

ACTAS

DE LAS

XXXVIII Jornadas de Automática

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Universidad de Oviedo
Universidá d'Uviéu
University of Oviedo



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Comité Español
de Automática

Colabora

Gijón

Convention Bureau

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Prefacio

Las *Jornadas de Automática* se celebran desde hace **40 años** en una universidad nacional facilitando el encuentro entre expertos en esta área en un foro que permite la puesta en común de las nuevas ideas y proyectos en desarrollo. Al mismo tiempo, propician la siempre necesaria colaboración entre investigadores del ámbito de la Ingeniería de Control y Automática, así como de campos afines, a la hora de abordar complejos proyectos de investigación multidisciplinares.

En esta ocasión, las Jornadas estarán organizadas por la Universidad de Oviedo y se han celebrado del 6 al 8 de septiembre de 2017 en el Palacio de Congresos de Gijón, colaborando tanto la Escuela Politécnica de Ingeniería de Gijón (EPI) como el Departamento de Ingeniería Eléctrica, Electrónica de Computadores y de Sistemas del que depende el Área de Ingeniería de Sistemas y Automática.

Además de las habituales actividades científicas y culturales, esta edición es muy especial al celebrarse el **50 aniversario de la creación de CEA**, Comité Español de Automática. Igualmente este año se conmemora el 60 aniversario de la Federación Internacional del Control Automático de la que depende CEA. Así se ha llevado a cabo la presentación del libro que se ha realizado bajo la coordinación de D. Sebastián Dormido, sobre la historia de la Automática en España en una sesión en la que han participado todos los ex-presidentes de CEA conjuntamente con el actual, D. Joseba Quevedo.

Igualmente hemos contado con la presencia de conferenciantes de prestigio para las sesiones plenarias, comunicaciones y ponencias orales en las reuniones de los 9 grupos temáticos, contribuciones en formato póster. Se ha celebrado también el concurso de CEABOT, así como una nueva Competición de Drones, con el ánimo de involucrar a más estudiantes de últimos cursos de Grado/Máster.

En el marco de las actividades culturales programadas se ha podido efectuar un recorrido en el casco antiguo situado en torno al Cerro de Santa Catalina y visitar la Laboral.

Gijón, septiembre de 2017

Hilario López
Presidente del Comité Organizador

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Table of Contents

Ingeniería de Control

TÚNEL DE AGUA PARA PRUEBAS Y CARACTERIZACIÓN DE DISEÑOS EXPERIMENTALES DE TURBINAS HIDROCINÉTICAS	1
<i>Eduardo Alvarez, Manuel Rico-Secades, Antonio Javier Calleja Rodríguez, Joaquín Fernández Francos, Aitor Fernández Jiménez, Mario Alvarez Fernández and Samuel Camba Fernández</i>	
Reduction of population variability in protein expression: A control engineering approach.	8
<i>Yadira Boada, Alejandro Vignoni and Jesús Picó</i>	
CONTROL ROBUSTO DEL PH EN FOTOBIORREACTORES MEDIANTE RECHAZO ACTIVO DE PERTURBACIONES	16
<i>José Carreño, Jose Luis Guzman, José Carlos Moreno and Rodolfo Villamizar</i>	
Control reset para maniobra de cambio de carril y validación con CarSim	23
<i>Miguel Cerdeira, Pablo Falcón, Antonio Barreiro, Emma Delgado and Miguel Díaz-Cacho</i>	
Maniobra de aterrizaje automática de una Cessna 172P modelada en FlightGear y controlada desde un programa en C	31
<i>Mario de La Rosa, Antonio Javier Gallego and Eduardo Fernández</i>	
Alternativas para el control de la red eléctrica aislada en parques eólicos marinos	38
<i>Carlos Díaz-Sanahuja, Ignacio Peñarrocha, Ricardo Vidal-Albalade and Ester Sales-Setién</i>	
CONTROL PREDICTIVO DISTRIBUIDO UTILIZANDO MODELOS DIFUSOS PARA LA NEGOCIACIÓN ENTRE AGENTES	46
<i>Lucía Fargallo, Silvana Roxani Revollar Chavez, Mario Francisco, Pastora Vega and Antonio Cembellín</i>	
Control Predictivo en el espacio de estados de un captador solar tipo Fresnel	54
<i>Antonio Javier Gallego, Mario de La Rosa and Eduardo Fernández</i>	
Control predictivo para la operación eficiente de una planta formada por un sistema de desalación solar y un invernadero	62
<i>Juan Diego Gil Vergel, Lidia Roca, Manuel Berenguel, Alba Ruiz Aguirre, Guillermo Zaragoza and Antonio Giménez</i>	
Depuración de Aguas Residuales en la Industria 4.0	70
<i>Jesus Manuel Gomez-De-Gabriel, Ana María Jiménez Arévalo, Laura Eiroa Mateo and Fco. Javier Fernández-De-Cañete-Rodríguez</i>	
Control robusto con QFT del pH en un fotobioreactor raceway	77
<i>Ángeles Hoyo Sánchez, Jose Luis Guzman, Jose Carlos Moreno and Manuel Berenguel</i>	
Revisión sistemática de la literatura en ingeniería de sistemas. Caso práctico: técnicas de estimación distribuida de sistemas ciberfísicos	84
<i>Carmelina Ierardi, Luis Orihuela Espina, Isabel Jurado Flores, Álvaro Rodríguez Del Nozal and Alejandro Tapia Córdoba</i>	
Desarrollo de un Controlador Predictivo para Autómatas programables basado en la normativa IEC 61131-3	92
<i>Pablo Krupa, Daniel Limon and Teodoro Alamo</i>	
Diseño de un emulador de aerogenerador de velocidad variable DFIG y control de pitch ...	100
<i>Manuel Lara Ortiz, Juan Garrido Jurado and Francisco Vázquez Serrano</i>	

Observación de la fracción de agua líquida en pilas de combustible tipo PEM de cátodo abierto.....	108
<i>Julio Luna and Ramon Costa-Castelló</i>	
Control Predictivo Basado en Datos.....	115
<i>José María Manzano, Daniel Limón, Teodoro Álamo and Jan Peter Calliess</i>	
Control MPC basado en un modelo LTV para seguimiento de trayectoria con estabilidad garantizada.....	122
<i>Sara Mata, Asier Zubizarreta, Ione Nieva, Itziar Cabanes and Charles Pinto</i>	
Implementación y evaluación de controladores basados en eventos en la norma IEC-61499.	130
<i>Oscar Miguel-Escrig, Julio-Ariel Romero-Pérez and Esteban Querol-Dolz</i>	
AUTOMATIZACIÓN Y MONITORIZACIÓN DE UNA INSTALACIÓN DE ENSAYO DE MOTORES.....	138
<i>Alfonso Poncela Méndez, Miguel Ochoa Vega, Eduardo J. Moya de La Torre and F. Javier García Ruíz</i>	
OPTIMIZACIÓN Y CONTROL EN CASCADA DE TEMPERATURA DE RECINTO MEDIANTE SISTEMAS DE REFRIGERACIÓN.....	146
<i>David Rodríguez, José Enrique Alonso Alfaya, Guillermo Bejarano Pellicer and Manuel G. Ortega</i>	
Diseño LQ e implementación distribuida para la estimación de estado.....	154
<i>Álvaro Rodríguez Del Nozal, Luis Orihuela, Pablo Millán Gata, Carmelina Ierardi and Alejandro Tapia Córdoba</i>	
Estimación de fugas en un sistema industrial real mediante modelado por señales aditivas.	160
<i>Ester Sales-Setién, Ignacio Peñarrocha and David Tena</i>	
Advanced control based on MPC ideas for offshore hydrogen production.....	167
<i>Alvaro Serna, Fernando Tadeo and Julio. E Normey-Rico</i>	
Transfer function parameters estimation by symmetric send-on-delta sampling.....	174
<i>José Sánchez, María Guinaldo, Sebastián Dormido and Antonio Visioli</i>	
An Estimation Approach for Process Control based on Asymmetric Oscillations.....	181
<i>José Sánchez, María Guinaldo Losada, Sebastian Dormido, José Luis Fernández Marrón and Antonio Visioli</i>	
Robust PI controller for disturbance attenuation and its application for voltage regulation in islanded microgrid.....	189
<i>Ramon Vilanova, Carles Pedret and Orlando Arrieta</i>	
Infraestructura para explotación de datos de un simulador azucarero.....	197
<i>Jesús M. Zamarreño, Cristian Pablos, Alejandro Merino, L. Felipe Acebes and De Prada César</i>	
<hr/>	
Automar	
<hr/>	
INFRAESTRUCTURA PARA ESTUDIAR ADAPTABILIDAD Y TRANSPARENCIA EN EL CENTRO DE CONTROL VERSÁTIL.....	203
<i>Juan Antonio Bonache Seco, José Antonio Lopez Orozco, Eva Besada Portas and Jesús Manuel de La Cruz</i>	
ARQUITECTURA DE CONTROL HÍBRIDA PARA LA NAVEGACIÓN DE VEHÍCULOS SUBMARINOS NO TRIPULADOS.....	211
<i>Francisco J. Lastra, Jesús A. Trujillo, Francisco J. Velasco and Elías Revestido</i>	

