Supplementary Material

Modelling Biological Clocks with Bio-PEPA: Stochasticity and Robustness for the *Neurospora crassa* Circadian Network

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The Bio-PEPA Model for the Circadian Clock

In this section we report the full Bio-PEPA model of the circadian clock studied in the main paper. First, the set of functional rates and the set of parameters are reported. The name of each action type describes the function of the associated reaction. The notation $fMA(r)$ indicates that the kinetic law is mass-action with constant rate r. Similarly, $fMM((v,K),S)$ stands for Michaelis-Menten kinetics with maximal reaction rate v, Michaelis constant K and substrate S, while $fH((v,K,h),S)$ stands for Hill kinetics with degree of cooperativity h. After that, there is the definition of species components and of the model component. Finally, the events describing entrainment are defined. Here we do not report the set of locations and the set $\mathcal{N}$ with auxiliary information for species as these are not considered in our study.

Note that in the Bio-PEPA model, species and parameters are given in terms of concentrations. However, in the mapping to the model for stochastic simulation, molecule numbers are derived by scaling the model by a factor Ω. The rescaled parameters are reported at the end of this section.

$$
\begin{aligned}
transcription\_MF\_by\_PWL &= [(a_1 \cdot PWL^n)/((1 + (PF/b_1)^g) \cdot (PWL^n + {b_2}^n))] \\
transcription\_MF\_by\_PW &= [(a_2 \cdot PW^m)/((1 + (PF/b_3)^h) \cdot (PW^m + {b_4}^m))] \\
degradation\_MF &= [fMM((d_1, b_5), MF)] \\
translation\_E1F &= [fMA(a_3)] \\
transformation\_E1F\_to\_E2F &= [fMA(f_1)] \\
degradation\_E1F &= [fMA(\gamma_1)] \\
degradation\_E2F &= [fMA(\gamma_1)] \\
transformation\_E2F\_to\_PF &= [fMA(f_1)] \\
degradation\_PF &= [fMM((d_2, b_6), PF)] \\
transcription\_MW\_simple &= [a_4] \\
transcription\_MW\_by\_PWL &= [fH((a_5, b_7, k), PWL)] \\
degradation\_MW &= [fMM((d_3, b_8), MW)] \\
translation\_E1W &= [fMA(a_6)] \\
translation\_E1W\_by\_PF &= [fMA(a_7)] \\
transformation\_E1W\_to\_E2W &= [fMA(f_2)] \\
degradation\_E1W &= [fMA(\gamma 2)] \\
degradation\_E2W &= [fMA(\gamma 2)] \\
transformation\_E2W\_to\_PW &= [fMA(f_2)] \\
transformation\_PW\_to\_PWL &= [fMA(r_1)] \\
transformation\_PWL\_to\_PW &= [fMA(r_2)] \\
degradation\_PW &= [fMM((d_4, b_9), PW)] \\
degradation\_PWL &= [fMM((d_5, b_{10}), PWL)]
\end{aligned}
$$

$a_1 = 8.3450$; $a_2 = 3.7925$; $a_3 = 0.3154$; $a_4 = 0.6787$; $a_5 = 10.0718$; $a_6 = 6.6644$;
$a_7 = 2.4695$; $b_1 = 4.1472$; $b_2 = 0.1560$; $b_3 = 0.7149$; $b_4 = 2.9415$;
$b_5 = 4.1075$; $b_6 = 0.4715$; $b_7 = 3.5676$; $b_8 = 0.5805$; $b_9 = 7.0233$; $b_{10} = 0.8218$;
$d_1 = 7.4608$; $d_2 = 0.4405$; $d_3 = 2.1710$; $d_4 = 3.0883$; $d_5 = 23.3120$;
$f_1 = 0.1962$; $f_2 = 0.1317$; $\gamma_1 = 0.0422$; $\gamma_2 = 0.0244$; $r_1 = 5.1759$; $r_2 = 5.0326$;
$n = 1.0168$; $m = 2.8134$; $k = 1.4135$; $g = 1.2730$; $h = 3.6978$

