

"Regulation of modular Cyclin and CDK feedback loops by an E2F transcription oscillator in the mammalian cell cycle"

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Supplementary files:

Table 1: Parameters space for CB (Eq.1) – A single parameter variation

Numerical stability analysis performed on four-variable system (Eq.1). The initial parameters used are: $P = [0.072543, 0.10186, 2.7971, 0.0059252, 1.1132, 0.46275, 0.017682, 0.029499, 83.653, 0.31339, 1.5928, 0.54378, 0]$. In each row of the table, only one single parameter varies and the system dynamic was examined by its number of possible steady states and its stability. The stability analysis was carried out by calculating the eigenvalues of the Jacobian around the fixed points using the aforementioned parameters (log scale between -23 to 23).

Parameter	Limit Cycle Rate (Limit Cycle occurrences divided by 10000 different parameter sets)	Limit Cycle Rate (Limit Cycle occurrences divided by total number of "legal" values)	Parameter Range for Limit Cycle [min, max]	Parameter Range for Limit Cycle – log scale [min, max]
P1	6284/10000=0.6284	6284/10000=0.6284	[7.25.e-12 26.7825]	[-25.6494 3.2877]
P2	1143/10000=0.1143	1143/6524=0.1751	[0.0137 2.6493]	[-4.2853 0.9743]
P3	1217/10000=0.1217	1217/5421=0.2244	[0.0104 14.7156]	[-4.5603 2.6889]
P4	1049/10000=0.1049	1049/10000=0.1049	[0.0003 0.0438]	[-7.9541 -3.1273]
P5	1572/10000=0.1572	1572/5479=0.2869	[0.0501 297.7254]	[-2.9900 5.6961]
P6	1143/10000=0.1143	1143/7539=0.1516	[0.0625 12.0361]	[-2.7717 2.4879]
P7	2016/10000=0.2016	2016/6524=0.3090	[3.58.e-5 0.3842]	[-10.2366 -0.9563]

P8	$6545/10000=0.6545$	$6545/6633=0.9867$	[2.95.e-12 36.2339]	[-26.5492 3.5899]
P9	$6214/10000=0.6214$	$6214/6217=0.9995$	[0.0313 8.36.e+11]	[-1.1622 27.4525]
P10	$6698/10000=0.6698$	$6698/7295=0.9181$	[3.1.e-11 778.7977]	[-24.1861 6.6577]
P11	$7295/10000=0.7295$	$7295/7295=1$	[0.0 1.59.e+10]	[-10.1021 23.4913]
P12	$6698/10000=0.6698$	$6698/7295=0.9181$	[5.e-11 1351.3341]	[-23.6350 7.2088]

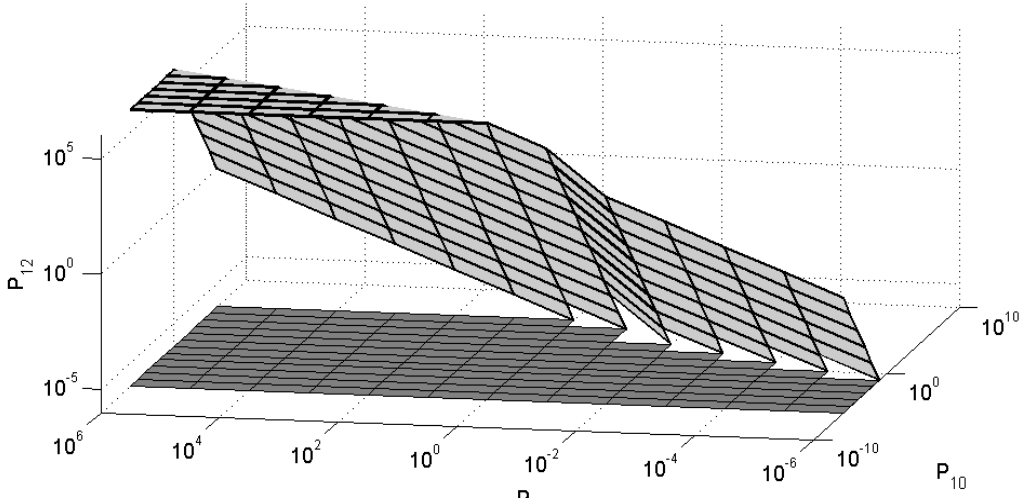
Table 2: Parameters space for the Modular Model (Eq.3) – A single parameter variation

We also have analyzed the full model (Eq.3) with the same assumptions and calculations. The initial parameters used are: $P = [24.586, 0.00083271, 2.6005, 0.032786, 301.93, 4.9728, 0.12421, 2.105, 4.9361e-005, 1.6223, 286.38, 0.28702, 61.761, 3.1502, 1.4648, 246.67, 0, 0]$.

