**“Multirhythmicity generated by coupling two cellular rhythms”**

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**Supporting information**

**Model for coupling the cell cycle to the circadian clock**

In this study, to investigate the possibility of a coexistence between multiple periodic attractors, we used a detailed mathematical model describing the dynamics of the Cdk network driving the mammalian cell cycle [1] and a mathematical model proposed for the mammalian circadian clock, in the version that includes the regulation of Bmal1 by the protein Rev-Erb [2,3]. With the exception of a few minor modifications described below we followed the approach developed in a previous study of entrainment of the cell cycle by the circadian clock [4].

The equations of the model for the mammalian circadian clock network are listed in the Supporting Information of [2]. Parameter values for the circadian clock model are listed in the legend to Fig. 8 in [2], with *K*ib =1 nM.

The equations of the model for the Cdk network are listed as eqs. [1]–[39] in Supporting Information of [1]. The definition and values of the parameters of the cell cycle model are listed in Table S2, with *vcb*=0.055m h-1.

The coupled model contains 60 variables: 19 variables for the circadian clock, 39 equations for the cell cycle model, to which we add equations (1) and (3) below.

1. **Three ways of coupling the cell cycle to the circadian clock**

A growing number of experiments have shown that some of the components of cell cycle can be regulated by the circadian clock, such as Wee1, cyclin E and p21. In this manuscript, following our previous approach [4], we considered three different ways of coupling the cell cycle to the circadian clock. In each situation, we explored the conditions in which multiple periodic attractors occur.

We first considered the coupling of the cell cycle to the circadian clock via Wee1, a protein kinase that inhibits cyclin-dependent kinases such as Cdk1 [5]. Previous experimental data indicated that the circadian clock can regulate the cell cycle by promoting the transcription of *wee1* mRNA through the Bmal1/Clock complexes [6]. Therefore, we incorporated an additional kinetic equation for the *Wee1* mRNA, to describe the coupling of the cell cycle to the circadian clock. The time evolution of the concentrations of Wee1 mRNA (Mw) and Wee1 protein is thus governed by eqs. (1) and (2), where the rate of synthesis of *Wee1* mRNA dependent on BMAL1 (*B*n), *vsw*, measures the coupling strength of the cell cycle to the circadian clock:

(1)

(2)

The coupling terms via Wee1 was slightly modified with respect to our previous study of coupling the cell cycle to the circadian clock, i.e. with respect to eqs. (1) and (2) in [4]. Here, we assumed that *v*swee1 is the basal rate of *Wee1* mRNA synthesis, rather than Wee1 protein. This is reasonable because the basal synthesis of Wee1 protein, which is independent of circadian clock, also depends on *Wee1* mRNA. The parameter values in eqs. (1) and (2) above are: *vswee1* =0.0117M h-1, *nmw*=4, *Kaw* =2 nM, *Vdmw*=0.5M h-1, *Kdmw* =0.5M.

The second way considered for coupling the cell cycle to the circadian clock is via cyclin E [4], since the Bmal1/Clock complex appears to repress the expression of cyclin E gene indirectly [7,8]. Therefore, we added a kinetic equation for *Cyclin E* mRNA in the model describing the coupling of the cell cycle to the circadian clock. The time evolution of the concentrations of cyclin E mRNA (*M*ce) and cyclin E protein (*C*e) is thus governed by eqs. (3) and (4), where the rate of synthesis of cyclin E mRNA inhibited by BMAL1, *vsce*, measures the coupling strength of the cell cycle to the circadian clock:

(3)

(4)

Equations (3) and (4) are the same as eqs. (5) and (6) considered in [4] by Gérard and Goldbeter for the coupling of the cell cycle to the circadian clock via cyclin E. Parameter values in eqs. (3) and (4) are *Kice*=1nM, *Vdmce* =0.5M h-1, *Kdmce* =0.5M, *nce*=4, *kce2* =5 h-1.

Finally we considered a third mode of coupling via both Wee1 and cyclin E. We multiply *vsw* and *vsce* by the same dimensionless parameter **. The values of *vsw* and *vsce* are equal to 1 nM h-1. The multiplicative factor ** measures the strength of coupling.

