Model for Positive Feedback in Nucleosome Modification

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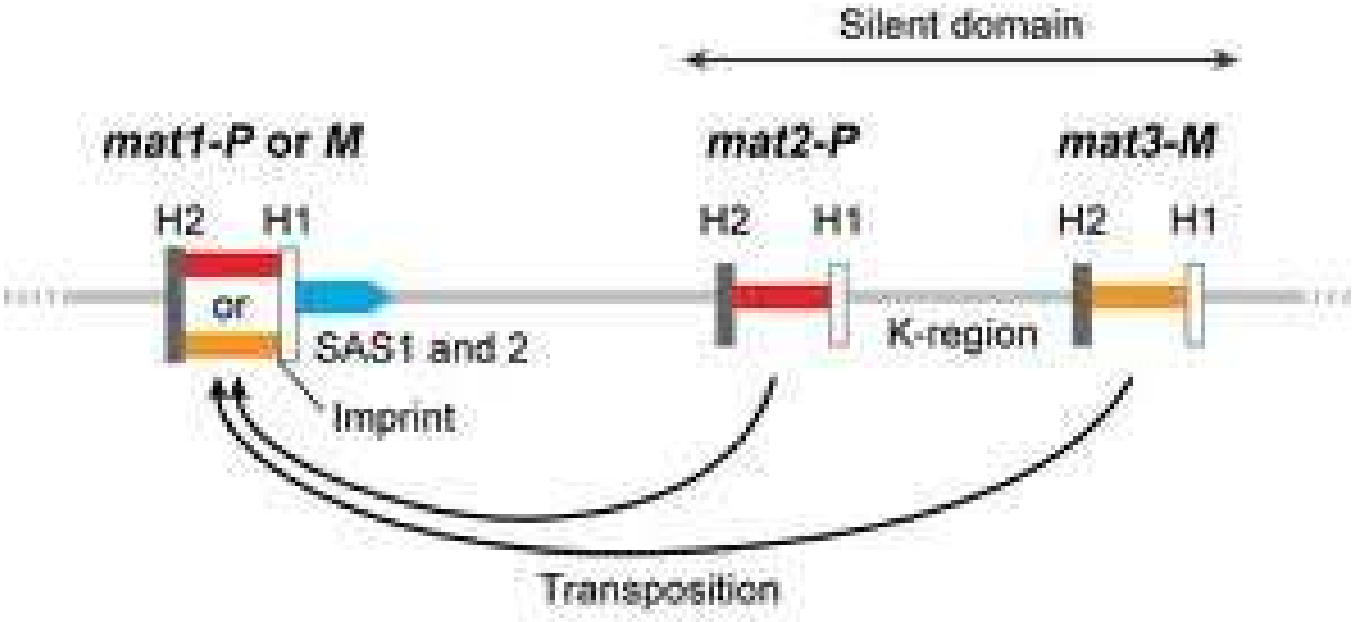
Epigenetics - an overview

