RNA-interference and Register Machines

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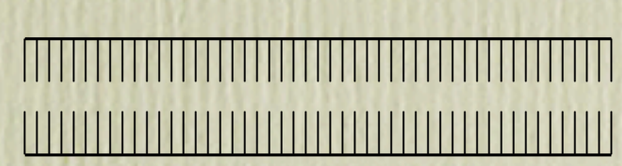
RNA interference

- RNAi (also known as RNA silencing) is a mechanism in which short interfering RNA's (siRNA's) (21～26 nt's) directly control gene expression.
- RNAi consists of three fundamental biochemical processes:

Step 1 RNAi

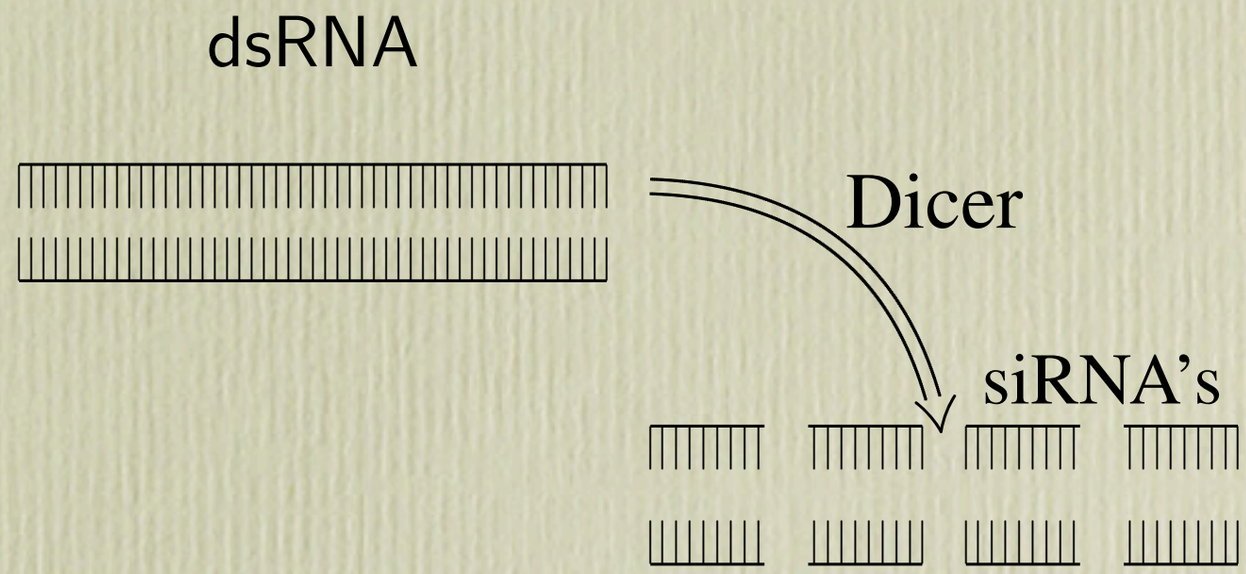
Formation of double stranded RNA (dsRNA)

