From simple to complex patterns of oscillatory behavior in a model for the mammalian cell cycle containing multiple oscillatory circuits

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We previously proposed an integrated computational model for the network of cyclin-dependent kinases (Cdks) that controls the dynamics of the mammalian cell cycle [C. Gérard and A. Goldbeter, "Temporal self-organization of the cyclin/Cdk network driving the mammalian cell cycle," Proc. Natl. Acad. Sci. U.S.A. **106**, 21643 (2009)]. The model contains four Cdk modules regulated by reversible phosphorylation, Cdk inhibitors, protein synthesis or degradation, and the balance between antagonistic effects of the tumor suppressor pRB and the transcription factor E2F. Increasing the level of a growth factor above a critical threshold triggers the transition from a quiescent, stable steady state to self-sustained oscillations in the Cdk network. These oscillations correspond to the repetitive, transient activation of cyclin D/Cdk4–6 in G1, cyclin E/Cdk2 at the G1/S transition, cyclin A/Cdk2 in S and at the S/G2 transition, and cyclin B/Cdk1 at the G2/M transition. This periodic, ordered activation of the various cyclin/Cdk complexes can be associated with cell proliferation. The multiplicity of feedback loops within the Cdk network is such that it contains at least four distinct circuits capable of producing oscillations. The tight coupling of these oscillatory circuits generally results in simple periodic behavior associated with repetitive cycles of mitosis or with endoreplication. The latter corresponds to multiple passages through the phase of DNA replication without mitosis. We show here that, as a result of the interaction between the multiple oscillatory circuits, particularly when attenuating the strength of the oscillatory module involving cyclin B/Cdk1, the model for the Cdk network can also produce complex periodic oscillations, quasiperiodic oscillations, and chaos. Numerical simulations based on limited explorations in parameter space nevertheless suggest that these complex modes of oscillatory behavior remain less common than the evolution to simple periodic oscillations of the limit cycle type, holding with the view that simple periodic oscillations in the Cdk network correspond to its physiological mode of dynamic behavior. © *2010 American Institute of Physics*. [doi:10.1063/1.3527998]

The mammalian cell cycle is composed of four different phases: G1, S (DNA replication), G2, and M (mitosis). A network of cyclin-dependent kinases (Cdks) controls the ordered progression through the successive phases of the cell cycle:[1–4] the cyclin D/Cdk4–6 and cyclin E/Cdk2 complexes promote progression in G1 and allow the G1/S transition, the cyclin A/Cdk2 complex ensures progression in S and elicits the S/G2 transition, while the cyclin B/Cdk1 complex brings about the G2/M transition. Cdk regulation is achieved through a variety of mechanisms that include association with cyclins and protein inhibitors, phosphorylation-dephosphorylation, and cyclin synthesis or degradation.[5–8] We recently proposed a model for the dynamics of the Cdk network that drives the mammalian cell cycle.[9] The model shows that in the presence of a suprathreshold amount of growth factor (GF), the Cdk network can self-organize in time in the form of sustained oscillations which correspond to the transient, ordered activation of the various cyclin/Cdk complexes. These oscillations can be associated with cell proliferation, while the stable steady state can be associated with a state of quiescence. The Cdk network contains at least four distinct oscillatory circuits. Here we show that each of these subnetworks can produce sustained oscillations. Generally, the tight coupling of the oscillatory circuits generates simple periodic behavior associated with repetitive cycles of mitosis. We also observe endoreplication, which corresponds to multiple rounds of DNA replication without mitosis. As a result of the interaction between the multiple oscillatory circuits present in the Cdk network, the model can also produce complex periodic oscillations, quasiperiodic oscillations, and chaos, particularly when the strength of the oscillatory module involving cyclin B/Cdk1 diminishes. Limited evidence from numerical simulations suggests, however, that these complex modes of oscillatory behavior are probably less common in parameter space than simple periodic oscillations.

I. INTRODUCTION

In a previous publication we constructed a detailed integrative model for the cyclin/Cdk network that drives the mammalian cell cycle and explored the conditions for its temporal self-organization.[9] Building on previous work that

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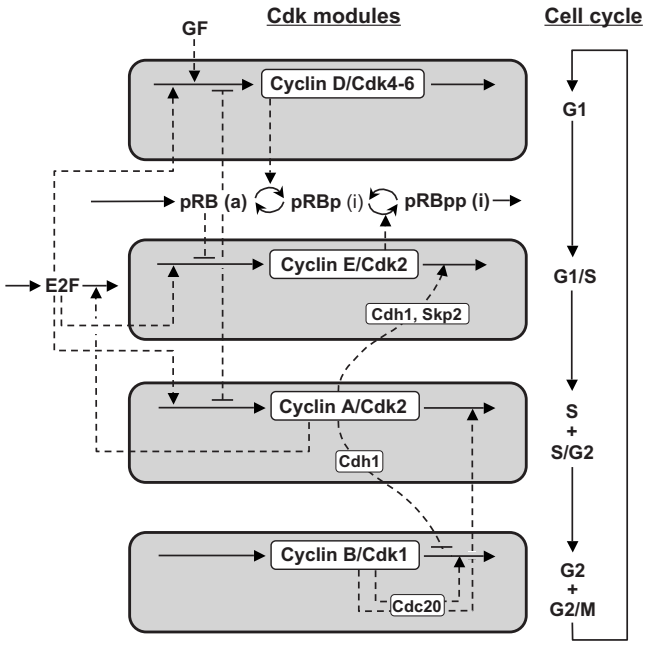