Stability and Heritability

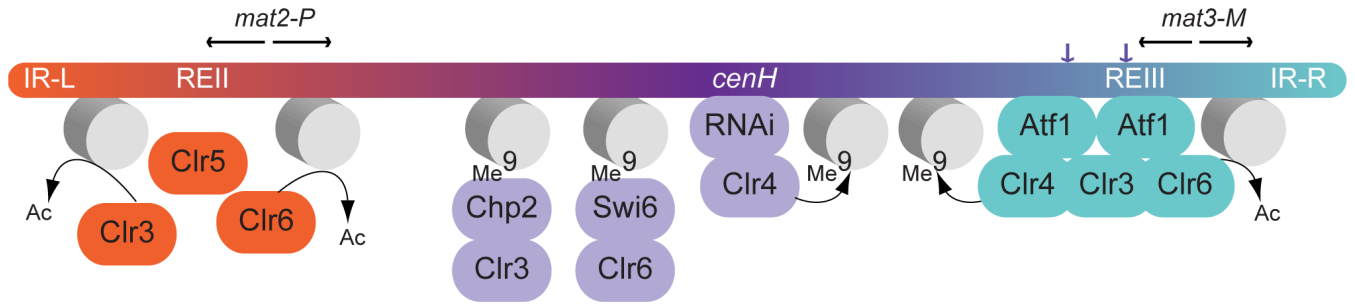
Positive Feedback

Bistability and Cooperativity

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



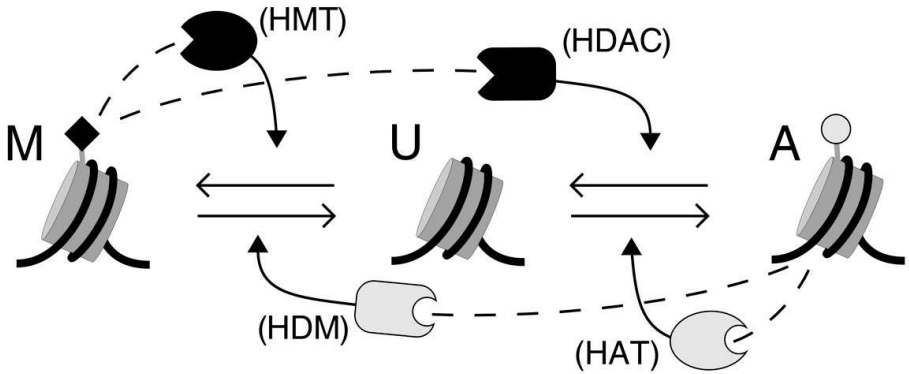
Klar AJS. 2007.
Annu. Rev. Genet. 41:213–36

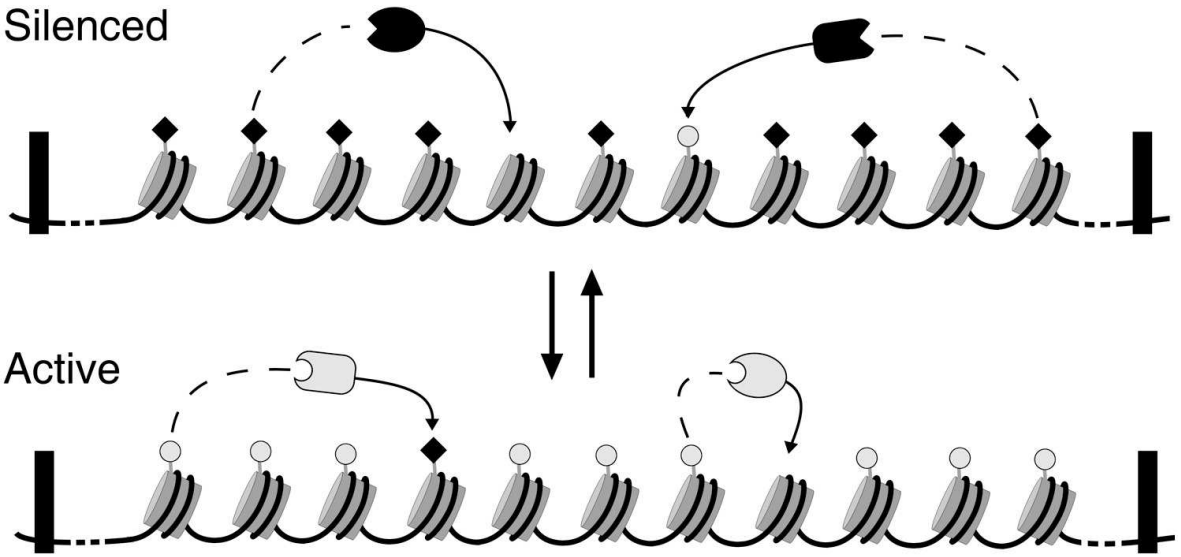


Basic Model Assumptions

- 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 recruitement-independent manner
- the rates of the interconversion reactions are the same for all nucleosomes

Basic Ingredients of the Model





Implementation

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 α a recruited concersion 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 torwards n_2"

n_1	A	A	A	U	U	U	M	M	M
n_2	A	U	M	A	U	M	A	U	M
new n_1	A	U	U	A	U	M	U	U	M

step 2B random conversion or noisy conversion

nucleosome n_1 is changed "one-step torwards" either of the other types with probability $1/3$

n_1	A	A	A	U	U	U	M	M	M
new n_1	A	U	M	A	U	M	A	U	M
probability	1/3	2/3	0	1/3	1/3	1/3	0	2/3	1/3