1. **Initial conditions** **for observing multiple periodic attractors**

The differential equations of the model were integrated numerically by means of the Runge-Kutta method provided in the program XPPAUTO developed by Dr. Bard Ermentrout at the University of Pittsburgh [9]. The observation of multiple periodic attractors is highly sensitive to initial conditions. Initial conditions for the figures in the text and in Supporting information are listed below (concentration units are expressed in nM for circadian variables (see Supporting information in [3]) and in M for cell cycle variables (see Supporting information in [1]) :

Fig.2b and Fig.7a: Mp=4.0342002, Mc=4.6187, Mbmal=8.4909, Pc=0.023964999, Cc=327.7673, Pcp=0.013851, Ccp=0.76131999, PCc=3.9844, PCn=1.0813,PCcp=5.3548002, PCnp=0.62621999, Bc=3.3185, Bcp=0.14084999, Bn=1.7053, Bnp=0.090561002, In=1.6584001, Mr=2.6716001, Rc=1.5322, Rn=1.1181999, AP1=6.0605998, pRB=1.4225, pRBc1=1.567, pRBp=12.2283, pRBc2=6.7241998, pRBpp=0.00099184003, E2F=11.1372, E2Fp=0.0077661001, Cd=0.094114996, Mdi=0.021430001, Md=0.74659997, Mdp27=0.59710002, Mce=0, Ce=0.0011064, Mei=0.0061730999, Me=0.019832, Skp2=21.161699, Mep27=0.012164, Pei=0.17065001, Pe=1.3978, Ca=0.003338, Mai=0.011651, Ma=0.0035418, Map27=0.0011525, p27=0.32516, p27p=0.018523, Cdh1i=0.54514003, Cdh1a=0.0093810996, Pai=0.59320003, Pa=0.21314, Cb=0.22935, Mbi=0.039067999, Mb=0.34164, Mbp27=0.062483002, Cdc20i=0.038474001, Cdc20a=1.8981, Pbi=0.081721999, Pb=1.0404, Mw=0.019308999, Wee1=0.20207, Wee1p=0.39875999.

Fig.2c and Fig. 7b: Mp=3.5994, Mc=4.1381998, Mbmal=10.0127, Pc=0.021329001, Cc=318.6214, Pcp=0.012222, Ccp=0.76115, PCc=3.1317999, PCn=0.62753999,PCcp=4.2498999, PCnp=0.31399, Bc=3.9242001, Bcp=0.14819001, Bn=2.5016, Bnp=0.10739, In=0.87125999, Mr=2.4974, Rc=1.0913, Rn=0.56395, AP1=6.0605998, pRB=1.3906, pRBc1=1.5869, pRBp=12.5438, pRBc2=7.1753001, pRBpp=0.014838, E2F=11.5112, E2Fp=0.058377001, Cd=0.094130002, Mdi=0.022756999, Md=1.2779, Mdp27=0.067538001, Mce=0, Ce=0.022678999, Mei=0.054009002, Me=0.26111999, Skp2=0.11388, Mep27=0.0084520001, Pei=0.052152999, Pe=1.6274, Ca=0.11267, Mai=0.29085001, Ma=0.026218001, Map27=0.00050924998, p27=0.016170001, p27p=0.043696001, Cdh1i=0.0028945, Cdh1a=1.0943, Pai=0.55353999, Pa=0.29100999, Cb=0.11101, Mbi=0.11006, Mb=0.0092435004, Mbp27=9.2194998e-05, Cdc20i=0.71082002, Cdc20a=0.010123, Pbi=0.55111003, Pb=0.097972997, Mw=0.023360001, Wee1=0.62681001, Wee1p=0.27224001.

Fig.3b: Mp=4.0342, Mc=4.6187, Mbmal=8.4909, Pc=0.02396, Cc=327.7673, Pcp=0.01385, Ccp=0.76132, PCc=3.9844, PCn=1.0813, PCcp=5.3548, PCnp=0.62622, Bc=3.3185, Bcp=0.14085, Bn=1.7053, Bnp=0.09056, In=1.6584, Mr=2.6716, Rc=1.5322, Rn=1.1182 AP1=6.0606, pRB=1.4878, pRBc1=2.2087, pRBp=12.227, pRBc2=9.0762, pRBpp=0.05742, E2F=14.9737, E2Fp=0.00819, Cd=0.09413, Mdi=0.02283, Md=1.3177, Mdp27=0.02085, Mce=0.00645, Ce=0.00278, Mei=0.02898, Me=0.73755, Skp2=17.427, Mep27=0.00825, Pei=0.02175, Pe=1.6906, Ca=0.00438, Mai=0.00979, Ma=0.00343, Map27=2.1468E-5, p27=0.0056, p27p=0.01954, Cdh1i=0.54659, Cdh1a=0.00675, Pai=0.59338, Pa=0.21284, Cb=0.2077, Mbi=0.03326, Mb=0.41118, Mbp27=0.00137, Cdc20i=0.0301, Cdc20a=1.9169, Pbi=0.06449, Pb=1.0719, Mw=0.01198, Wee1=0.11797, Wee1p=0.2403.