FIG. 1. Scheme of the model for the Cdk network. The model incorporates the four main cyclin/Cdk complexes centered on cyclin D/Cdk4–6, cyclin E/Cdk2, cyclin A/Cdk2, and cyclin B/Cdk1. Also considered are the effect of the growth factor GF and the role of the pRB/E2F pathway, which controls cell cycle progression. Cyclin D/Cdk4–6 and cyclin E/Cdk2 elicit progression in G1 and the G1/S transition by phosphorylating and inhibiting pRB. The active, unphosphorylated form of pRB inhibits the transcription factor E2F, which promotes cell cycle progression by inducing the synthesis of cyclins D, E, and A. The protein Cdh1, inhibited by cyclin A/Cdk2, promotes the degradation of cyclin B and inhibits Skp2 which promotes the degradation of cyclin E; thereby, the activation of cyclin A/Cdk2 leads to the activation of cyclin B/Cdk1 and to the inhibition of cyclin E/Cdk2. The protein Cdc20, activated by cyclin B/Cdk1, promotes the degradation of cyclins A and B, leading to the decrease in cyclin A/Cdk2 and cyclin B/Cdk1. The combined effect of regulatory interactions between the four modules allows the cell to progress in a repetitive, oscillatory manner along the successive phases of the cell cycle, as depicted on the right part of the figure (see supporting information of Ref. 9 for more detailed schemes of the Cdk network).

showed the occurrence of oscillations in models for the cell cycle in embryos[10–14] and yeast,[15] and in less detailed or partial models for the mammalian cell cycle,[16–20] we focused on the conditions in which the cyclin/Cdk network may function as a self-sustained biochemical oscillator solely as a result of its regulatory structure. To this end we disregarded the control by cell mass, which appears less stringent in mammalian cells than in yeast.[21] The model for the Cdk network (Fig. 1) contains four coupled modules centered on cyclin D/Cdk4–6, cyclin E/Cdk2, cyclin A/Cdk2, and cyclin B/Cdk1, respectively (for more detailed schemes of the four modules, see Supporting information in Ref. 9). The activity of the cyclin/Cdk complexes is regulated both through phosphorylation-dephosphorylation and reversible association with the protein inhibitors p21 or p27.[6,22] The model includes the Retinoblastoma protein pRB and the transcription factor E2F, which respectively inhibit[23] and promote[24] progression in the cell cycle. The Cdk network itself controls the balance between pRB and E2F through phosphorylation. Additional regulations of cyclin/Cdk complexes occur in the form of negative feedback, which arises from Cdk-induced cyclin degradation,[7] and positive feedback, which originates from the fact that Cdks indirectly promote their own activation.[25]

The model is described by a set of 39 ordinary differential equations. Five additional equations are needed to incorporate into the model a checkpoint on DNA replication.[9] The model predicts that in the presence of suprathreshold amounts of growth factor (GF), the regulatory interactions within the Cdk network can spontaneously give rise to sustained oscillations corresponding to the repetitive, ordered activation of the various cyclin/Cdk complexes along the cell cycle phases. We proposed to associate such self-sustained oscillations with cell proliferation. When GF decreases below a critical level, oscillations stop and the system evolves to a stable steady state, which can be associated with the quiescent, G0 phase of the cell cycle. We showed in Ref. 9 that the model accounts for key properties of the mammalian cell cycle such as the need for a fine-tuned balance between pRB and E2F for oscillations to occur, and the existence of a restriction point in G1, which is a point of no return beyond which cells are irreversibly engaged in the cycle and do not require the presence of growth factor to complete mitosis.[26–28] By including the role of a DNA replication checkpoint, we showed that such a checkpoint slows down the dynamics of the network without modifying its oscillatory nature. The model further accounts for the possibility of truncated cell cycles corresponding to endoreplication, in which multiple rounds of DNA replication occur in the absence of mitosis.[29,30]

The multiplicity of regulatory loops within the Cdk network is such that it contains several oscillatory circuits, which, if isolated, could produce oscillations on their own. Because of their tight coupling, these oscillatory subnetworks generally synchronize with each other to produce limit cycle oscillations. We focus here on the possibility that the interactions between the oscillatory circuits can nevertheless produce complex oscillatory behavior in the form of complex periodic oscillations (bursting), quasiperiodic oscillations, or chaos.

II. SIMPLE PERIODIC OSCILLATIONS IN THE CDK NETWORK: EVOLUTION TO A LIMIT CYCLE

The model, schematized in Fig. 1, contains four modules corresponding to the sequential activation of the various cyclin/Cdk complexes. Modules 1–3 are centered on cyclin D/Cdk4–6, cyclin E/Cdk2, and cyclin A/Cdk2, respectively, whereas cyclin B/Cdk1 is at the core of module 4. The modules are coupled through multiple regulatory interactions, which are depicted in a more detailed manner in Supporting information in Ref. 9, where more comprehensive schemes for modules 1–4 are presented in Figs. S1 and S2, together with a detailed description of the reactions and regulations considered for each module; variables are defined in Table S1, while a definition of parameters and a list of their numerical values are given in Table S2. The temporal evolution of the model is governed by a set of 39 kinetic equations, which are listed in Sec. II in the Supporting information of Ref. 9. These equations are based on mass action or Michae-