feedback-to-noise ratio

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

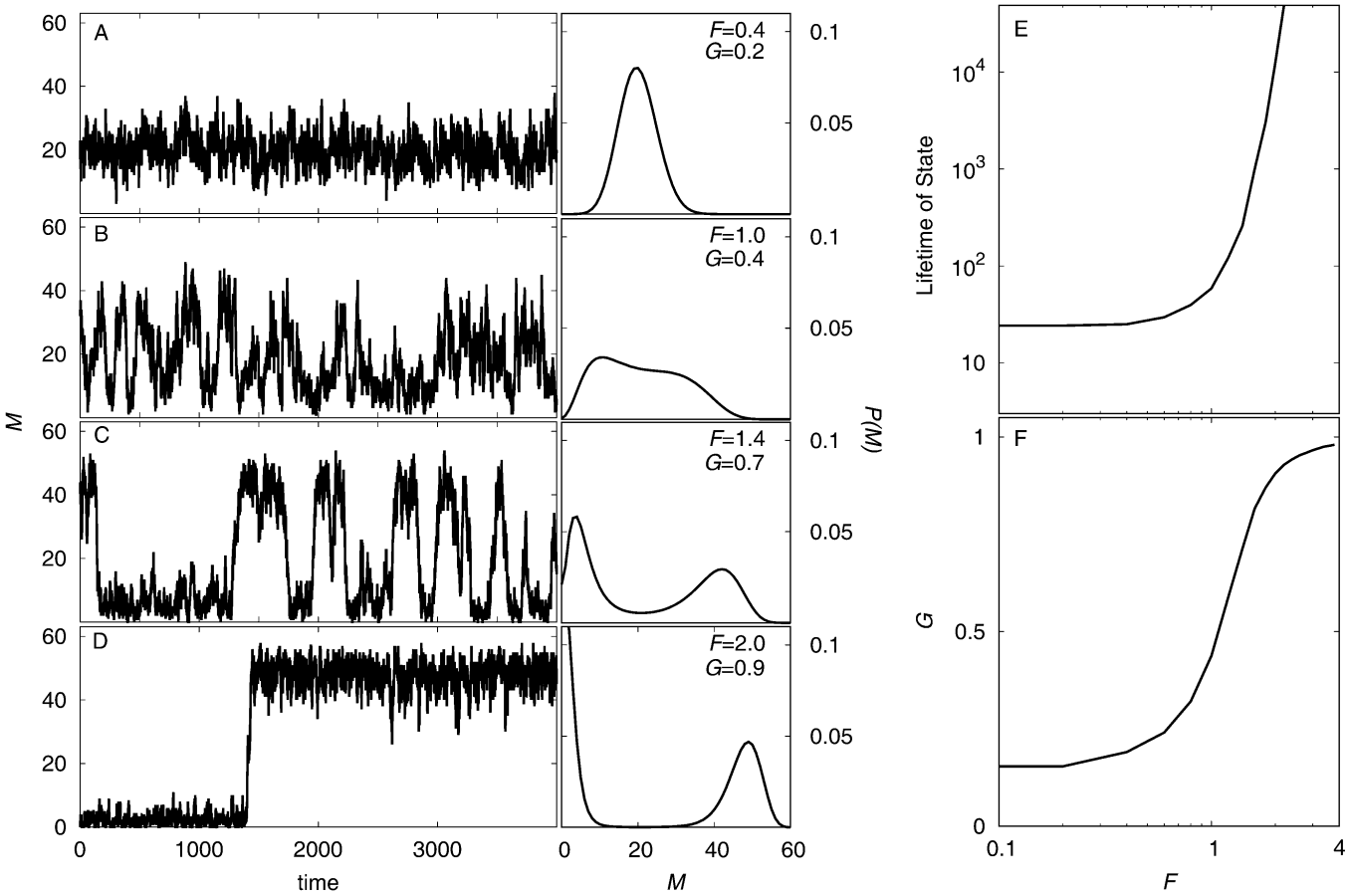
more feedback-dependent conversions than noisy conversions if $F > 1$

“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 nucelosomes in the M state at timepoint t

$P(M)$ . . . probability to observe M nucleosomes in state M over time δt

When feedback is only twice as strong as noise ($F = 2.0$) –

Bistability Is a Function of Noise

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/`

What is the Origin of Cooperativity in the Model?

- 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 $n_1 = U$.