Fig.3c: Mp=3.2219, Mc=4.0914, Mbmal=8.8284, Pc=0.0151, Cc=412.95889, Pcp=0.0086, Ccp=0.7633, PCc=3.0569, PCn=0.8567, PCcp=11.8592, PCnp=0.5722, Bc=3.0471, Bcp=0.1358, Bn=1.5129, Bnp=0.0841, In=0.7315, Mr=2.0935, Rc=0.7221, Rn=0.3503, AP1=0.1, pRB=0.1, pRBc1=0.1, pRBp=0.1, pRBc2=0.1, pRBpp=0.1, E2F=0.1, E2Fp=0.1, Cd=0.1, Mdi=0.1, Md=0.1, Mdp27=0.1, Mce=0.1, Ce=0.1, Mei=0.1, Me=0.1, Skp2=0.1, Mep27=0.1, Pei=0.1, Pe=0.1, Ca=0.1, Mai=0.1, Ma=0.1, Map27=0.1, p27=0.1, p27p=0.1, Cdh1i=0.1, Cdh1a=0.1, Pai=0.1, Pa=0.1, Cb=0.1, Mbi=0.1, Mb=0.1, Mbp27=0.1, Cdc20i=0.1, Cdc20a=0.1, Pbi=0.1, Pb=0.1, Mw=0.1, Wee1=0.1, Wee1p=0.1.

Fig.3d: Mp=4.0342, Mc=4.6187, Mbmal=8.4909, Pc=0.02396, Cc=327.7673, Pcp=0.01385, Ccp=0.76132, PCc=3.9844, PCn=1.0813, PCcp=5.3548, PCnp=0.62622, Bc=3.3185, Bcp=0.14085, Bn=1.7053, Bnp=0.09056, In=1.6584, Mr=2.6716, Rc=1.5322, Rn=1.1182, AP1=6.0606, pRB=1.4932, pRBc1=2.6417, pRBp=12.2706, pRBc2=10.854, pRBpp=0.05735, E2F=17.8103, E2Fp=0.01016, Cd=0.09414, Mdi=0.02283, Md=1.3176, Mdp27=0.02092, Mce=0.00429, Ce=0.00262, Mei=0.02917, Me=0.7369, Skp2=18.4977, Mep27=0.00827, Pei=0.02176, Pe=1.6906, Ca=0.0052, Mai=0.01174, Ma=0.00408, Map27=2.58E-5, p27=0.00562, p27p=0.0196, Cdh1i=0.54633, Cdh1a=0.00724, Pai=0.59243, Pa=0.21474, Cb=0.14998, Mbi=0.03339, Mb=1, Mbp27=0.00132, Cdc20i=0.03185, Cdc20a=1.9128, Pbi=0.06812, Pb=1.0651, Mw=0.01198, Wee1=0.12131, Wee1p=0.23855.

Fig.3e: Mp=3.2219, Mc=4.0914, Mbmal=8.8284, Pc=0.0151, Cc=412.95889, Pcp=0.0086, Ccp=0.7633, PCc=3.0569, PCn=0.8567, PCcp=11.8592, PCnp=0.5722, Bc=3.0471, Bcp=0.1358, Bn=1.5129, Bnp=0.0841, In=0.7315, Mr=2.0935, Rc=0.7221, Rn=0.3503, AP1=0.1, pRB=0.1, pRBc1=0.1, pRBp=0.1, pRBc2=0.1, pRBpp=0.1, E2F=0.1, E2Fp=0.1, Cd=0.1, Mdi=0.1, Md=0.1, Mdp27=0.1, Mce=0.1, Ce=0.1, Mei=0.1, Me=0.1, Skp2=0.1, Mep27=0.1, Pei=0.1, Pe=0.1, Ca=0.1, Mai=0.1, Ma=0.1, Map27=0.1, p27=0.1, p27p=0.1, Cdh1i=0.1, Cdh1a=0.1, Pai=0.1, Pa=0.1, Cb=0.1, Mbi=0.1, Mb=0.1, Mbp27=0.1, Cdc20i=0.1, Cdc20a=0.1, Pbi=0.1, Pb=0.1, Mw=0.1, Wee1=0.1, Wee1p=0.1.