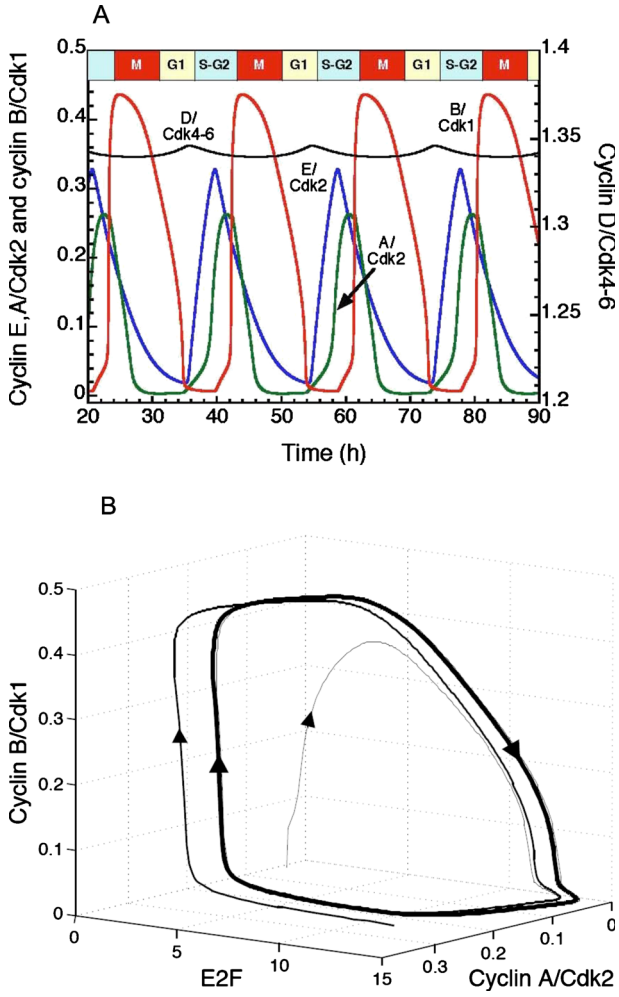

FIG. 2. (Color online) Limit cycle oscillations (temporal series and phase space). (a) In the presence of a suprathreshold amount of GF, sustained oscillations correspond to the repetitive, ordered activation of the four cyclin/Cdk complexes. Cyclin D/Cdk4–6 and cyclin E/Cdk2 control progression in G1 and elicit the G1/S transition, whereas cyclin A/Cdk2 allows progression into S and G2. Finally, the peak in cyclin B/Cdk1 brings about the G2/M transition. The curves were generated by numerical integration of the kinetic equations (1)–(39) listed in Sec. II in the supporting information of Ref. 9, for the parameter values listed in Table S2. Shown are the oscillations in the active forms of the cyclin/Cdk complexes. For cyclin D/Cdk4–6 the curve shows the evolution of the sum of the free form of the complex and of its form bound to p21/p27. The oscillations in (a) are of the limit cycle type, i.e., they correspond in the phase space to a unique closed curve that can be reached regardless of initial conditions. The same closed curve is accordingly reached in (b) for two distinct initial conditions when the trajectory of the 39-variable system is projected onto the three-variable phase space formed by the concentrations of E2F, cyclin A/Cdk2, and cyclin B/Cdk1.

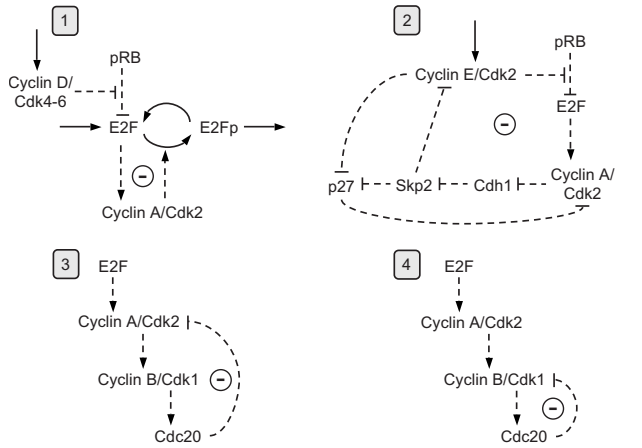

FIG. 3. Multiple oscillatory circuits in the Cdk network. Schematized are four circuits containing negative feedback loops that are capable of generating sustained oscillations in the model for the mammalian cell cycle (Ref. 9), as shown in Fig. 4. Cyclin A/Cdk2 is present in the four circuits, each of which can generate on its own sustained oscillations. In circuits 1 and 2, oscillations can occur in the absence of cyclin B/Cdk1, which is responsible for the entry of cells into mitosis. Oscillations in Cdk2, which controls DNA replication, occur in these circuits without any peak in Cdk1, a phenomenon known as endoreplication (see text). In oscillatory circuits 3 and 4, mitotic oscillations involving repetitive activation of cyclin B/Cdk1 can occur, based on a negative feedback exerted via the protein Cdc20, which allows the degradation of either cyclin A or cyclin B in these circuits. In physiological conditions, all four oscillatory circuits synchronize to produce the ordered, repetitive activation of the different modules forming the Cdk network that drives the mammalian cell cycle.

lian kinetics. To limit the complexity of the model, we only considered the variation of protein levels without incorporating explicitly changes in the mRNAs.

The model indicates that when GF exceeds a critical threshold value, repetitive activation of the cyclin/Cdk complexes occurs in the form of self-sustained oscillations [Fig. 2(a)]. The ordered activation of the cyclin/Cdk complexes corresponds to the passage through the successive phases of the cell cycle. The peaks in the activity of cyclin D/Cdk4–6 and cyclin E/Cdk2 allow progression from G1 to S. The activity of cyclin A/Cdk2 rises in S and G2, while at the end of the cycle, the peak in cyclin B/Cdk1 brings about the G2/M transition. The level of cyclin D/Cdk4–6 remains elevated throughout the cycle, in agreement with experimental observations,[31] and falls only when GF is removed.

Below the threshold level of GF, cells are in a stable steady state, which can be associated with the quiescent phase, G0. Above the threshold the repetitive activation of the Cdks can be associated with cell proliferation. Oscillations only occur in a bounded range of parameter values, as illustrated by stability diagrams that can be found in Ref. 9.

Sustained oscillations shown in Fig. 2(a) correspond to the evolution to a stable limit cycle [Fig. 2(b)]. The latter can be reached regardless of initial conditions. Thus, Fig. 2(b) illustrates how trajectories starting from two distinct initial conditions converge to the same closed curve in the phase space.