Conversions in the Single-Feedback Models

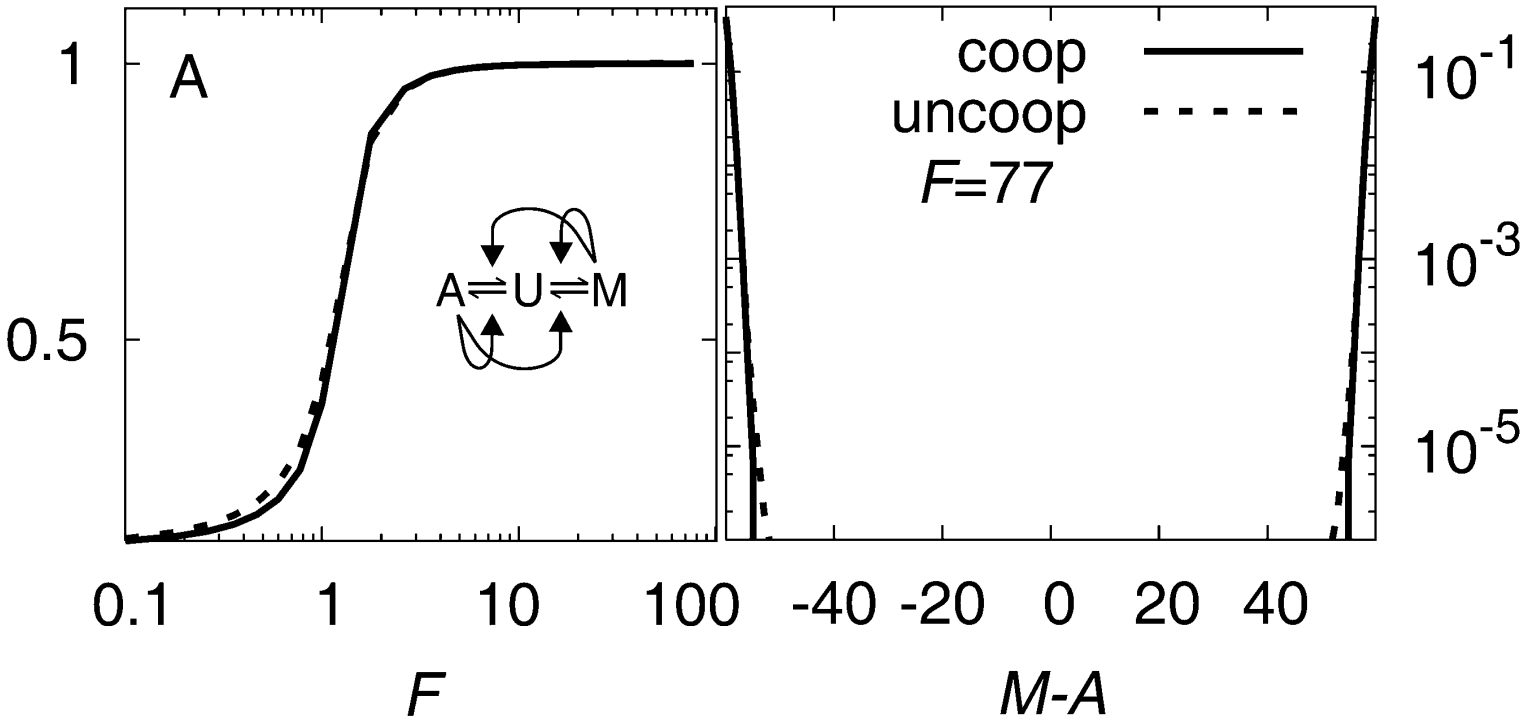
The instruction specified under **cooperative modification** (coop. mod. vers.) and **cooperative de-modification** (coop. demod. vers.) specify variants to the standard version of `step 2A` in the implementation.

n_1 n_2	A A	A U	A M	U A	U U	U M	M A	M U	M M	
standard version	A	**U**	**U**	**A**	U	**M**	**U**	**U**	M	Fig A
coop. mod. vers.	A	A	A	**A**	U	**M**	M	M	M	Fig B
coop. demod. vers.	A	**U**	**U**	U	U	U	**U**	**U**	M	Fig C

See Figures A,B and C on the following pages.