dsRNA



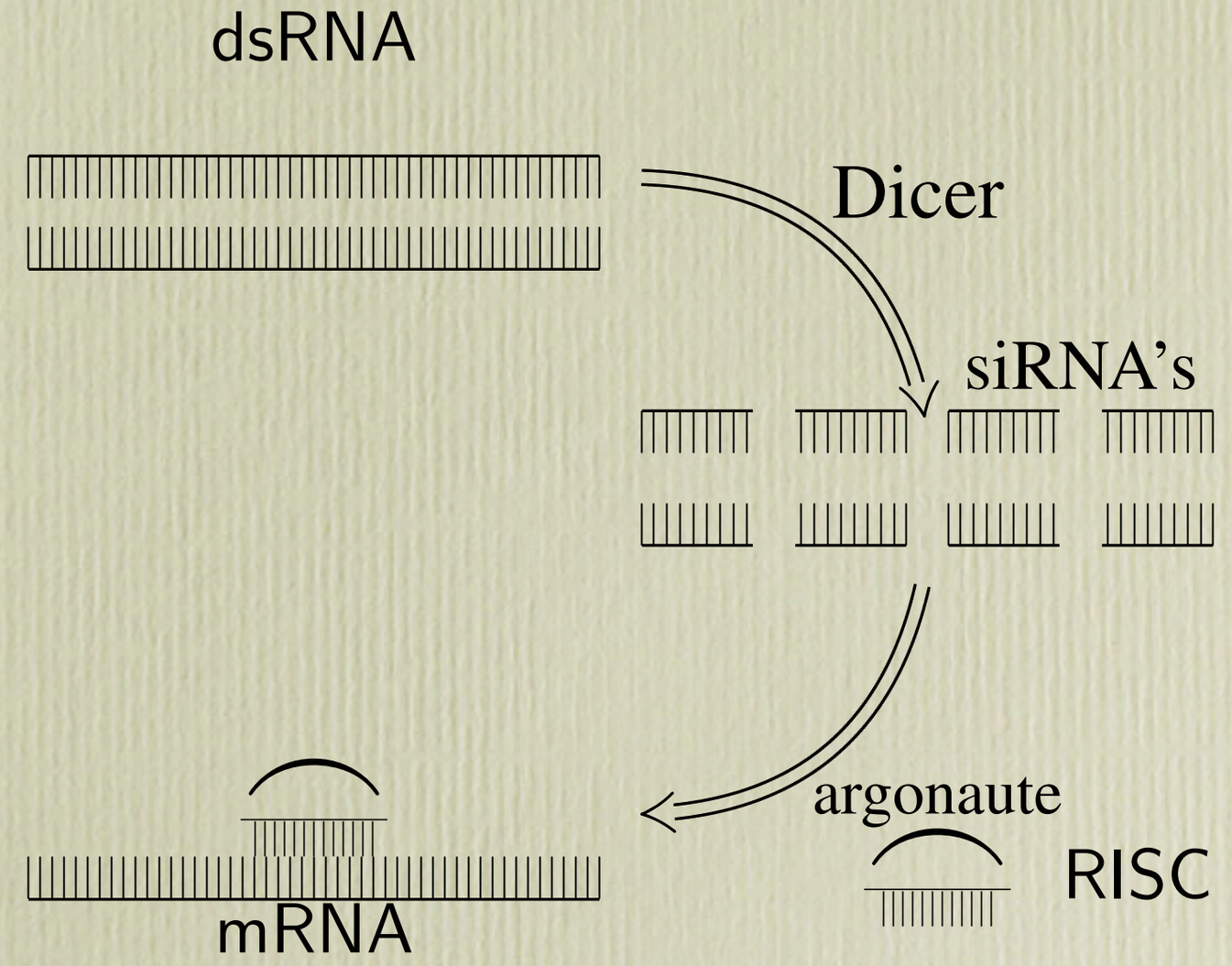
Step 2 RNAi

Dicer enzyme cleaves dsRNA into siRNA's:

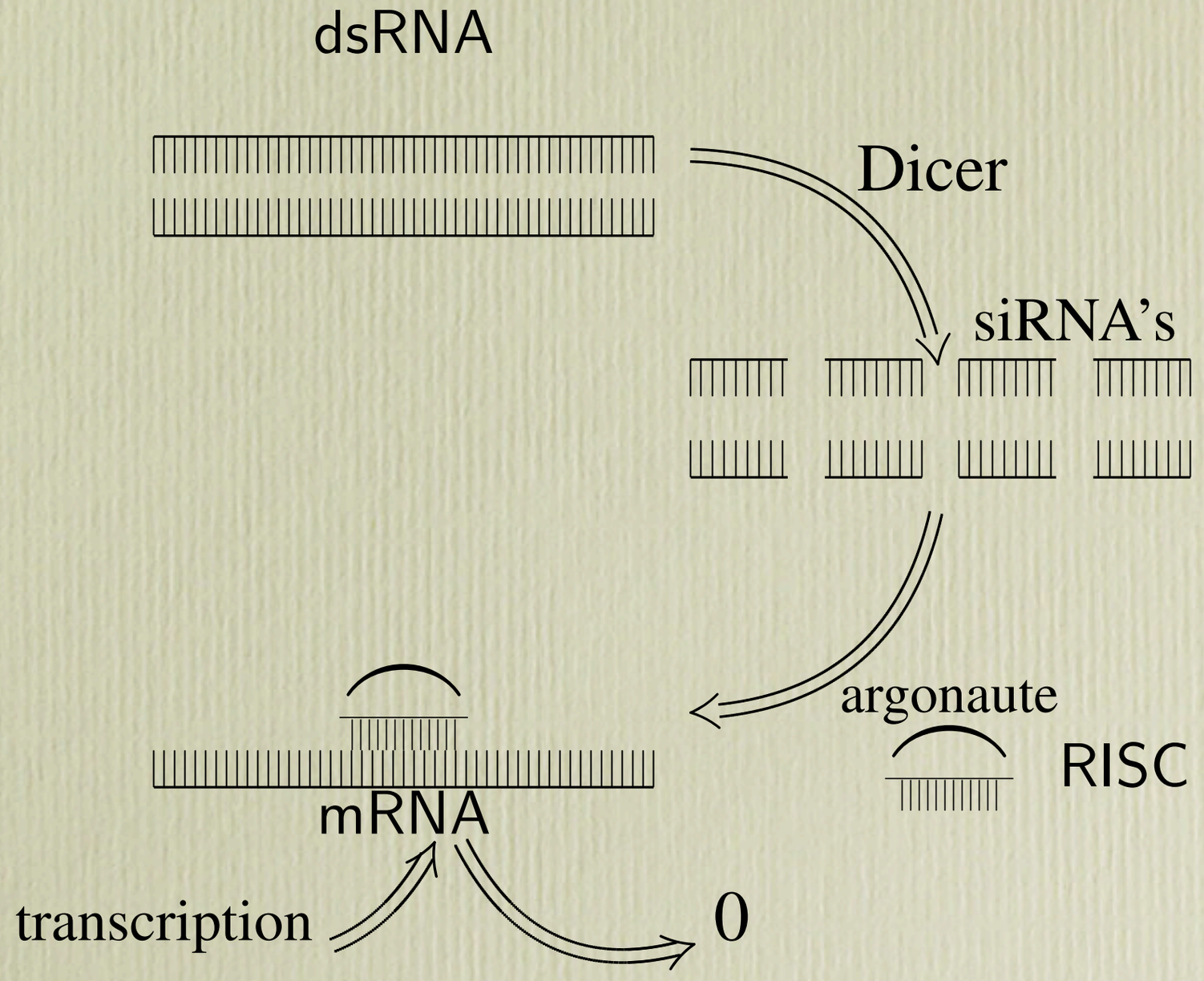


Step 3 RNAi

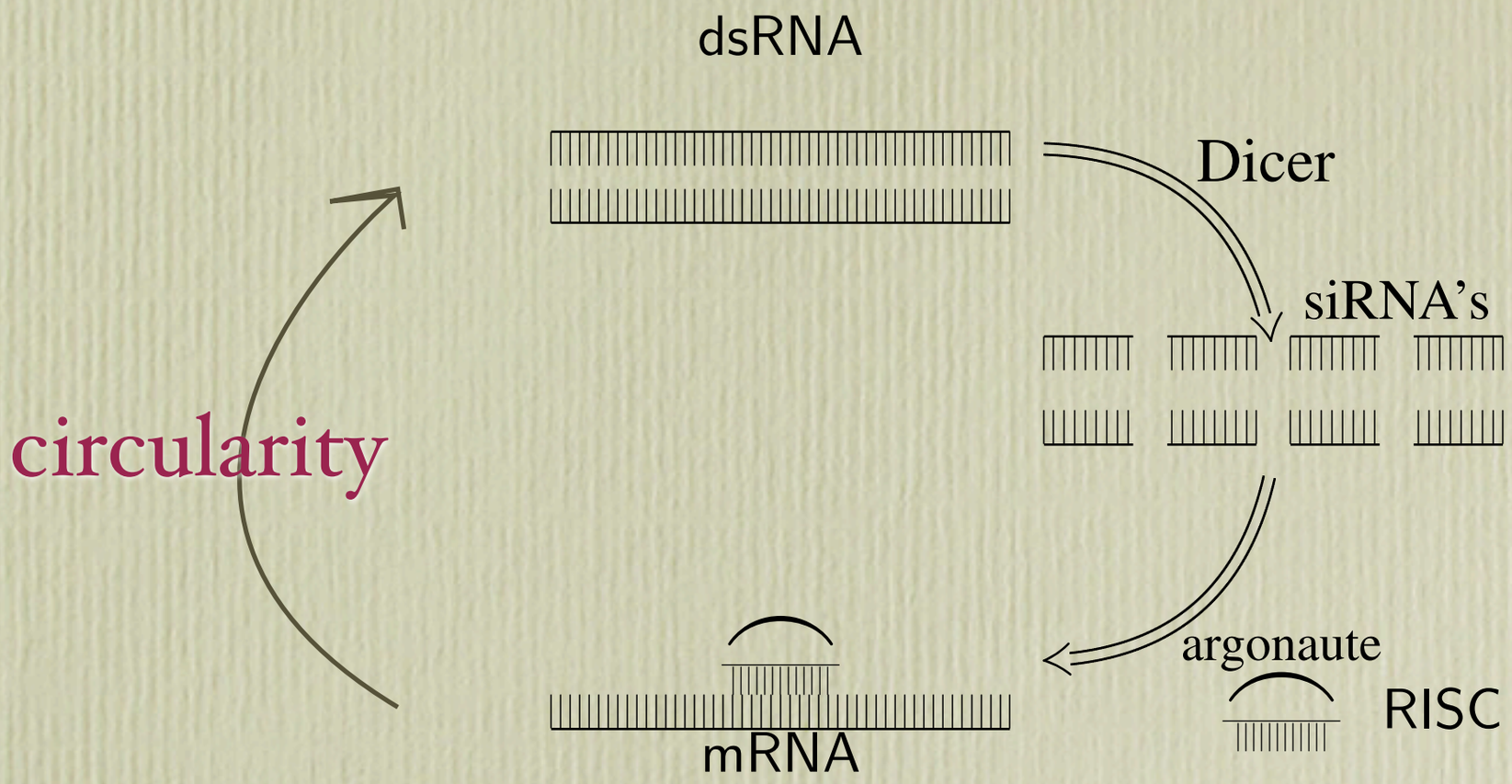
Incorporation of siRNA into RNA-induced silencing complex (RISC), targeting a long single-stranded mRNA by complementarity.



Finally, RISC degrades mRNA.