III. MULTIPLE OSCILLATORY CIRCUITS IN THE CDK NETWORK

If the model for the mammalian cell cycle can globally operate in a periodic manner, the Cdk network, nevertheless, contains at least four oscillatory circuits, each of which can produce sustained oscillations on its own.[9] When coupled, as occurs in physiological conditions, these circuits generally cooperate to produce the periodic, ordered activation of the cyclin/Cdk complexes that drive the successive phases of the cell cycle. The four oscillatory circuits in the Cdk network are schematized in Fig. 3. The oscillators are all based on negative feedback regulation and were identified by numerical simulations. Shown in Fig. 4 are the different types of

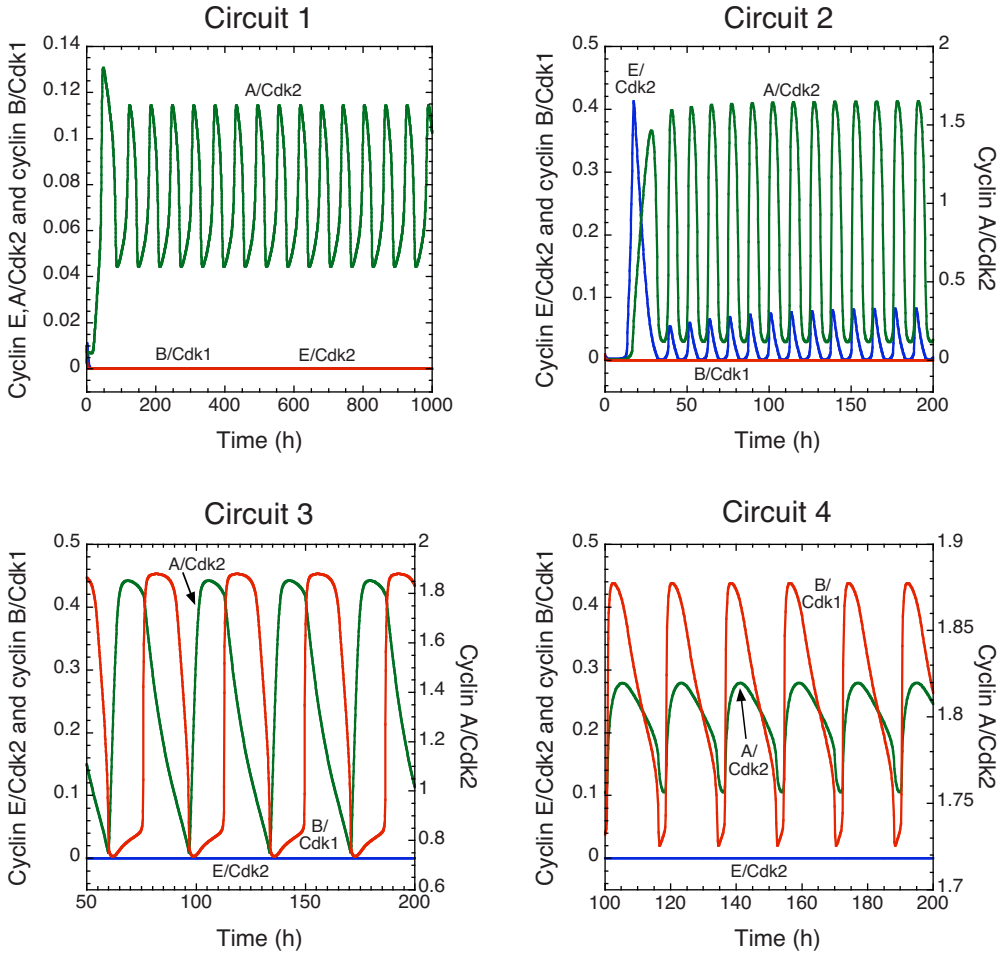

FIG. 4. (Color online) Oscillations generated by the different oscillatory circuits embedded in the Cdk network. The four circuits are schematized in Fig. 3. In circuit 1, $k_{ce}=v_{s1p27}=v_{s2p27}=v_{cb}=0$, $v_{se2f}=0.025$ μM h^{-1}. In circuit 2, $v_{cb}=V_{1e2f}=0$. For circuits 3 and 4, $V_{1e2f}=k_{ce}=v_{s1p27}=v_{s2p27}=0$. Moreover, in circuit 3, $V_{db}=0.5$ μM h^{-1}, $K_{dbcdh1}=0.01$ μM, and the term of activation of the degradation of cyclin B by the protein Cdc20 is suppressed [see Eq. (30) in the supporting information of Ref. 9]. In circuit 4, $V_{da}=0.1$ μM h^{-1}, $K_{dbcdc20}=0.1$ μM, and the term of activation of the degradation of cyclin A protein by the protein Cdc20 is suppressed [see Eq. (20) in the supporting information of Ref. 9]. The values of the other parameters of the model are the same as in Table S2 of Ref. 9 where the different parameters of the model are defined.

sustained oscillations generated by each of the four circuits isolated from the rest of the network. This isolation can readily be achieved in the model by setting relevant parameters equal to zero, as explained in the legend to Fig. 4. For example, for the oscillatory circuit 1, we put the rate of synthesis of cyclin B, v_{cb}, and the rate constant for the synthesis of cyclin E, k_{ce}, equal to zero in order to suppress negative feedback loops and bypass oscillators 3 and 4 and oscillator 2, respectively.

We see in Fig. 3 that the four oscillators all contain cyclin A/Cdk2, but only circuits 3 and 4 also contain cyclin B/Cdk1 and can thus be viewed as mitotic oscillators producing a peak in cyclin B/Cdk1, as shown in Fig. 4. In contrast, the subnetworks 1 and 2 predict oscillations in cyclin A/Cdk2 in the absence of coupling to Cdk1, i.e., even when the latter remains constant (Fig. 4).

The oscillatory circuits 1 and 2 produce Cdk1-independent Cdk2 oscillations and are therefore associated with endoreplication, while circuits 3 and 4 involve Cdk1 oscillations and are associated with periodic cell division. The possibility of endoreplication was previously reported in a model for the yeast cell cycle[32] and in a generic model for the eukaryotic cell cycle.[20] The oscillatory circuit 4 is, in fact, closely related to the mitotic oscillator driving the early cell cycles in amphibian embryos.[10–14] Rapid cycling likely associated with an oscillatory subnetwork involving cyclin B/Cdk1 has been revealed by treatments perturbing the normal operation of the Cdk network.[33]

The present results suggest that the sequential activation of the Cdk modules in the Cdk network is brought about by temporal self-organization corresponding to the global, periodic operation of the mammalian cell cycle. The first three modules of the network (see Fig. 1) centered on cyclin D/Cdk4–6, cyclin E/Cdk2, and cyclin A/Cdk2 cooperate to induce the transient firing of the last, embryonic-like, oscillatory module centered on cyclin B/Cdk1. The two modules at the top of the network elicit the increase in cyclin A/Cdk2 in module 3 that transiently drives circuit 4 into the domain of sustained oscillations. The resulting pulse in cyclin B/Cdk1 triggers successively the decrease in cyclin A/Cdk2, the associated exit of circuit 4 from the oscillatory domain, and the return to conditions leading to the resumption of a new cell cycle.