Fig.4b: Mp=1.0003, Mc=1.698, Mbmal=6.805, Pc=0.0055822, Cc=328.4629, Pcp=0.0031028, Ccp=0.76158, PCc=0.75418, PCn=0.2771, PCcp=5.8789, PCnp=0.44121, Bc=1.9198, Bcp=0.1102, Bn=1.0386, Bnp=0.065823, In=0.070079, Mr=0.82908, Rc=0.12613, Rn=0.036569 AP1=6.0606, pRB=1.5921, pRBc1=0.20208, pRBp=13.5477, pRBc2=0.86082, pRBpp=0.091333, E2F=1.2949, E2Fp=0.11011, Cd=0.094086, Mdi=0.022841, Md=1.3225, Mdp27=0.016087, Mce=0.028122, Ce=0.006114, Mei=0.029935, Me=0.96505, Skp2=10.6707, Mep27=0.0081096, Pei=0.017005, Pe=1.6997, Ca=0.0044513, Mai=0.051508, Ma=0.16472, Map27=0.00099041, p27=0.0042028, p27p=0.019275, Cdh1i=0.54806, Cdh1a=0.0037106, Pai=0.20488, Pa=1.0414, Cb=1.0856, Mbi=0.033732, Mb=0.45296, Mbp27=0.0011308, Cdc20i=0.026537, Cdc20a=1.8263, Pbi=0.057179, Pb=1.0824, Mw=0.013442, Wee1=0.11901, Wee1p=0.26963.

Fig.4c: Mp=3.4509, Mc=3.984, Mbmal=10.0391, Pc=0.020401, Cc=317.3298, Pcp=0.011662, Ccp=0.76114, PCc=2.9193, PCn=0.56669, PCcp=4.0657, PCnp=0.27604, Bc=3.9105, Bcp=0.14791, Bn=2.5688, Bnp=0.10847, In=0.7199, Mr=2.4211, Rc=0.98579, Rn=0.47282, AP1=6.0606, pRB=1.576, pRBc1=10.4992, pRBp=12.81, pRBc2=42.6575, pRBpp=0.29481, E2F=66.6106, E2Fp=0.018566, Cd=0.094285, Mdi=0.022849, Md=1.3276, Mdp27=0.011106, Mce=0.00088102, Ce=8.783, Mei=0.34986, Me=1.5161, Skp2=0.11373, Mep27=0.0086715, Pei=0.011127,Pe=1.7112, Ca=2.7717, Mai=0.099727, Ma=0.006256, Map27=2.053e-05, p27=0.0028624, p27p=0.047187, Cdh1i=0.00074166, Cdh1a=1.0985, Pai=0.58913, Pa=0.22117, Cb=0.1207, Mbi=0.11404, Mb=0.0046496, Mbp27=7.936e-06, Cdc20i=0.71255, Cdc20a=0.0048493, Pbi=0.55448, Pb=0.091041, Mw=0.044751, Wee1=1.5275, Wee1p=0.35309.