Moreover RNAi has a circularity to synthesize dsRNA

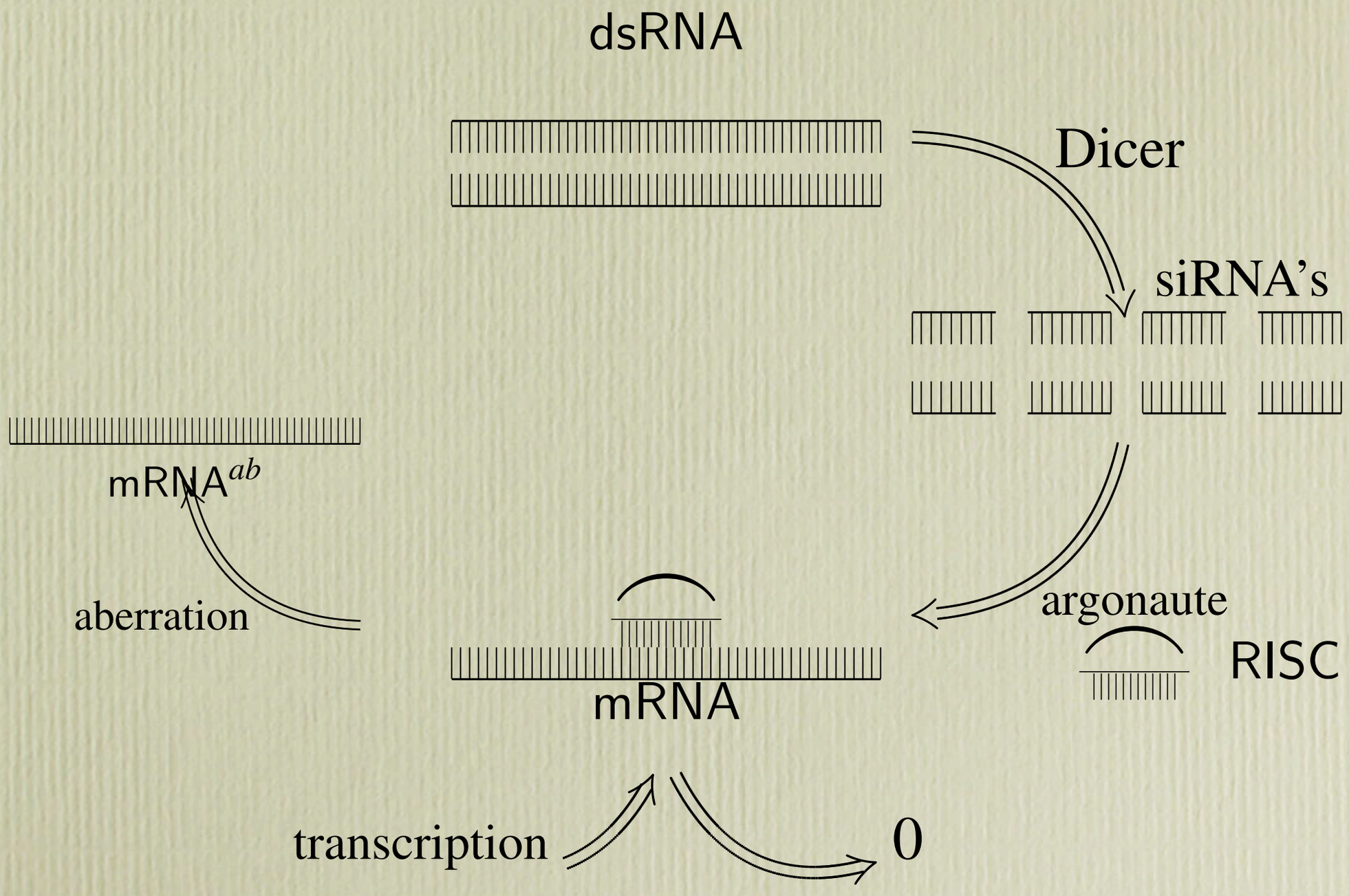


This is realized by

polymerization

of aberrant mRNA caused by RISC degradation

That is, RISC degrades mRNA or makes it aberrated.