Exploración y Reconstrucción 3D de Fondos Marinos Mediante AUVs y Sensores Acústicos	218
<i>Oscar L. Manrique Garcia, Mario Andrei Garzon Oviedo and Antonio Barrientos</i>	
AUTOMATIZACIÓN DE MANIOBRAS PARA UN TEC DE 2GdL	226
<i>Marina Pérez de La Portilla, José Andrés Somolinos Sánchez, Amable López Piñeiro, Rafael Morales Herrera and Eva Segura</i>	
MERBOTS PROJECT: OVERALL DESCRIPTION, MULTISENSORY AUTONOMOUS PERCEPTION AND GRASPING FOR UNDERWATER ROBOTICS INTERVENTIONS	232
<i>Pedro J. Sanz, Raul Marin, Antonio Peñalver, David Fornas and Diego Centelles</i>	
<hr/> Bioingeniería <hr/>	
MARCADORES CUADRADOS Y DEFORMACIÓN DE OBJETOS EN NAVEGACIÓN QUIRÚRGICA CON REALIDAD AUMENTADA	238
<i>Eliana Aguilar, Oscar Andres Vivas and Jose Maria Sabater-Navarro</i>	
Entrenamiento robótico de la marcha en pacientes con Parálisis Cerebral: definición de objetivos, propuesta de tratamiento e implementación clínica preliminar	244
<i>Cristina Bayón, Teresa Martín-Lorenzo, Beatriz Moral-Saiz, Óscar Ramírez, Álvaro Pérez-Somarriba, Sergio Lerma-Lara, Ignacio Martínez and Eduardo Rocon</i>	
PREDICCIÓN DE ACTIVIDADES DE LA VIDA DIARIA EN ENTORNOS INTELIGENTES PARA PERSONAS CON MOVILIDAD REDUCIDA	251
<i>Arturo Bertomeu-Motos, Santiago Ezquerro, Juan Antonio Barios, Luis Daniel Lledó, Francisco Javier Badesa and Nicolas Garcia-Aracil</i>	
Sistema de Visión Estereoscópico para el guiado de un Robot Quirúrgico en Operaciones de Cirugía Laparoscópica HALS.....	256
<i>Carlos Castedo Hernández, Rafael Estop Remacha, Eusebio de La Fuente López and Lidia Santos Del Blanco</i>	
Head movement assessment of cerebral palsy users with severe motor disorders when they control a computer thought eye movements.....	264
<i>Alejandro Clemotte, Miguel A. Velasco and Eduardo Rocon</i>	
Diseño de un sensor óptico de fuerza para exoesqueletos de mano.....	270
<i>Jorge Diez Pomares, Andrea Blanco Ivorra, José María Catalan Orts, Francisco Javier Badesa Clemente, José María Sabater and Nicolas Garcia Aracil</i>	
POSIBILIDADES DEL USO DE TRAMAS ARTIFICIALES DE IMAGEN MOTORA PARA UN BCI BASADO EN EEG	276
<i>Josep Dinarès-Ferran, Christoph Guger and Jordi Solé-Casals</i>	
EFFECTOS SOBRE LA ERD EN TAREAS DE CONTROL DE EXOESQUELETO DE MANO EMPLEANDO BCI.....	282
<i>Santiago Ezquerro, Juan Antonio Barios, Arturo Bertomeu-Motos, Luisa Lorente, Nuria Requena, Irene Delegido, Francisco Javier Badesa and Nicolas Garcia-Aracil</i>	
Formulación Topológica Adaptada para la Simulación y Control de Exoesqueletos Accionados con Transmisiones Harmonic Drive.....	288
<i>Andres Hidalgo Romero and Eduardo Rocon</i>	

Identificación de contracciones isométricas de la extremidad superior en pacientes con lesión medular incompleta mediante características espectrales de la electromiografía de alta densidad (HD-EMG)	296
<i>Mislav Jordanic, Mónica Rojas-Martínez, Joan Francesc Alonso, Carolina Migliorelli and Miguel Ángel Mañanas</i>	
Diseño de una plataforma para analizar el efecto de la estimulación mecánica aferente en el temblor de pacientes con temblor esencial	302
<i>Julio S. Lora, Roberto López, Jesús González de La Aleja and Eduardo Rocon</i>	
DEFINICIÓN DE UN PROTOCOLO PARA LA MEDIDA PRECISA DEL RANGO CERVICAL EMPLEANDO TECNOLOGÍA INERCIAL	308
<i>Álvaro Martín, Rafael Raya, Cristina Sánchez, Rodrigo Garcia-Carmona, Oscar Ramirez and Abraham Otero</i>	
SISTEMA BRAIN-COMPUTER INTEFACE DE NAVEGACIÓN WEB ORIENTADO A PERSONAS CON GRAVE DISCAPACIDAD.....	313
<i>Víctor Martínez-Cagigal, Javier Gómez-Pilar, Daniel Álvarez, Eduardo Santamaría-Vázquez and Roberto Hornero</i>	
ESTRATEGIAS DE NEUROESTIMULACIÓN TRANSCRANEAL POR CORRIENTE DIRECTA PARA MEJORA COGNITIVA	320
<i>Silvia Moreno Serrano, Mario Ortiz and José María Azorín Poveda</i>	
COMPARATIVA DE ALGORITMOS PARA LA DETECCIÓN ONLINE DE IMAGINACIÓN MOTORA DE LA MARCHA BASADO EN SEÑALES DE EEG	328
<i>Marisol Rodriguez-Ugarte, Irma Nayeli Angulo Sherman, Eduardo Iáñez and Jose M. Azorin</i>	
DETECCIÓN, MEDIANTE UN GUANTE SENSORIZADO, DE MOVIMIENTOS SELECCIONADOS EN UN SISTEMA ROBOTIZADO COLABORATIVO PARA HALS	334
<i>Lidia Santos, José Luis González, Eusebio de La Fuente, Juan Carlos Fraile and Javier Pérez Turiel</i>	
BIOSENSORES PARA CONTROL Y SEGUIMIENTO PATOLOGÍAS REUMATOIDES	340
<i>Amparo Tirado, Raúl Marín, José V Martí, Miguel Belmonte and Pedro Sanz</i>	
Assessment of tremor severity in patients with essential tremor using smartwatches	347
<i>Miguel A. Velasco, Roberto López-Blanco, Juan P. Romero, M. Dolores Del Castillo, J. Ignacio Serrano, Julián Benito-León and Eduardo Rocon</i>	
INTERFAZ CEREBRO-ORDENADOR PARA EL CONTROL DE UNA SILLA DE RUEDAS A TRAVÉS DE DOS PARADIGMAS DE NAVEGACIÓN	353
<i>Fernández-Rodríguez Álvaro, Velasco-Álvarez Francisco and Ricardo Ron-Angevin</i>	
<hr/>	
Control Inteligente	
Aprendizaje por Refuerzo para sistemas lineales discretos con dinámica desconocida: Simulación y Aplicación a un Sistema Electromecánico	360
<i>Henry Diaz, Antonio Sala and Leopoldo Armesto</i>	
Diseño de sistemas de control en cascada clásico y borroso para el seguimiento de trayectorias	368
<i>Javier G. Gonzalez, Rodolfo Haber, Fernando Matia and Marcelino Novo</i>	