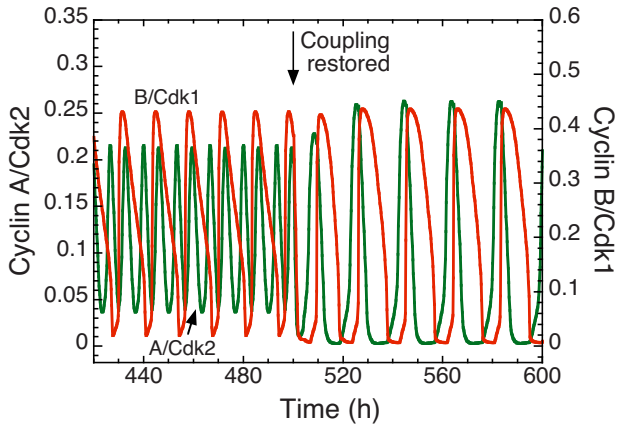

FIG. 5. (Color online) Coupling and phase-locking of the Cdk2 and Cdk1 oscillators. Intrinsically, the Cdk network contains multiple oscillatory circuits (see Figs. 3 and 4). When these are coupled to each other, the Cdk network can self-organize in time to generate sustained oscillations that occur, sequentially, with the same period, in the various cyclin/Cdk complexes [Fig. 2(a)]. If the Cdk1 module, responsible for the entry into mitosis, is silenced, endoreplication oscillators can be expressed (see Fig. 6). Upon decreasing the coupling between the Cdk2 and Cdk1 oscillators, the latter produce sustained oscillations with distinct periods (see $t<500$ h). In these conditions, the phase of DNA replication is not anymore constant with respect to the phase of mitosis. Upon restoring the tight coupling between the Cdk2 and Cdk1 oscillators ($t>500$ h), their phase-locking ensures the sequential activation of cyclin A/Cdk2 and cyclin B/Cdk1, which corresponds to the successive passage through DNA replication and mitosis. For $t>500$ h, parameter values are the same as in the Table S2 in Ref. 9. For $t<500$ h, $v_{se2f}=0.26$ μM h^{-1}, $V_{1e2f}=7$ h^{-1}, $K_{1e2f}=K_{2e2f}=0.01$ μM, $k_{ca}=1$ h^{-1}, $K_{acdc20}=0$, $v_{s1p27}=v_{s2p27}=0$, $v_{cb}=0.09$ μM h^{-1}, $K_{dbcdc20}=0.5$ μM, $K_{dbcdh1}=0$.

We previously mentioned that the four Cdk modules and the different oscillators present in the Cdk network must be tightly coupled in order to produce the successive activation of the various cyclin/Cdk complexes corresponding to the correct progression along the different cell cycle phases.[9] This view holds with the phase locking concept of the cell cycle control, which suggests that in yeast the Cdk oscillator could order cell cycle events by phase-locking various peripheral oscillators responsible for specific phases of the cell cycle.[34–36] The model proposed for the Cdk network driving the mammalian cell cycle contains multiple oscillators (see Figs. 3 and 4), which must be tightly coupled in order to produce correct progression into the various cell cycle phases. The model shows that if the Cdk1 module is not tightly coupled to the Cdk2 modules, oscillations with distinct periods can occur in Cdk2 and Cdk1 (see Fig. 5 for $t<500$ h). As explained in the legend to Fig. 5, the uncoupling is achieved by modifying the values of several parameters linking the Cdk1 module to the other modules of the network. When the coupling is restored (see Fig. 5 for $t>500$ h), the Cdk2 and Cdk1 oscillators become synchronized; their phase locking ensures a correct progression from DNA replication to mitosis.

IV. FROM SIMPLE TO COMPLEX PATTERNS OF OSCILLATORY BEHAVIOR

Even when the four oscillatory circuits are coupled, and thus include Cdk1, simulations indicate that the interactions between the oscillatory subnetworks may sometimes produce complex oscillations. Thus, upon decreasing progressively the rate of inactivation of protein Cdh1 that promotes cyclin B degradation, the rate of cyclin B hydrolysis increases and the Cdk1 module is progressively inactivated. Such a change leads to the transition from mitotic oscillations to endoreplication (Fig. 6). This result fits with the observation that constitutive activation of the protein Cdh1 can uncouple DNA replication from mitosis.[37] We observed that several peaks in Cdk2 may sometimes be produced for each peak in Cdk1. These periodic oscillations are more or less complex [Figs. 6(b) and 6(c)]. Sometimes they may become highly complex [Fig. 7(a)], leading to folded limit cycles in phase space [Fig. 7(b)]. The periodic nature of the trajectory can be ascertained by the construction of a Poincaré section, which shows a limited number of fixed points [Fig. 7(c)].

Other modes of complex oscillatory behavior can be observed in the Cdk network. Thus, upon varying the rate of synthesis of the transcription factor E2F, measured by parameter v_{se2f}, in the conditions of Fig. 7, we observed the transition from complex periodic to quasiperiodic oscillations (Fig. 8). The latter yield a Poincaré section corresponding to a closed curve [Fig. 8(c)].

Chaotic oscillations [Fig. 9(a)] can also occur for parameter values close to those producing quasiperiodic or complex periodic behavior. These aperiodic oscillations correspond to the evolution to a strange attractor in phase space [Fig. 9(c)]. The chaotic nature of such dynamic behavior was determined by its sensitivity to initial conditions [Fig. 9(b)] and by the structure of the associated Poincaré section [Fig. 9(d)], which differs from that shown in Figs. 7(c) and 8(c) for complex periodic and quasiperiodic oscillations, respectively.