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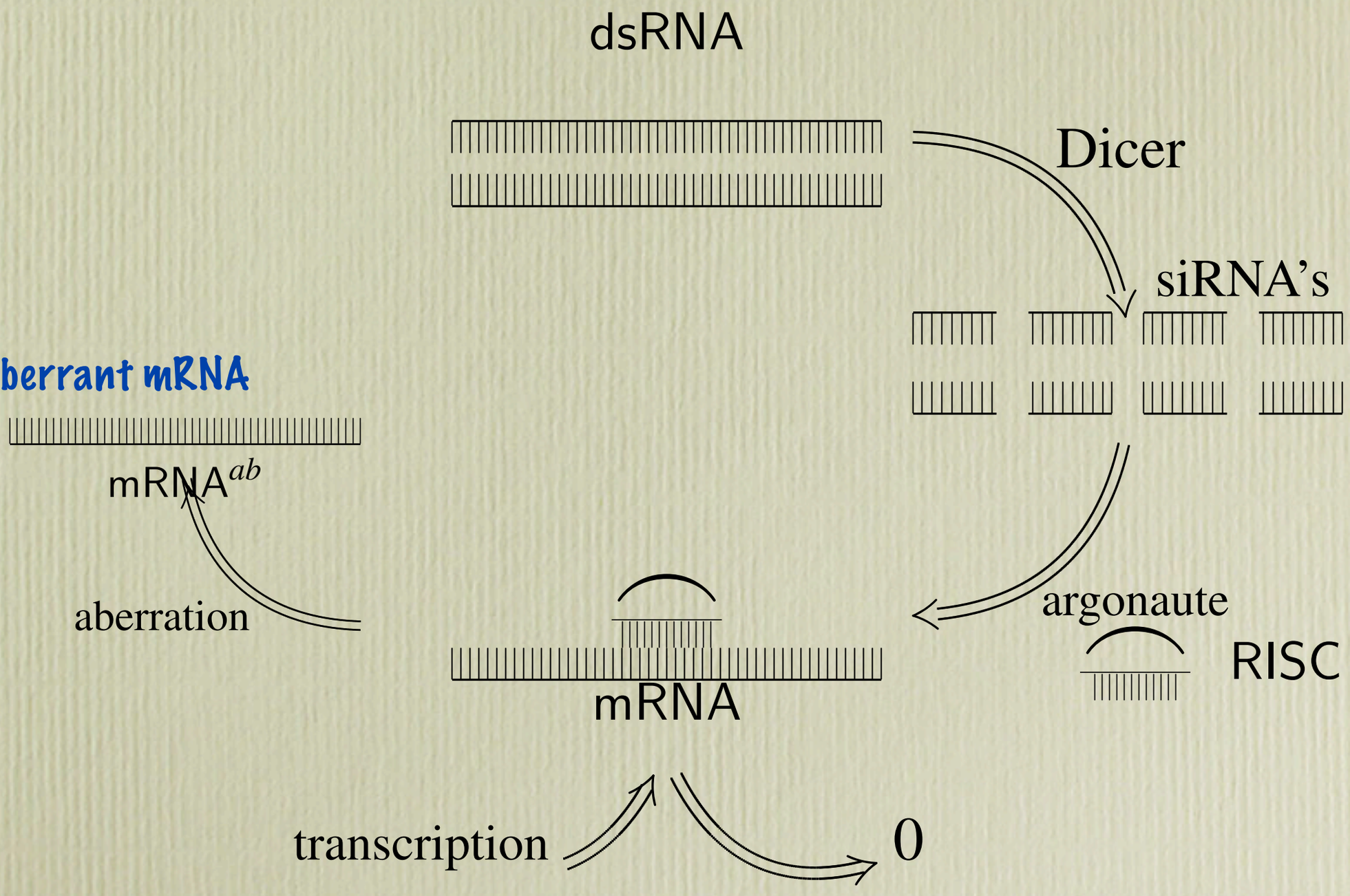
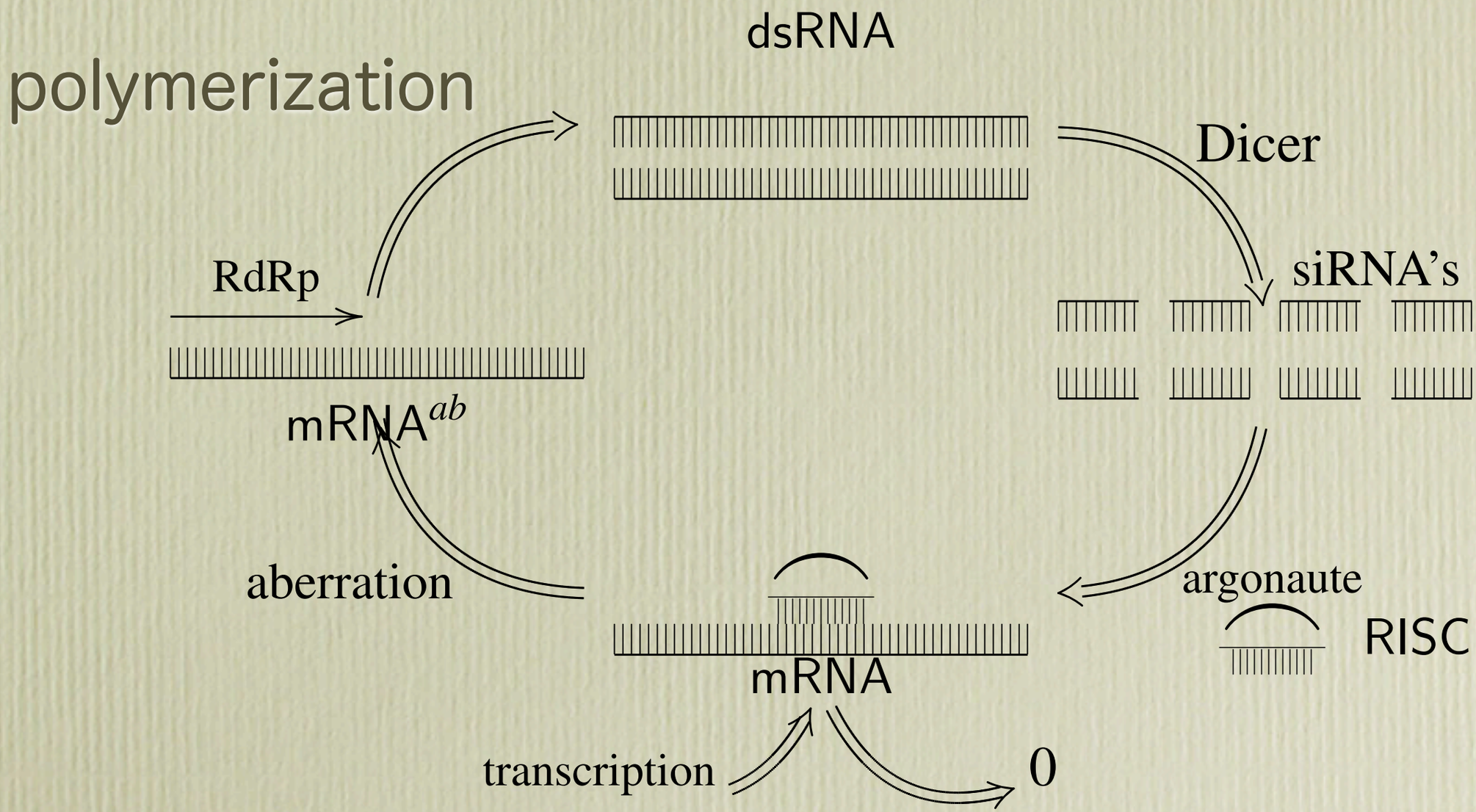


Circularity of RNAi
by polymerization to duplicate dsRNA



Starting Point of Our Wotk

Given that

- Each Step of RNAi is digital
- Their combination maintains the circularity,

RNAi resembles a kind of (digital) computation !

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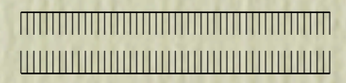
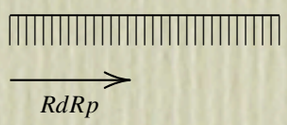
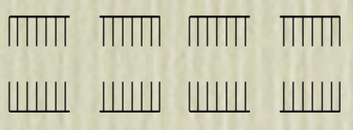
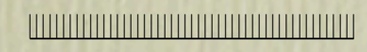
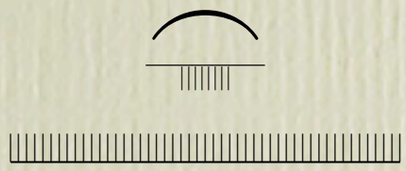
A Naive Interpretation of RNAi in Register Machine

register	values	increment/decrement
r_1	$\overbrace{\text{dsRNA} \mid \cdots \mid \text{dsRNA}}^{m_1}$ **dsRNA** 	$\text{Inc}(r_1) := RdRp$  $\text{Dec}(r_1) := Dicer$ 

