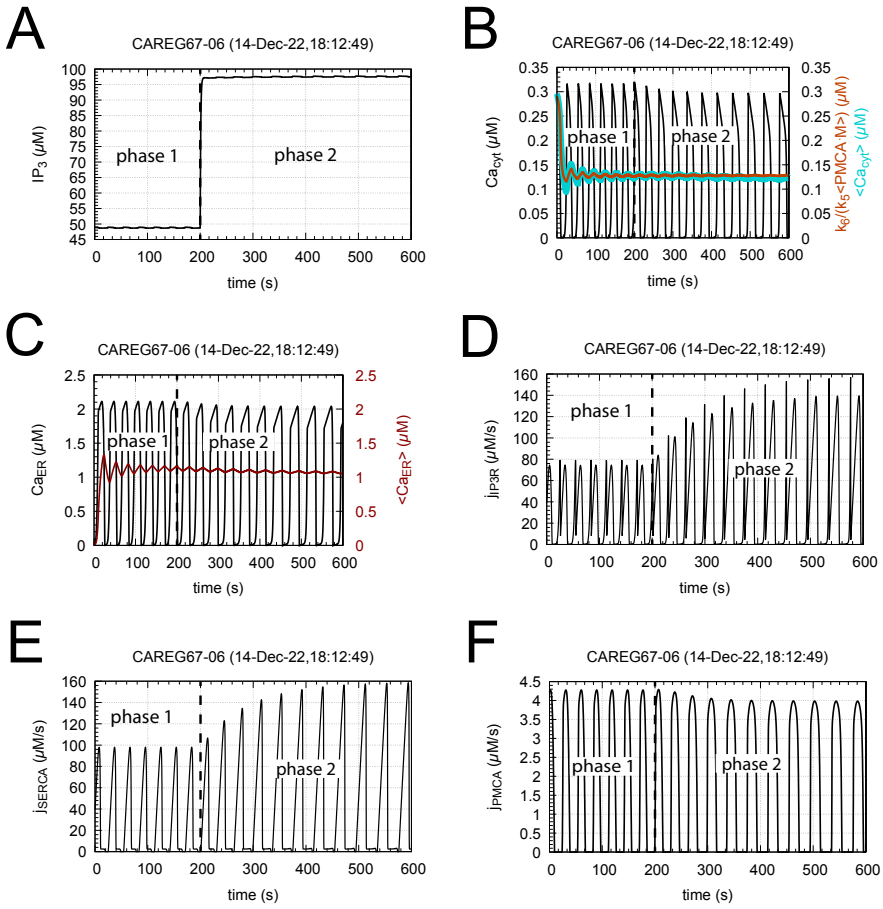

Figure S5. Influence of increased IP_3 concentration on period. See text for description. The folder `CAREG67-06` contains the source file for this calculation, `CAREG67.f`, the input file `CAREG67.INP` and the binaries `careg67.exe` (Win) and `careg67.exe` (Mac). See descriptions above on how to execute the binaries via the script files `careg67.cmd` (Win) or `careg67.sh` (Mac). Rate parameters and initial concentrations are given in the input file `CAREG67.INP`. Note that in panel A the IP_3 oscillations are barely seen due to the relative large change in the IP_3 concentration from phase 1 to phase 2.

Finally, in Fig S6 k_{46} is reduced from $50s^{-1}$ in phase 1 to $10s^{-1}$ in phase 2. The corresponding decrease in concentrations of IP_3 and $IP_3R{\bullet}IP_3$ causes a decrease in the average j_{IP3R} concentration in phase 2 and a corresponding decrease in the j_{IP3R} oscillations' amplitude. The period is reduced from 29.3s (phase 1) to 22.7s (phase 2). Also in this calculation we have in both phases that $k_{77}{=}k_{78}{=}1\mu Ms^{-1}$.

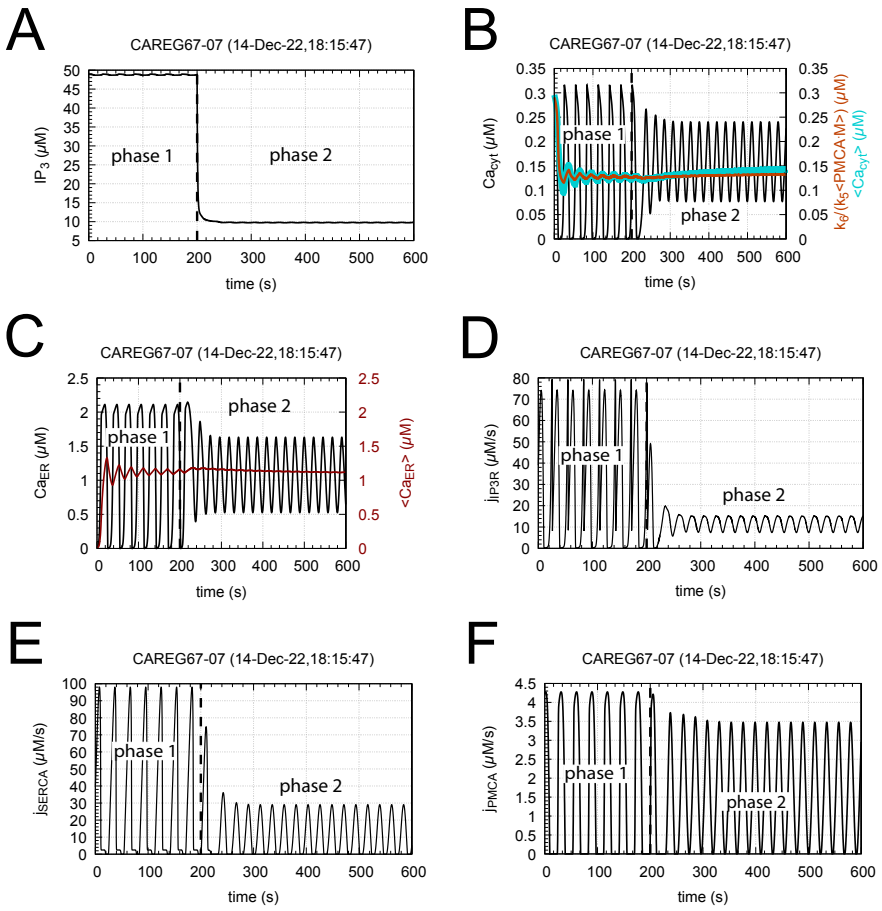

Figure S6. Influence of decreased IP_3 concentration on period. See text for description. The folder `CAREG67-07` contains the source file for this calculation, `CAREG67.f`, the input file `CAREG67.INP` and the binaries `careg67.exe` (Win) and `careg67.exe` (Mac). Please note that the binaries relate only to this calculation. See descriptions above on how to execute the binaries via the script files `careg67.cmd` (Win) or `careg67.sh` (Mac). Rate parameters and initial concentrations are given in the input file `CAREG67.INP`. Note that in panel A the IP_3 oscillations are barely seen due to the relative large change in the IP_3 concentration from phase 1 to phase 2.