Implicit Cooperation – Fig A

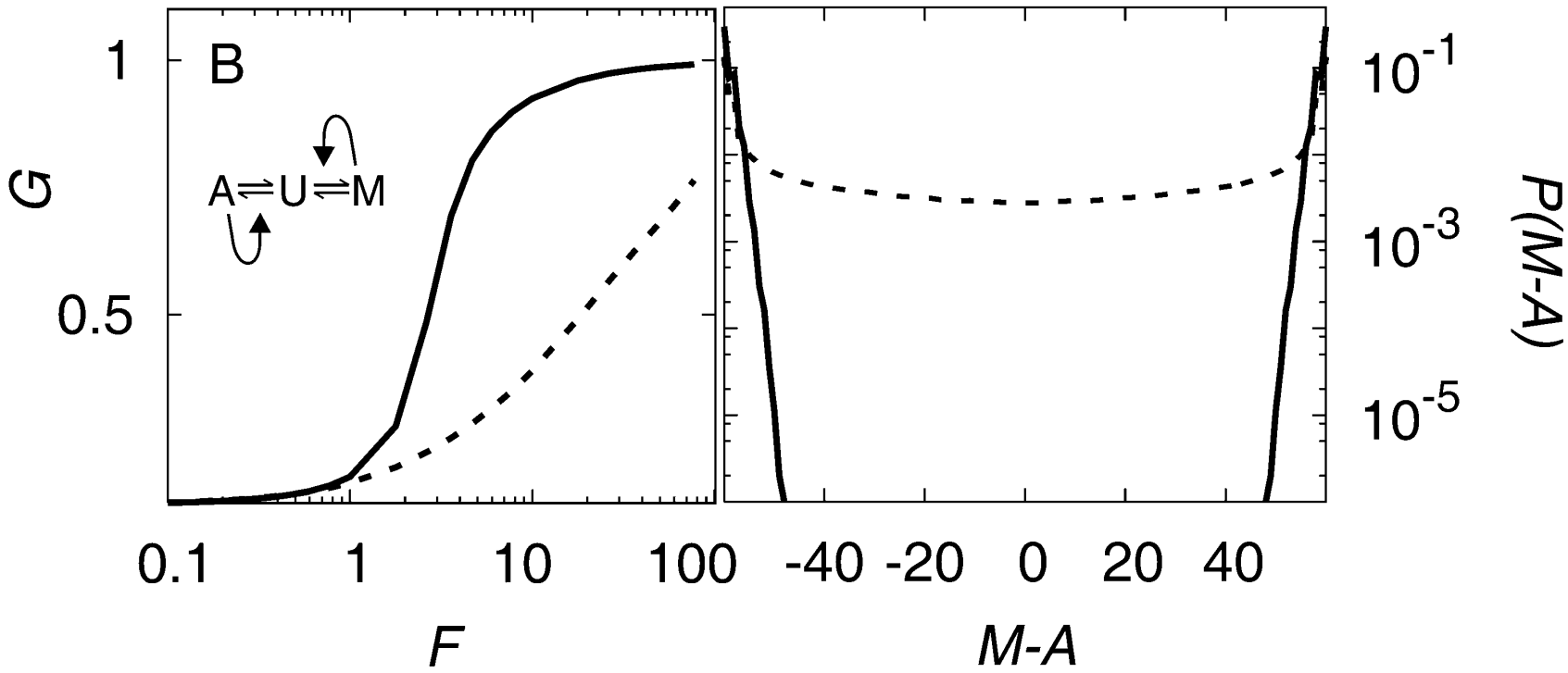
standard version



Adding additional cooperativity to the standard version of the model has little effect on the bistability. (Compare the solid and dashed lines.)

