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Stochastic bursts in the kinetics of gene expression with regulation by long non-coding RNAs

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One of the main recent breakthroughs in cellular biology is a discovery of numerous non-coding RNAs (ncRNAs). We outline abilities of long ncRNAs and articulate that the corresponding kinetics may frequently exhibit stochastic bursts. For example, we scrutinize one of the generic cases when the gene transcription is regulated by competitive attachment of ncRNA and protein to a regulatory site. Our Monte Carlo simulations show that in this case one can observe huge long transcriptional bursts consisting of short bursts.

1. In cells, genes are transcribed to mRNAs which are in turn translated to proteins. Many genes exist in a single copy and the populations of mRNAs and proteins are often relatively low [1]. For these reasons, the kinetics of gene expression frequently exhibit stochastic features (see, e.g., reviews [2, 3]) or, more specifically, bursts representing sequential periods of high and low transcriptional and/or translational activity. Such features of the kinetics of gene expression have long attracted appreciable attention because this phenomenon is obviously of high interest from very different perspectives. The corresponding experimental and theoretical studies are focused on the interplay of mRNAs and proteins. These species are central in prokaryotes whose genomes consist of tightly packed sequences transcribed to protein-coding RNAs (e.g., to mRNAs). In eukaryotic cells, the situation is more complex, because their genomes contain relatively rare protein-coding sequences while many sequences of the rest of the genome are transcribed to ncRNAs forming the cornerstone of a regulatory network that operates in concert with the protein network [4 – 7]. Structurally, ncRNAs are divided into two groups including (i) long ncRNAs obtained directly after gene transcription and (ii) small ncRNAs (from 20 to 200 nucleotides) obtained by cleavage of long ncRNAs. The functions of small ncRNAs are based primarily on their ability to pair with specific mRNAs and inhibit their translation and/or facilitate degradation [7]. The abilities of long ncRNAs are much more diverse [4 – 6].

The important role of ncRNAs has recently been tracked out in a wide variety of cellular processes. One can safely say that in one or another way the ncRNAs influence almost every intracellular process. For example, thousands of mammalian mRNAs are highly expressed at developmental stages before ncRNAs expression and their levels tend to fall as the ncRNAs that target them begin to accumulate [8]. Abnormal levels of ncRNA expression were observed in many types of human cancer [9]. Misexpression of ncRNAs occurs also in many other diseases including diabetes, obesity, heart disease and inflammation [10].

Despite the current boom in the studies of ncRNAs, the experimental data on the corresponding kinetics are still limited. In particular, to our knowledge, there are no experimental reports on observation of stochastic bursts related to ncRNAs. The theoretical works available in this field are based primarily on the mean-field kinetic equations (see Refs. [11] and [12, 13], focused, respectively, on the situations without and with protein-mediated feedbacks) and do not predict stochastic bursts. The bursts related to bistability in the mRNA-ncRNA-protein interplay have been illustrated by using Monte Carlo simulations [14]. The latter model includes negative regulation of the ncRNA synthesis by protein. The other scenarios of bursts were not discussed there.

Taking high current interest in ncRNAs into account, it is now timely to overview the likely mechanisms of burst formation in gene expression occurring with participation of ncRNAs in order to stimulate further experimental and theoretical studies in this field. Following this line, we recall the main types of stochastic bursts in the interplay of mRNAs and proteins (Sec.2), outline the key abilities of long ncRNAs and briefly comment on the likely associated stochastic effects (Sec.3), and present an analytical treatment and Monte Carlo simulations illustrating explicitly stochastic bursts in one of the novel generic situations (Sec.4).

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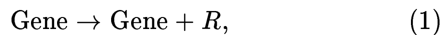
2. In genetic networks including mRNAs and proteins, there are three scenarios of stochastic bursts (for the numerous corresponding models, we may refer to the already mentioned reviews [2, 3], one of the formative articles [15], more recent articles [16 – 19], and references therein):

(i) *Translational bursts* [2]. The simplest scheme of gene expression consists of gene transcription to mRNA (R), mRNA translation to protein (P), and mRNA and protein degradation,



$$\text{Gene} \to \text{Gene} + R, \tag{1}$$

$$R \to R + P, \tag{2}$$

$$R \to \emptyset, \tag{3}$$

$$P \to \emptyset. \tag{4}$$

Stochastic bursts can be observed even if a network contains only these four steps and there is no any regulation. This is possible provided that the rate constant of step (2) is high compared to that of step (4). In this case, the synthesis of each R results in a stochastic burst in the P population. These bursts are well manifested provided that the R population is low and step (1) is slow compared to steps (2) and (4). The former is the case provided that the rate constant of step (3) is comparable to or higher than the rate of step (1).