Fig.4d: Mp=3.2463, Mc=3.7733, Mbmal=9.9569, Pc=0.019106, Cc=316.0825, Pcp=0.010885, Ccp=0.76114, PCc=2.6433, PCn=0.49884, PCcp=3.8667, PCnp=0.23522, Bc=3.8409, Bcp=0.14693, Bn=2.6083, Bnp=0.10903, In=0.55564, Mr=2.3117, Rc=0.85671, Rn=0.37449, AP1=6.0606, pRB=1.4825, pRBc1=3.6321, pRBp=12.9241, pRBc2=15.8455, pRBpp=0.020356, E2F=24.4996, E2Fp=0.1303, Cd=0.094164, Mdi=0.022624, Md=1.1951, Mdp27=0.14775, Mce=0.00015657, Ce=0.048424, Mei=0.044671, Me=0.34226, Skp2=0.11407, Mep27=0.0087755, Pei=0.042149, Pe=1.6245, Ca=0.11943, Mai=0.26814, Ma=0.049825, Map27=0.00089792, p27=0.012494, p27p=0.044846, Cdh1i=0.0060408, Cdh1a=1.0884, Pai=0.49116, Pa=0.38889, Cb=0.078423, Mbi=0.080046, Mb=0.0097357, Mbp27=8.9043e-05, Cdc20i=0.7109, Cdc20a=0.010715, Pbi=0.55065, Pb=0.098727, Mw=0.017414, Wee1=0.41881, Wee1p=0.22374.

Fig.4e: Mp=2.2664, Mc=3.0602, Mbmal=5.5945, Pc=0.014097, Cc=336.1068, Pcp=0.0081348, Ccp=0.7616, PCc=2.8863, PCn=1.421, PCcp=6.6519, PCnp=1.3352, Bc=1.7368, Bcp=0.10665, Bn=0.64466, Bnp=0.048635, In=0.78818, Mr=1.4611, Rc=0.47082, Rn=0.59183, AP1=6.0606, pRB=1.4098, pRBc1=2.5732, pRBp=12.392, pRBc2=11.3029, pRBpp=0.0015619, E2F=18.3528, E2Fp=0.016924, Cd=0.094145, Mdi=0.021792, Md=0.84884, Mdp27=0.49618, Mce=0.0052342, Ce=0.0028096, Mei=0.0083613, Me=0.03108, Skp2=21.094, Mep27=0.011245, Pei=0.15506, Pe=1.4204, Ca=0.0057082, Mai=0.020964, Ma=0.0067488, Map27=0.0014917, p27=0.17749, p27p=0.019447, Cdh1i=0.54031, Cdh1a=0.018351, Pai=0.58841, Pa=0.22268, Cb=0.043767, Mbi=0.035965, Mb=0.2511, Mbp27=0.028654, Cdc20i=0.060229, Cdc20a=1.8437, Pbi=0.12412, Pb=0.95896, Mw=0.012206, Wee1=0.15976, Wee1p=0.22679.

Fig.5b and Fig. S1a: Mp=1.1569999, Mc=1.7789, Mbmal=7.2195001, Pc=0.0062671001, Cc=325.28311, Pcp=0.0034558999, Ccp=0.76152998, PCc=0.70789999, PCn=0.19575, PCcp=5.2571998, PCnp=0.12734, Bc=2.1372001, Bcp=0.11593, Bn=1.3151, Bnp=0.076318003, In=0.055312, Mr=0.96881002, Rc=0.1548, Rn=0.041343, AP1=6.0605998, pRB=1.5329, pRBc1=0.48471999, pRBp=12.9828, pRBc2=2.0545001, pRBpp=0.13319001, E2F=3.2801001, E2Fp=0.026215, Cd=0.094091997, Mdi=0.022845, Md=1.325, Mdp27=0.013466, Mce=0.024901001, Ce=0.005537, Mei=0.031500999, Me=1.1559, Skp2=11.8677, Mep27=0.0081121, Pei=0.014376, Pe=1.7049, Ca=0.0046791998, Mai=0.046822, Ma=0.019317999, Map27=0.0002039, p27=0.0035139001, p27p=0.019300999, Cdh1i=0.54710001, Cdh1a=0.0055264998, Pai=0.63407999, Pa=0.29585001, Cb=0.95919001, Mbi=0.034823999, Mb=0.45019999, Mbp27=0.00094055, Cdc20i=0.026786, Cdc20a=1.8816, Pbi=0.057624999, Pb=1.0843, Mw=0.016368, Wee1=0.13579001, Wee1p=0.32049.