Explicit or No Cooperation – Fig B

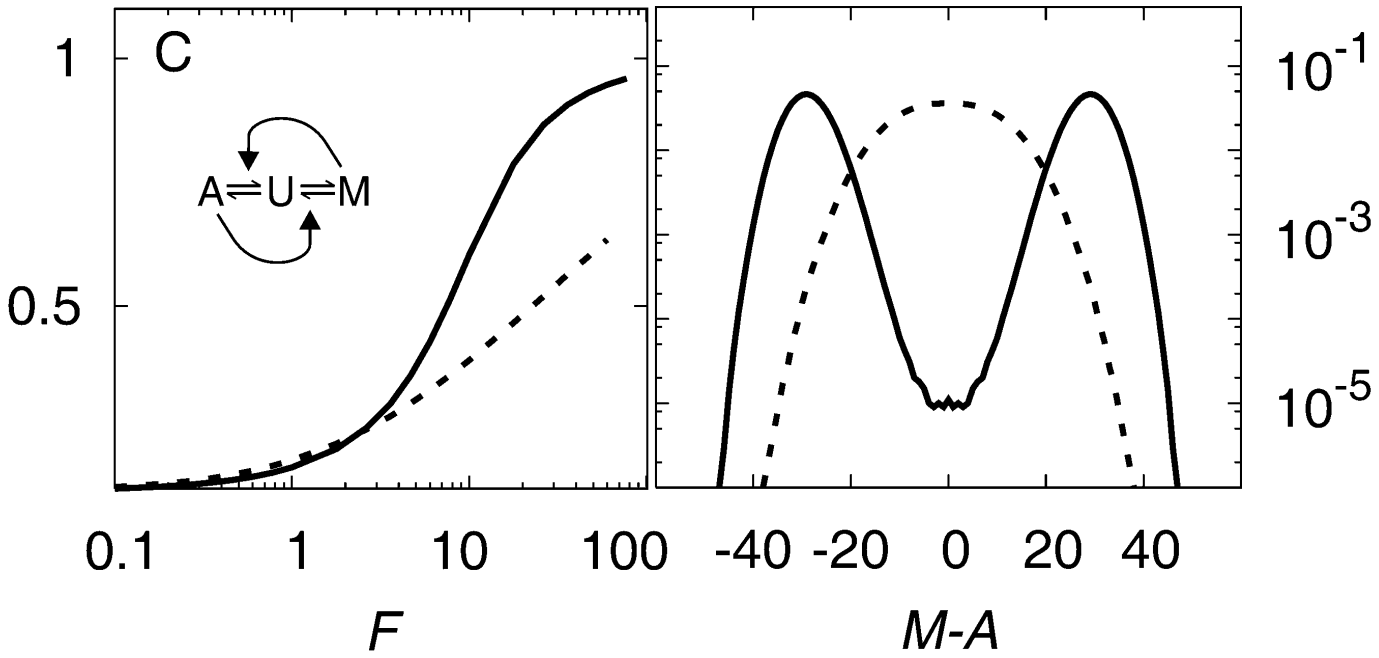
cooperative modification version



Strong bistability is achieved by cooperation in the modification reaction as depicted here.