(a) register r_1

register	values	increment/decrement
r_2	$\overbrace{\text{mRNA} \mid \cdots \mid \text{mRNA}}^{m_2}$ **mRNA** 	$\text{Inc}(r_2) := \text{transcription}$  $\text{Dec}(r_2) := \text{RISC}$ 

(b) register r_2

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Chemical Ground Form (Cardelli 2008)

(a minimal stochastic process calculus describing chemical reactions)

- Interaction Prefix $\tau_{(r)} \vdots ?a_{(r)} \vdots !a_{(r)}$
- Parallel Composition $\mid$ and choice $\oplus$

Molecule-decay

$$\cdots \oplus \tau_{(r)}.Q \oplus \cdots \longrightarrow Q$$

Molecules-collision

$$\cdots \oplus ?a_{(r)}.Q \oplus \cdots \mid \cdots \oplus !a_{(r)}.R \oplus \cdots \longrightarrow Q \mid R$$

RNAi as Chemical Reactions

- Increment

$$\mathsf{RdRp} + \mathsf{mRNA}^{ab} \longrightarrow \mathsf{dsRNA}$$

$$\longrightarrow \mathsf{mRNA}$$

- Decrement

$$\mathsf{dsRNA} + \mathsf{Dicer} \longrightarrow \mathsf{siRNA}'s$$

$$\mathsf{mRNA} + \mathsf{RISC} \longrightarrow \widetilde{\mathsf{mRNA}} + \mathsf{RISC}$$

RNAi in CGF

- Registers $r_1 = \prod_{l_1}^{\mathsf{dsRNA}}$ $r_2 = \prod_{l_2}^{\mathsf{mRNA}}$

$$\mathsf{dsRNA} := ?a_1.(\mathsf{siRNA} \mid \cdots \mid \mathsf{siRNA})$$

$$\mathsf{mRNA} := ?a_2.(\tau.0 \oplus \tau.\mathsf{mRNA}^{ab})$$

- Increment $I_i = \mathsf{Inc}(r_j)$

$I_i = \mathsf{RdRp} \mid \tau.I_{i+1}$ j=1

$I_i = \mathsf{mRNA} \mid \tau.I_{i+1}$ j=2

- Decrement $I_i = \mathsf{DecJump}(r_j, s)$

$I_i = !a_1.(0 \mid I_{i+1}) \oplus \tau.I_s$ with Dicer $= !a_1.(0 \mid I_{i+1})$ j=1

$I_i = !a_2.(\mathsf{RISC} \mid I_{i+1}) \oplus \tau.I_s$ with RISC $= !a_2.(\mathsf{RISC} \mid I_{i+1})$ j=2

Decrement Instruction Ii makes an error !

$I_i = \mathsf{DecJump}(r_j, s)$

wrongly jumps to Is even if the register rj ≠0.

$$I_i \quad = !a_{\mathbf{j}}.(0 \mid I_{i+1}) \oplus \tau.I_s$$

decrement　　jump

Register $= \prod ?a_{\mathbf{j}}. \ldots$

Due to the absence of zero-test against the registers,

which is related to Turing Incompleteness of CGF.

Zavattaro-Cardelli (2008) Soloveichik-Winfree, et al. (2008)

Question:
How to probabilistically moderate the error jumps of RNAi in CGF ?

We propose:

- Theoretical idea of Inhibitors for the decrement instructions (motivated by Zavattaro-Cardelli 2008)

- The inhibitors are realized by a biological extension of Recursive RNAi !

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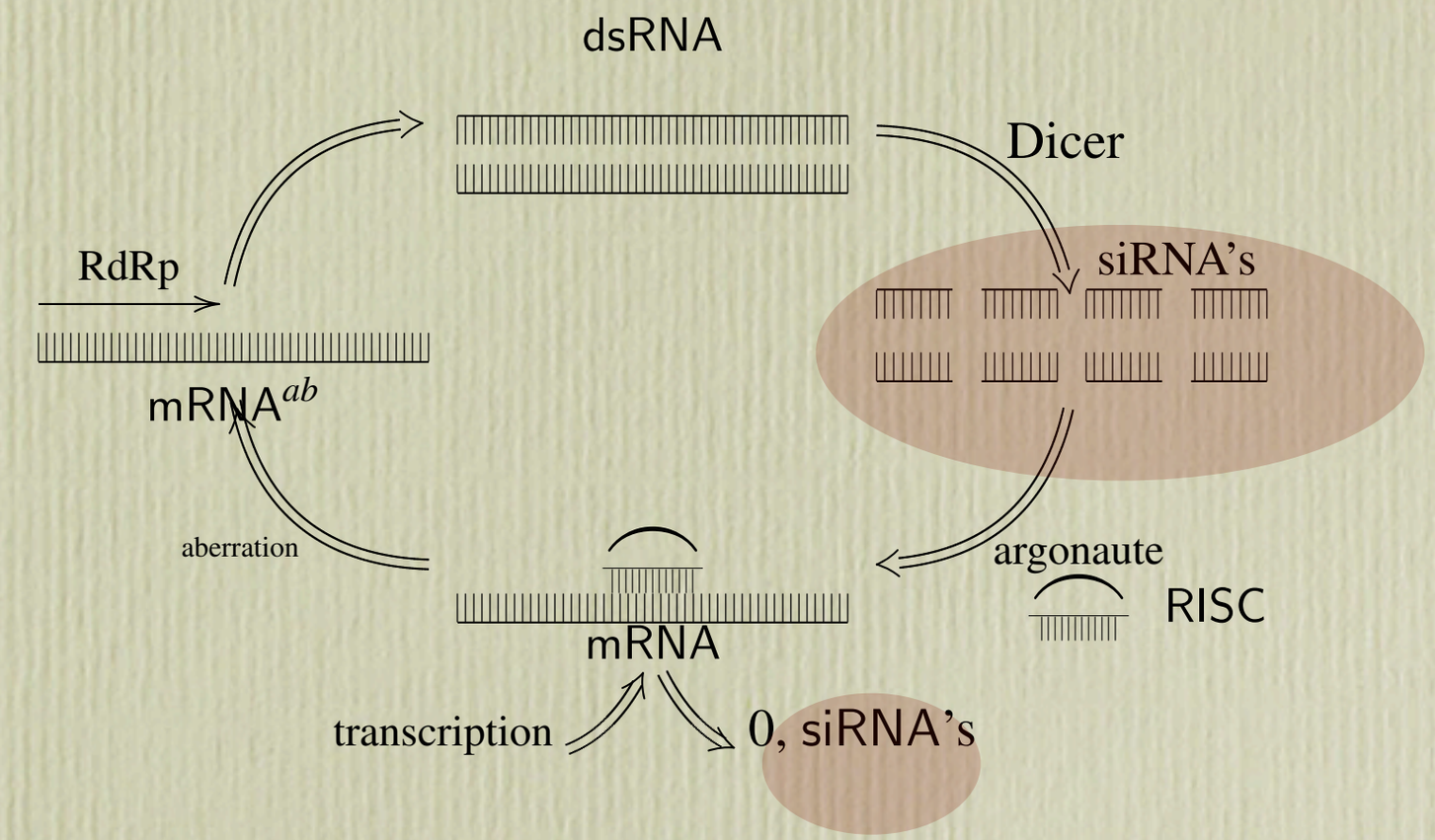
For recursive RNAi,