ANÁLISIS FORMAL DE LA DINÁMICA DE SISTEMAS NO LINEALES MEDIANTE REDES NEURONALES.....	376
<i>Eloy Irigoyen, Mikel Larrea, A. Javier Barragán, Miguel Ángel Martínez and José Manuel Andújar</i>	
Predicción de la energía renovable proveniente del oleaje en las islas de Fuerteventura y Lanzarote.	384
<i>G.Nicolás Marichal, Deivis Avila, Ángela Hernández, Isidro Padrón and José Ángel Rodríguez</i>	
Aplicación de Redes Neuronales para la Estimación de la Resistencia al Avance en Buques	393
<i>Daniel Marón Blanco and Matilde Santos</i>	
Novel Fuzzy Torque Vectoring Controller for Electric Vehicles with per-wheel Motors.....	401
<i>Alberto Parra, Martín Dendaluze, Asier Zubizarreta and Joshué Pérez</i>	
REPOSTAJE EN TIERRA DE UN AVIÓN MEDIANTE ALGORITMOS GENÉTICOS .	408
<i>Elías Plaza and Matilde Santos</i>	
VISUALIZACIÓN WEB INTERACTIVA PARA EL ANÁLISIS DEL CHATTER EN LAMINACIÓN EN FRÍO.....	416
<i>Daniel Pérez López, Abel Alberto Cuadrado Vega and Ignacio Díaz Blanco</i>	
BANCADA PARA ANÁLISIS INTELIGENTE DE DATOS EN MONITORIZACIÓN DE SALUD ESTRUCTURAL.....	424
<i>Daniel Pérez López, Diego García Pérez, Ignacio Díaz Blanco and Abel Alberto Cuadrado Vega</i>	
CONTROL DE UN VEHÍCULO CUATRIRROTOR BASADO EN REDES NEURONALES.....	431
<i>Jesus Enrique Sierra and Matilde Santos</i>	
CONTROL PREDICTIVO FUZZY CON APLICACIÓN A LA DEPURACIÓN BIOLÓGICA DE FANGOS ACTIVADOS.....	437
<i>Pedro M. Vallejo Llamas and Pastora Vega Cruz</i>	
<hr/> Educación en Automática <hr/>	
REFLEXIONES SOBRE EL VALOR DOCENTE DE UNA COMPETICION DE DRONES EN LA EDUCACIÓN PARA EL CONTROL.....	445
<i>Ignacio Díaz Blanco, Alvaro Escanciano Urigüen, Antonio Robles Alvarez and Hilario López García</i>	
Uso del Haptic Paddle con aprendizaje basado en proyectos.....	451
<i>Juan M. Gandarias, Antonio José Muñoz-Ramírez and Jesus Manuel Gomez-De-Gabriel</i>	
REPRESENTACION INTEGRADA DE ACCIONAMIENTOS MECANICOS Y CONTROL DE EJES ORIENTADA A LA COMUNICACIÓN Y DOCENCIA EN MECATRONICA.....	457
<i>Julio Garrido Campos, David Santos Esterán, Juan Sáez López and José Ignacio Armesto Quiroga</i>	
Construcción y modelado de un prototipo fan & plate para prácticas de control automático	465
<i>Cristina Lampon, Javier Martin, Ramon Costa-Castelló and Muppaneni Lokesh Chowdary</i>	

EDUCACION EN AUTOMATICA E INDUSTRIA 4.0 MEDIANTE LA APLICACIÓN DE TECNOLOGÍAS 3D	471
<i>Jose Ramon Llata, Esther Gonzalez-Sarabia, Carlos Torre-Ferrero and Ramon Sancibrian</i>	
Desarrollo e implementación de un sistema de control en una planta piloto hibrida.....	479
<i>Maria P. Marcos, Cesar de Prada and Jose Luis Pitarch</i>	
LA INFORMÁTICA INDUSTRIAL EN LAS INGENIERÍAS INDUSTRIALES	486
<i>Rogelio Mazaeda, Eusebio de La Fuente López, José Luis González, Eduardo J. Moya de La Torre, Miguel Angel García Blanco, Javier García Ruiz, María Jesús de La Fuente Aparicio, Gregorio Sainz Palmero and Smaranda Cristea</i>	
Ventajas docentes de un flotador magnético para la experimentación de técnicas control ..	495
<i>Eduardo Montijano, Carlos Bernal, Carlos Sagües, Antonio Bono and Jesús Sergio Artal</i>	
PROGRAMACIÓN ATRACTIVA DE PLC	502
<i>Eduardo J. Moya de La Torre, F. Javier García Ruíz, Alfonso Poncela Méndez and Victor Barrio Lángara</i>	
MODERNIZACIÓN DE EQUIPO FEEDBACK MS-150 PARA EL APRENDIZAJE ACTIVO EN INGENIERÍA DE CONTROL	510
<i>Perfecto Reguera Acevedo, Miguel Ángel Prada Medrano, Antonio Morán Álvarez, Juan José Fuertes Martínez, Manuel Domínguez González and Serafín Alonso Castro</i>	
INNOVACIÓN PEDAGÓGICA EN LA FORMACIÓN DEL PERFIL PROFESIONAL PARA EL DESARROLLO DE PROYECTOS DE AUTOMATIZACIÓN INDUSTRIAL A TRAVÉS DE UNA APROXIMACIÓN HOLÍSTICA.	517
<i>Juan Carlos Ríos, Zaneta Babel, Daniel Martínez, José María Paredes, Luis Alonso, Pablo Hernández, Alejandro García, David Álvarez, Jorge Miranda, Constantino Manuel Valdés and Jesús Alonso</i>	
Aprendiendo Simulación de Eventos Discretos con JaamSim	522
<i>Enrique Teruel and Rosario Aragüés</i>	
RED NEURONAL AUTORREGRESIVA NO LINEAL CON ENTRADAS EXÓGENAS PARA LA PREDICCIÓN DEL ELECTROENCEFALOGRAMA FETAL...	528
<i>Rosa M Aguilar, Jesús Torres and Carlos Martín</i>	
ANÁLISIS DEL COEFICIENTE DE TRANSFERENCIA DE MATERIA EN REACTORES RACEWAYS.....	534
<i>Marta Barceló, Jose Luis Guzman, Francisco Gabriel Acién, Ismael Martín and Jorge Antonio Sánchez</i>	
MODELADO DINÁMICO DE UN SISTEMA DE ALMACENAMIENTO DE FRÍO VINCULADO A UN CICLO DE REFRIGERACIÓN	539
<i>Guillermo Bejarano Pellicer, José Joaquín Suffo, Manuel Vargas and Manuel G. Ortega</i>	
Predictor Intervalar basado en hiperplano soporte	547
<i>José Manuel Bravo Caro, Manuel Vasallo Vázquez, Emilian Cojocarú and Teodoro Alamo Cantarero</i>	
Dynamic simulation applied to refinery hydrogen networks	555
<i>Anibal Galan Prado, Cesar De Prada, Gloria Gutierrez, Rafael Gonzalez and Daniel Sarabia</i>	

APROXIMACIÓN DE MODELOS ALGEBRAICOS MEDIANTE ALAMO Y ECOSIMPRO	563
<i>Carlos Gómez Palacín, José Luis Pitarch, Gloria Gutiérrez and Cesar De Prada</i>	
A Causal Model to Analyze Aircraft Collision Avoidance Deadlock Scenarios	569
<i>Miquel Àngel Piera Eroles, Julia de Homdedeu, Maria Del Mar Tous, Thimjo Koca and Marko Radanovic</i>	
ONLINE DECISION SUPPORT FOR AN EVAPORATION NETWORK	575
<i>José Luis Pitarch, Marc Kalliski, Carlos Gómez Palacín, Christian Jasch and Cesar De Prada</i>	
Predicción de la irradiancia a partir de datos de satélite mediante deep learning	582
<i>Javier Pérez, Jorge Segarra-Tamarit, Hector Beltran, Carlos Ariño, José Carlos Alfonso Gil, Aleks Attanasio and Emilio Pérez</i>	
MODELO DINÁMICO ORIENTADO AL TRATAMIENTO Y SEGUIMIENTO DE LA LEUCEMIA MIELOIDE CRÓNICA	589
<i>Gabriel Pérez Rodríguez and Fernando Morilla</i>	
Modelado y optimización de la operación de un sistema de bombeo de múltiples depósitos	596
<i>Roberto Sanchis Llopis and Ignacio Peñarrocha</i>	
DEVELOPMENT OF A GREY MODEL FOR A MEDIUM DENSITY FIBREBOARD DRYER IN ECOSIMPRO	604
<i>Pedro Santos, Jose Luis Pitarch and César de Prada</i>	
DETECCIÓN AUTOMÁTICA DE FALLOS MEDIANTE MONITORIZACIÓN Y OPTIMIZACIÓN DE LAS FECHAS DE LIMPIEZA PARA INSTALACIONES FOTOVOLTAICAS	611
<i>Jorge Segarra-Tamarit, Emilio Pérez, Hector Beltran, Enrique Belenguer and José Luis Gandía</i>	
Modelado de micro-central hidráulica para el diseño de controladores con aplicación en regiones aisladas de Honduras	618
<i>Alejandro Tapia Córdoba, Pablo Millán Gata, Fabio Gómez-Estern Aguilar, Carmelina Ierardi and Álvaro Rodríguez Del Nozal</i>	
FRAMEWORK PARA EL MODELADO DE UN LAGO DE DATOS	626
<i>J.M Torres, R.M. Aguilar, C.A. Martin and S. Diaz</i>	
SIMULADOR CARDIOVASCULAR PARA ENSAYO DE ROBOTS DE NAVEGACION AUTONOMA	633
<i>José Emilio Traver, Juan Francisco Ortega Morán, Ines Tejado, J. Blas Pagador, Fei Sun, Raquel Pérez-Aloe, Blas M. Vinagre and F. Miguel Sánchez Margallo</i>	
PLANIFICACION DE LA PRODUCCION BASADA EN CONTROL PREDICTIVO PARA PLANTAS TERMOSOLARES	641
<i>Manuel Jesús Vasallo Vázquez, José Manuel Bravo Caro, Emilian Cojocarú and Manuel Emilio Gegundez Arias</i>	
Evaluación multicriterio para la optimización de redes de energía	649
<i>Ascensión Zafra Cabeza, Rafael Espinosa, Miguel Àngel Ridao Carlini and Carlos Bordóns Alba</i>	
Percibiendo el entorno en los robots sociales del RoboticsLab	657
<i>Fernando Alonso Martín, Jose Carlos Castillo Montoya, Àlvaro Castro-Gonzalez, Juan José Gamboa, Marcos Maroto Gómez, Sara Marqués Villaroya, Antonio J. Pérez Vidal and Miguel Àngel Salichs</i>	

