gene \( (n_1) \) \quad mRNA \quad \quad (n_2) \quad \quad \text{Protein} \quad (n_3)
The mRNA Life Cycle

Cytoplasm

Nucleus
GENE ACTIVATION:

GENE INACTIVATION:

TRANSCRIPTION:

mRNA DEGRADATION:

TRANSLATION:

PROTEOLYSIS:
\[ n_1 \xrightarrow{\lambda_1^+ (n_1^{\text{max}} - n_1)} n_1 + 1 \]
\[ n_1 \xrightarrow{\lambda_1^- n_1} n_1 - 1 \]
\[ n_2 \xrightarrow{\lambda_2 n_1} n_2 + 1 \]
\[ n_2 \xrightarrow{n_2/\tau_2} n_2 - 1 \]
\[ n_3 \xrightarrow{\lambda_3 n_2} n_3 + 1 \]
\[ n_3 \xrightarrow{n_3/\tau_3} n_3 - 1 \]
Direct kinetic measurements are missing.

A possible test: 
HOW the feedback mechanism influences protein fluctuation?
CIRCULAR GENE
EXPRESSION HYPOTHESIS
(M. Choder and coworkers :)

The circular
gene
expression
hypothesis: feedback effects and protein
fluctuations

The circular gene expression hypotheses

Molecular genetic facts

Canonical stochastic models of gene expression

The skeleton network model of the coordinated mRNA degradation and synthesis

Stochastic chemical kinetics: theory and simulations

Comparative studies
SIMULATION RESULTS:

Statistical analysis

WHERE are we now?

Coordination between Transcription and Decay:
A conceptual model: gene expression is a circular process

Specific Mutations in XRN1 Similarly Affect mRNA Decay, Yet Have Different Effects on Transcription: Schematic model of the suggested linkage between mRNA decay, nuclear import of DFs and transcription.
From: Gene expression is circular: factors for mRNA degradation also foster mRNA synthesis.
Haimovich G1, Medina DA, Causse SZ, Garber M, Millán-Zambrano G, Barkai O, Chávez S, Pérez-Ortín JE, Darzacq X, Choder M.
(a) WT cells. Following full degradation of the mRNA by Xrn1p, the decaysome is imported to the nucleus as a complex or subcomplexes. In the nucleus, at least some DFs (Xrn1p, Dep2p and Lsm1p) associate with chromatin, 30 bp upstream to transcription start site (red arrowhead) — the same location as the preinitiation complex (PIC), and stimulate transcription initiation as well as transcription elongation. Transcription is efficient (illustrated artistically by three Pol II molecules per ORF). The elongating Pol II is properly phosphorylated on Ser-2 of its C-terminal domain (data not shown).

(b) An \textit{xrn1}^{D208A} cell. Xrn1^{D208A}p is able to bind the 5'-phosphate of the decapped mRNA but cannot degrade it. This mutant form exerts its adverse effects on transcription and import only if its active site properly binds the decapped RNA at the 5' end. Bound Xrn1^{D208A}p is trapped in the cytoplasm and does not permit import of other DFs as well. Therefore, DFs that are confined in the cytoplasm, are unable to stimulate both transcription initiation and elongation, resulting in a severe defect of transcription (artistically illustrated by showing only one Pol II per ORF).

(c) An \textit{\Delta xrn1} cell. Since Xrn1p normally represses import as long as the RNA is not fully degraded, its absence permits import. In the absence of Xrn1p, the other decay factors are released from the mRNA, possibly following its degradation by the exosome, and are imported to the nucleus in an Xrn1p-independent manner. Because \textit{\Delta xrn1} cells are only partially defective in transcription, it seems that the imported DFs are able to stimulate transcription initiation, at least partially. Because transcription elongation of \textit{\Delta xrn1} is almost as defective as elongation in \textit{xrn1}^{D208A} cells, we surmise that the elongation stage is especially vulnerable to the absence of Xrn1p, leading to accumulation of hypophosphorylated (backtracked?) Pol II and intermediate transcription rates (artistically illustrated by showing two Pol II molecules per ORF).