(ii) *Bursts related to regulation of transcription* [2, 15, 16]. If step (1) is controlled, e.g., by slow attachment of a transcription factor [protein ($\mathcal{P}$)] to and detachment from a regulatory site, one can observe stochastic bursts in the R and P population. In particular, these populations will be relatively small or large depending on the state of a regulatory site. In addition or alternatively to the protein attachment, the transition between the active and inactive gene states can be related, e.g., to chromatin remodeling.

(iii) *Bursts related to bistability* [15, 17, 18, 19]. In the presence of feedbacks between the mRNA and protein synthesis, the kinetics of gene expression are often bistable (in the mean-field approximation). For example, steps (1)–(4) may result in bistability provided that step (1) is positively regulated by P and the number of the corresponding regulatory sites is equal or larger than 2. If, in addition, the mRNA and protein populations are relatively small, one can observe stochastic bursts representing sequential transitions between the states which are close to the stable mean-field steady states. These bursts are more collective compared to those described in item (ii). In particular, the periods of high and low activity cannot be expressed in terms of the rate of one of the steps.

3. Reading recent reviews [4 – 6], one can find that the examples illustrating the role of long ncRNAs in gene expression are now limited. Below, we outline of the emerging paradigms in this area in combination with our commentaries focused on stochastic bursts.

(i) *Chromatin modification.* In eukaryotic cells, chromosomes are packaged by histones (positevely charged proteins) into a condensed structure called chromatin. ncRNAs can silence gene expression by recruitment of chromatin modifying complexes, exclusion of the transcription machinery from the chromosome, modification of histones, and subsequent changes in the chromatin structure [5]. There are also other scenarios of the ncRNA-induced chromatin modification resulting in transcriptional activation [6]. In general, chromatin modification seems to occur via a few steps. The simplest coarse-grained description of this process can be based on the two-state ("unmodified" and "modified") approximation. Following this line, one can conclude that the ncRNA-induced chromatin modification may result in stochastic bursts (like in Sec.2(ii)).

(ii) *Transcriptional interference.* The transcription of a ncRNA across the promoter region of a protein-coding gene can interfere with transcription factor binding and prevent this gene from the mRNA synthesis [6]. In this case, the gene-expression kinetics can exhibit stochastic bursts similar to those described in Sec.2(ii).

(iii) *Direct regulation of transcription.* ncRNAs can directly regulate transcription through a range of mechanisms [4]: ncRNA can associate with a gene and recruit a ncRNA-binding protein with subsequent regulation of the gene activity by this protein or the ncRNa-protein complex; ncRNA can associate with protein, and the ncRNa-protein complex can then associate with a gene and regulate transcription; ncRNA and regulatory protein can competitively adsorb on a regulatory site of a gene and the transcription rate can depend on the state of this site. Under suitable conditions, all these scenarios may result in stochastic bursts similar to those described in Sec. 2(ii). In the presence of feedbacks, stochastic bursts similar to those described in Sec. 2(iii) are possible as well.

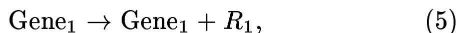
(iv) *Indirect regulation of transcription.* ncRNAs can associate with mRNAs, other ncRNAs or proteins and reduce the population of these species and/or affect their processing [6]. In addition, long ncRNAs can be processed to yield small RNAs [6]. Such diverse processes can indirectly regulate the transcription of many genes and result in stochastic bursts similar to

those described in Sec. 2(iii). As already noticed in the introduction, the MC simulations illustrating such bursts in the case of association of mRNA and ncRNA have been presented in Ref. [14].