DISEÑO DE UNA PRÓTESIS DE MANO ADAPTABLE AL CRECIMIENTO	664
<i>Marta Ayats and Raul Suarez</i>	
COOPERATIVISMO BIOINSPIRADO BASADO EN EL COMPORTAMIENTO DE LAS HORMIGAS	672
<i>Brayan Bermudez, Kristel Novoa and Miguel Valbuena</i>	
PROCEDIMIENTO DE DISEÑO DE UN EXOESQUELETO DE MIEMBRO SUPERIOR PARA SOPORTE DE CARGAS	680
<i>Andrea Blanco Ivorra, Jorge Diez Pomares, David Lopez Perez, Francisco Javier Badesa Clemente, Miguel Ignacio Sanchez and Nicolas Garcia Aracil</i>	
Estructura de control en ROS y modos de marcha basados en máquinas de estados de un robot hexápodo	686
<i>Raúl Cebolla Arroyo, Jorge De Leon Rivas and Antonio Barrientos</i>	
USING AN UAV TO GUIDE THE TELEOPERATION OF A MOBILE MANIPULATOR	694
<i>Josep Arnau Claret and Luis Basañez</i>	
Estudio de los patrones de marcha para un robot hexápodo en tareas de búsqueda y rescate	701
<i>Jorge De León Rivas and Antonio Barrientos</i>	
SISTEMA DE INTERACCIÓN VISUAL PARA UN ROBOT SOCIAL	709
<i>Mario Domínguez López, Eduardo Zalama Casanova, Jaime Gómez García-Bermejo and Samuel Marcos Pablos</i>	
Mejora del Comportamiento Proxémico de un Robot Autónomo mediante Motores de Inteligencia Artificial Desarrollados para Plataformas de Videojuegos	717
<i>David Fernández Chaves, Javier Monroy and Javier Gonzalez-Jimenez</i>	
Micrófonos de contacto: una alternativa para sensado táctil en robots sociales	724
<i>Juan José Gamboa, Fernando Alonso Martín, Jose Carlos Castillo, Marcos Maroto Gómez and Miguel A. Salichs</i>	
Clasificación de información táctil para la detección de personas	732
<i>Juan M. Gandarias, Jesús M. Gómez-De-Gabriel and Alfonso García-Cerezo</i>	
Planificación para interceptación de objetivos: Integración del Método Fast Marching y Risk-RRT	738
<i>David Alfredo Garzon Ramos, Mario Andrei Garzon Oviedo and Antonio Barrientos</i>	
ESTABILIZACIÓN DE UNA BOLA SOBRE UN PLANO UTILIZANDO UN ROBOT PARALELO 6-RSS	746
<i>Daniel González, Lluís Ros and Federico Thomas</i>	
TELEOPERACIÓN DE INSTRUMENTOS QUIRÚRGICOS ARTICULADOS	754
<i>Ana Gómez Delgado, Carlos Perez-Del-Pulgar, Antonio Reina Terol and Victor Muñoz Martinez</i>	
CONTROL OF A ROBOTIC ARM FOR TRANSPORTING OBJECTS BASED ON NEURO-FUZZY LEARNING VISUAL INFORMATION	760
<i>Juan Hernández Vicén, Santiago Martínez de La Casa Díaz and Carlos Balaguer</i>	
PLATAFORMA BASADA EN LA INTEGRACIÓN DE MATLAB Y ROS PARA LA DOCENCIA DE ROBÓTICA DE SERVICIO	766
<i>Carlos G. Juan, Jose Maria Vicente, Alvaro Garcia and Jose Maria Sabater-Navarro</i>	

Estimadores de fuerza y movimiento para el control de un robot de rehabilitación de extremidad superior.....	772
<i>Aitziber Mancisidor, Asier Zubizarreta, Itziar Cabanes, Pablo Bengoa and Asier Brull</i>	
Definiendo los elementos que constituyen un robot social portable de bajo coste	780
<i>Marcos Maroto Gómez, José Carlos Castillo, Fernando Alonso-Martín, Juan José Gamboa, Sara Marqués Villarroya and Miguel Ángel Salichs</i>	
Interfaces táctiles para Interacción Humano-Robot	787
<i>Sara Marqués Villarroya, Jose Carlos Castillo Montoya, Fernando Alonso Martín, Marcos Maroto Gómez, Juan José Gamboa and Miguel A. Salichs</i>	
HERRAMIENTAS DE ENTRENAMIENTO Y MONITORIZACIÓN PARA EL DESMINADO HUMANITARIO	793
<i>Hector Montes, Roemi Fernandez, Pablo Gonzalez de Santos and Manuel Armada</i>	
Control a Baja Velocidad de una Rueda con Motor de Accionamiento Directo mediante Ingeniería Basada en Modelos	799
<i>Antonio José Muñoz-Ramírez, Jesús Manuel Luque-Bedmar, Jesus Manuel Gomez-De-Gabriel, Anthony Mandow, Javier Serón and Alfonso Garcia-Cerezo</i>	
SIMULACIÓN DE VEHÍCULOS AUTÓNOMOS USANDO V-REP BAJO ROS	806
<i>Cándido Otero Moreira, Enrique Paz Domonte, Rafael Sanz Dominguez, Joaquín López Fernández, Rafael Barea, Eduardo Romera, Eduardo Molinos, Roberto Arroyo, Luís Miguel Bergasa and Elena López</i>	
Cinemática y prototipado de un manipulador paralelo con centro de rotación remoto para robótica quirúrgica.....	814
<i>Francisco Pastor, Juan M. Gandarias and Jesús M. Gómez-De-Gabriel</i>	
ANÁLISIS DE ESTABILIDAD DE SINGULARIDADES AISLADAS EN ROBOTS PARALELOS MEDIANTE DESARROLLOS DE TAYLOR DE SEGUNDO ORDEN.....	821
<i>Adrián Peidro Vidal, Óscar Reinoso, Arturo Gil, José María Marín and Luis Payá</i>	
INTERFAZ DE CONTROL PARA UN ROBOT MANIPULADOR MEDIANTE REALIDAD VIRTUAL	829
<i>Elena Peña-Tapia, Juan Jesús Roldán, Mario Garzón, Andrés Martín-Barrio and Antonio Barrientos</i>	
Evolución de la robótica social y nuevas tendencias.....	836
<i>Antonio J. Pérez Vidal, Alvaro Castro-Gonzalez, Fernando Alonso Martín, Jose Carlos Castillo Montoya and Miguel A. Salichs</i>	
DISEÑO MECÁNICO DE UN ASISTENTE ROBÓTICO CAMARÓGRAFO CON APRENDIZAJE COGNITIVO	844
<i>Irene Rivas-Blanco, M Carmen López-Casado, Carlos Pérez-Del-Pulgar, Francisco García-Vacas, Víctor Fernando Muñoz, Enrique Bauzano and Juan Carlos Fraile</i>	
CÁLCULO DE FUERZAS DE CONTACTO PARA PRENSIONES BIMANUALES.....	852
<i>Francisco Abiud Rojas-De-Silva and Raul Suarez</i>	
Modelado del Contexto Geométrico para el Reconocimiento de Objetos.....	860
<i>José Raúl Ruiz Sarmiento, Cipriano Galindo and Javier Gonzalez-Jimenez</i>	
Estimación Probabilística de Áreas de Emisión de Gases con un Robot Móvil Mediante la Integración Temporal de Observaciones de Gas y Viento	868
<i>Carlos Sanchez-Garrido, Javier Monroy and Javier Gonzalez-Jimenez</i>	