V. DISCUSSION

The model for the cyclin/Cdk network brings to light the various modes of dynamic behavior that emerge from the intertwined regulations of the different modules that drive the successive phases of the mammalian cell cycle. When the growth factor that induces progression in the cycle exceeds a critical value, repetitive activation of the cyclin/Cdk complexes occurs in the form of self-sustained oscillations. The ordered activation of the cyclin/Cdk complexes corresponds to the passage through the successive phases of the cell cycle. Much as in models containing but a few variables,[11] such periodic oscillations correspond to the evolution to a limit cycle (Fig. 2) even though the system contains 39 variables! The Cdk network is thus capable of temporal self-organization in the form of limit cycle oscillations.

Because of its relatively complex structure built along four Cdk modules and of the large number of variables and regulations involved, the Cdk network contains multiple oscillatory circuits. We have identified by numerical simulations at least four oscillatory circuits,[9] represented in Fig. 3. As shown in Fig. 4, each of these circuits, when isolated from the rest of the network, can produce sustained oscillations on its own. Two circuits generate oscillations in Cdk2 without oscillations in Cdk1, which behavior corresponds to endoreplication. In spite of the multiplicity of oscillatory circuits, their tight coupling within the Cdk network ensures

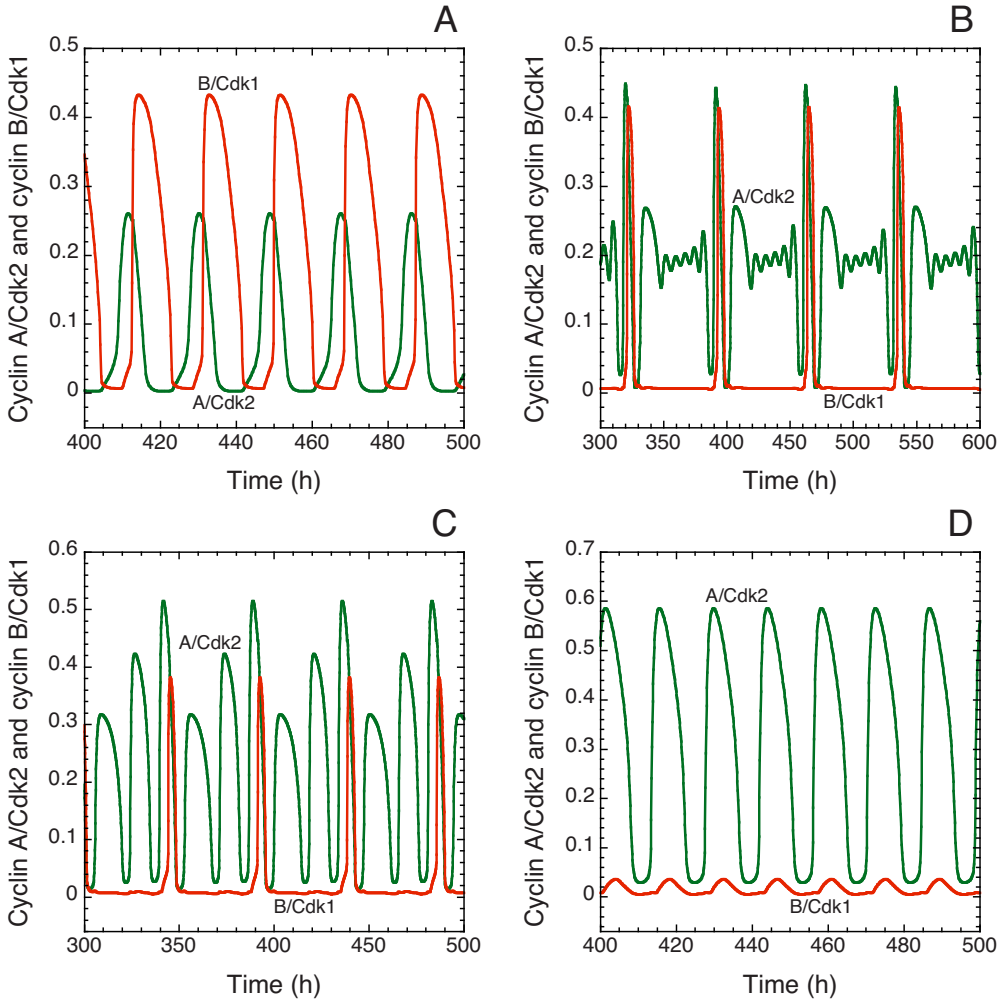

FIG. 6. (Color online) Progressive shift from mitotic oscillations to endoreplication. From (a) to (d) the rate constant for inactivation of Cdh1, V_{2cdh1}, decreases progressively from (a) 7 h^{-1} (simple periodic, large-amplitude oscillations in cyclin A/Cdk2 and cyclin B/Cdk1) to (b) 4.5 h^{-1} (complex periodic oscillations particularly noticeable for cyclin A/Cdk2), (c) 3 h^{-1} (yet another type of complex periodic oscillations), and (d) 2.5 h^{-1} (simple periodic oscillations corresponding to endoreplication, with large-amplitude oscillations in cyclin A/Cdk2 and small-amplitude oscillations in cyclin B/Cdk1). In each case, the rate of synthesis of p27 v_{s1p27} equals 1.2 μM h^{-1}. Other parameter values are those listed in the Table S2 of Ref. 9.

that periodic oscillations represent its most common mode of temporal self-organization. Periodic oscillations involving large-amplitude changes in Cdk2 and Cdk1 occur in large regions in parameter space, which often extend over several orders of magnitude of the control parameters.[9]

The interaction between the oscillatory circuits within the full Cdk network may nevertheless lead to complex patterns of oscillatory behavior. This result is not astonishing since we know, from the study of a variety of other models, that the interaction between multiple oscillatory mechanisms within the same system can lead to complex oscillatory behavior, including chaos. This was observed, for example, in models for circadian rhythms for oscillations of Ca^{2+} or cyclic AMP.[38–40] In each case complex patterns of oscillatory behavior originate from the interplay between two instability-generating mechanisms in a domain in parameter space where both mechanisms are active at the same time. In the model for the mammalian cell cycle, no less than four oscillatory circuits are present. This situation is prone to produce complex oscillations. Here we showed, accordingly, the occurrence of three distinct modes of complex oscillatory behavior: bursting in the form of more or less complex periodic oscillations (Figs. 6 and 7), quasiperiodic oscillations (Fig. 8), and chaos (Fig. 9). Poincaré sections established for these various modes of complex oscillatory behavior confer to each of them a distinct signature.