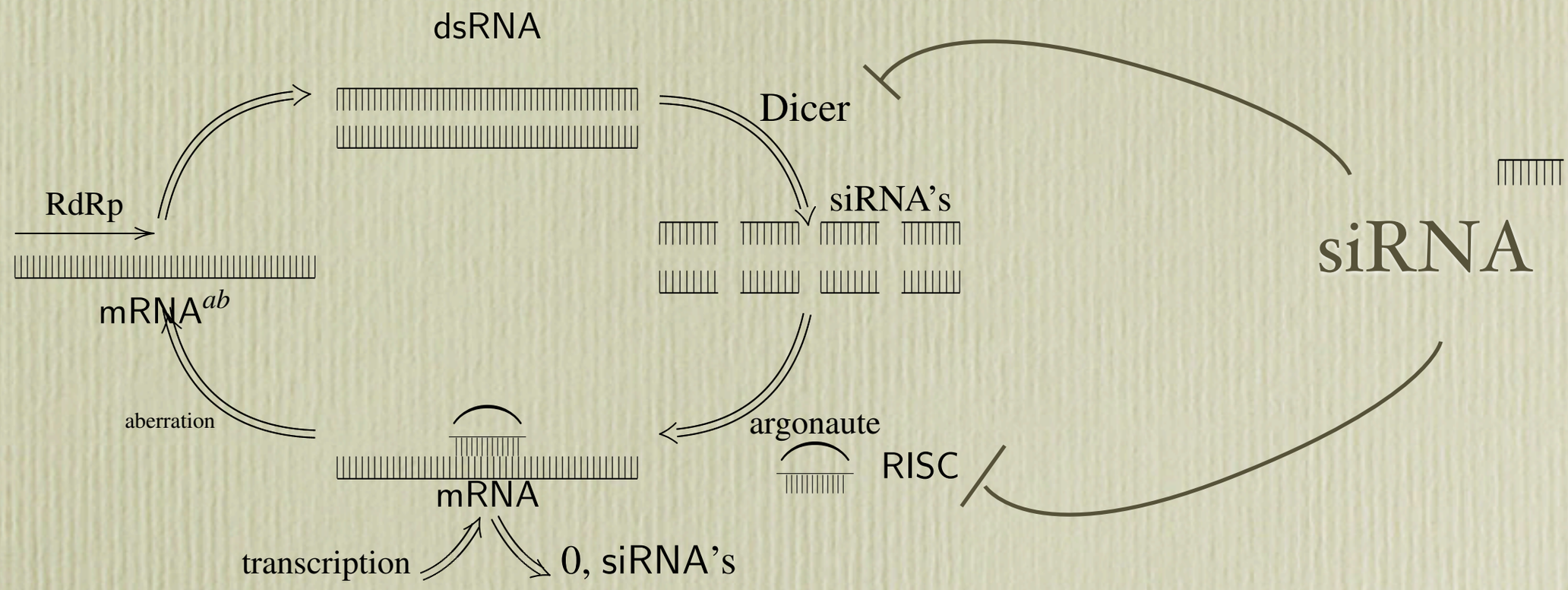


siRNAs floating/growing during the interference are to be taken into account !

Recursive RNAi (recRNAi)

Xie Z, Kasschau KD, Carrington JC, Negative feedback regulation of Dicer-like1 in Arabidopsis by microRNA-guided mRNA degradation. Curr Biol (2003)

feedback linkage in RNAi



siRNA inhibits (not only mRNA but also) Dicer and RISC.