MANIPULADOR AÉREO CON BRAZOS ANTROPOMÓRFICOS DE ARTICULACIONES FLEXIBLES	876
<i>Alejandro Suarez, Guillermo Heredia and Anibal Ollero</i>	
EVALUACIÓN DE UN ENTORNO DE TELEOPERACIÓN CON ROS	864
<i>David Vargas Frutos, Juan Carlos Ramos Martínez, José Luis Samper Escudero, Miguel Ángel Sánchez-Urán González and Manuel Ferre Pérez</i>	

Sistemas de Tiempo Real

GENERACIÓN DE CÓDIGO IEC 61131-3 A PARTIR DE DISEÑOS EN GRAFCET....	892
<i>María Luz Alvarez Gutierrez, Isabel Sarachaga Gonzalez, Arantzazu Burgos Fernandez, Nagore Iriondo Urbistazu and Marga Marcos Muñoz</i>	
CONTROL EN TIEMPO REAL Y SUPERVISIÓN DE PROCESOS MEDIANTE SERVIDORES OPC-UA	900
<i>Francisco Blanes Noguera and Andrés Benlloch Faus</i>	
Control de la Ejecución en Sistemas de Criticidad Mixta	906
<i>Alfons Crespo, Patricia Balbastre, Jose Simo and Javier Coronel</i>	
GENERACIÓN AUTOMÁTICA DEL PROYECTO DE AUTOMATIZACIÓN TIA PORTAL PARA MÁQUINAS MODULARES	913
<i>Darío Orive, Aintzane Armentia, Eneko Fernandez and Marga Marcos</i>	
DDS en el desarrollo de sistemas distribuidos heterogéneos con soporte para criticidad mixta	921
<i>Hector Perez and J. Javier Gutiérrez</i>	
ARQUITECTURA DISTRIBUIDA PARA EL CONTROL AUTÓNOMO DE DRONES EN INTERIOR	929
<i>Jose-Luis Poza-Luján, Juan-Luis Posadas-Yaguë, Giovanni-Javier Tipantuña-Topanta, Francisco Abad and Ramón Mollá</i>	
Ingeniería Conducida por Modelos en Sistemas de Automatización Flexibles	935
<i>Rafael Priego, Elisabet Estévez, Darío Orive, Isabel Sarachaga and Marga Marcos</i>	
Estudio e implementación de Middleware para aplicaciones de control distribuido	942
<i>Jose Simo, Jose-Luis Poza-Lujan, Juan-Luis Posadas-Yaguë and Francisco Blanes</i>	

Visión por Computador

Real-Time Image Mosaicking for Mapping and Exploration Purposes	948
<i>Abdulla Al-Kaff, Juan Camilo Soto Triviño, Raúl Sosa San Frutos, Arturo de La Escalera and José María Armingol Moreno</i>	
ALGORITMO DE SLAM UTILIZANDO APARIENCIA GLOBAL DE IMÁGENES OMNIDIRECCIONALES	956
<i>Yerai Berenguer, Luis Payá, Mónica Ballesta, Luis Miguel Jiménez, Sergio Cebollada and Oscar Reinoso</i>	
Medición de Oximetría de Pulso mediante Imagen fotopletismográfica.....	964
<i>Juan-Carlos Cobos-Torres, Jordan Ortega Rodríguez, Pablo J. Alhama Blanco and Mohamed Abderrahim</i>	
Algoritmo de captura de movimiento basado en visión por computador para la teleoperación de robots humanoides.....	970
<i>Juan Miguel Garcia Haro and Santiago Martinez de La Casa</i>	

COMPARACIÓN DE MÉTODOS DE DETECCIÓN DE ROSTROS EN IMÁGENES DIGITALES	976
<i>Natalia García Del Prado, Victor Gonzalez Castro, Enrique Alegre and Eduardo Fidalgo Fernández</i>	
LOCALIZACIÓN DEL PUNTO DE FUGA PARA SISTEMA DE DETECCIÓN DE LÍNEAS DE CARRIL	983
<i>Manuel Ibarra-Arenado, Tardi Tjahjadi, Sandra Robla-Gómez and Juan Pérez-Oria</i>	
Oculus-Crawl, a Software Tool for Building Datasets for Computer Vision Tasks	991
<i>Iván De Paz Centeno, Eduardo Fidalgo Fernández, Enrique Alegre Gutiérrez and Wesam Al Nabki</i>	
Clasificación automática de obstáculos empleando escáner láser y visión por computador ..	999
<i>Aurelio Ponz, Fernando Garcia, David Martin, Arturo de La Escalera and Jose Maria Armingol</i>	
T-SCAN: OBTENCIÓN DE NUBES DE PUNTOS CON COLOR Y TEMPERATURA EN INTERIOR DE EDIFICIOS	1007
<i>Tomás Prado, Blanca Quintana, Samuel A. Prieto and Antonio Adan</i>	
EVALUACIÓN DE MÉTODOS PARA REALIZAR RESÚMENES AUTOMÁTICOS DE VÍDEOS	1015
<i>Pablo Rubio, Eduardo Fidalgo, Enrique Alegre and Víctor González</i>	
SIMULADOR PARA LA CREACIÓN DE MUNDOS VIRTUALES PARA LA ASISTENCIA A PERSONAS CON MOVILIDAD REDUCIDA EN SILLA DE RUEDAS .	1023
<i>Carlos Sánchez Sánchez, María Cidoncha Jiménez, Emiliano Pérez, Ines Tejado and Blas M. Vinagre</i>	
Calibración Extrínseca de un Conjunto de Cámaras RGB-D sobre un Robot Móvil	1031
<i>David Zúñiga-Nöel, Rubén Gómez Ojeda, Francisco-Ángel Moreno and Javier González Jiménez</i>	

Reduction of population variability in protein expression: A control engineering approach.

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Resumen

Controlling protein expression level is of interest in many applications. Yet, the stochastic nature of gene expression plays an important role and cannot be disregarded. We propose a gene synthetic circuit designed to control the mean gene expression in a population of cells and its variance. The circuit combines an intracellular negative feedback loop and quorum sensing based cell-to-cell communication system. Our *in silico* analysis using stochastic simulations reveals significant noise attenuation in gene expression through the interplay between quorum sensing and negative feedback, and explain their different roles for different noise sources. Preliminary *in vivo* results agree well with the computational results.

Palabras clave: cellular noise, noise attenuation, protein expression control, quorum sensing, feedback control.

1. Introduction

Noise is pervasive in the cellular mechanisms underlying gene expression [26]. It propagates to downstream genes at the single cell level, and eventually causes variation within an isogenic population [25, 19] that may determine the fate of individual cells and that of a whole population [8, 19].

At the gene level, noise can be traced back to intrinsic sources due to stochastic fluctuations in transcription and translation mechanisms, and extrinsic ones corresponding to gene independent fluctuations in protein expression due to external factors [8, 3, 14]. To minimize the deleterious effects of noise, cells have evolved different strategies at the single-cell level: from different transcription and translation efficiency so as to reduce translation burst rates in key genes [16] to more elaborated strategies, such as negative feedback regulation to reduce noise by shifting the noise spectrum to a higher frequency region [26]. Yet, cells live in communities, forming a population. At this

level, extracellular signaling propagates intracellular stochastic fluctuations across the population [34]. Thus, cells have adapted their communication mechanisms in order to improve the signal-to-noise ratio [40]. One of such communication mechanisms is quorum sensing.

Quorum sensing (QS), initially discovered in *V. fischeri* and *P. putida*, is a cell-to-cell communication mechanism whereby bacteria exchange chemical signaling molecules, called autoinducers, whose external concentration depends on the cell population density. It is known that synchronization and consensus protect from noise [33]. Cells detect a threshold concentration of QS autoinducers and alter gene expression accordingly [10], driving the population as a whole to achieve a desired consensus gene expression level despite the individual noise of each member of the population. Cells consensus induced by QS is thought to reduce extrinsic noise by reducing the transmission of fluctuating signals in the low-frequency domain [35], enhances intrinsic stochastic fluctuations [34], and allows entrainment of a noisy population when faced to environmental changing signals [22]. Therefore QS seems an effective tool to control the phenotypic variability in a population of cells [40].