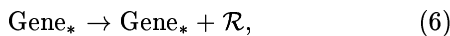
(v) *Spatial aspects.* ncRNAs can serve as structural RNAs. Within the nucleus, for example, a number of RNA-binding proteins localize to paraspeckles. These irregularly shaped compartments seem to be partly formed of ncRNAs [6]. More globally, ncRNAs have been found to participate in the organization and maintenance of the cellular cytoskeleton [6]. At present, the manifestation of such ncRNA functions in the kinetics of gene expression is open for studies and debates.

Above, we have outlined numerous abilities of ncRNAs and articulated that the corresponding kinetics may frequently exhibit stochastic bursts similar to those observed in and/or predicted for the mRNA-protein networks. "Similar" used here does not, however, mean "identical". Although some of the models including ncRNAs can be mapped to those describing the mRNA-protein interplay, as a rule this is not the case, because the former models usually contain the ingredients specific to ncRNAs. For this reason, the analysis of stochastic bursts in the models including ncRNAs is expected to be one of the new subfields of the theory of genetic networks.

4. As already noted in Sec. 3(iii), ncRNA and regulatory protein can competitively associate to a regulatory site of a gene and the transcription rate can depend on the state of this site. For example, a ncRNA transcribed from the *DHFR* minor promoter in humans can associate with the major promoter, occlude the binding of the general transcription factor TFIID, and thereby silence *DHFR* gene expression (see experiments [20] and review [4]). Our generic kinetic model of gene expression with this type of the regulation includes synthesis of mRNA (R_1) and ncRNA ($\mathcal{R}$),



$$\mathrm{Gene}_1 \to \mathrm{Gene}_1 + R_1, \tag{5}$$

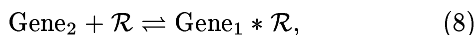


$$\mathrm{Gene}_* \to \mathrm{Gene}_* + \mathcal{R}, \tag{6}$$

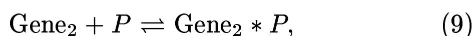
translation of mRNA to protein (P),

$$R_1 \to R_1 + P, \tag{7}$$

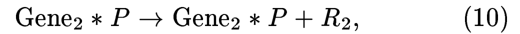
reversible association of ncRNA and protein with the regulatory site of the gene transcribed to RNA (R_2; the type of this RNA does not matter),



$$\mathrm{Gene}_2 + \mathcal{R} \rightleftharpoons \mathrm{Gene}_1 * \mathcal{R}, \tag{8}$$

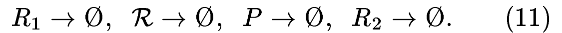


$$\mathrm{Gene}_2 + P \rightleftharpoons \mathrm{Gene}_2 * P, \tag{9}$$



$$\mathrm{Gene}_2 * P \to \mathrm{Gene}_2 * P + R_2, \tag{10}$$

and degradation of all these species,



$$R_1 \to \emptyset,\ \ \mathcal{R} \to \emptyset,\ \ P \to \emptyset,\ \ R_2 \to \emptyset. \tag{11}$$

The synthesis of R_2 [step (10)] is assumed to occur only in the presence of P on the regulatory site. Association of $\mathcal{R}$ and P with the regulatory site is considered to be competitive, i.e., the site can be occupied either by ncRNA or by protein (as in the case of the *DHFR* gene [20]). To focus on this type of regulation, we assume that $\mathcal{R}$ and R_2 are formed on different genes.

To illustrate stochastic bursts, we will employ MC simulations of steps (5)-(11). First, it is instructive, however, to describe these steps by using the simplest mean-field kinetic equations for the R_1, $\mathcal{R}$, P and R_2 populations in a cell. In particular, for the R_1 population, we have

$$dN_{R1}/dt = w_{R1} - k_{R1}N_{R1}, \tag{12}$$

where w_{R1} and k_{R1} are the corresponding synthesis rate and degradation rate constant. To describe $\mathcal{R}$ and P, we assume that the corresponding populations, N_* and N_P, are relatively large ($\gg 1$). In this case, the contribution a single $\mathcal{R}$ or P, participating in steps (8) and (9), to the population of these species is negligible, and we can write

$$dN_*/dt = w_* - k_*N_*, \tag{13}$$

$$dN_P/dt = \kappa_{R1}N_{R1} - k_PN_P, \tag{14}$$

where w_* is the $\mathcal{R}$ synthesis rate, and κ_{R1}, k_* and k_P are the R_1-translation and $\mathcal{R}$- and P-degradation rate constants. The R_2 population is described as