$$
\begin{aligned}
MF &\stackrel{def}{=} (transcription\_MF\_by\_PWL, 1)\uparrow \; + \; (transcription\_MF\_by\_PW, 1)\uparrow \; + \\
&\quad (degradation\_MF, 1)\downarrow \; + (translation\_E1F, 1) \odot \\
PF &\stackrel{def}{=} (transcription\_MF\_by\_PWL, 1) \odot \; + (transcription\_MF\_by\_PW, 1) \odot + \\
&\quad (transformation\_E2F\_to\_PF, 1)\uparrow \; + \; (degradation\_PF, 1)\downarrow \; + \\
&\quad (translation\_E1W\_by\_PF, 1) \odot \\
E1F &\stackrel{def}{=} (translation\_E1F, 1)\uparrow \; + \; (transformation\_E1F\_to\_E2F, 1)\downarrow \; + \\
&\quad (degradation\_E1F, 1)\downarrow \\
E2F &\stackrel{def}{=} (transformation\_E2F\_to\_PF, 1)\downarrow \; + \; (transformation\_E1F\_to\_E2F, 1)\uparrow \; + \\
&\quad (degradation\_E2F, 1)\downarrow \\
MW &\stackrel{def}{=} (transcription\_MW\_simple, 1)\uparrow \; + \; (transcription\_MW\_by\_PWL, 1)\uparrow \; + \\
&\quad (degradation\_MW, 1)\downarrow \; + \; (translation\_E1W, 1) \odot \; + \\
&\quad (translation\_E1W\_by\_PF, 1) \odot \\
PW &\stackrel{def}{=} (transcription\_MF\_by\_PW, 1) \odot \; + (transformation\_E2W\_to\_PW, 1)\uparrow \; + \\
&\quad (transformation\_PW\_to\_PWL, 1)\downarrow \; + \; (transformation\_PWL\_to\_PW, 1)\uparrow \; + \\
&\quad (degradation\_PW, 1)\downarrow \\
E1W &\stackrel{def}{=} (translation\_E1W, 1)\uparrow \; + \; (translation\_E1W\_by\_PF, 1)\uparrow \; + \\
&\quad (transformation\_E1W\_to\_E2W, 1)\downarrow \; + \; (degradation\_E1W, 1)\downarrow \\
E2W &\stackrel{def}{=} (transformation\_E2W\_to\_PW, 1)\downarrow \; + \; (transformation\_E1W\_to\_E2W, 1)\uparrow \; + \\
&\quad (degradation\_E2W, 1)\downarrow \\
PWL &\stackrel{def}{=} (transcription\_MF\_by\_PWL, 1) \odot \; + (transcription\_MW\_by\_PWL, 1) \odot \; + \\
&\quad (transformation\_PW\_to\_PWL, 1)\uparrow \; + \; (transformation\_PWL\_to\_PW, 1)\downarrow \; + \\
&\quad (degradation\_PWL, 1)\downarrow
\end{aligned}
$$

$$
\begin{aligned}
&MF(0.2053) \underset{*}{\bowtie} E1F(0.7839) \underset{*}{\bowtie} E2F(1.2629) \underset{*}{\bowtie} PF(1.2210) \underset{*}{\bowtie} MW(0.2640) \underset{*}{\bowtie} \\
&PW(5.6253) \underset{*}{\bowtie} PWL(0) \underset{*}{\bowtie} E1W(16.6588) \underset{*}{\bowtie} E2W(14.1157)
\end{aligned}
$$

$$
\begin{aligned}
Events \; = \; [&(dawn_i \,; \;\; t \, = \, t_{dawn} \cdot i \,; \;\; r_1 \, = \, 1 \,; \;\; 0), \\
&(dusk_i \,; \;\; t \, = \, t_{dusk} \cdot i \,; \;\; r_1 \, = \, 0 \,; \;\; 0), \;\; i \, = \, 1, 2, \ldots, D \;\;]
\end{aligned}
$$

where D is the number of days, and t_{dawn} and t_{dusk} are the time of the day at which dawn and dusk occur, respectively.

Rescaling by Ω

The stochastic version of the clock is obtained by rescaling the deterministic model by the factor Ω in the following way:

- all the initial species concentrations are multiplied by Ω;
- some parameters are modified in order to take molecule numbers into account.