Phenotypic variability has important practical relevance in many applications in the areas of biomedicine, biotechnology and other branches of biological science [11] as the presence of heterogeneous subpopulations may have significant impact on the yield and productivity of industrial cultures [21, 9, 2]. Thus, improving homogeneity of protein expression in industrial cultures is a goal of economic relevance for microbial cell factory processes. that has traditionally been attempted either by optimizing environmental conditions in the culture or by careful selection of the strain. Open loop strategies based on sensitivity analysis have been used to provide guides as to how properly tune transcriptional and translational parameters so that the noise levels can be controlled while the mean values can be simultaneously adjusted to desired values [18]. While sensitivity analysis gives very valuable insights, open loop control is

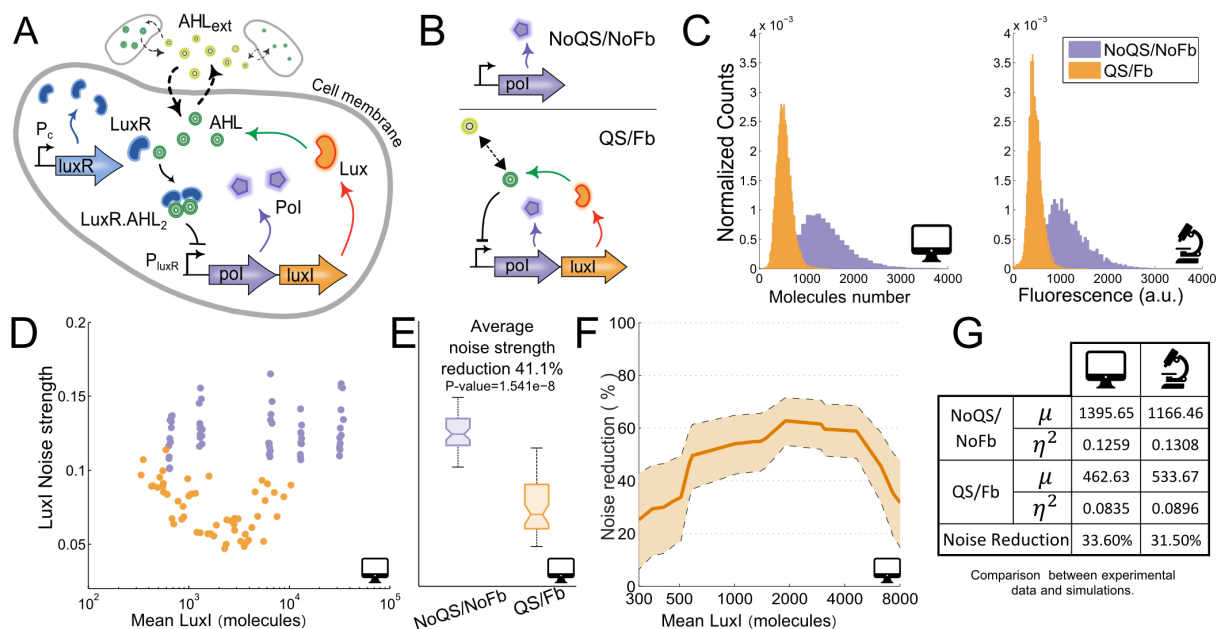


Figura 1: LuxI noise strength under presence/absence of quorum sensing and negative feedback. (A). Proposed synthetic gene circuit. (B) Circuits topologies: NoQS/NoFb (top) and QS/Fb (bottom). (C) Representative computational (left) and experimental (right) population histograms of LuxI noise strength for QS/Fb (orange) presenting a narrower gaussian-like distribution as compared to the Poisson-like one of NoQS/NoFb (purple). From computational simulations: (D) Sampled combinations of LuxI expression parameters for fixed LuxR ones show larger values of LuxI noise strength *vs.* mean for NoQS/NoFb (purple dots) than for QS/Fb (orange dots). (E) The QS/Fb circuit significantly reduces the average noise strength for the sampled parameters space by 41%, from $\langle \eta_{\text{NoQS/NoFb}}^2 \rangle = 0.1263$ down to $\langle \eta_{\text{QS/Fb}}^2 \rangle = 0.0744$. (F) For varying LuxI parameters the average reduction of noise strength in LuxI ranges from 30% up to 60% and shows dependence on the mean expression level. Data shown for LuxI means between the biotechnological relevant range [300, 8000] molecules/cell. (G) Comparison of experimental and computational statistical moments.

not robust against system uncertainty and/or variations. There is an ever-growing appreciation that biological complexity requires new bioprocess design principles.

Synthetic biology, sometimes defined as the engineering of biology, has the potential to engineer genetic circuits to perform new functions for useful purposes in a systematic, predictable, robust, and efficient way [38]. In the last years, several synthetic circuits have been proposed with the ultimate goal of dealing with gene expression noise [43, 44]. Though circuits using negative feedback have been proved to decrease gene expression noise [5], single-cell intracellular feedback loops do not take into account that in practice one is interested in controlling gene expression mean value and noise across a population of cells. Feedback across a population of cells can be implemented by means of quorum sensing-based strategies, and has been shown to reduce noise effects [35, 39, 40]. Indeed, cell-to-cell communication by means of quorum sensing induces consensus among cells [27], that is, contributes to reduce the difference of internal state among cells in a population. This, in turn, may contribute to protect from noise [33]. Thus,

the idea of joining both intracellular negative feedback and extracellular feedback via quorum sensing is a natural one, that has been suggested in [1, 37, 42].

In this work we analyze the synthetic gene circuit designed previously in [1] depicted in Fig 1A, designed to reduce gene expression noise while achieving a desired mean expression level in a protein of interest [37]. The circuit uses the repressible promoter P_{lux} designed in [7] to implement a negative feedback loop over the gene of interest, and adds a QS mechanism based on N-acyl-L-homoserine lactone (AHL) [31, 10] to induce population consensus (Section 2). We used the stochastic Chemical Langevin Equation [13] to explore the impact of some key circuit parameters on noise strength (Section 3). To assess the role played by feedback and QS we compared the proposed circuit, denoted as QS/Fb, with constitutive expression (NoQS/NoFb) (Fig. 1B). Extrinsic noise was modeled by randomizing values of the model parameters [15, 36]. Our *in silico* analysis (Section 4) reveals significant noise attenuation in gene expression through the interplay between quorum sensing and negative feedback, and explain their

different roles for different noise sources, highlighting the need for proper characterization of extrinsic noise. Preliminary *in vivo* (Section 5) results agree with the computational ones.

2. Circuit description

The synthetic gene circuit (Fig. 1A) combines two functional subsystems already implemented in *E. coli*. The first subsystem implements a cell-to-cell communication mechanism via quorum sensing, based on exchange of the small signaling autoinducer molecule N-acyl-L-homoserine lactone (AHL) [17, 10]. This autoinducer molecule passively diffuses across the cellular membrane to and from the external environment. Intracellular AHL is synthesized by the protein LuxI expressed by an homolog of the gene *luxI* of *V. fischeri* [31]. The second subsystem uses the synthetic repressible promoter P_{lux} designed in [7] to control transcription of the gene *luxI*. This promoter is repressed by the transcription factor $(\text{LuxR.AHL})_2$. Protein LuxR is expressed by gene *luxR* under the constitutive promoter P_c . Proteins LuxR and AHL bind creating the heterodimer (LuxR.AHL) , which subsequently dimerizes forming the heterotetramer $(\text{LuxR.AHL})_2$. This way, the negative feedback control of the LuxI expression is effectively implemented.

3. Mathematical model

To analyze how our genetic circuit affects intrinsic and extrinsic noise, we needed an appropriate model and a computationally efficient method. Both aspects are intertwined. We considered an equivalent set of pseudo-reactions resulting from the deterministic model of the circuit, and then derived a stochastic model for a population of N cells whose mean corresponds to that of the deterministic one. We used the Chemical Langevin Equation approach (CLE). Though computationally much more efficient than the Chemical master equation (CME) or even the Gillespie algorithm, the CLE is still computationally demanding when the goal is to simulate a whole population of cells. Since the CLE approximates the CME by a system of stochastic differential equations of order equal to the number of species, a reduced deterministic model with as few species per cell as possible was desirable.

3.1. Reduced deterministic model

We aimed at obtaining a reduced model more amenable for computational analysis, but avoiding excessive reduction that would lead to lack

of biological relevance. In particular, the species we obtained in the reduced model are not lumped ones. Reduced models accounting for total mRNA and total transcription factor have been proposed to match modeled species with measurable ones [12]. In our case we explicitly modeled bound and unbound forms of the transcription factor, but the model accounts for the total LuxI protein. For our circuit this is a good proxy for the amount of protein of interest if both are co-expressed, and transcriptional noise dominates.