$$dN_{R2}/dt = w_{R2}p_P - k_{R2}N_{R2}, \tag{15}$$

where w_{R2} is the R_2 synthesis rate in the presence of P on the regulatory site, p_P is the probability that the regulatory site is occupied by P, and k_{R2} is the R_2 degradation rate constant. The probability that the regulatory site is occupied by $\mathcal{R}$ is defined to be p_*. The equations for p_P and p_* are determined by the rates of steps (8) and (9),

$$dp_P/dt = (1 - p_P - p_*)r_P^aN_P - r_P^dp_P, \tag{16}$$

$$dp_*/dt = (1 - p_P - p_*)r_*^aN_* - r_*^dp_*, \tag{17}$$

where r_P^a, r_*^a, r_P^d and r_*^d are the rate constants of the P and $\mathcal{R}$ attachment to and detachment from the regulatory site, and $1 - p_P - p_*$ is the probability that this site is vacant.

Under the steady-state conditions, Eqs. (12)–(14) yield

$$N_{R1} = \frac{w_{R1}}{k_{R1}}, \quad N_* = \frac{w_*}{k_*}, \quad N_P = \frac{\kappa_{R1} w_{R1}}{k_{R1} k_P}. \tag{18}$$

According to Eqs. (16) and (17), the probability p_P is represented as

$$p_P = \frac{r_P^a N_P}{r_P^d (1 + r_P^a N_P / r_P^d + r_*^a N_* / r_*^d)}. \tag{19}$$

Using expressions (18) for N_P and N_*, we get

$$p_P = \frac{r_P^a \kappa_{R1} w_{R1}}{r_P^d k_{R1} k_P + r_P^a \kappa_{R1} w_{R1} + r_P^d k_{R1} k_P r_*^a w_* / (k_* r_*^d)}. \tag{20}$$

The R_2 population is determined by Eq. (15),

$$N_{R2} = w_{R2} p_P / k_{R2}. \tag{21}$$

The total number of R_2, transcribed during the time interval t, is given by

$$N_{R2}^{\text{tot}} = w_{R2} p_P t. \tag{22}$$

According to the mean-field equations, the kinetics under consideration are simple. In particular, the steady state is unique and the populations of all the species monotonously depend on the model parameters. With fluctuations, the model can, however, predict distinct stochastic bursts of the synthesis of R_2 by Gene$_2$. Although the bursts are basically of the type described in Sec. 2(ii), some of their features are novel. In particular, the R_2 population as a function of time can exhibit relatively long bursts composed of short bursts. This feature can be observed provided that the rates of the $\mathcal{R}$ attachment to and detachment from the regulatory site of Gene$_2$ are much lower than the corresponding rates for P.

To illustrate explicitly the bursts described above, we should specify the model parameters. For validation of the parameters, we notice that the degradation of RNAs and proteins in eukaryotic cells often occurs on the time scale from a few minutes to one hour. Following this guideline, we use $k_{R1} = k_* = 0.1\,\text{min}^{-1}$, $k_{R2} = 0.2\,\text{min}^{-1}$, and $k_P = 0.02\,\text{min}^{-1}$. To have biologically reasonable reactant populations, we employ $w_{R1} = w_{R2} = 20\,\text{min}^{-1}$, $w_* = 10\,\text{min}^{-1}$, and $\kappa_{R1} = 0.05\,\text{min}^{-1}$. The attachment and detachment rate constants are chosen to be $r_*^a = 10^{-4}\,\text{min}^{-1}$, $r_*^d = 0.01\,\text{min}^{-1}$, $r_P^a = 2 \cdot 10^{-4}\,\text{min}^{-1}$, and $r_P^d = 0.1\,\text{min}^{-1}$.

To perform MC simulations, we use the standard Gillespie algorithm based on the calculation of the total rate of all the possible steps, $w_t = \sum_{i=1} w_i$, realization of one of the steps chosen with probability w_i/w_t, and the corresponding increment of time by $|\ln(\rho)|/w_t$, where ρ $(0 < \rho \leq 1)$ is a random number.