Explicit or No Cooperation – Fig C

cooperative demodification version



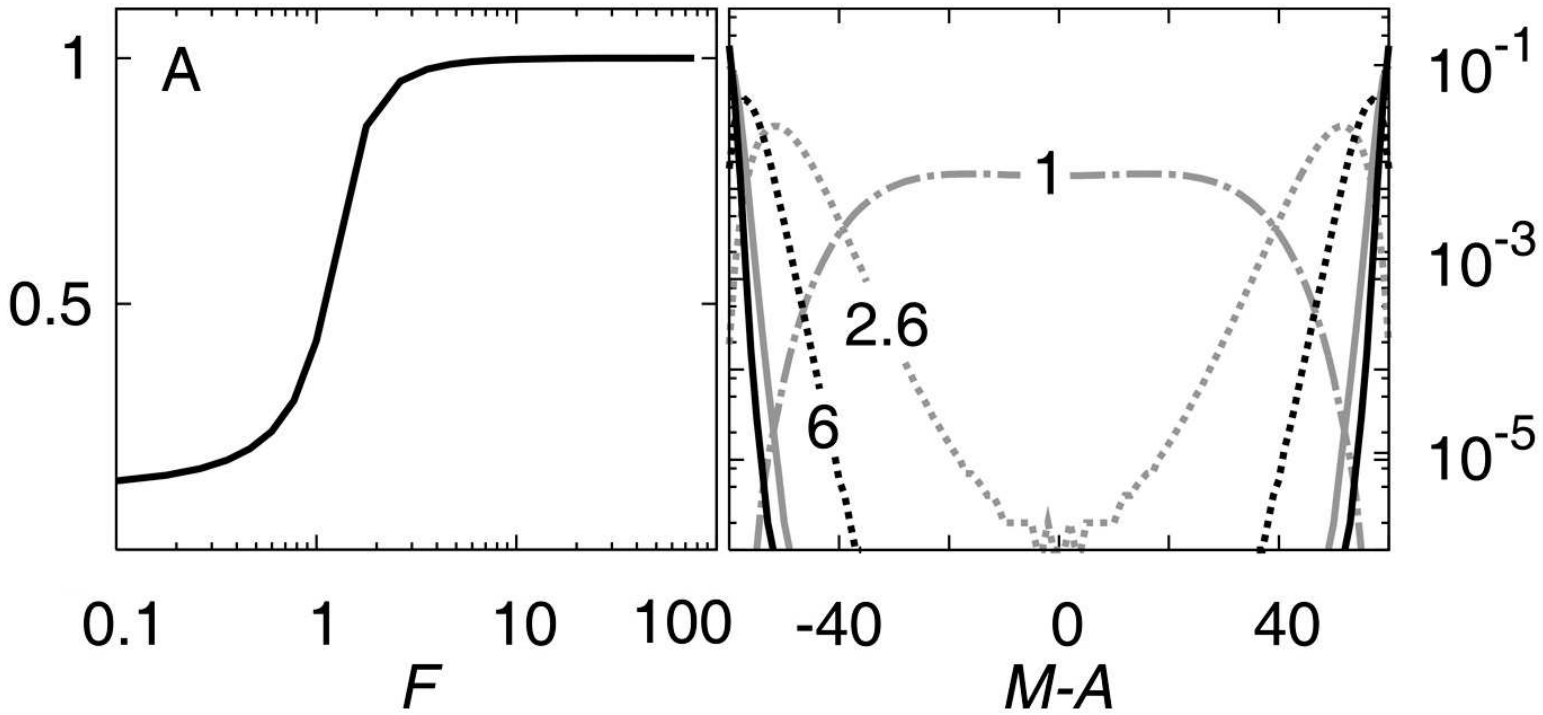
Weak bistability is achieved by cooperation in the de-modification reaction as depicted here.

A Need for "Beyond-Neighbor" Interactions

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.