Exploring the dynamic behavior of the model in parameter space is a daunting task because the model counts no less than 164 parameters (see Ref. 9). It is therefore difficult to reach definitive conclusions about the relative occurrence of simple versus complex oscillatory behavior in parameter space. In our experience of running hundreds of numerical simulations of this model, it is much more difficult to find parameter settings for complex periodic oscillations than for simple periodic oscillations with a single peak of Cdk1 and Cdk2 per period. This observation holds with the view that the latter mode of periodic behavior represents the physiological mode of operation of the Cdk network, whereas complex oscillations, particularly quasiperiodic or chaotic behavior, would correspond to unphysiological or pathologi-

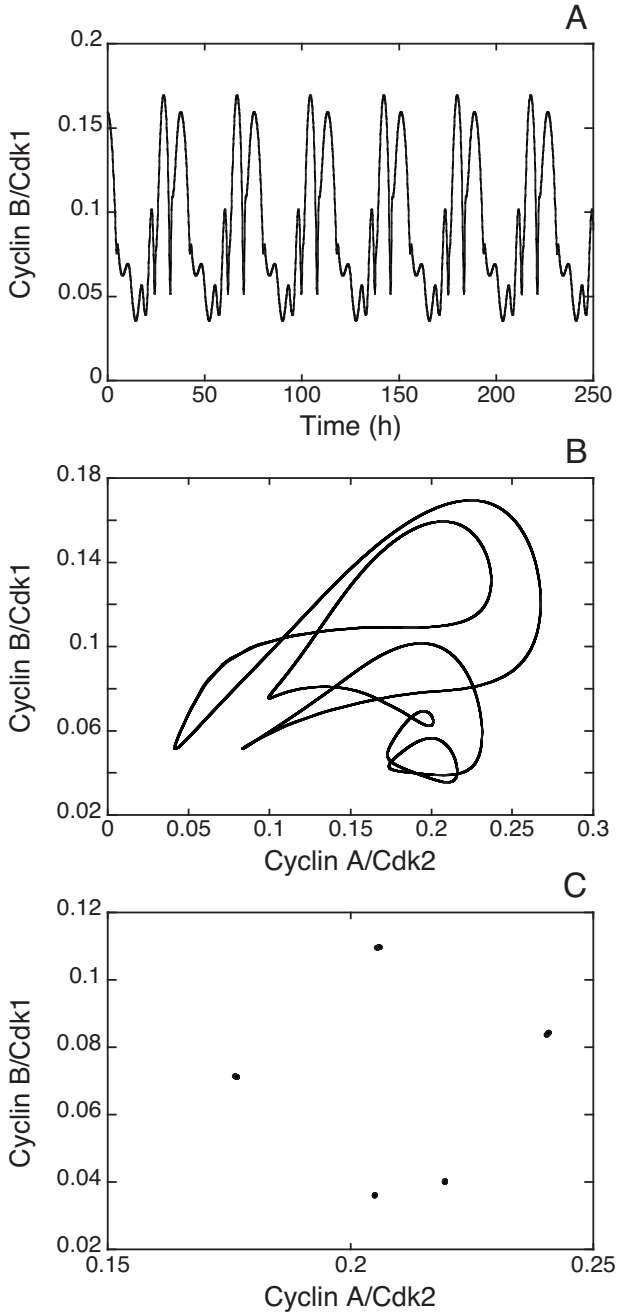

FIG. 7. Complex periodic oscillations. (a) Time evolution of cyclin B/Cdk1. (b) Projection of the trajectory of the 39-variable system onto the phase plane formed by cyclin A/Cdk2 and cyclin B/Cdk1. (c) Poincaré section established by plotting the level of cyclin B/Cdk1 vs the level of cyclin A/Cdk2 corresponding to the passage through a maximum in the level of cyclin E/Cdk2. The curves were established for the following parameter values: $v_{se2f}=0.255\ \mu M\ h^{-1}$, $k_{ce}=0.35\ h^{-1}$, $K_{dceskp2}=2.5\ \mu M$, $v_{sskp2}=0.1\ \mu M\ h^{-1}$, $V_{M5e}=24\ h^{-1}$, $k_{ca}=0.05\ h^{-1}$, $v_{s1p27}=1\ \mu M\ h^{-1}$, $v_{scdh1a}=0.3\ \mu M\ h^{-1}$, $V_{2cdh1}=7\ h^{-1}$, $v_{spai}=0.11\ \mu M\ h^{-1}$, $v_{cb}=0.025\ \mu M\ h^{-1}$, $k_{com4}=0.2\ \mu M^{-1}\ h^{-1}$, $V_{M1b}=4.5\ h^{-1}$, $v_{scdc20i}=0.01\ \mu M\ h^{-1}$, $k_{dcdc20i}=0.12\ h^{-1}$, $V_{M5b}=10\ h^{-1}$. Other parameter values are those listed in Table S2 of Ref. 9.