Fig.5c and Fig. S1b, d: Mp=1.0568, Mc=1.8480999, Mbmal=6.3362999, Pc=0.0063677998, Cc=331.87189, Pcp=0.0036138999, Ccp=0.76160997, PCc=1.1508, PCn=0.53987998, PCcp=6.4289999, PCnp=0.9738, Bc=1.7359, Bcp=0.10505, Bn=0.78301001, Bnp=0.054529, In=0.13778999, Mr=0.80400997, Rc=0.12732001, Rn=0.056669999, AP1=6.0605998, pRB=1.6623, pRBc1=0.064092003, pRBp=14.2593, pRBc2=0.27438, pRBpp=0.073599003, E2F=0.38652, E2Fp=0.13256, Cd=0.094083004, Mdi=0.022838, Md=1.3206, Mdp27=0.017968001 Mce=0.043490998, Ce=0.0096067004, Mei=0.029376, Me=0.85652, Skp2=10.3268, Mep27=0.0081107998, Pei=0.01898, Pe=1.6959, Ca=0.0052708001, Mai=0.058660999, Ma=0.57453001, Map27=0.0034302, p27=0.0047358, p27p=0.019261001, Cdh1i=0.54900002, Cdh1a=0.001937, Pai=0.049509, Pa=1.3054, Cb=1.5501, Mbi=0.034116, Mb=0.45583999, Mbp27=0.0012757001, Cdc20i=0.026214, Cdc20a=1.6991, Pbi=0.056650002, Pb=1.0693001, Mw=0.012853, Wee1=0.11596, Wee1p=0.26273999.

Fig.5d and Fid. S1c: Mp=3.8206, Mc=4.4591999, Mbmal=7.0496998, Pc=0.022822, Cc=332.95831, Pcp=0.013212, Ccp=0.76144999, PCc=4.0913, PCn=1.4298, PCcp=5.9698, PCnp=0.91716999, Bc=2.6282001, Bcp=0.12933999, Bn=1.1401, Bnp=0.072456002, In=1.7034, Mr=2.4809999, Rc=1.4744999, Rn=1.2787, AP1=6.0605998, pRB=1.5723, pRBc1=10.3337, pRBp=12.772, pRBc2=42.0023, pRBpp=0.72290999, E2F=65.723701, E2Fp=0.026629999, Cd=0.094283, Mdi=0.022849999 Md=1.3284, Mdp27=0.010303 Mce=0.012209, Ce=6.1146002, Mei=0.093232997, Me=1.8104, Skp2=0.11376, Mep27=0.0086570997, Pei=0.0093919998, Pe=1.7142, Ca=2.9912, Mai=0.069659002, Ma=0.0089255003, Map27=2.6543001e-05, p27=0.0023914999, p27p=0.047150999, Cdh1i=0.001224, Cdh1a=1.0976, Pai=0.58535999, Pa=0.22962999, Cb=0.1178, Mbi=0.11398, Mb=0.0083007999, Mbp27=1.1417e-05, Cdc20i=0.71063, Cdc20a=0.0089766998, Pbi=0.55146003, Pb=0.096436001, Mw=0.02376, Wee1=0.74412, Wee1p=0.29271001.

Fig.6b and Fig.8a, b: Mp=2.4993, Mc=3.0172, Mbmal=9.1559, Pc=0.014313, Cc=315.34851, Pcp=0.0080521004, Ccp=0.76121002, PCc=1.7591, PCn=0.32752001, PCcp=3.6020999, PCnp=0.14058, Bc=3.3485, Bcp=0.1399, Bn=2.4319999, Bnp=0.1055, In=0.22218999, Mr=1.8796, Rc=0.50357997, Rn=0.16938999, AP1=6.0605998, pRB=2.0323999, pRBc1=2.8015001, pRBp=15.9921, pRBc2=11.0375, pRBpp=0.17736, E2F=13.3293, E2Fp=0.57766998, Cd=0.094108999, Mdi=0.022846, Md=1.3261, Mdp27=0.012429, Mce=0.0025329001, Ce=0.0020113001, Mei=0.039349001, Me=1.2926, Skp2=3.2623, Mep27=0.0081824996, Pei=0.012941, Pe=1.7078, Ca=0.10244, Mai=0.077680998, Ma=0.24383, Map27=0.00087791, p27=0.0031552999, p27p=0.019941, Cdh1i=0.54447001, Cdh1a=0.013721, Pai=0.12989999, Pa=1.1174001, Cb=0.83148003, Mbi=0.29302001, Mb=0.044936001, Mbp27=7.1399998e-05, Cdc20i=0.67309999, Cdc20a=0.076699004, Pbi=0.50858998, Pb=0.1675, Mw=0.01198, Wee1=0.24507999, Wee1p=0.1787