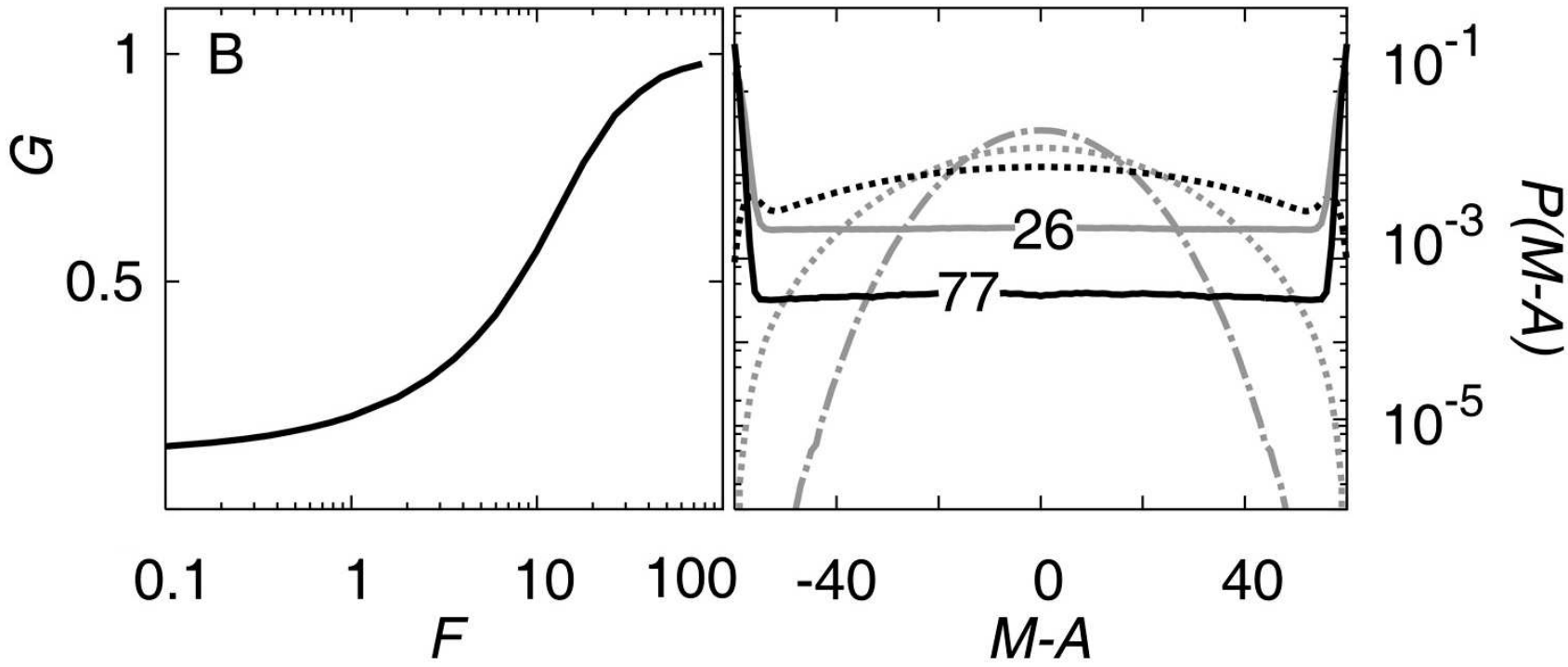
Standard Model



Curves for different F-values (1, 2.6, 6, 26, 77) are given in the right panels.

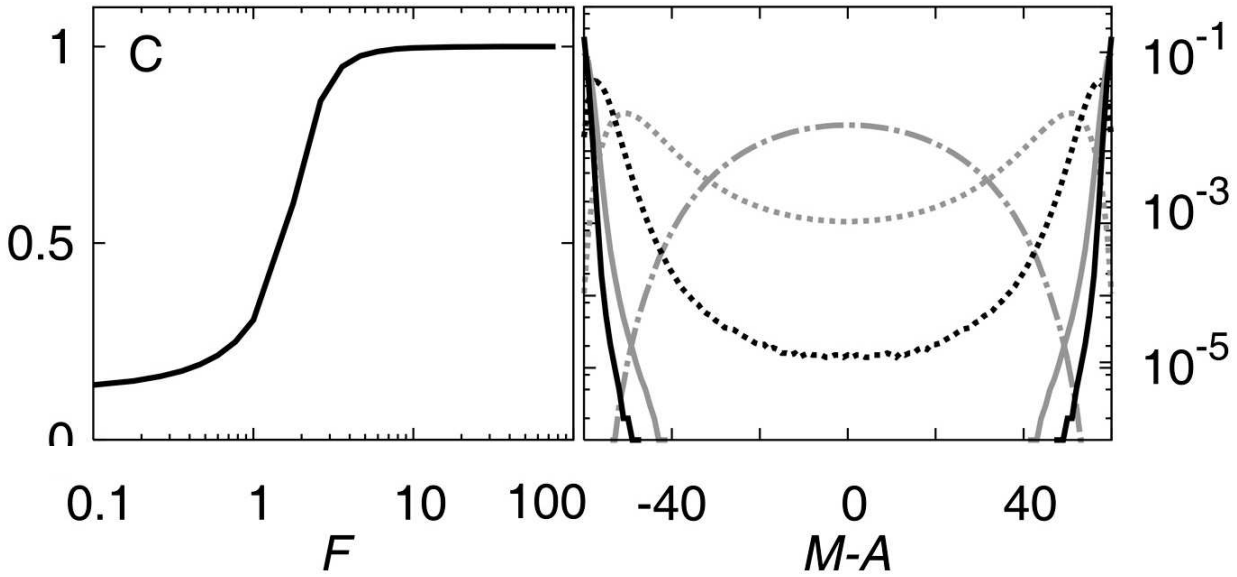
At nearly all time points nucleosomes are either in all-M or all-A state for $F = 2.6$.

Neighbor-limited Model



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.

Power-law Contact Model



The existance 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

The Role of the Region Length

Literature

- [Dodd, 2007] Ian B. Dodd, Mille A. Micheelsen, Kim Sneppen and Geneviève Thon. *Theoretical Analysis of Epigenetic Cell Memory by Nucleosome Modification*. Cell 2007, 129(4):813-822
- [Sneppen, 2008] Kim Sneppen, Mille A. Micheelsen and Ian B. Dodd. *Ultrasensitive gene regulation by positive feedback loops in nucleosome modification*. Mol. Sys. Biol. 2008, 4:182.