I.e., siRNA inhibits the decrement instructions.

recRNAi in CGF with Fixed Points

$I_i = \mathsf{DecJump}(r_j, I_s)$ $\qquad$ $\mathsf{siRNA} = ?s.\mathsf{siRNA}$

$$I_i = !a_j.(0 \mid I_{i+1}) \oplus \tau.(!s.I_i \oplus \tau.I_s)$$

Dicer cleaving dsRNA $\qquad$ Dicer being degraded by siRNA

$$(= \mathsf{fix}_X.[a.(0 \mid I_{i+1}) \oplus \tau.(!s.X \oplus \tau.I_s)])$$

State with h-inhibitors of siRNAs

Given a state $(I_i, r_1 = l_1, r_2 = l_2)$ and a natural number h,

$$[\![(I_i, r_1 = l_1, r_2 = l_2)]\!]_h \quad := \quad I_i \mid \prod_{l_1} \mathsf{dsRNA} \mid \prod_{l_2} \mathsf{mRNA} \mid \prod_{h} \mathsf{siRNA}$$

recRNAi probabilistically computes

Given machine's one step computation

$$(I_i, r_1 = l_1, r_2 = l_2) \quad \longmapsto \quad (I_j, r_1 = l_1', r_2 = l_2')$$

- Inc is precise

$[\![(I_i, r_1 = l_1, r_2 = l_2)]\!]_h$ is reachable to $[\![(I_j, r_1 = l_1', r_2 = l_2')]\!]_h$

with probability 1

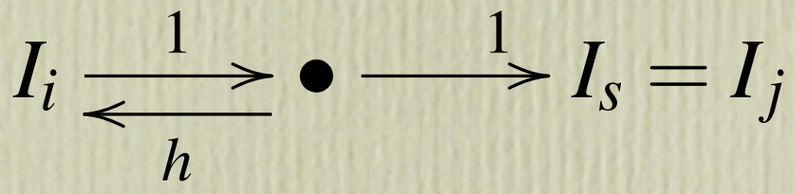
- DecJump is probabilistic $> 1 - 1/h$

$[\![(I_i, r_1 = l_1, r_2 = l_2)]\!]_h$ is reachable to $[\![(I_j, r_1 = l_1', r_2 = l_2')]\!]_k$

for some $k \geq h+1$ with probability $> 1 - 1/h$

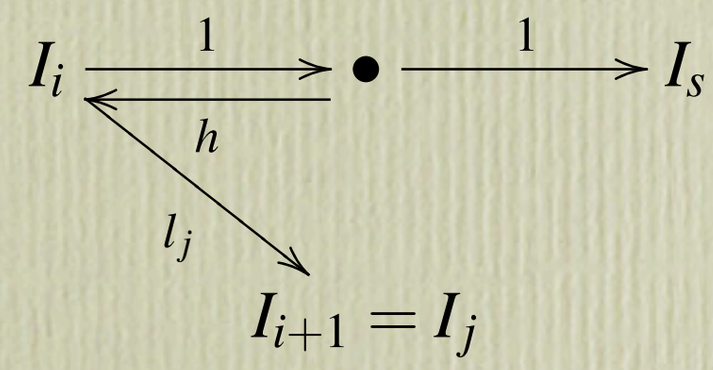
DecJump is probabilistic $> 1 - 1/h$

$l_j = 0$



$$\sum_{i=0}^{\infty} \left(\frac{h}{h+1}\right)^i \times \frac{1}{(h+1)} = 1$$

$l_j \neq 0$



$$\sum_{i=0}^{\infty} \left(\frac{1}{l_j+1} \times \frac{h}{h+1}\right)^i \times \frac{l_j}{l_j+1} > 1 - \frac{1}{h}$$

Probabilistic Termination

The following is equivalent

- Register Machine starting from $(I_j, r_1 = l_1, r_2 = l_2)$ terminates.
- RecRNAI starting from $[\![(I_j, r_1 = l_1, r_2 = l_2)]\!]_h$ probabilistically terminates with probability

$$> 1 - \sum_{k=h}^{\infty} \frac{1}{k}.$$

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Turing Complete Extensions of CGF

Cardelli-Zavattaro (2010)

BGF

(Biochemical GF)

association/dissociation
of agents

We propose

CGF

with delayed Inputs

CGF

Delayed Inputs

(for Π-calculus) van Breugel '97 , Merro-Sangiorgi '98

- Self Communication

$$!a.\,(?a.\,P \oplus M) \rightarrow P$$

- Guarding

$$?b.\,R \oplus N \mid !a.\,(?a.\,P \oplus M) \rightarrow ?b.\,R \oplus N \mid P$$

only if $b \neq a$.

Precise Encoding of RM into CGF with Delayed Inputs

By entanglling channels,

- DecJump Instruction Ii

$$I_i = \mathsf{DecJump}(r_j, s) \quad = \quad !a_j.(?a_j.I_s \oplus !b.I_{i+1})$$

- Registers

$$r_j = \overbrace{?a_j.?b.0 \,\big|\, \cdots \,\big|\, ?a_j.?b.0}^{l_j}$$

Preciseness

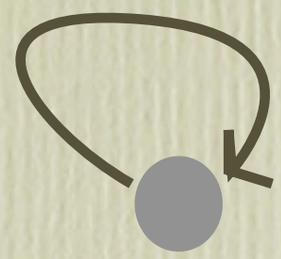
- Register hold ≠0

DecJump

Register

$$?a_j.?b.0 \,|\, !a_j.(?a_j.I_s \oplus !b.I_{i+1})$$
$$\longrightarrow \; ?b.0 \,|\, ?a_j.I_s \oplus !b.I_{i+1}$$
$$\longrightarrow \; 0 \,|\, I_{i+1}$$

- Register holds 0



$$!a_j.(?a_j.I_s \oplus ?b.I_{i+1})$$
$$\longrightarrow \; I_s$$

CGF with delayed input is Turing complete.

Future Work

- Computational meaning of RNAi with another pathway of polymerization ?