Fig.6c and Fig. 8e, f: Mp=2.1944001, Mc=2.7155001, Mbmal=8.7518997, Pc=0.01238, Cc=316.4129, Pcp=0.0069275, Ccp=0.76126999, PCc=1.4507, PCn=0.27621001, PCcp=3.7061999, PCnp=0.11497, Bc=3.0973001, Bcp=0.13585, Bn=2.2598, Bnp=0.102, In=0.15332, Mr=1.6896, Rc=0.39939001, Rn=0.12418, AP1=6.0605998, pRB=1.8511, pRBc1=3.49, pRBp=14.8012, pRBc2=13.9825, pRBpp=0.16383, E2F=18.4433, E2Fp=0.5887, Cd=0.094125003, Mdi=0.022843, Md=1.3241, Mdp27=0.014482, Mce=0.0040384, Ce=0.0048019998, Mei=0.040137, Me=1.2557, Skp2=1.4085, Mep27=0.0082513001, Pei=0.013299, Pe=1.7065001, Ca=0.15322, Mai=0.088518001, Ma=0.23305, Map27=0.00077024999, p27=0.0032674, p27p=0.021024, Cdh1i=0.57270998, Cdh1a=0.018758001, Pai=0.13643, Pa=1.0465, Cb=0.38834, Mbi=0.17692, Mb=0.023291999, Mbp27=3.5796002e-05, Cdc20i=0.69796002, Cdc20a=0.029544, Pbi=0.53530002, Pb=0.12092, Mw=0.01198, Wee1=0.25659001, Wee1p=0.17239

Fig.6d and Fig. 8c, d: Mp=2.3504, Mc=3.1379001, Mbmal=5.5969, Pc=0.014588, Cc=336.16791, Pcp=0.0084201004, Ccp=0.76159, PCc=2.9741001, PCn=1.4513, PCcp=6.6378999, PCnp=1.3285, Bc=1.7568001, Bcp=0.10734, Bn=0.65192997, Bnp=0.049095999, In=0.83809, Mr=1.5125, Rc=0.51437998, Rn=0.64007998, AP1=6.0605998, pRB=1.5642, pRBc1=11.2912, pRBp=12.1498, pRBc2=43.853199, pRBpp=1.408, E2F=72.184402, E2Fp=0.0053323, Cd=0.094313003, Mdi=0.022852, Md=1.3297, Mdp27=0.0089892, Mce=0.046331, Ce=18.3297, Mei=0.041972999, Me=1.9401, Skp2=0.11374, Mep27=0.0087379003, Pei=0.0087884003, Pe=1.7158, Ca=2.4066999, Mai=0.0062527, Ma=0.0017703, Map27=5.0844001e-06, p27=0.0022541001, p27p=0.047812998, Cdh1i=0.00091857999, Cdh1a=1.0982, Pai=0.59601998, Pa=0.20821001, Cb=0.068705998, Mbi=0.071603, Mb=0.011518, Mbp27=1.5565e-05, Cdc20i=0.70967001, Cdc20a=0.012924, Pbi=0.54922003, Pb=0.10155, Mw=0.01198, Wee1=0.26192999, Wee1p=0.16855

1. **Legends to supplementary figures S1 to S6**

**Figure S1:** Trirhythmicity: switching between multiple periodic attractors when the cell cycle is coupled to the circadian clock via both Wee1 and Cyclin E, in the conditions of Fig. 5b-d. (a) Switch from simple oscillations of 24h-period to complex oscillations of 48h-period when the basal synthesis rate of cyclin B (*v*cb) transiently decreases from 0.055Mh-1 to 0.005Mh-1 at t=480h; as in all panels in this figure, the transient change in *v*cb lasts for 1h. (b) Complex oscillations can also switch back to simple oscillations when *v*cb decreases transiently from 0.055Mh-1 to 0.005Mh-1 at t=480h. (c) Endoreplication can switch to complex oscillations when *v*cb increases from 0.055Mh-1 to 0.5Mh-1 at t=478h. (d) Complex oscillations can also switch back to endoreplication when *v*cb increases from 0.055Mh-1 to 1Mh-1 at t=455h. The autonomous period of the cell cycle is 20.08h (*eps*=21.4) and the coupling strength **=0.05.

