Model for Positive Feedback in Nucleosome Modification

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Silencing of the mating-type cassettes in *S. pombe*

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Basic Model Assumptions

- DNA region consisting of \( N = 60 \) nucleosomes isolated by boundary elements
- three kinds of nucleosomes exist:
  - unmodified (U)
  - methylated or modified (M)
  - acetylated or anti-modified (A)
- nucleosomes are actively interconverted by recruited (de-)modifications enzymes
  Enzymes are recruited by a selected nucleosome.
- nucleosomes are randomly interconverted in a recruitment-independent manner
- the rates of the interconversion reactions are the same for all nucleosomes
Basic Ingredients of the Model

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Nucleosome Modification Model
step 1  Selection of a random nucleosome \( n_1 \) to be modified

A specific \( n_1 \) is selected with probability \( 1/N \) (here: \( N = 60 \))

With probability \( \alpha \) a recruited conversion will be attempted

With probability \( (1 - \alpha) \) a random conversion will be attempted

step 2A recruited conversion

**standard version**: A second random nucleosome \( n_2 \) is selected from anywhere and is changed “one-step towards \( n_2 \)”

\[
\begin{array}{cccc|cccc|cccc}
\end{array}
\]

new \( n_1 \) | A | U | U | A | U | M | U | U | M

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### Implementation

**step 2B** random conversion or noisy conversion

nucleosome $n_1$ is changed “one-step towards” either of the other types with probability $1/3$

<table>
<thead>
<tr>
<th>$n_1$</th>
<th>A</th>
<th>A</th>
<th>A</th>
<th>U</th>
<th>U</th>
<th>U</th>
<th>M</th>
<th>M</th>
<th>M</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>new $n_1$</td>
<td>A</td>
<td>U</td>
<td>M</td>
<td>A</td>
<td>U</td>
<td>M</td>
<td>A</td>
<td>U</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>probability</td>
<td>1/3</td>
<td>2/3</td>
<td>0</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>0</td>
<td>2/3</td>
<td>1/3</td>
<td></td>
</tr>
</tbody>
</table>
feedback-to-noise ratio

\[ F = \frac{\alpha}{(1 - \alpha)} \text{ for } \alpha \in [0, 1] \]

more feedback-dependent conversions than noisy conversions if \( F > 1 \)

“gap” measure

\[ G = \frac{1}{t} \sum_{i=1}^{t} \frac{|M - A|}{|M + A|} \]

measures the size of the “gap” between the peeks in the probability distribution
Bistability Is a Function of Noise

$M$ ... number of nucleosomes in the M state at timepoint $t$

$P(M)$ ... probability to observe $M$ nucleosomes in state M over time $\delta t$

When feedback is only twice as strong as noise ($F = 2.0$) –
The left panels of A-D are samples of the time development of the number $M$ of nucleosomes in state M. The right panels of A-D show the corresponding probability distribution of $M$ obtained from long simulations.

Figure E measures the lifetime of the high-M or high-A state, while the system is said to be in the high-M state when $M > 1.5A$ and in the high-A state when $A > 1.5M$.

Figure F: relationship between the feedback-to-noise ratio and the average “gap” between the numbers of M and A nucleosomes at any time point.

Run the simulation yourself!
http://cmol.nbi.dk/models/epigen/
Bistability not only requires positive feedback but also nonlinearity in the feedback loop. This is usually achieved by cooperativity.

There is no explicit cooperativity in the model.

**Hypothesis**

The model is implicitly cooperative with respect to the conversion from A to M (and *vice versa*) since the transition require an M \( (n_2 = M) \) for the deacetylation \( A \rightarrow U \) and an M \( (n_2 = M) \) for the methylation \( U \rightarrow M \). The conversion thus has a rate proportional to \( M^2 \).
Eliminating Bistability

- remove the recruited modification reactions \((U \rightarrow A, U \rightarrow M)\) \(\Rightarrow\) no cooperativity, no bistability
- remove the recruited de-modification reactions \((A \rightarrow U, M \rightarrow U)\) \(\Rightarrow\) no cooperativity, no bistability

Restoring Bistability

introduce explicit cooperativity by introducing dependence on two nucleosomes \(n_2\) and \(n_3\) into the remaining recruited reactions.

recruited conversion

- **cooperative modification version:**
  - if \(n_2 = n_3 = M\), then \(n_1 = U\) is changed to \(n_1 = M\) and
  - if \(n_2 = n_3 = A\), then \(n_1 = U\) is changed to \(n_1 = A\).

- **cooperative de-modification version:**
  - if \(n_2 = n_3 = U\), then \(n_1\) is changed to \(n_1 = U\) and
  - if \(n_2 = n_3 = A\), then \(n_1 = M\) is changed to \(n_1 = U\) and
  - if \(n_2 = n_3 = M\), then \(n_1 = A\) is changed to \(n_1 = U\).
The instruction specified under **cooperative modification** (coop. mod. vers.) and **cooperative de-modification** (coop. demod. vers.) specify variants to the standard version of step 2A in the implementation.

\[
\begin{array}{c|ccc|ccc|ccc}
\hline
n_2 & A & U & M & A & U & M & A & U & M \\
\hline
\text{standard version} & A & U & U & A & U & M & U & U & M & \text{Fig A} \\
\text{coop. mod. vers.} & A & A & A & A & U & M & M & M & M & \text{Fig B} \\
\text{coop. demod. vers.} & A & U & U & U & U & U & U & U & M & \text{Fig C} \\
\hline
\end{array}
\]

See Figures A,B and C on the following pages.
Adding additional cooperativity to the standard version of the model has little effect on the bistability. (Compare the solid and dashed lines.)
Strong bistability is achieved by cooperation in the modification reaction as depicted here.
Weak bistability is achieved by cooperation in the de-modification reaction as depicted here.
Consider where $n_2$ nucleosomes come from that are involved in recruitment of enzymes to $n_1$.

- **Standard model**: All nucleosomes in the region have the same capability to stimulate enzyme recruitment to $n_1$.

- **Neighbor-limited model**: Only the two nearest neighbors of $n_1$ have the capability to stimulate enzyme recruitment to $n_1$.

- **Power-law contact model**: The capability of stimulating enzyme recruitment to $n_1$ depends on the distance of $n_2$ and $n_1$. The probability of contact is proportional to $\frac{1}{d^{1.5}}$ and therefore power-law distributed.
Curves for different $F$-values (1, 2.6, 6, 26, 77) are given in the right panels.

At nearly all time points nucleosomes are either in all-M or all-A state for $F = 2.6$. 
Bistability is difficult to achieve. Even a large majority of nucleosomes with one kind of modification is unable to prevent the random growth of patches of nucleosomes carrying the competing modification.
The existence of a low rate of long-range contacts is all that is necessary to allow robust stability of both states (here at $F = 7$).
Heritability of Nucleosome Modifications

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Nucleosome Modification Model