The parameters are rescaled according to the relations between deterministic and stochastic rates shown in [1]. The bimolecular reaction rate constants in mass-action are divided by Ω and zero-order reaction rate constants (for instance the transcription of *wc-1* mRNA, MW) are multiplied by Ω. Rate constants for monomolecular reactions do not need to be rescaled.

In our model there are complex kinetic laws different from mass-action, representing approximations obtained by applying the quasi-steady-state assumption to enzyme-substrate or gene-repressor interactions [2]. For these reactions also it is necessary to rescale some parameters, multiplying them by Ω in order to take molecule number into account instead of concentration.

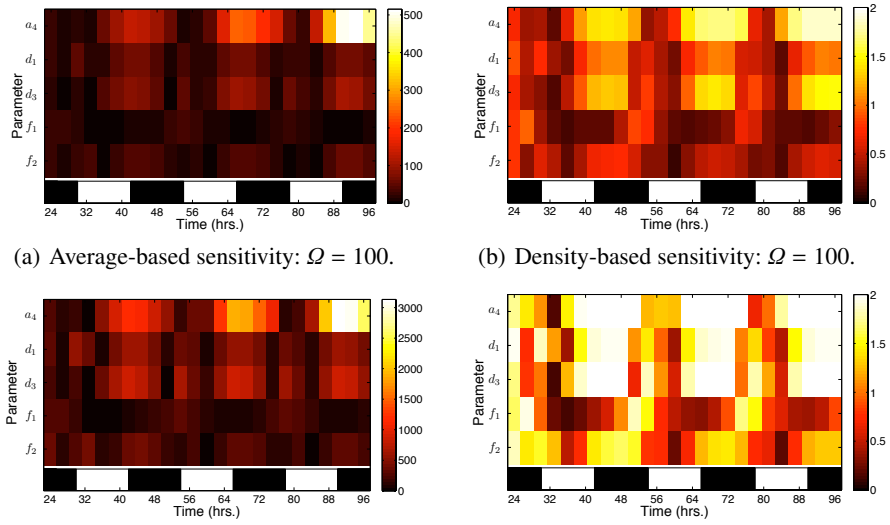
Below we report how the parameters are rescaled; just the modified ones are shown.

$$
\begin{array}{llll}
a_1 = 8.3450 \cdot \Omega; & a_2 = 3.7925 \cdot \Omega; & a_4 = 0.6787 \cdot \Omega; & a_5 = 10.0718 \cdot \Omega; \\
a_7 = 2.4695 \cdot \Omega; & b_1 = 4.1472 \cdot \Omega; & b_2 = 0.1560 \cdot \Omega; & b_3 = 0.7149 \cdot \Omega; \\
b_4 = 2.9415 \cdot \Omega; & b_5 = 4.1075 \cdot \Omega; & b_6 = 0.4715 \cdot \Omega; & b_7 = 3.5676 \cdot \Omega; \\
b_8 = 0.5805 \cdot \Omega; & b_9 = 7.0233 \cdot \Omega; & b_{10} = 0.8218 \cdot \Omega; & d_1 = 7.4608 \cdot \Omega; \\
d_2 = 0.4405 \cdot \Omega; & d_3 = 2.1710 \cdot \Omega; & d_4 = 3.0883 \cdot \Omega; & d_5 = 23.3120 \cdot \Omega
\end{array}
$$

References

1. Gillespie, D.: Exact stochastic simulation of coupled chemical reactions. J Phys Chem **81**(25) (1977) 2340–2361
2. Murray, J.: Mathematical Biology. Springer-Verlag (2003)

Supplementary Figures



(a) Average-based sensitivity: $\Omega = 100$.

(b) Density-based sensitivity: $\Omega = 100$.

(c) Average-based sensitivity: $\Omega = 1000$.

(d) Density-based sensitivity: $\Omega = 1000$.

Fig. S1. Local sensitivity to parameter variation over 3 successive circadian cycles ($24 \leq t \leq 96$). Sensitivities were computed every 3 hours. As in Fig. 6 of the main paper, the color gradients in each panel denote the magnitude of the change in FP.