**Figure S2:** Sensitivity to duration of the transient perturbation for switching between periodic regimes. In the conditions of Fig 8b, when *v*cb increases transiently from 0.055Mh-1 to 0.5Mh-1 at t=480h, simple oscillations fail to switch to another periodic attractor if the duration of the change is 0.1h-0.3h, 0.7-0.8h, 1.4-1.5h, or 1.7-1.9h,. If the duration of the change is 1h-1.2h, simple oscillations will switch to endoreplication (Fig. S2a, duration=1h). If the duration of the change is 0.4h-0.6h, 0.9h, 1.3h, 1.6h and 2h, simple oscillations will switch to complex oscillation (Fig. S2b, duration=0.4h). Initial conditions are as in Fig. 8b.

**Figure S3:** Sensitivity to magnitude of the transient perturbation for switching between periodic regimes. In the condition of Fig. S1a, at t=480h, if the magnitude of *v*cb transiently changes for 1h, simple oscillations may switch to another periodic attractor. If the value of *v*cb is increased up to 0.026-0.064, 0.954-1.57, 1.584-1.595 or 1.598-2, simple oscillations fail to switch. If *v*cb is transiently changed to 0-0.025, 0.065-0.953, 1.571-1.583 or 1.596-1.597, simple oscillations switch to complex oscillations (Figure S3a, magnitude =0.005). If the magnitude is increased to 1.598-2, simple oscillations switch to endoreplication (Fig. S3b, magnitude =1.6). Initial conditions are as in Fig. S1a.

**Figure S4:** Parameters other than *v*cb can also cause the transition between multiple periodic attractors. (a) In the same initial conditions as in Fig. 6c, if the total Cdk2 (Cdk2tot) is decreased from 2 M to 1 M at t=480h for 1 hour, the complex oscillation can switch to simple oscillation of 24h. (b) If the basal rate of wee1 mRNA (*vswee1*) synthesis increases at t=480h from 0.0117Mh-1 to 0.05 Mh-1 for 1 hour, the complex oscillations can also change to simple oscillations. (c) With the same initial conditions as in Fig. 6b, the simple oscillations can switch back to complex oscillations by decreasing the total Cdk1 (Cdk1tot) from 0.5 M to 0.1 M for 1 hour at t=485h.

**Figure S5:** Final state sensitivity in two cases of trithyrhmicity. (a) Starting from the same initial condition as in Fig. 6d (small amplitude oscillations of 24h period), we progressively change the value of Cyclin B/Cdk1 at t=480h from 0.1 M to 31.6228 M. The green domain represents the initial values of Cyclin B/Cdk1 leading to complex oscillations of 72h and the red domain represents the initial values of Cyclin B/Cdk1 that lead to simple oscillations of 24h period. The blue domain indicates the initial values of Cyclin B/Cdk1 that maintain small amplitude oscillations. (b) Starting from the initial conditions in Fig. 5d (endoreplication), we only change the value of Cyclin B/Cdk1 by progressively increasing it at t=478h from 0.1 M to 12.5893M. The green domain represents the initial values of Cyclin B/Cdk1 leading to complex oscillations of 48h period and the red domain represents the initial values of Cyclin B/Cdk1 that lead to simple oscillation of 24h period. The blue domain indicates the initial values of Cyclin B/Cdk1 that still cause endoreplication.

**Figure S6:** Bifurcation scenario for the onset of birhythmicity and trirhythmicity. The schematic bifurcation diagram shows the origin of multiple periodic attractors in a 3-variable model for a multiply regulated biochemical system [27]. The solid lines represents the stable oscillatory regimes (limit cycles LC1, LC2 or LC3) or the stable steady state of one of the variables, denoted X0. The dashed line indicates an unstable steady state or unstable periodic trajectories. As the control parameter increases, the coupled system could switch from a single periodic solution (LC1) to birhythmicity (coexistence of LC1 and LC2) and trirhythmicity (coexistence of LC1, LC2 and LC3). The relevance of this bifurcation diagram to the occurrence of multirhythmicity in the coupled circadian clock-cell cycle model remains to be established; this question might be investigated more easily by means of reduced models for the two cellular oscillators. The results shown in Fig. 5A suggest that the coupling strength can play the role of control parameter whose increase leads successively from monorhythmicity to birhythmicity and trirhythmicity.

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