Thus, in a first step we used the mass-action kinetics formalism [4] to get a deterministic model of the full reactions network corresponding to the genetic circuit [1]. We then got a reduced order model by applying the *Quasi Steady-State Approximation* (QSSA) on the fast chemical reactions and taking into account invariant moieties [1, 20, 24]. The resulting deterministic reduced model is described by equations (1)-(2).

$$\begin{aligned}
 \dot{n}_1^i &= \frac{C_{\text{IPI}}}{d_{\text{mI}}} \left(\frac{k_{\text{dLux}} + \alpha n_3^i}{k_{\text{dLux}} + n_3^i} \right) - d_{\text{I}} n_1^i \\
 \dot{n}_2^i &= \frac{C_{\text{RPR}}}{d_{\text{mR}}} + k_{-1} n_6^i - \left(\frac{k_{-1}}{k_{\text{d1}}} n_4^i + d_{\text{R}} \right) n_2^i \\
 \dot{n}_3^i &= \frac{k_{-2}}{k_{\text{d2}}} (n_6^i)^2 - (k_{-2} + d_{\text{RA}2}) n_3^i \\
 \dot{n}_4^i &= k_{-1} n_6^i + k_{\text{A}} n_1^i + D (V_c n_5 - n_4^i) - \left(\frac{k_{-1}}{k_{\text{d1}}} n_2^i + d_{\text{A}} \right) n_4^i \\
 \dot{n}_5 &= D \left(-N V_c n_5 + \sum_{i=1}^N n_4^i \right) - d_{\text{Ae}} n_5
 \end{aligned} \tag{1}$$

with:

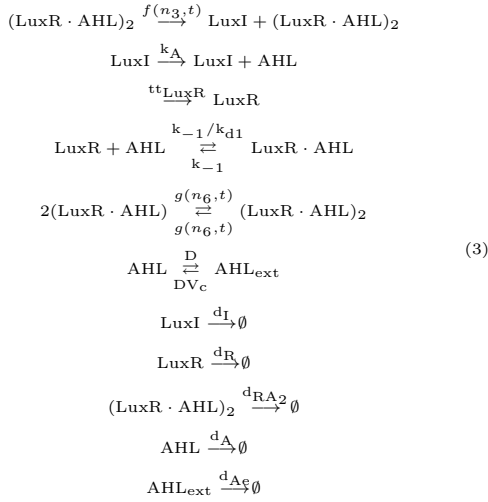
$$n_6^i = \frac{k_{\text{d2}}(d_{\text{RA}} + k_{-1})}{4k_2} \left[\sqrt{\frac{8k_{-2}(2k_{-2}k_{\text{d1}}n_3^i + k_{-1}n_2^in_4^i)}{k_{\text{d1}}k_{\text{d2}}(d_{\text{RA}} + k_{-1})^2} + 1} - 1 \right] \tag{2}$$

where $\mathbf{n}(t)^i = [n_1(t)^i, n_2(t)^i, n_3(t)^i, n_4(t)^i, n_6(t)^i]^T$ is the vector of species LuxI, LuxR, $(\text{LuxR.AHL})_2$, intracellular AHL and (LuxR.AHL) for the i^{th} cell respectively, and n_5 is the extracellular AHL_{ext} .

3.2. Stochastic model

To model gene expression intrinsic noise we derived a stochastic CLE-based model whose mean corresponds to that of the deterministic reduced model (1)-(2). To this end we first considered the equivalent set of pseudo-reactions (3) for the de-

terministic model in the i^{th} cell.



where we denoted $f(n_3^i, t) \triangleq \frac{C_{\text{IPI}}}{d_{\text{mI}}} \left(\frac{k_{d\text{lux}} + \alpha_I n_3^i}{k_{d\text{lux}} + n_3^i} \right)$ as the Hill-like function associated to LuxI expression, $g(n_6^i, t)$ corresponds to the dimerization reflected in equation (2), and $\text{tt}_{\text{LuxR}} = \frac{C_{\text{RPR}}}{d_{\text{mR}}}$ represent the transcription-translation activity of *luxI* and *luxR* respectively, $V_c = \frac{V_{\text{cell}}}{V_{\text{ext}}}$ is the ratio between the cell volume and the culture medium volume, and \emptyset denotes species degradation.

For the computational analysis we used the Euler-Maruyama discretization (4) of the stochastic model resulting from the set of pseudo-reactions (3) :

$$\mathbf{n}(t+\delta t) = \mathbf{n}(t) + \mathbf{S} \cdot \mathbf{a}(\mathbf{n}) \delta t + \mathbf{S} \cdot \mathcal{N} \cdot \sqrt{\mathbf{a}(\mathbf{n})} \sqrt{\delta t}, \tag{4}$$

where $\mathbf{n}(t) = [\mathbf{n}(t)^i, \dots, \mathbf{n}(t)^N, n_5]^T$ are the number of molecules of each species in the population. The stoichiometry matrix \mathbf{S} , whose elements are the stoichiometry submatrices for each cell \mathbf{S}_{cell} and the external stoichiometry \mathbf{S}_{ext} , has structure:

$$\mathbf{S} = \left[\begin{array}{c|c} \mathbf{S}_{\text{cell}} \otimes \mathbf{I}_N & \mathbf{0}_{N \times 1} \\ \hline \mathbf{S}_{\text{ext}} \otimes \mathbf{1}_{1 \times N} & -1 \end{array} \right], \tag{5}$$

where \otimes is the Kronecker product, \mathbf{I}_N the identity matrix of dimension $N \times N$, $\mathbf{0}_{N \times 1}$ and $\mathbf{1}_{1 \times N}$ are vectors of zeroes and ones respectively, and the coefficients in the stoichiometry matrices \mathbf{S}_{cell} and \mathbf{S}_{ext} , obtained from the set of pseudo-reactions (3), are:

$$\begin{aligned}
 \mathbf{S}_{\text{cell}} &= \begin{bmatrix} 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & -1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 & 1 \end{bmatrix} \\
 \mathbf{S}_{\text{ext}} &= [0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 1 \ -1].
 \end{aligned}$$

The term $\mathbf{a}(\mathbf{n})$ in (4) is the associated vector of reaction propensities for the whole population of

cells, with:

$$\begin{aligned}
 \mathbf{a}(\mathbf{n}) &= \left[\mathbf{a}(\mathbf{n})^1 \quad \mathbf{a}(\mathbf{n})^2 \quad \dots \quad \mathbf{a}(\mathbf{n})^N \quad | \quad d_{\text{Ae}} n_5 \right]^T \\
 \mathbf{a}(\mathbf{n})^i &= \left[f(n_3^i, t) \quad d_I n_1^i \quad \frac{C_{\text{RPR}}}{d_{\text{mR}}} \quad k_{-1} n_6^i \quad \frac{k_{-1}}{k_{d1}} n_2^i n_4^i \right. \\
 & \quad d_R n_2^i \quad \frac{k_{-2}}{k_{d2}} (n_6^i)^2 \quad k_{-2} n_3^i \quad d_{\text{RA}_2} n_3^i \quad k_A n_1^i \\
 & \quad \left. d_A n_4^i \quad D n_4^i \quad D V_c n_5 \right]^T
 \end{aligned}$$

Finally, $\mathcal{N}_{(JN+1) \times (JN+1)}$, where $J = 13$ is the number of reactions for the i^{th} cell, is a diagonal matrix of continuous normal random variables with zero mean and unit variance.

Notice we used lumped propensity functions derived from the reduced model, like the $f(n_3)$ Hill-like function associated to LuxI repression. This approach has already been used in [41]. We validated it for our model by simulating the pseudo-reaction associated to $f(n_3^i)$ using CLE, and comparing the result with that obtained by simulating the set of corresponding original reactions using Gillespie's direct method SSA [1].

Extrinsic noise was modeled by randomizing the values of the model parameters [15, 36], an approach that can easily be integrated within the CLE framework. We assumed a normal distribution to generate the model parameters of the i^{th} cell in the population.

The stochastic simulations we performed for 400 min using $\delta t = 25 \cdot 10^{-4}$ sec.

4. Computational analysis

We used the stochastic model (4) of the proposed circuit, hereafter denoted as circuit QS/Fb, to explore the impact of some key circuit parameters on noise. As control circuit to compare with, we considered a second circuit which removes both QS and the feedback loop, denoted as NoQS/NoFb. For the computational analysis, this accounts to setting the synthesis of AHL to zero ($k_A = 0 \text{ min}^{-1}$) in model (4). This condition is achieved in the lab experimental implementation by taking out the gene coding for LuxI (Section 5).

Gene expression noise was evaluated using the squared coefficient of variation, i.e. the noise strength measure ($\eta^2 = (\sigma/\mu)^2$). This measure properly captures the contributions of both intrinsic and extrinsic noise [23], and allows comparisons for different expression rates.