Parameter	Limit Cycle Rate (Limit Cycle occurrences divided by 1000 different parameter sets)	Limit Cycle Rate (Limit Cycle occurrences divided by total number of "legal" values)	Parameter Range for Limit Cycle [min, max]	Parameter Range for Limit Cycle – log scale [min, max]
P1	999/1000=0.999	999/999=1	[0.0 2.34.e+11]	[-19.8236 26.1819]
P2	181/1000=0.181	181/602=0.3006	[7.38.e-6 0.0296]	[-11.8158 -3.5182]
P3	592/1000=0.592	592/604=0.9801	[2.6.e-10 306.9933]	[-22.0701 5.7268]
P4	592/1000=0.592	592/604=0.9801	[3.28.e-12 3.8704]	[-26.4436 1.3533]
P5	591/1000=0.591	591/603=0.9801	[2.56 2.88.e+12]	[0.9390 28.6899]
P6	181/1000=0.181	181/603=0.3001	[0.0461 185.4268]	[-3.0749 5.2226]
P7	181/1000=0.181	181/603=0.3001	[0.0034 14.0025]	[-5.6583 2.6392]
P8	612/1000=0.612	612/999=0.6126	[2.11.e-10 359.3224]	[-22.2815 5.8842]
P9	826/1000=0.826	826/826=1	[0.0 162.1438]	[-32.9422 5.0884]
P10	679/1000=0.679	679/680=0.9985	[1.6.e-10 6077.2169]	[-22.5420 8.7123]
P11	678/1000=0.678	678/679=0.9985	[0.08 2.73.e+12]	[-2.5711 28.6370]
P12	679/1000=0.679	679/680=0.9985	[3.e-11 1075.1912]	[-24.2740 6.9802]
P13	588/1000=0.588	588/596=0.9865	[0.0436 27.1030]	[1.045 5.89.e+11]
P14	155/1000=0.155	155/999=0.1551	[0.0351 42.6058]	[-3.3470 3.7519]
P15	162/1000=0.162	162/597=0.2713	[1.68.e-10 54.6197]	[-22.5058 4.0003]
P16	157/1000=0.157	157/999=0.1571	[19.0987 25358.7794]	[2.9496 10.1408]

Figure 1: Single CB - Parameters space for CKI activity (P_{10}, P_{11}, P_{12})

Stability was analyzed in the plane of CKI parameters: P_{10}, P_{11} and P_{12} (Eq.1). The initial parameters used are: $P = [0.072543, 0.10186, 2.7971, 0.0059252, 1.1132, 0.46275, 0.017682, 0.029499, 83.653, 0.31339, 1.5928, 0.54378, 0]$; Each parameter was varied over a large range of parameter space (10 magnitudes of order). The synthesis rate of CKI is assumed to be const (P_{10}); the Cyclin/CDK/CKI complex rate can occasionally effect differently over Cyclin and CKI concentrations; without the loss of generality we assumed not necessarily equal values of rate constants (e.g., P_{11} and P_{12} , respectively). The stably kinase activity is the area between the two surfaces. Robust oscillated kinase activity (limit cycle) is the area above the lower surface and below the upper surface, while the other activities are outside this area.



Model: Modular system with shared CKI for all CB (Eq.4)

Cyclin E box:

$$x_1' = k_1 P_1 x_{13} - P_2 x_1 x_3 + P_3 x_1 x_2 - P_{12} x_1 x_4$$

$$(4a) \quad x_2' = P_9 + P_4 x_1 - P_5 x_2$$

$$x_3' = P_8 + P_6 x_1 - P_7 x_3$$

CKI:

$$(4b) \quad x_4' = P_{10} - P_{11} x_4 (S_1 x_1 + S_2 x_5 + S_3 x_9) - P_{17} x_4$$

Cyclin A box:

$$\begin{aligned}
x_5' &= k_2 P_1 x_{13} - P_2 x_5 x_7 + P_3 x_5 x_6 - P_{12} x_5 x_4 \\
(4c) \quad x_6' &= P_9 + P_4 x_5 - P_5 x_6 \\
x_7' &= P_8 + P_6 x_5 - P_7 x_7 \\
x_8 &\text{ was canceled}
\end{aligned}$$

Cyclin B box:

$$\begin{aligned}
x_9' &= k_3 P_1 x_{13} - P_2 x_9 x_{11} + P_3 x_9 x_{10} - P_{12} x_9 x_4 \\
(4d) \quad x_{10}' &= P_9 + P_4 x_9 - P_5 x_{10} \\
x_{11}' &= P_8 + P_6 x_9 - P_7 x_{11} \\
x_{12} &\text{ was canceled}
\end{aligned}$$

E2F box.

$$\begin{aligned}
(4e) \quad x_{13}' &= P_{13} x_{13} + P_{14} x_1 x_{14} - P_{15} x_{13} x_5 - P_{16} x_{13} x_9 - P_{18} x_{13} \\
x_{14}' &= P_{16} x_{13} x_9 - P_{14} x_1 x_{14}
\end{aligned}$$

In order to examine the validation of our modular system, a more realistic demand was applied: the use of single CKI that shared all CB control (Eq.4b).

Figure 2: Numerical solution of modular system with single CKI described by Eq.4

These ODEs solved using the ode45 MATLAB function. The top drawing shows the phase space of E2F (y axis) versus Cyclin A (x axis), while the bottom drawing shows the variation of concentrations over time.

The parameter sets used are: $k=[150, 80, 1]$, $S=[0.9, 0.1, 0.01]$, $P=[0.0356, 0.4416, 1.3013, 0.203, 0.5467, 0.6108, 0.2844, 0.1952, 0.7739, 0.2782, 0.4302, 0.1691, 0.02291, 3.02887e-05, 9.6660e-06, 0.0996, 1, 0.06]$