According to our MC simulations, the fluctuations in the R_1, $\mathcal{R}$ and P populations (Fig.1a) are modest as expected, while the R_2 population exhibits huge long bursts (Fig.1b) related primarily to sequential $\mathcal{R}$

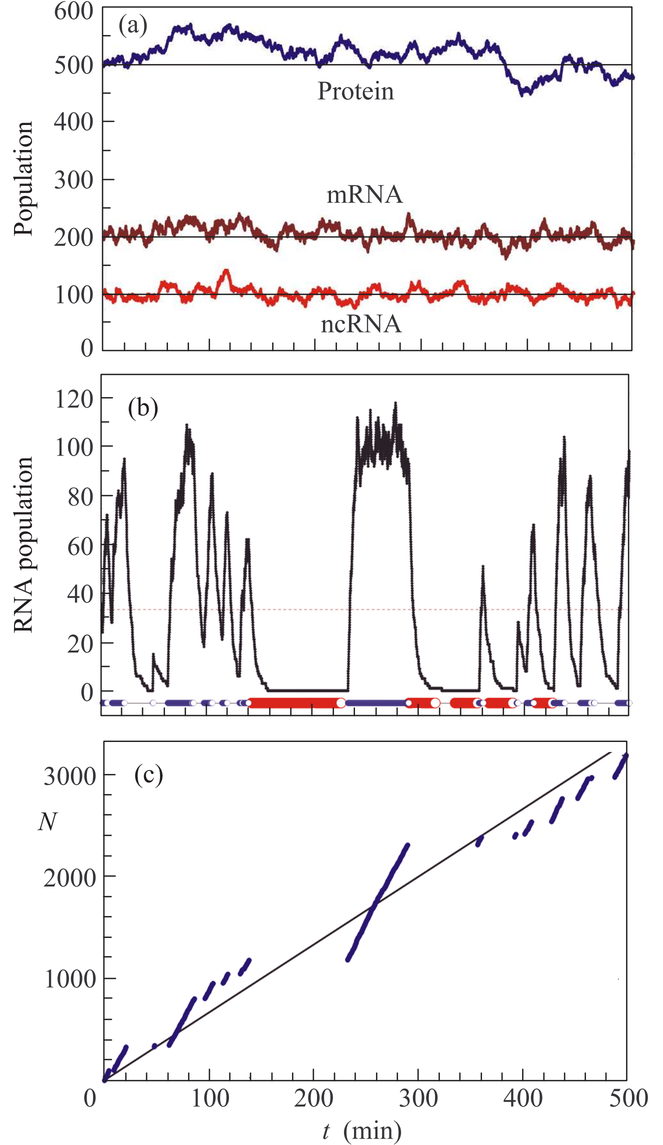


Fig.1. [(a) and (b)] Populations of mRNA, ncRNA, protein and RNA and (c) the total number of synthesized RNA as a function of time. The state of the regulatory site of Gene$_2$ is shown on the bottom line in panel (b) (the large and small circles correspond to occupation of this site by ncRNA and protein, respectively). The predictions of the mean-field kinetic equations (18) and (20)–(22) are indicated by straight solid or dashed lines

attachments to and detachments from the regulatory site of $Gene_2$. The bursts are also distinctly visible in the dependence of the total number of transcripts on time (Fig.1c). Scrutinizing Fig.1b, c, one can observe (Fig.2) that the long bursts consist of short bursts related mainly to P attachments to and detachments from the same regulatory site.

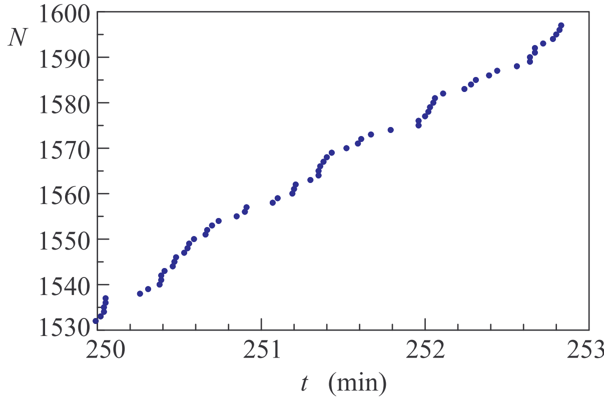


Fig.2. Fragment of Fig.1c

Stochastic bursts in the RNA population (Fig.1b) can be quantitatively characterized by using the normalized stationary variance of this variable, $\sigma^2/\langle N_{R2}\rangle^2$, where σ^2 is the square of the deviation from the mean value, $\langle N_{R2}\rangle$. For the Poissonian distribution, the normalized variance is well known to equal $1/\langle N_{R2}\rangle$. The bursts shown in Fig.1b are, however, far from Poissonian, and the corresponding variance is obviously much larger compared to the Poissonian case.