We followed the following general procedure. First, for different combinations of the model parameters, we performed temporal simulations of the number of molecules of each species in the circuit for every cell in the population of our sys-

tem. Extrinsic noise was modeled by randomizing the values of the model parameters using a normal distribution with a variance of 15%. The models were implemented using OpenFPM (<http://openfpm.mpi-cbg.de>), a C++ version of the Parallel Particle Mesh (PPM) library allowing efficient computational particle-mesh simulations [30]. The code is available in (<http://sb2c1.ai2.upv.es/content/software>). In all simulations we used a population of $N = 240$ cells in a culture volume of $10^{-3} \mu\text{l}$, corresponding to an optical cell density $\text{OD}_{600} = 0.3$.

Then, we obtained the first two statistical moments μ and σ^2 for each species in the cell population at every time t_k . We used the laws of total expectation and total variance. From these moments, we calculated long-term distributions to infer the noise strength of each species.

Finally, we explored the effect of variations in parameters associated to expression of LuxI and LuxR, as they are as key parameters in our circuit. For LuxI, we considered the dissociation constant k_{dLux} between the transcription factor $(\text{LuxR} \cdot \text{AHL})_2$ and the repressible P_{lux} promoter, the translation rate p_I , and the basal expression α_I of the P_{lux} promoter. We sampled in the ranges $k_{\text{dLux}} = [10 - 2000]$ molecules, $\alpha = [0.01 - 0.1]$, and $p_I = [0.2 - 10] \text{ min}^{-1}$ selected from the literature [28, 6, 32] and experimentally achievable in the lab. As for LuxR, we considered two values for the the translation rate p_R : a strong RBS ($p_R = 10 \text{ min}^{-1}$), and a medium-weak one ($p_R = 2 \text{ min}^{-1}$).

5. Strains, plasmids and experimental protocol

To validate the *in silico* computational results, we implemented the QS/Fb and NoQS/NoFb circuits *in vivo*. We used components from the iGEM Registry of Standard Biological Parts. All parts were cloned using the Biobrick's foundation 3 Antibiotic Assembly method. All coding sequences have the double-terminator BBA_B0015, and were confirmed by sequencing. The circuit QS/Fb couples both QS-based cell-to-cell communication and the negative feedback subsystems. It was split in two subunits integrated in different plasmids.

On the one hand, plasmid pCB2tc contains the gene *luxR* (part BBA_C0062) coding for the protein LuxR constitutively expressed under the control of a medium strength promoter (part BBA_J23106), and a strong RBS (part BBA_B0034).

This insert was cloned into the pACYC184 plasmid cloning vector (p15A origin, 10-12 copies/cell, chloramphenicol/tetracycline [29]).

On the other hand, plasmid pYB06ta contains gene *luxI* (part BBA_C0161) under control of the P_{luxR} repressible promoter (part BBA_R0062) and a strong RBS (part BBA_B0034). The strong RBS BBA_B0034 and the green fluorescent protein (GFP, part BBA_E0040) were inserted using GIBSON assembly (NEB Catalog Number E2611S) upstream of *luxI*, right after the P_{luxR} promoter. This way, GFP, used as protein of interest (PoI in Fig. 1A) is co-expressed with LuxI.

They were inserted into the pBR322 plasmid cloning vector (pMB1 origin, 15-20 copies/cell, ampicillin/tetracycline [29]). Finally, both plasmids pCB2tc and pYB06ta were co-transformed in competent cells (DH-5 α , Invitrogen). Notice being both plasmids low copy ones, they do not introduce a big metabolic burden on the cell. On the other hand, their variability is quite narrow so gene copy number will not be the only relevant extrinsic noise source in the experimental setup.

As control network, we implemented the circuit NoQS/NoFb which removes both QS and the feedback loop. To this end, the plasmid pCB2tc above was co-transformed with the plasmid pAV02ta (pMB1 origin, ampicillin/tetracycline) containing only GFP downstream of the P_{luxR} repressible promoter (part BBA_R0062) and the the strong RBS (part BBA_B0034). Both were cloned in the pBR322 plasmid cloning vector.

5.1. Experimental protocol

For the experimental validation of the circuit (protocol details are in [1]), two sets of *E. coli* cells (cloning strain DH-5 α) carrying the QS/Fb and NoQS/NoFb circuits respectively, were inoculated from -80°C stocks into 3 mL of LB with appropriate antibiotics, followed by an overnight incubation at 37°C and 250 rpm in 14 ml culture tubes. When the cultures reached an optical density (OD) of 4 (600 nm, Eppendorf BioPhotometer D30), the overnight cultures were diluted 500-fold (OD_{600} of 0.02) into M9 medium with appropriate antibiotics. These were used to inoculate new cultures, which were incubated for 7 hours (37°C , 250 rpm, 14 ml culture tubes) until they reached an OD_{600} between 0.2–0.3. At this point, cell growth and protein expression were interrupted by transferring the culture into an ice-water bath for 10 min. Next, 50 μL of each tube were transferred into 1 ml of phosphate-buffered saline with 500 $\mu\text{g}/\text{mL}$ of the transcription inhibitor rifampicin (PBS + Rif) in one 5 mL cytometer tube, and incubated during 1 hour in a water bath at 37°C , so that transcription kept blocked and GFP had time to mature and fold properly. Samples were measured at different time points using the BD

FACSCalibur flow cytometer (original default configuration parameters), and flow cytometry data analyzed with custom scripts.

6. Results

We first addressed the question whether the proposed QS/Fb circuit effectively reduces noise strength with respect to the circuit NoQS/NoFb (Fig. 1B). The last one consists of the LuxR expression on the one hand, and the protein of interest (PoI) downstream the P_{lux} repressible promoter, without the luxI gene coding for LuxI protein, on the other. Since no autoinducer *AHL* is neither produced nor externally introduced, there is no repression, so the expression of PoI is essentially a constitutive one (Section 2). This corresponds to the Poisson distribution observed in the purple population histogram in the left panel of Fig. 1C. Contrarily, the QS/Fb histogram departs from the Poisson distribution to become a narrow Gaussian-like one in the orange population histogram in the left panel of Fig. 1C. This fact, and the reduction in the mean expression value, indicate the strong presence of regulation. In both cases we used the nominal circuit parameters [1].

Reduction in noise strength was not due to a particular choice of the circuit parameter values, but a property of the proposed topology. Fig. 1D depicts LuxI noise strength *vs.* mean expression for 60 different combinations of the P_{LuxR} characteristics for both QS/Fb (orange points) and NoQS/NoFb (purple points). The points in the figure correspond to the mean values across the cells population for each combination of parameters (Section 4). The magnitude of noise strength reduction was larger for medium values of mean protein expression. Noise strength levels were similar for all mean expression values in the case of the NoQS/NoFb circuit. Mean expression values in this case depend only on the translation rate p_I for which five discrete values were used, inducing the five mean values seen in the figure. On the contrary, the QS/Fb circuit showed lower values of noise strength and more graded values of the mean expression level, as it depends on the combination of all three parameters varied.

More important, noise strength was consistently lower for the QS/Fb circuit. Taking together all the different combinations of promoter parameters for each circuit, and the average noise strength was significantly reduced by 41 % in the presence of quorum sensing and negative feedback as shown in Fig. 1E.

For the given fixed LuxR expression parameters, the noise strength reduction in LuxI showed a

clear dependence on its mean expression level. In Fig. 1F the minimum and maximum values of LuxI noise reduction are plotted as a function of its mean value. In the range between 600 and 6000 LuxI molecules it was possible to reduce the noise variance at least in 35 % in the worst case scenario, with a maximum reduction of around 70 % for means between 2000 and 3000 molecules.

7. Conclusion

Our results show that gene synthetic circuits benefiting from the interplay between feedback and cell-to-cell communication allow control of the mean expression level and noise strength of a protein of interest. A few circuit parameters easy to tune in the wet-lab can be used to achieve noise strength reductions up to a 60 % with respect to constitutive expression of the protein of interest.

Mean expression level and noise strength are not independent goals. At low mean values intrinsic noise dominates and sets the minimum noise strength attainable. At high mean values extrinsic noise dominates. Thus, there is a trade-off between expression level and noise strength, as revealed both by system-wide experimental data and theoretical analysis reported in the literature. Our computational results fitted well in this scenario, and suggest that tuning synthetic gene circuits to minimize noise while achieving a desired expression level will require a multi-objective optimization approach.

The experimental results, though preliminary, showed a high concordance the computational ones and confirmed the capability of the proposed circuit to reduce noise strength.

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