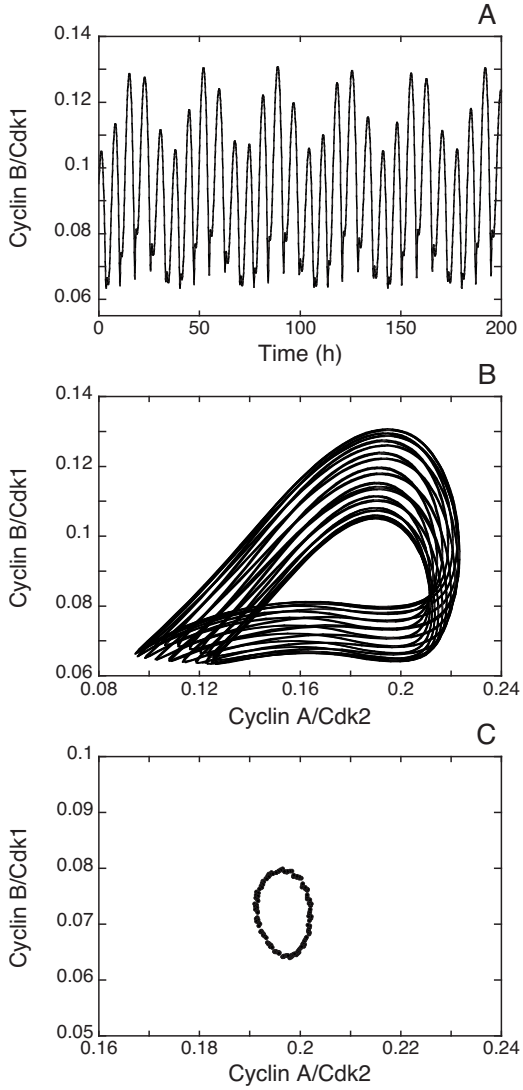

FIG. 8. Quasiperiodic behavior. (a) Time evolution of cyclin B/Cdk1. (b) Projection of the trajectory of the 39-variable system onto the phase plane formed by cyclin A/Cdk2 and cyclin B/Cdk1. (c) Poincaré section established by plotting the level of cyclin B/Cdk1 vs the level of cyclin A/Cdk2 corresponding to the passage through a maximum in the level of cyclin E/Cdk2. Here, $v_{se2f}=0.2575\ \mu M\ h^{-1}$. Other parameter values are as in Fig. 7.

cal conditions. Complex oscillations occur when the strength of the fourth module of the Cdk network becomes attenuated, so that the preceding modules have more freedom to express their own oscillatory properties. The model for the mammalian cell cycle allows us to investigate how the internal synchronization between multiple oscillatory circuits generally produces periodic behavior rather than chaos or quasiperiodic oscillations.

We recently presented a skeleton version of the model for the Cdk network driving the mammalian cell cycle, which contains only 5 (instead of 39) variables and 24 (instead of 164) parameters.[41] This reduced version of the model lacks many of the biochemical details of the present, more comprehensive model, but it retains the same modes of dynamic behavior including simple or complex periodic oscillations, quasiperiodic oscillations, and chaos. In addition, it can display birhythmicity, i.e., the coexistence between two stable modes of sustained oscillations. Given its much smaller number of parameters, it should prove easier to characterize the domains of occurrence of simple versus complex

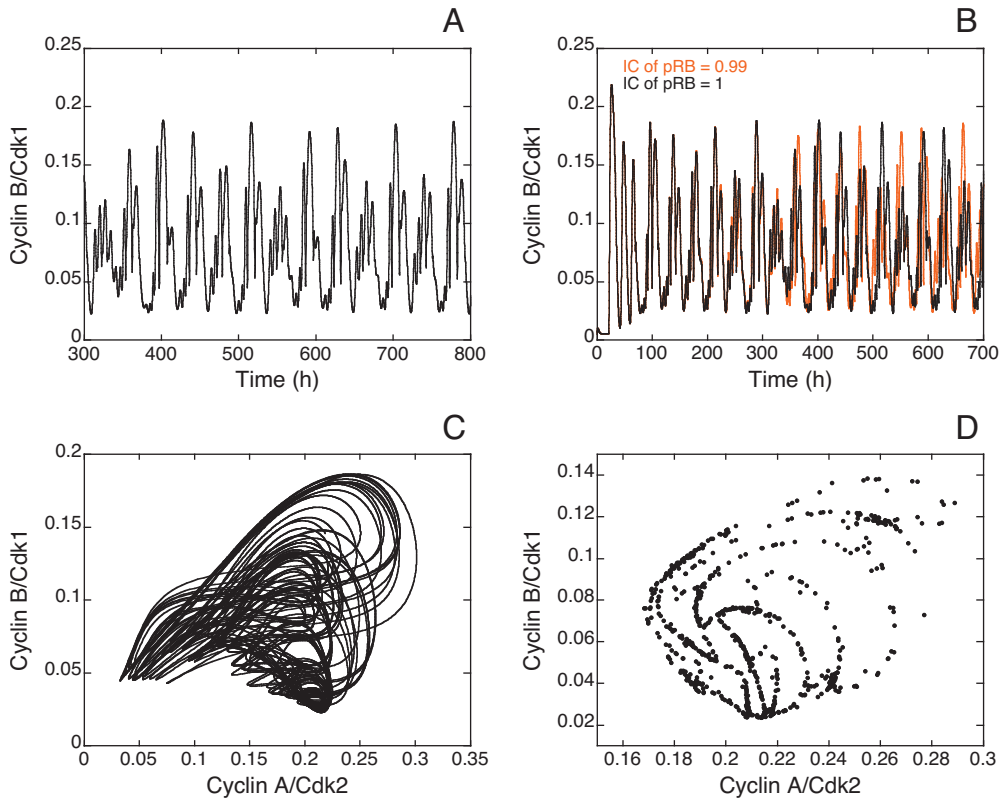

FIG. 9. (Color) Chaos. (a) Time evolution of cyclin B/Cdk1. (b) Time evolution of cyclin B/Cdk1 for two slightly different initial values of pRB (tentatively expressed in μM): 0.99 and 1 (as in Figs. 2 and 4–8, other initial conditions are listed in the Supporting information of Ref. 9). The sensitivity to initial conditions is a signature of chaotic behavior. (c) Strange attractor obtained by projection of the trajectory of the 39-variable system onto the phase plane formed by cyclin A/Cdk2 and cyclin B/Cdk1. (d) Poincaré section established by plotting the level of cyclin B/Cdk1 vs the level of cyclin A/Cdk2 corresponding to the passage through a maximum in the level of cyclin E/Cdk2. Here, v_{se2f}=0.24 μM h^{-1}. Other parameter values are as in Fig. 7.

oscillatory behavior in the skeleton version of the model. These results could then guide the systematic search for complex modes of oscillatory behavior in the comprehensive model for the Cdk network.

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