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Title: The Continuum Model: Regulation of the mammalian cell cycle is related to a continuous accumulation process and not dependent on phase-specific cascades of gene expression.

The Continuum Model of the eukaryotic cell cycle proposes that the principal, fundamental, and ultimate control of the cell cycle is a continuous accumulation process occurring in all phases of the cell cycle. The Continuum Model proposes that there are no G1-phase specific events (1), that there is no G1-phase restriction point controlling passage through the G1 phase (2), and that the G0 phase—a postulated phase into which cells have been proposed to enter when conditions for growth are not favorable—is an anthropomorphic construct that has no existence and no biological meaning (1-5). The Continuum Model proposes that there are no events unique to the G1 phase; processes occurring in the G1 phase occur in the other phases as well (1, 6). Events unique to the S- and G2/M-phases can and do occur; these events are superimposed upon the continuous regulatory process or processes occurring throughout the cell cycle. The Continuum Model explains the well-known variability of G1 phase duration, as well as the existence of G1-less cells (7, 8). The Continuum Model prompted experiments defining, identifying, and explaining artifacts that led to the widely-accepted proposal of G1-phase dependent Rb protein phosphorylation (6, 9). These experiments supported the Continuum Model prediction of no G1-phase Rb phosphorylation. The Continuum Model led to a reexamination and reinterpretation of the microarray data on G1-phase specific gene expression as studied using microarrays (10-12). The Continuum Model proposes that whole-culture synchronization, the dominant and near-prevalent approach to cell-cycle analysis, cannot synchronize cells at all (1, 13-17). Time-lapse studies have supported the Continuum Model prediction that whole-culture, non-selective methods of "synchronization" cannot synchronize cells (13). The widespread and near-universal use of whole-culture synchronization methods—methods that neither synchronize cells nor avoid unwanted and deviant perturbations—have led to the current view of the cell cycle with myriad proposed variations in gene expression occurring during G1 phase. The Continuum Model does not postulate any metabolic switches during the G1 phase when certain genes are turned on leading to the initiation of subsequent events such as S phase. No metabolic cascade with G1-phase specific gene expression regulates the cell cycle. Rather, the continuous accumulation of material leads to initiation of S phase, the subsequent passage through S phase, and then mitosis and cytokinesis. Theoretical, mathematical, and formal studies and analyses of cell cycle control should always consider problems with data based on questionable experimental approaches, particularly experiments using whole-culture synchronization.

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(Many of the cited references can be read directly at www.umich.edu/~cooper; just click on the appropriate article title. The experimental data supporting the Continuum Model are described in more detail in these references.)