To calculate $\sigma^2/\langle N_{R2}\rangle^2$ analytically, we notice that our mean-field analysis above is valid on average, i.e., we have (cf. Eq. (21))

$$\langle N_{R2}\rangle = N_{R2}^{\max} p_P, \tag{23}$$

where $N_{R2}^{\max} = w_{R2}/k_{R2}$ is the maximum mean-field value of N_{R2}. Taking into account that N_{R2} is close to $N_{R2}^{\max}$ during the bursts while between the bursts N_{R2} is negligible (Fig.1b) and that the probabilities of occurrence of these periods are p_P and $1-p_P$, respectively, we can represent the variance as

$$\sigma^2 \simeq p_P(N_{R2}^{\max} - \langle N_{R2}\rangle)^2 + (1-p_P)\langle N_{R2}\rangle^2. \tag{24}$$

Using Eqs. (23) and (24), we obtain

$$\frac{\sigma^2}{\langle N_{R2}\rangle^2} \simeq \frac{1-p_P}{p_P}. \tag{25}$$

Employing expression (20) for p_P, we can rewrite Eq. (25) as

$$\frac{\sigma^2}{\langle N_{R2}\rangle^2} \simeq \frac{r_P^d k_{R1} k_P + r_P^d k_{R1} k_P r_*^a w_*/(k_* r_*^d)}{r_P^a \kappa_{R1} w_{R1}}. \tag{26}$$

This expression describes the dependence of the normalized stationary variance of N_{R2} on the model parameters.

For the parameters used to construct Fig. 1, for example, Eq. (23) and (26) yield $\langle N_{R2}\rangle = 33$ and $\sigma^2/\langle N_{R2}\rangle^2 = 2.0$. For comparison, the direct numerical processing of the kinetics shown in Fig.1b results in $\langle N_{R2}\rangle = 32$ and $\sigma^2/\langle N_{R2}\rangle^2 = 1.3$, while the Poissonian distribution (with $\langle N_{R2}\rangle = 32$) predicts $\sigma^2/\langle N_{R2}\rangle^2 = 0.03$. As expected, the average values of N_{R2} predicted analytically [Eq. (23)] and calculated numerically are in very good agreement. The normalized variances predicted analytically [Eq. (26)] and calculated numerically are in good agreement as well, while the Poissonian distribution appreciably underestimates the variance.

5. In eukaryotic cells, many genes are transcribed to long ncRNAs. Our overview presented in Sec. 3 indicates that the kinetics of gene expression including such RNAs may exhibit stochastic bursts similar to those earlier found in the mRNA-protein interplay and that the analysis of such bursts in the models including ncRNAs is expected to be one of the new subfields of the theory of genetic networks.

For example, we have scrutinized one of the generic cases when the gene transcription is regulated by competitive attachment of ncRNA and protein to a regulatory site. In this case, in addition to already known stochastic features, our model predicts novel peculiarities. Specifically, we have shown that the huge long bursts, related primarily to sequential ncRNA attachments to and detachments from the regulatory site, may consist of short bursts, related mainly to protein attachments to the same site. In the available studies of the mRNA-protein interplay (Sec.2), the bursts of this type were not observed or predicted.

Our study was motivated by the experiments [20]. The types of the gene regulations were there firmly identified by using various schemes of measurements. The temporal kinetics were, however, not studied. The rate constants for various steps were not measured either. For these reasons, direct comparison of the results of our calculations with the experiment is now hardly possible. In the field of the ncRNA biochemistry, this situation is typical because quantitative information on kinetic processes occurring with participation of ncRNAs is still very limited despite high current interest in ncRNAs.

In summary, our present work in combination earlier MC simulations [14] of stochastic bursts related to bistability is indicative of richness of the stochastic kinetics of gene expression including ncRNAs and many open avenues in this field.

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