Modeling the Cell Cycle

References

1. A. Goldbeter's book, "Biochemical Oscillations and Cellular Rhythms" (we have a copy) - see Chap. 10.


Goldbeter's Minimal Cascade Model

**Ultrasensitivity**: Way to generate steep thresholds

Consider simple cycle:

![Diagram of the cascade model]

- $p^*$: inactive protein
- $p$: active protein
- $v_1, v_2$: reaction velocities

We have:

\[
\frac{p}{p_T} + \frac{p^*}{p_T} = 1
\]

\[
\Rightarrow \frac{p^*}{p_T} = 1 - \frac{p}{p_T} = x
\]

\[
\Rightarrow \frac{p^*}{p_T} = 1 - x
\]

\[
\frac{v_1}{p} \rightarrow p \rightarrow \frac{v_2}{p} \Rightarrow \frac{dp}{dt} = v_1 - v_2
\]

Assume MM kinetics:

\[
v_1 = \frac{v_1 (1-x)}{K_1 + (1-x)}
\]

\[
v_2 = \frac{v_2 x}{K_2 + (1-x)}
\]

Note: $K_1, K_2$ normalized by $p_T$, as are $v_1, v_2$.\[V_{max} = K_2 E_{total}^*\]
At steady state: \[
\frac{dP}{dt} = 0
\]
\[
\Rightarrow 2v_1 = 2v_2
\]
\[
\Rightarrow \frac{v_1 (1-X)}{k_1 + (1-X)} = \frac{v_2 X}{k_2 + X}
\]
\[
\Rightarrow X_{ss} = \phi + \left[ \phi^2 + 4 k_2 (\frac{v_1}{v_2} - 1) (\frac{v_1}{v_2}) \right]^{\frac{1}{2}}
\]
\[
\frac{2 (\frac{v_1}{v_2} - 1)}{2 (\frac{v_1}{v_2} - 1)}
\]

\[
\text{with } \phi = (\frac{v_1}{v_2} - 1) - k_2 (\frac{v_1}{k_2} + \frac{v_1}{v_2})
\]

\[
X_{ss}
\]

\[
\frac{V_1}{V_2} \left( \frac{E_1^{tot}}{E_2^{tot}} \right)
\]

Note: \( k_1 = \frac{k_{m1}}{P_T} \), \( k_2 = \frac{k_{m2}}{P_T} \)

\( K_1, K_2 \ll 1 \)\ (i.e. \( K_{m1}, K_{m2} \ll P_T \))

\( K_1, K_2 \gg 1 \)\ (i.e. \( K_{m1}, K_{m2} \gg P_T \))
Assumptions in the minimal model (Fig 3)

- The model focused on the cell cycle in early amphibian embryos where 2 main factors are cyclin and cdc2 kinase. Assume is synthesized at a constant rate and it triggers the activation of cdc2 kinase.
- Ignore complex formation between cyclin and cdc2.
- Assume that the maximum activity of wee1 (kinase) remains constant throughout the cell cycle.

### Kinetic equations

For cyclin:  
\[
\frac{dC}{dt} = \frac{K_a}{K_d + C} - k_d C
\]

- **Constant rate of cyclin synthesis**
- **Max. rate of cyclin degradation by Protase X.**
- **Non-specific degradation of cyclin**
  - \(<<\) than that due to \(X\).
- **Michaelis constant for cyclin deg.**
For cdc2 kinase $M$:

$$
\dot{M} = \frac{V_1 (1-M)}{K_1 + (1-M)} - \frac{V_2 M}{K_2 + M}
$$

$V_1 = \frac{C}{K_c + C}$

Michaelis constant for cyclin activation

Note: $M = \frac{[M]}{M_T}$

$V_1, V_2$ effective mass rate for $E_1, E_2$

$K_1, K_2$ effective Michaelis constant for $E_1, E_2$

For protease $X$:

$$
\dot{X} = \frac{V_3 (1-X)}{K_x + (1-X)} - \frac{V_4 X}{K_4 + X}
$$

$V_3 = M V_{M_3}$

Coupling of $M$ with change of $X$

With the simple model, we have an explanation for the origin of thresholds in the control of cdc2 activity by cyclin and in the activation of the protease $(X)$ by cdc2 kinase. (See Fig 4)
Role of thresholds and time delays

1. The simple model provides a plausible explanation for the origin of threshold levels observed in the action of cyclin and cdk2 kinase during the mitotic cycle.

2. Links these thresholds to time delays that play a primary role in the onset of oscillations.

See Fig. 6 and Fig. 7.

See Goldbeter, for extensions to the model (i.e. extending the cascade, testing the effect of autocatalysts, etc.).

Note: Main results:

1. Time lags associated with thresholds in covalent modification are required for inducing oscillations.

2. Thresholds provide increased responsiveness to small changes in cyclin concentration.
Fig 2.

Novak et al.
DNA replication

Rule: replication and segregation of chromosomes must alternate.
Goldbeter's Minimal Cascade Model for Mitotic Oscillation.

- $C$: Cyclin
- $M$: Active cdc2
- $X$: Active protease
- $cde25$: phosphatase ($E_1$)
- $weel$: kinase ($E_2$)

Idea: Cell-cycle is driven by continuous biochemical oscillations and that the triggering by cdc2 kinase of cyclin degradation creates a (ve) feedback loop on which a minimum cell-cycle oscillator could be based.

"Building a cell cycle oscillator: hysteresis and bistability in the activation of Cdc2."


Fig 5
**Minimal Cascade Model** - Goldbeter et. al.

Note: threshold for M, X and time delays

* Use Matlab and graph to explore this. *(cell-cycle.m)*

**Fig 6.**
Fig 7