switch and light steerage stochastic electric switch exemplifies a long-term intellectual effort in integrating electronic functions based on individual molecules into electrical nanocircuits. Moreover, as the decoupling of molecule leads to a decrease in the on-current (0.3 nA), the clock frequency of a practical device will be much lower than today's Si switches (GHz). It is still necessary to design new conceptual circuit architectures and new concepts of data processing to integrate these conceptual molecular devices into ICs.

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REFERENCES

1. Xiang D, Wang XL and Jia CC *et al. Chem Rev* 2016; **116**: 4318–440.
2. Jia CC and Guo XF. *Chem Soc Rev* 2013; **42**: 5642–60.
3. Dulic D, van der Molen SJ and Kudernac T *et al. Phys Rev Lett* 2003; **91**: 207402.
4. Jia C, Migliore A and Xin N *et al. Science* 2016; **352**: 1443–5.
5. Cao Y, Dong SH and Liu S *et al. Angew Chem Int Ed* 2012; **51**: 12228–32.

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IMMUNOLOGY

New evidence on the antiviral role of RNA interference in mammals

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Unique among the multitude of host defense systems evolved to combat viral pathogens, RNA molecules serve as both the inducer and the specificity determinant of the antiviral immunity mechanism mediated by RNA interference (RNAi). Consistently with predictions from studies in plants and invertebrates [1], recent reports have provided evidence for an antiviral function of RNAi against several RNA viruses in mammals [2–4]. However, little is known about the mechanism of antiviral RNAi or whether it is widespread among mammalian viral infections.

The study by Yang Qiu and colleagues [5] focused on human enterovirus 71 (HEV71), which causes fatal neurological illness in infants and young children. HEV71 is a positive-strand RNA virus of the genus *Enterovirus* that also includes poliovirus. The authors began by determining whether any of the virus-encoded proteins could suppress RNAi induced after a short hairpin RNA is processed into small interfering RNA (siRNA) by Dicer. This led to the identification of the 3A protein as the viral suppressor of RNAi (VSR). Surprisingly, VSR-3A binds viral dsRNA replicative intermediates in infected cells and suppresses *in vitro* Dicer processing of long dsRNA into siRNA, similar to the nodaviral VSR-B2 [2,3,6]. Several VSR-3A mutants defective in RNAi suppression were identified. One such mutant carries Asp to Ala substitution at position 23 (D23A), known to disrupt dimerization of the enteroviral 3A protein and cause severe defects in enterovirus RNA replication [7]. Notably, Dicer-dependent production of virus-derived siRNAs (vsiRNAs) was detected in human somatic cells and primary murine lung fibroblasts (MLFs) after infection with $HEV71_{D23A}$, which expressed the mutant VSR-3A, but not wild-type HEV71, indicating active suppression of the biogenesis of vsiRNAs during HEV71 infection [5]. The 22-nt vsiRNAs sequenced from the infected cells exhibited the canonical properties of siRNA, were present in Argonaute complexes and accumulated high levels readily detectable by Northern blot hybridization. However, the sequenced libraries of HEV71-derived small RNAs also included abundant small RNAs outside of the size range for Dicer products [5]. Removal of these non-specific small RNAs may require an extra step in the library construction to enrich the vsiRNAs by co-immunoprecipitation with Argonautes as shown recently for the influenza vsiRNAs [4].

The authors further provided several lines of evidence to illustrate the antiviral activity of the vsiRNAs produced during HEV71 infection. They found that $HEV71_{D23A}$ replicated to significantly enhanced levels after Dicer knockout or knock-down in human somatic cells and primary MLFs. Higher titers of $HEV71_{D23A}$ were also detected following ectopic expression of VSR-3A or VSR-B2 and were correlated with a reduced biogenesis of vsiRNAs. Similarly to a recent study [4], antiviral RNAi acted additively with the interferon antiviral response to enhance $HEV71_{D23A}$ titers [5]. Moreover, the vsiRNAs produced in $HEV71_{D23A}$-infected 293T cells to target the 5'-terminal region of the viral genomic RNA were capable of directing specific degradation of a chimeric cellular mRNA [5]. Strikingly, rapid clearance of $HEV71_{D23A}$ infection in newborn mice was associated with the production of abundant vsiRNAs, indicating induction and suppression of antiviral RNAi during *in vivo* infection.

These findings represent a landmark accomplishment, by illustrating a fundamental role for vsiRNAs and RNAi in natural defense against a human viral pathogen. Importantly, this study provides an experimental strategy to tease

apart the mammalian antiviral RNAi response against other important human viruses.

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REFERENCES

1. Ding SW. *Nat Rev Immunol* 2010; **10**: 632–44.
2. Li Y, Lu J and Han Y *et al. Science* 2013; **342**: 231–4.
3. Maillard PV, Claudo C and Marchais A *et al. Science* 2013; **342**: 235–8.
4. Li Y, Basavappa M and Lu J *et al. Nature Microbiology* 2016; **2**: 16250.
5. Qiu Y, Xu Y and Zhang Y *et al. Immunity* 2017; **46**: 992–1004.
6. Aliyari R, Wu Q and Li HW *et al. Cell Host Microbe* 2008; **4**: 387–97.
7. Wessels E, Notebaart RA and Duijsings D *et al. J Biol Chem* 2006; **281**: 28232–43.

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INFORMATION SCIENCE

On the applicability of PID control to nonlinear second-order systems

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Proportional-integral-derivative (PID) controllers, which react to the regulated signal's present, past and predicted future behavior, are popular, for two reasons. First, they are model-free and require minimal background and preliminary effort from the user. Second, they possess the capability—albeit limited—of shaping the system's both transient and asymptotic performance.

The great popularity of PID controllers goes hand in hand with their widespread misuse. With only one degree of freedom to influence asymptotic performance (the I part), PID controllers are capable of only the rejection of constant disturbances and tracking of constant commands. With only two degrees of freedom for shaping the system's transients (the PD part), PID controllers are sufficiently general only for systems that have up to two states, namely second-order systems.

Zhao and Guo [1] from the Chinese Academy of Sciences provide a highly valuable paper for both the control practitioner and for the theorist, by developing a detailed analysis of applying PID control to general second-order systems. They note that fully actuated mechanical systems, modeled by Newton's second law, are second-order and, therefore, the rigorous focus of their work comes with little sacrifice in terms of relevance.

In Theorem 1, the authors prove that, if the proportional gain is larger than an 'anti-stiffness' function of the plant, and the derivative gain is larger than an 'anti-damping' function of the plant, then the integral gain can be chosen sufficiently small, but positive, so that global output regulation is achieved. The general result of Theorem 1 is both specialized in Proposition 1 and Corollary 1 and further generalized in Theorem 2 but in the absence of the I-term for plants for which the setpoint is an equilibrium.

The results are strong and their proofs are not elementary. The most general results are proved using Lyapunov-like techniques, including those by LaSalle and Yoshizawa, as well as by eigenvalue-based techniques. For the case in which the I-action is not needed, a theorem based on the Markus-Yanabe Jacobian-based conjecture is employed in the proof.

The authors provide conditions on the PID gains such that global regulation is guaranteed independently of the output setpoint. Such results are highly valuable for the practitioner by giving large ranges of 'safe' controller parameters. However, as the authors indicate in the introduction, from the early days of PID control, there has, additionally, been interest in providing recipes to the user for not only safe choices, but the *best* choices of the three parameters. The Ziegler-Nichols procedure is the best-known recipe, but also known to exhibit interior transients while asymptotically rejecting constant disturbances. Most of the nine methods listed by the authors are developed based on the assumption of linearity of the plant.

The only method known to us in which the parameter optimization is conducted regardless of the plant's linearity or nonlinearity, or event the plant's dimension, is the extremum-seeking (ES) method in [2]. This method views the system's response as a map from the three gains into a functional of the system's response over a time interval of interest. For linear systems, ES matches or beats the best performance attainable by linearity-based methods. An alternative to deterministic ES [2] is the stochastic ES method in [3]. Hence, the papers [2,3] can be viewed as companion references for the practical user of the results in the highlighted paper. However, the user should be aware that, for nonlinear plants, optimal parameter choices will be dependent on the plant's initial condition and the setpoint value.

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REFERENCES

1. Zhao C and Guo L. *Sci China Inf Sci* 2017; **60**: 022201.
2. Killingsworth N and Krstic M. *Contr Syst Mag* 2006; **26**: 70–9.
3. Liu S-J and Krstic M. *IEEE T Automat Contr* 2016; **61**: 90–102.

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